

Refocusing Priorities in Alcohol Research

A Report by the Physicians Committee for Responsible Medicine

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Alcohol consumption has many effects on health. It was with those consequences in mind that Congress and President Nixon enacted the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970,¹ authorizing a comprehensive, federally funded program to address prevention and treatment of alcohol abuse and alcoholism. From this Act grew the National Institute of Alcohol Abuse and Alcoholism (NIAAA), which now stands as the largest funder of alcohol research in the world, administering nearly \$500 million in grants in FY 2013.²

NIAAA funds a broad range of alcohol research, including studies on genetics, neuroscience, epidemiology, prevention, and treatment.³ In addition to addressing health risks associated with alcohol consumption, NIAAA grant-funded research projects examine potential health benefits of alcohol and seek to understand the causes of addiction. NIAAA also funds research to develop effective prevention and treatment strategies to address excessive and underage alcohol consumption.

Alcohol and Health

Alcohol use has well-known short- and long-term health consequences. Short-term risks include acute alcohol poisoning, drunk driving and other risky behaviors, and increased violence. Chronic alcohol abuse has been linked with liver, heart, and intestinal diseases, certain cancers, fetal abnormalities, neurologic and psychiatric disorders, and many social problems.

Past efforts to address these problems have focused especially on legal and social measures: limiting alcohol availability (e.g., reducing the number of outlets selling alcohol), increased taxation, increasing the minimum drinking age, and strengthening blood alcohol content laws. Each of these has had a demonstrable effect on reducing alcohol abuse.⁴⁻⁶ Underage drinking has declined annually, since 2002, from 28.8% to 25.1%.⁷ Rates of drunk driving are also declining; dropping over 20% in the last 10 years to 11.1%.⁷ While this decline is encouraging, alcohol-related deaths have remained steady at nearly 80,000 per year, since 2002.⁸ Furthermore, the Centers for Disease Control estimated that in 2006 there were over 1.2 million emergency room visits and over 2.7 million physician office visits due to excessive drinking.⁸ The economic impact of the excessive drinking was estimated at \$223.5 billion.⁸

Current NIAAA Research Priorities

NIAAA research programs focus on 6 priority areas:⁹

1. **Medications development:** NIAAA's Medications Development Program focuses on expanding safe and effective medication options for alcohol use disorders and alcohol-induced organ damage.
2. **Underage and College Drinking Program:** The goal of this program is to understand the factors leading to the onset of drinking and progression to abuse and dependence. NIAAA supports more than 30 projects that target college-age youth.
3. **Fetal Alcohol Spectrum Disorders Program:** Accounting for nearly 10% of NIAAA's research and training budget, this program includes projects on pre-pregnancy prevention of alcohol abuse,

treatment of women with alcohol use disorders during pregnancy, improving diagnosis of FASD, and interventions for children with FASD.

4. **Combined Pharmacotherapies and Behavioral Intervention Study:** The COMBINE Study was the largest pharmacotherapy trial conducted for alcoholism in the United States. This study tested the efficacy of two currently approved drugs (naltrexone and acamprosate) for reducing alcoholic dependency.
5. **Collaborative Study on the Genetics of Alcoholism:** Data have been collected on more than 3000 people from over 300 extended families, in which many members are affected by alcoholism. The researchers have collected extensive physiologic and genetic data from these individuals to elucidate the role of genetics in alcohol use disorders. The researchers also have established a repository of cell lines from these individuals to serve as a permanent source of DNA for genetic studies.
6. **NIAAA-Funded Research Centers:** NIAAA has established a nationwide program of 27 Alcohol Research Centers. The Alcohol Research Centers provide long-term support for interdisciplinary research focusing on aspects of alcohol abuse, alcoholism, or other related problems.

Of these priority areas, two have obvious urgency. Underage drinking and fetal alcohol syndrome are overlapping problems affecting large numbers of people with consequences extending far into the future. Alcohol is the most commonly used and abused drug among youth in the United States, accounting for more than 4,700 annual deaths and 189,000 emergency room visits in 2010.⁸ However, there are important signs of progress. Since 2002, there has been a 30% decrease in binge drinking rates among adolescents, from 10.7% to 7.4%, and a concurrent increase in the perceived risk of binge drinking (i.e. understanding that binge drinking has health risks) from 38.2% to 40.7%, suggesting that prevention and education campaigns have been effective.¹⁰

Fetal alcohol syndrome (FAS) is the leading preventable cause of mental retardation. Although a 2005 Surgeon General's report¹¹ and many other authoritative reports have recommended that women who are pregnant or may become pregnant abstain from alcohol use, there has been little change in alcohol consumption or binge drinking rates among pregnant women in the past 30 years.¹² FAS incidence has also remained steady at about 1 per 1000 live births. Treatment of FAS is a lifelong process. FAS is a highly variable syndrome that can present with physical, intellectual, and behavioral components. Clinical (human) research has demonstrated that early intervention is the most effective treatment and has the most marked effect on the child's development.¹³ Behavioral therapies, such as executive functioning training, socializing skills, specialized tutoring, and parent-child interactive training, are consistently the most effective treatments for children with FAS. Some children benefit from alternative therapies, such as nutritional supplementation, biofeedback, and relaxation therapy. Medication does play a role in treatment of children with FAS; however, no medications are specifically approved to treat children with FAS.¹³ Medication is used only to treat symptoms, and due to its variability, no single medication is effective for all children.

In all of the above cases, the key contributions to understanding, preventing, and treating the outcomes of alcohol consumption have come from human-based studies.

Refocusing Research on Humans

NIAAA administers nearly 1,400 grants at 250 institutions, annually, with a total budget of approximately \$491 million.² While about \$145 million of NIAAA funding goes to clinical (human) research programs in prevention, treatment, and health services;¹⁴ nearly 700 NIAAA grants totaling \$216 million, include animal experiments.² Most animal experiments fall into three general categories: (1) design and testing of medications to reduce alcohol craving and treat organ damage due to alcohol, (2) testing neurologic effects of alcohol throughout the lifecycle, and (3) examining genetic markers of alcoholism through behavioral studies.

Medications: The role of animal experimentation in the development of medications for alcohol abuse and alcoholism is based upon the assumption that modeling specific characteristics of alcoholic disease will lead to identification of clinically effective compounds.¹⁵ Despite significant and ongoing efforts, medications development research has born little fruit. Over the past 20 years, over 100 different drugs have had positive results in animal experiments. Based upon results from the animal experiments, NIAAA has sponsored over 130 clinical trials of drugs to treat alcohol use disorder, involving over 25,000 people.¹⁶ From those trials, only one new drug has been approved by the FDA.¹⁷

Although animals and humans have many similar physiological processes, there are also many differences. Medication development for alcohol use disorder has primarily relied on examining, in an animal, a single metabolic process that is relevant to alcohol use. To model the effect of alcohol use, experiments may need to create animals with significant genetic mutations and use interventions that have little to do with alcohol consumption. For example, in an experiment funded by NIAAA and conducted at Duke University, researchers attempted to create a model of alcoholic cirrhosis, hoping to find a compound to minimize liver scarring.¹⁸ In this experiment, they first created 9 different genetically mutant mouse strains, with 3 – 8 different mutations per strain. Then, liver damage was created by feeding a diet deficient in methionine and choline. Alcohol was never administered to the mice. While liver damage was created, it required a method fundamentally different from the course of alcoholic liver cirrhosis in humans. Differences in disease onset, course, physiology, duration, and pathology may result in promising therapies in animal experiments, that later fail in human trials.

Medications have a role in alcohol treatment, but their importance in relation to other treatment factors remains a matter of discussion. NIAAA animal-based grants specifically searching for new drugs have a combined annual budget of approximately \$20 million (average grant budget ~ \$358,000 per year).² Six of the grants, representing five institutions (University of North Carolina, NIAAA, Angion Biomedica, Medical University of South Carolina, and University of Wisconsin) have annual budgets greater than \$1 million.² Many other NIAAA-funded grants are not specifically testing new medications, but state a goal of eventually developing one with their findings. The need for new medications and the value of animal models in producing useful candidate drugs remain in question.

Neurologic Effects: Alcohol consumption has significant effects on the brain. Global effects, such as changes in emotions, personality, impaired perception, learning, and memory are all well-known in alcoholic humans.¹⁹ Human studies have also established specific neurologic effects associated with alcohol consumption, including reward, stimulation, sleep disturbance, and hyperexcitability.¹⁹ Health problems associated with alcoholism, particularly vitamin deficiencies and liver disease, also contribute to neurologic disorders. Animal experiments attempt to replicate components of both the global and specific neurologic actions.

Neurologic experiments associated with alcohol use often focus on behavior, with the goal of using animal behavior to understand specific changes in the brain; yet, often requiring assumptions about similarities between animals and humans.²⁰ For instance, the dependent-Wistar strain of rat, having gone through periods of intoxication and withdrawal, will consume large quantities of alcohol if it is available during the withdrawal period.²¹ While this appears to be similar to heavy drinking in humans, the rats must first be selectively bred to be predisposed to drinking large quantities of alcohol. Not only are the subjects rodents with innumerable differences from humans, but they must be a specific genetic mutant rat, suggesting that findings may not even apply to other rats.

An example from Scripps Research Institute involved training monkeys to drink sweetened alcohol, followed by an experiment designed to test dexterity and memory.²² The results of these tests were interpreted in the context of human adolescent cognitive impairment and only suggested the possibility of a prolonged response time to stimuli; unlike human studies which have repeatedly demonstrated the significant relationship between alcohol consumption and prolonged response time. A mismatch between human and animal studies can delay and misinform human therapies.

A study from Oregon Health Sciences University examined the neurologic effects associated with withdrawal tremors by placing mice on a rotating rod following chronic alcohol vapor inhalation.²³ The duration the mice remained on the rod before falling off was interpreted to be related to alcoholic tremors, even though tremors were never observed and the method of alcohol delivery was very different from human consumption. None of these models fully parallels human alcoholism in etiology, symptoms, or prognosis, particularly in cognitive and social domains, yet all of the experiments described above aimed to relate their results to the human condition.

NIAAA funds many animal-based grants which examine various neurologic aspects of alcohol abuse and alcoholism. In FY 2013, 157 grants had neurologic experiments as a primary goal. These grants accounted for 20% of all animal-based grants, with a total annual budget of over \$40 million.² Ten of the grants, representing just four institutions (NIAAA, Oregon Health Sciences University, Scripps Research Institute, and Yale), had annual budgets greater than \$1 million.²

Genetic Markers: Numerous human studies have examined the role of genetics in alcohol-related conditions. Typically, these studies rely on matching a population, currently being treated for alcoholic disease, with a similar non-alcoholic population.²³ The results of these studies have not shown major effects of specific genes to alcoholism. Further, even very large studies, including twins and family members, have not demonstrated that genes play a decisive role in alcoholic disease.²³

These findings contrast with results from animal experiments, which have reported genetic links to alcohol use and abuse, primarily in mice.²³ Many genetic links have been described in animals, including tolerance, withdrawal, devotion of time to obtaining alcohol, impulsivity, and cognitive decline.

Analysis of NIAAA administered animal-based grants for FY 2013 revealed that over 90% (over \$180 million annual budget²), utilized some form of genetically modified mouse or rat. Virtually every significant area of alcohol research, including neurologic, developmental, immunity, organ damage, and medication development and testing involved creating genetically mutant and inbred mice to attempt to model a specific portion of alcoholic disease and/or determine the impact of genetics on alcoholism. The consistency of human studies in showing no major genetic component of alcohol disease lends significant question to the outcomes of animal-based genetic studies.

There are no truly homologous animal models of alcoholism.^{22,23} Animals can only model simple facets of alcoholism. Even then, "the animal model is only designed to be predictive and does not need to resemble the etiology or symptoms of human alcoholism."²² NIAAA funding of this approach to alcohol research has resulted in many animal-based experiments lasting over a decade (Table 1), with no improvement in human therapeutic outcomes.

Grant Question	Institution	Annual Budget	Grant duration (yrs)	How are animals used	Human related studies
How does alcohol bind to receptors in the brain? Could these receptors be targets for new drugs?	University of Texas, Austin	\$475,647	31	Mice are inbred to have one of six different forms of a neuron receptor (GABA). Mice were then intravenously injected with alcohol and placed on a rotating rod. The time they stayed on the rod is used as a measure of motor coordination. To confirm the changes were related to motor coordination, mice are placed in elevated mazes and hung on bars to measure grip strength. Mice were also exposed to hypothermic conditions to measure the effect of alcohol on body temperature. ²⁴	Since 2003, 34 clinical trials, with 3800 people, have been conducted with 4 different drugs in this class. One study suggested Baclofen might decrease the need for other drugs to treat withdrawal. ¹⁶ No new drugs have been approved in this class.
How does alcohol exposure during pregnancy affect sensory function in the baby?	University of Maryland, Baltimore	\$346,176	13	Ten-day old ferrets were given intraperitoneal injections of alcohol every other day for three weeks to get blood alcohol content to 0.25. They were then left alcohol-free for 10 days. One eye was then sewn shut for 4 days. Later, the eye was then re-opened and optical responses were compared with ferrets not receiving the alcohol. ²⁵	Ocular abnormalities have been linked to fetal alcohol syndrome in human babies for at least 40 years. ²⁶
How does alcohol consumption, during pregnancy affect neurologic development in the baby?	Texas Agrilife	\$313,667	14	Pregnant sheep were given intravenous alcohol infusions three days a week for four weeks. Their blood alcohol content was increased to 0.2 – 0.26 (In a human, this level is associated with severe impairment of all mental, physical, and sensory functions). The ewe was then killed, the lamb removed, and the brain removed for examination. ²⁷	Neurologic effects of alcohol on the fetus have been known and repeatedly described in human infants since 1973. ²⁶
Do genetics play a role in causing severe alcohol withdrawal symptoms?	Oregon Health Sciences University	\$1,774,468	18	Inbred mice were given sweetened alcohol to drink. They drank 5-10 times as much alcohol, on a per-weight basis, as a human. Withdrawal symptoms were determined by picking the mouse up by the tail and twirling it around in an arc to elicit convulsions. ²⁸	Genes associated with alcohol withdrawal syndrome were identified in human alcoholics in 1998. ²⁹
Does alcohol consumption contribute to increased AIDS-virus replication	Louisiana State University	\$1,682,020	20	Monkeys had a tube surgically implanted into their stomach, through which alcohol was administered. Three months later, they were infected with Simian Immunodeficiency Virus. Four months later, they were infected with pneumonia. Lung samples were taken from the monkeys 7 times over the next 3 months. ³⁰	A human-based link between alcohol and HIV infectivity has been repeatedly confirmed in humans since 1995. ³¹
How does alcohol consumption complicate burn injury	Loyola University, Chicago	\$411,997	13	Mice had alcohol administered by a stomach tube. Four hours later, 15% of their body was shaved and then they were placed in scalding hot water for 8 seconds. One day later they were killed. ³²	These studies have confirmed the findings from humans, but have not produced improvements in therapy for burn victims.

Table 1: Representative NIAAA-administered grants, from FY 2013, which use animals and have been funded for more than 10 years. Nearly 20% of the 672 NIAAA-administered grants using animals have been funded for more than 10 years.

Animal Welfare in Alcohol Experiments

From the standpoint of animal welfare, experiments in alcohol research can be highly stressful (Appendix 1). Because animals do not naturally consume alcohol, it is often administered in ways that are not representative of human consumption patterns. For example, alcohol can be delivered via a tube inserted into the stomach or administered as an aerosol.²⁰ Implantation of a stomach tube carries a significant risk of pain and peritonitis. Aerosolized alcohol is an irritant to the eyes and to any wounds. Alcohol may also be mixed in a solution to be the sole source of calories.²⁰ A totally liquid diet is unnatural to the animals receiving it and causes digestive problems.

Due to significant species differences in metabolism; the quantities of alcohol administered may be far greater than would be consumed by a human. Experiments with rats at the National Institute of Drug Abuse describe the administration of over 10 grams of alcohol per kilogram of body weight every day.³³ For an average adult human, this would be equivalent to drinking over one-half gallon of whiskey daily.³⁴ For monkeys, experiments at Scripps Research Institute involved administration of 2 grams of alcohol per kilogram of body weight, equivalent to an average-sized human consuming 10 glasses of whiskey per day.³⁵ This volume of whiskey is double that of the definition of binge drinking.³⁶ These significant differences indicate the highly artificial nature of many animal studies in alcohol research.

Because environmental, social, and cultural cues roles in the development of alcoholism, many animal experiments have subjected animals to highly stressful environments in attempts to model the antecedents of human alcoholism. For example, multiple experiments have examined the effect of removing infant monkeys from their mothers to illustrate the role of stress.³⁷ In other experiments, researchers have placed animals in physical isolation and/or barren environments. Similarly, the stress-inducing effects of overcrowding have been modeled by putting eight water-deprived rats (each rat would have approximately 8.5 in² of cage space; about one-third the regulatory standard and only 2 in² greater than the floor space covered by the rat³⁸) into a cage with alcohol to measure increased consumption.³⁹ Human cultural and social cues are modeled by putting monkeys and rats in stressful situations of dominance and subordination.³⁷ All of these experiments awkwardly mimic well-documented factors in human alcohol abuse. All are severely hampered by artificiality, as it is impossible to discern a social response from a generalized stress response, in an animal.³⁷

Re-establishing priorities

Alcoholism is a complex disease, caused by many factors that can change markedly over time. To the extent these complexities are clinically relevant; they merit investigation in the species of interest, humans. The toxic effects of alcohol and many of the factors that influence the success of treatment are already well known. Future research should aim to find ways modify the complex web of social, behavioral, neurologic, and physical factors that sustain drinking.

At their best, research efforts identify shortcomings in public-health interventions and clinical treatments and find ways to improve them. It may be especially valuable to link research efforts with public health policy initiatives to investigate their effectiveness and to explore ways to improve them. To this end, the 2011 *National Prevention Strategy* of the Surgeon General⁴⁰ made three specific recommendations towards preventing excess alcohol consumption:

1. Support state, tribal, local, and territorial implementation and enforcement of alcohol control policies.
2. Create environments that empower young people not to drink alcohol.
3. Identify alcohol disorders early and provide rapid intervention, referral, and treatment.

The Surgeon General's report lists nine specific actions that the federal government will take related to preventing drug abuse and excessive alcohol use. These actions include fostering the development of a nationwide community prevention system; monitoring youth exposure to alcohol marketing; and improve links between drug prevention, substance abuse, mental health, and juvenile and criminal justice agencies in order to develop and share effective methods of prevention. There is an important role for research in assessing the efficacy of these interventions and improving them when necessary.

A human-based approach to alcohol research will have the advantage of applicability to clinical problems without the need for extrapolation from animal models, as well as the obvious benefit from the standpoint of animal welfare.

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Appendix 1: Examples of Animal Experiments funded by NIAAA

1. Alcohol consumption decreases a person's ability to concentrate and increases response time. A 2013 manuscript, from Scripps Research Institute, described an experiment which was funded by the NIAAA (Grants: AA016807 & AA007456), seeking to determine the short- and long-term effects of alcohol consumption on the response time of young monkeys, as a model for adolescent humans. In this experiment, young monkeys were given alcohol sweetened with fruit flavors. Each monkey drank, on average, 2.0 g/kg of alcohol, five days a week for 10 months. The amount of alcohol consumed daily by the monkeys was equivalent to an adolescent child consuming about 7 shots of whiskey. Every day, before they drank their alcohol, the monkeys were required to touch a LCD panel in response to visual stimuli. After 10 months of alcohol consumption, the alcohol was stopped and then the monkeys were tested again 30 days later. The results demonstrated that alcohol prolonged response time to visual stimuli even one month after the onset of abstinence.

That alcohol consumption increases response time and decreases concentration is well-documented. Determination of the effects of alcohol on cognition has been done repeatedly in adult and juvenile human beings. The authors of this manuscript cited 11 human studies describing effects of alcohol on cognition, but stated "Animal models are necessary to determine the specific effects of controlled alcohol exposure and to distinguish affected from spared cognitive domains."

Scripps Research Institute has received over \$4 million from NIAAA since 2009 for the grants that supported these experiments.

Wright MJ, SA Vandewater, MA Taffe. The influence of acute and chronic alcohol consumption on response time distribution in adolescent rhesus macaques". *Neuropharm.* 2013: 70;12-18.

2. A 2013 manuscript from the Intramural Research Program of the National Institute of Drug Abuse described the development of an animal model of alcoholic relapse that was suppressed by negative consequences. One-month-old rats were given alcohol every other day for two weeks until they preferentially sought out alcohol over water. The rats were drinking about 12.8 g/kg per day of alcohol during the days it was available. The amount of alcohol consumed daily by the rats was equivalent to an adult human consuming over 10 gallons of whiskey every day. Once the rats preferentially drank alcohol, they were subjected to electric shocks if they drank alcohol instead of water. This was done repeatedly, at increasing intensities, until the rats stopped drinking alcohol. Over time, these rats were shown to drink less, even when the alcohol was presented without an electric shock.

This experiment demonstrated that a negative consequence can suppress alcohol use. There is a large body of literature describing the effects of negative consequences on alcohol consumption in humans. The authors cited 5 different studies describing this finding and noted that physical punishment (i.e. electric shock) is not used to deter alcoholics from drinking.

Marchant NJ, TN Khuc, CL Pickens, A Bonci, Y Shaham. Context-induced relapse to alcohol seeking after punishment in a rat model. *Bio Psychiatry.* 2013;73;256-62.

3. Over time, many alcoholics develop tolerance, apparently due to a change in the sensitivity of cells to alcohol. Some scientists theorize that changes in genes could be responsible for increased tolerance. A 2012 manuscript from the University of Texas describes an experiment using fruit flies, funded by the NIAAA (grant #: AA018037). Eight- to ten-day-old flies were exposed to aerosolized alcohol until they were sedated and lost postural control (i.e. fell over). After each exposure, the time was measured until the flies could stand. An increase in time spent standing was interpreted as increased tolerance. Since it was impossible to measure alcohol consumption, flies were instead crushed in a test-tube and "whole body" alcohol content was measured. Changes to neuronal genes were measured by removing the fly's head. The experimenters found that in flies, the activity of certain genes are changed after two exposures to alcohol.

The authors stated that there is virtually no similarity between the neural organization of a fly and any vertebrate animal, including humans. They also noted they could not determine if a fly is addicted to alcohol. Nonetheless, the authors identified two genes that they believed might be required for the acquisition of alcohol tolerance, even though there is no physical evidence the gene products interact with alcohol.

The University of Texas has received \$1.6 million from NIAAA since 2008 to fund these fruit-fly experiments.

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