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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

FDA EXAMINED NIAAA-SUPPORTED RESEARCH IN ITS CAFFEINATED ALCOHOLIC BEVERAGE REVIEW

Drinkers of caffeinated alcoholic beverages found to be much more likely to get injured enough to require medical care as a result of their drinking than people who drank only alcohol.

Fans of Four Loko—most of them college age—are in mourning. They are expressing their grief through YouTube tribute videos. They are connecting on Facebook groups. They are holding candlelight vigils. Some are even buying and selling Four Loko jewelry on eBay.

Others are more in agreement with the decision by the Food and Drug Administration (FDA) to warn Four Loko's manufacturers, as well as three other makers of alcoholic energy drinks, that the caffeine in their products is an "unsafe food additive." This past November, the FDA gave the companies 15 days to "remedy the violation" of the Federal Food, Drug, and Cosmetic Act.

The FDA based its decision on scientific research, much of it supported by NIAAA, about the effects of combining alcohol and caffeine.

What Is Four Loko?

Four Loko is a fruity-flavored beverage that comes in 23.5-ounce cans and is about 12 percent alcohol, meaning that each can contains the equivalent of nearly five standard alcoholic drinks.

"Essentially, this is a bottle of wine in a can—when you drink a can, you've just chugged a bottle of wine," said Aaron White, Ph.D., health scientist administrator at NIAAA.

In addition, the drinks contained a large—though unspecified—amount of caffeine. Whereas a 6-ounce cup of brewed coffee has about 100 milligrams of caffeine, these alcoholic energy drinks contained 150 milligrams or more. (1)

Continued on page 3

IN THIS ISSUE

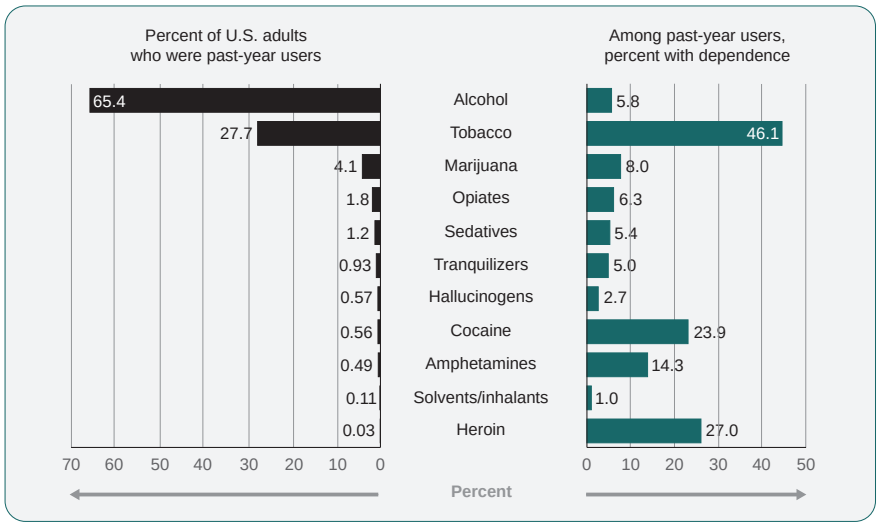
CHARTICLE

POPULARITY AND "ADDICTABILITY" OF DRUGS AMONG U.S. ADULTS

Among drugs used by U.S. adults, alcohol ranks first, by far, in popularity and seventh in "addictability," according to a nationwide survey of 43,000 adults. More than 6 in 10 U.S. adults reported past-year use of alcohol and, of them, about 6 percent were dependent. Though far less addictive than some other drugs, alcohol's popularity boosts the number of dependent users to 8 million per year, nearly five times the number of people dependent on all illicit drugs combined.

Tobacco is second in popularity and by far the most addictive drug, with nearly half of past-year users being dependent. After tobacco, heroin is most addictive (27 percent of past-year users), followed by cocaine (24 percent) and amphetamines (14 percent). Fewer than 1 in 10 past-year users were dependent on marijuana (8 percent); opiates; that is, prescription painkillers used without or beyond the bounds of a prescription (6.3 percent); alcohol (5.8 percent); sedatives (5.4 percent); tranquilizers (5 percent); hallucinogens (2.7 percent); or solvents/inhalants (1 percent).

What makes some drugs more likely to lead to addiction? One factor appears to be the speed with which a drug enters the brain, with faster delivery increasing a drug's "addictive potential." The speed of entry into the brain varies by a drug's chemistry and its route of administration, that is, whether it is smoked, sniffed, injected, or ingested. Many other factors influence the development of addiction, and the full picture is not yet known. Investigators are currently looking into mechanisms involving individual vulnerability, including genetics; drug properties, including effects on brain targets; and environmental variables such as availability.



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FEATURE

WHEN TOO MUCH ALCOHOL TURNS INTO ALCOHOL POISONING

There is only a small safety window when it comes to alcohol. You can quickly go from too much to way too much.
— Aaron White, Ph.D., health scientist administrator, NIAAA

Research shows that when people drink alcohol and caffeine together, they are less aware of how drunk they are getting. People who do not "feel drunk" tend to drink more and often miss the telltale signs of alcohol overdose.

"People feel less sleepy and less impaired, but when you look at their performance—like their ability to drive a car—they are still just as impaired by the alcohol" as without the caffeine, explained Aaron White, Ph.D., health scientist administrator at NIAAA.

But what are the signs of an alcohol overdose? And is there a difference between an overdose and alcohol poisoning?

Continued on page 4

Continued from page 1

Caffeine masks the key sensory warning signs of intoxication—like slowed reaction time and drowsiness—alerting drinkers that their body has had enough alcohol.

"Alcohol slows our reaction time. Caffeine increases our reaction time. So caffeine counteracts some of the effects on reaction time, but doesn't ameliorate the other impairments that alcohol causes," explained Dr. White.

Studies show that people who drink nonalcoholic caffeinated energy drinks consume more alcohol when they drink than people who do not consume energy drinks. Research also indicates that college students who drink caffeinated alcoholic beverages are more likely to drink larger quantities of alcohol when they drink and to drink more often. These same students are also more likely to commit sexual assault, sustain an unintentional injury, and need medical attention.

"There is an extremely strong association between drinking alcoholic energy drinks and serious injury," explained Mary Claire O'Brien, M.D., associate professor of emergency medicine at Wake Forest University School of Medicine. Dr. O'Brien, an emergency medicine physician, collaborates on the NIAAA-funded *Study to Prevent Alcohol Related Consequences* (SPARC), a multicommunity trial testing the impact of an environmental approach to high-risk drinking by college students. (Mark Wolfson, Ph.D., a professor in the Department of Social Sciences and Health Policy at Wake Forest University, is the principal investigator for the SPARC study.) One of the SPARC outcome measures is an annual cross-sectional survey of more than 4,000 college students that examines the use of alcohol, drugs, and tobacco.

After caring for a college student in the emergency department who was practically comatose from drinking large amounts of alcohol and caffeine in an attempt to "drink more and party longer," Dr. O'Brien added questions about drinking both premixed alcoholic caffeinated beverages and the "mix-your-own" varieties to the SPARC survey.

Dr. O'Brien and her colleagues found that drinkers of caffeinated alcoholic beverages "are much more likely [than drinkers of alcohol alone] to get injured enough to require medical care as a result of their drinking." When this research, also supported by NIAAA, was publicized in 2007, "it caused a firestorm of interest, not just nationally, but internationally," Dr. O'Brien said.

Dr. O'Brien credits NIAAA with allowing her and her colleagues to expand the SPARC study to investigate the implications of these drinks.

"In 2001, [when we began SPARC], these drinks weren't there. NIAAA allowed us to modify the study as time went on, giving us support and latitude to investigate in ways that were relevant—even as the environment changed," she said. "The SPARC study has been a sort of 'living laboratory.'"

How Did the Research Inform Policy?

Dr. O'Brien's findings, combined with the findings of a group of experts, got the attention of the FDA.

The FDA found that the evidence "showed a broad range of concern about safety that was supported by credible scientists," said Joshua Sharfstein, M.D., principal deputy commissioner at the FDA. Dr. Sharfstein and his team believed "the evidence [the group of experts] presented about harms associated with these drinks demonstrated a risk to public health. That led us to respond by taking a closer look."

As a result, in 2009, the FDA contacted 30 manufacturers of caffeinated alcoholic beverages. "We asked them to submit materials. We reviewed existing scientific literature. We consulted with external experts. And we tested the products here in our labs at the FDA," said Dr. Sharfstein.

After its extensive investigation, the FDA determined that the use of caffeine in alcoholic beverages did not meet its "generally recognized as safe" standard. To meet this standard, products must demonstrate technical evidence of safety that is accepted by qualified experts. The FDA communicated with four companies whose products failed to meet the legal standard.

As a result, the makers of Four Loko reformulated its product to remove the caffeine. The caffeinated alcoholic beverages made by the other three manufacturers that received warnings will no longer be available for sale.

"We at the FDA looked at our role, but we just have one role in all of this. This issue is a lot broader than the FDA," said Dr. Sharfstein.

From Dr. O'Brien's perspective, though, the FDA's actions have broad implications. She believes that "this research has changed national policy in a way that improves health."

1. O'Brien MC, McCoy TP, Rhodes SD, Wagoner A, Wolfson M. Caffeinated cocktails: Energy drink consumption, high-risk drinking, and alcohol-related consequences among college students. *Academy of Emergency Medicine.* 2008 May;15(5):453–60.

Continued from page 2

Dr. White explained that the two conditions lie along a spectrum of adverse alcohol effects and can overlap. An "effective" dose of any drug promotes a positive or desired response. For example, an appropriate dose of alcohol for those who choose to drink—no more than one drink for women or two drinks for men—may promote relaxation. "An overdose is what happens when the negative effects of a drug outweigh its positive or therapeutic effects," Dr. White explained.

When it comes to alcohol, which people take more for desired effects than for medicinal effects, an overdose can mean that you have taken "so much of a substance that it produces impairments that increase the risk of harm," said Dr. White. An alcohol overdose can cause you to stumble around, feel sleepy, and slur your words. These side effects can interfere with your ability to function.

Caffeine masks these symptoms and may give people the impression that they can continue to drink. But consuming more alcohol at this stage can push a drinker over the edge from alcohol overdose to alcohol poisoning. "Poisoning is a specific type of overdose where the amount you consume becomes toxic and threatens your life," explained Dr. White. Symptoms of alcohol poisoning include mental confusion, vomiting, seizures, breathing problems, and extremely low body temperatures.

There is a toxic threshold for all drugs, including alcohol. With alcohol, though, the difference between a dose that produces a desired effect and a dose that can cause immediate harm is far less than for many other drugs. "There is only a small safety window when it comes to alcohol. You can quickly go from too much to way too much," said Dr. White.

To learn more about the health effects of alcohol, please download NIAAA's newest publication, *Beyond Hangovers: Understanding Alcohol's Impact on Your Health. http://pubs.niaaa.nih.gov/publications/Hangovers/beyondHangovers.htm*

IN YOUR FACE? WE HOPE NOT.

This is an example of a handheld alcohol breath-testing instrument that police use for roadside tests of drivers they suspect of intoxication. In recent years, many handheld units (such as this one by Intoximeters, Inc.) have become accurate and reliable enough for their results to be admissible in court. Most jurisdictions, however, still use handheld units as screening tools that tell police which drivers to take to the station for further testing on larger, highly accurate desktop units.

Why test the breath for alcohol? When people drink more alcohol than the liver can break down at a given time, the leftover alcohol enters the bloodstream. The alcohol circulates and distributes itself evenly throughout the water in all the body's tissues and fluids, including water vapor in the lungs. Thus, alcohol content in the breath parallels that in the blood.

The breath sensor converts the amount of alcohol in the breath to an equivalent blood alcohol concentration (BAC).

BACs form the backbone of drunk driving laws. The legal BAC limit in all States is .08, a point at which driving skills are impaired in all drivers, regardless of age, gender, driving experience, or drinking history. Health policy research shows that basic drunk driving laws, including BAC limits and associated driver's license removals, have resulted in a substantial reduction in alcohol-related traffic fatalities.

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National Highway Traffic Safety Administration. Highway safety programs; conforming products list of evidential breath alcohol measurement devices. A notice by the National Highway Traffic Safety Administration on 03/11/2010. *Federal Register.*

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PHOTO ESSAY

Permission to use photo granted by Intoximeters, Inc. The pictured device, the Alco-Sensor FST, is one of many mobile units approved by the National Highway Traffic Safety Administration as an "evidential breath alcohol measurement device."

NEWS FROM THE FIELD

REDUCING OFF-CAMPUS DRINKING

Collaborative, community-based interventions successfully reduce off-campus drinking.

Highly visible cooperative projects, in which colleges and their surrounding communities target off-campus drinking settings, can reduce harmful alcohol use among college students, according to a report by researchers supported by NIAAA.

As reported online in the *American Journal of Preventive Medicine,* researchers led by Robert Saltz, Ph.D., conducted the Safer California Universities study of college and community alcohol prevention strategies at 14 large public universities in California. Beginning in 2003, Dr. Saltz and his colleagues conducted random surveys of students from each of the participating schools. The survey documented that heavy drinking at off-campus parties was a common problem.

Policy and enforcement interventions were implemented in 2005 and 2006 at half of the universities, with the other half also monitored for comparison. Interventions included nuisance party enforcement operations and surveillance to prevent alcohol sales to minors.

To assess the effectiveness of the interventions, the researchers measured the proportion of drinking occasions in which students got drunk in various settings. The researchers found significantly greater reductions in the incidence and likelihood of intoxication at off-campus parties and at bars and restaurants for students at the intervention universities. Students at intervention universities also reported a lower likelihood of drinking to intoxication the last time they attended an off-campus party, a bar or restaurant, or other drinking settings.

The greatest reductions were found at universities with the highest intensity of intervention implementation, achieved through heavy publicity and highly visible enforcement activities.

"These findings should give college administrators and surrounding communities some degree of optimism that student drinking is amenable to a

combination of well-chosen, evidence-based universal prevention strategies," said Dr. Saltz. "Here, one set of alcohol control strategies was found to be effective, but other combinations may work as well, or even better."

The article abstract can be found here:

Alcohol Risk Management in College Settings: The Safer California Universities Randomized Trial. http://www.nc bi.nlm.nih.gov/pubmed/21084068

NEWS FROM THE FIELD

BRAIN'S REWARD CIRCUITS MAY CONTRIBUTE TO ALCOHOL ABUSE

Targeting the mTORC1 pathway appears to be an innovative strategy for treating alcohol abuse disorders.

A molecular pathway within the brain's reward circuitry appears to contribute to alcohol abuse, according to laboratory mouse research supported by NIAAA. The findings, published online in *Proceedings of the National Academy of Sciences*, also provide evidence that the pathway may be a promising new target for the treatment of alcohol problems.

The mammalian target of rapamycin complex 1, or mTORC1, is a group of proteins found in cells throughout the body. An important part of the cellular machinery, mTORC1 sends signals that help regulate the size and number of cells. Scientists have also found that it is involved in other cellular processes. For example, in the central nervous system, mTORC1 has been

Continued on page 6

linked to processes related to learning and memory. Because problems in the cellular mechanisms that underlie learning and memory can contribute to alcohol abuse disorders, NIAAA-supported researchers at the Ernest Gallo Clinic and Research Center of the University of California, San Francisco (UCSF) hypothesized that mTORC1 might be involved in alcohol problems.

In laboratory studies conducted with mice, researchers led by Dorit Ron, Ph.D., a Gallo Center principal investigator and a professor of neurology at UCSF, measured an increase in mTORC1 cellular products in the nucleus accumbens of mice that had consumed alcohol—an indication that alcohol activates the mTORC1 pathway. The nucleus accumbens is a brain region that in rodents and humans is part of the reward system that affects cravings for alcohol and other addictive substances. They then showed that rapamycin, an immunosuppressant drug that blocks the mTORC1 pathway, decreased excessive alcohol consumption, binge drinking, and alcohol-seeking behavior in the rodents.

"Our findings show that the mTORC1 pathway is an important contributor to mechanisms that underlie alcohol-seeking behavior," said Dr. Ron. "They also suggest that novel rapamycin-like compounds might be useful treatments for alcohol use disorders."

The article abstract can be found here:

Role for Mammalian Target of Rapamycin Complex 1 Signaling in Neuroadaptations Underlying Alcohol-Related Disorders. http://www.ncbi.nlm.nih.gov/pubmed/21041654

IMPULSIVITY, ALCOHOL, AND VIOLENCE

Alcohol may trigger violence in those with a genetic variant linked to impulsivity.

Research led by scientists at NIAAA has found that a genetic variant of a brain receptor molecule may contribute to violently impulsive behavior when people who carry it are under the influence of alcohol. A report of the findings, which include human genetic analyses and gene knockout studies in animals, appears in the December 23, 2010, issue of *Nature*.

In collaboration with researchers in Finland and France, David Goldman, M.D., chief of the Laboratory of Neurogenetics at NIAAA, and colleagues studied a sample of violent criminal offenders in Finland. The hallmark of the violent crimes committed by individuals in the study sample was that they were spontaneous and purposeless.

The researchers sequenced DNA of the impulsive subjects and compared those sequences with DNA from an equal number of nonimpulsive Finnish control subjects. They found that a single DNA change that blocks a gene known as HTR2B was predictive of highly impulsive behavior. HTR2B encodes one type of serotonin receptor in the brain. Serotonin is a neurotransmitter known to influence many behaviors, including impulsivity.

"Interestingly, we found that the genetic variant alone was insufficient to cause people to act in such ways," noted Dr. Goldman. "Carriers of the HTR2B variant who had committed impulsive crimes were male, and all had become violent only while drunk from alcohol, which itself leads to behavioral disinhibition."

The researchers then conducted studies in mice and found that, when the equivalent HTR2B gene is knocked out or turned off, mice also become more impulsive. Taken together, the findings could lead to a better understanding of some aspects of impulsivity and ultimately may lead to strategies for diagnosing and treating some clinically important manifestations of impulsive behavior. The researchers caution, however, that impulsivity is a complex trait with multiple genetic and environmental causes.

The article abstract can be found here:

A Population-Specific HTR2B Stop Codon Predisposes To Severe Impulsivity.http://www.ncbi.nlm.nih.gov/pubmed/21179162

NEWS FROM THE FIELD

WHY ARE ADOLESCENTS LESS SENSITIVE TO ALCOHOL?

In adolescent rats, firing rate of cerebellar Purkinje neurons appears insensitive to alcohol's effects.

Researchers from Baylor University Addictions Research Consortium and other institutions have helped to explain why adolescents are less sensitive to alcohol's impairing effects on motor skills than are adults. The researchers examined the effects of alcohol on rats' motor skills by recording distance traveled before and after the rats were administered alcohol. They also tested the animals' righting reflex with and without alcohol.

The experiments were performed on rats of all ages and confirmed that adolescent rats experienced significantly less alcohol-induced movement inhibition than did adult rats. In addition to monitoring the rats' motor skills, the researchers recorded Purkinje neurons from adolescent and adult rats. They also determined protein kinase C (PKCγ) expression in three brain regions in the adolescent and adult rats.

Researchers found that the in vivo firing rate of cerebellar Purkinje neurons recorded from adolescent rats was insensitive to alcohol's effects, while the firing rate of adult cerebellar Purkinje neurons was significantly depressed by alcohol. They also noted that PKCγ expression in the cortex and cerebellum mirrors the age-dependent effect of ethanol in that adolescents have significantly less PKCγ expression compared to adults.

"It stands to reason that reduced sensitivity to alcohol-induced motor impairments, which serve as cues to moderate alcohol intake, may contribute to amplified alcohol use during adolescence," noted the researchers. Since reduced initial sensitivity to alcohol and tolerance to alcohol are risk factors for developing alcoholism, the researchers believe that a greater "understanding [of] the mechanisms that underlie the reduced sensitivity to alcohol during adolescence is critical."

The article abstract can be found here:

Behavioral Effects of Ethanol in Cerebellum Are Age Dependent: Potential System and Molecular Mechanisms. http://www.ncbi.nlm.nih.gov/pubmed/20860615

5 QUESTIONS WITH...

RALPH HINGSON, Sc.D.

Dr. Hingson is director of NIAAA's Division of Epidemiology and Prevention Research

1. There is so much discussion in the news and in our communities about underage drinking. What is the most important thing we should remember?

There are so many statistics that show the dangers of underage drinking that we can sometimes miss the forest for the trees. We have statistics on fatal traffic crashes, injuries, assaults, academic problems, unplanned pregnancies, and many others. And while all of these are significant in their own right, they also—collectively—illustrate an important issue in public health: Alcohol is the leading contributor to some of the leading causes of death and injury among young Americans. And it's entirely preventable.

Additionally, we know that the earlier one starts to drink, the greater the likelihood one will experience alcohol dependence, dependence at an earlier age, and chronic relapsing dependence. One million high school students binge drink six or more times per month. One-third of them drink and smoke marijuana on school property. And they are four times more likely to report D's and F's on their report cards. Alcohol misuse also disproportionately affects the developing brain. Even if the damage is not permanent, it represents lost opportunities.

2. How about colleges? What can they do?

Much has been written, and will continue to be written, about the seemingly intractable nature of underage and abusive drinking among college students. But in this area, too, we have learned much about the types of activities that can make a difference

under the right circumstances. Clearly, we have enough information to make recommendations to college presidents, as we did in the *NIAAA College Drinking Task Force* report several years ago. At that time, existing research permitted us to strongly recommend individual-oriented approaches, such as screening and brief interventions, as well as other types of counseling, both voluntary and mandated. The problem is that, while 20 percent of college students meet the alcohol use disorder criteria, only 5 percent of them receive counseling. Since the report was released in 2002, research results have helped us refine our recommendations even further. Recent findings are showing positive outcomes from Internet and face-to-face normative reduction interventions, family interventions, and targeted environmental actions, such as price, drinking age, drinking and driving laws, and reduction of outlet density in the surrounding communities. The fact is, we know how to make meaningful interventions; we just need to muster the will to do it.

3. Have we learned anything new in recent years about effective comprehensive community partnerships?

Quite a bit, and it's very encouraging. Comprehensive community partnerships typically involve collaboration and strategic planning by officials from multiple local departments, schools, health agencies, police, alcohol beverage control agencies, and concerned citizens. Often, multiple strategies are incorporated, including school and family-based initiatives, community organizing, media advocacy, and police enforcement of alcohol and drunk driving laws, as well as expansion of screening, brief interventions, and counseling. A growing body of research is demonstrating success in reducing drinking or alcohol-related problems among underage and college youth as a result of selected community programs.

This research continues to reinforce the recommendation that the most promising plan of attack is to combine individual, family, and school approaches (such as social norms) with environmental/community-based interventions.

4. What about the minimum legal drinking age?

This issue has been studied extensively, using multiple methodologies. The preponderance of research indicates that the legal drinking age of 21 has had positive effects on health and safety in America, primarily in decreasing traffic crashes and fatalities, suicide, and consumption by those under age 21. Jim Fell, M.S., identified a 16 percent decline in fatal crashes involving drinking drivers under age 21 as being associated with raising the drinking age after controlling for numerous other policies.(1) He also found that laws targeting adults also independently reduced alcohol-related deaths among people under age 21. Karen Norberg, M.D., found that a drinking age of 21 was linked to reduced alcohol and drug abuse dependence during adult years.(2)

5. You're a native of Cleveland but your home base has been Boston for many years. How have these circumstances affected your support for the professional teams in those cities?

Upon moving to Boston, I became a Boston Red Sox fan, which will make me a better person for the rest of my life.

1. Fell J, Fisher DA, Voas RB, et al. The impact of underage drinking laws on alcohol-related fatal crashes of young drivers. *Alcoholism: Clinical and Experimental Research.* 2009 Jul;33(7):1208–1219.
2. Norberg KE, Bierut LJ, Grucza RA. Long-term effects of minimum drinking age laws on past-year alcohol and drug use disorders. *Alcoholism: Clinical and Experimental Research.* 2009 Dec;33(12):2180–2190.

ABOUT US

NIAAA Spectrum is NIAAA's first-ever webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences. Each issue includes feature-length stories, news updates from the field, charticles and photo essays, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

CONTACT US

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

5635 Fishers Lane, MSC 9304
Bethesda, MD 20892-9304
Communications/Public Info:
301–443–3860
http://www.spectrum.niaaa.nih.gov