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

FEATURE

ANTISMOKING MEDICATION SHOWS PROMISE FOR TREATING ALCOHOL DEPENDENCE

A smoking cessation medication may be a viable option for the treatment of alcohol use disorders, according to a new study by NIAAA scientists and grantees. The study found that varenicline, a drug approved by the Food and Drug Administration (FDA) in 2006 to help people stop smoking, significantly reduced alcohol consumption and craving among alcohol-dependent individuals. The new findings were published recently in the *Journal of Addiction Medicine*.

"Drinking and smoking often co-occur, and common genetic components underlie alcohol and nicotine dependence," notes lead author Raye Z. Litten, Ph.D., associate director of the NIAAA Division of Treatment and Recovery Research. It is perhaps unsurprising that a smoking cessation treatment might serve to treat alcohol problems.

Varenicline works by partially stimulating receptors for nicotinic acetylcholine, which scientists believe is a promising molecular target for treating both nicotine and alcohol use disorders. Studies have shown that varenicline decreases alcohol consumption in animals, and early studies conducted in humans have also suggested varenicline's possible effectiveness for treating alcohol problems. For example, studies conducted among smokers who also were heavy drinkers found that varenicline reduced alcohol drinking, craving, and the pleasant effects of alcohol and that varenicline treatment led to a greater reduction in alcohol craving and fewer heavy drinking days, compared to placebo treatment.

"Our current study is the first clinical trial to test the effectiveness and safety of varenicline in a population of smokers and nonsmokers with alcohol use disorders," said Dr. Litten.

Dr. Litten and colleagues from NIAAA worked with NIAAA's Clinical Investigations Group, a multicenter team of researchers at Boston Medical Center, the University of Virginia, Dartmouth University, the University of Pennsylvania, and The Johns Hopkins University School of Medicine. The researchers randomized 200 alcohol-dependent adults to receive either varenicline or placebo each day for 13 weeks.

Study participants had reported drinking an average of at least 28 drinks per week for females or 35 drinks per week for males prior to the study, with women and men

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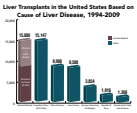

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FEATURE

BRAIN PATTERNS MAY HELP PREDICT RELAPSE RISK FOR ALCOHOLISM

Relapse is common for those in recovery from alcoholism, but spotting who may be most at risk can be difficult. A new brain scan study may give clues about which people in recovery are more likely to return to heavy drinking.

The NIAAA study, published in *JAMA Psychiatry*, found that distinct patterns of brain activity are linked to greater rates of relapse among alcohol-dependent patients in early recovery. Those with abnormally high levels of activity in the prefrontal region of the brain while in a relaxed state were eight times as likely to relapse and return to heavy drinking as those with normal brain patterns or healthy controls.

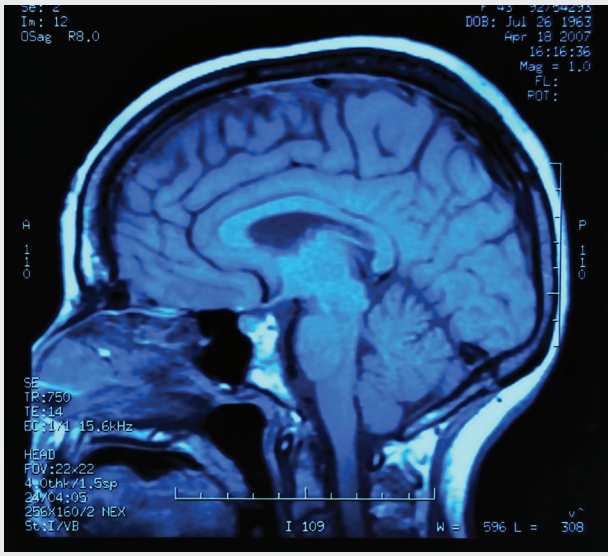
Abnormally low prefrontal activity while imagining a stressful scenario was also linked to greater number of days drinking after relapse.

> ***The patterns of brain activity we observed may one day serve as a neural marker that could help clinicians identify alcohol-dependent patients in recovery who are most at risk of relapse.***
>
> — Rajita Sinha, Ph.D.

The prefrontal brain plays a role in regulating emotion, the ability to suppress urges, and decision-making. Chronic drinking may damage regions involved in self-control, affecting the ability to regulate cravings and resist relapse.

"The patterns of brain activity we observed may one day serve as a neural marker that could help clinicians identify alcohol-dependent patients in recovery who are most at risk of relapse," said Rajita Sinha, Ph.D., the study's senior author, who is Foundations Fund Professor of Psychiatry and professor in the Child Study Center and of neurobiology at Yale University.

"Our findings may also have implications for the use of medications and behavioral treatments that restore prefrontal function, as they could potentially benefit people at high risk of relapse," Dr. Sinha said.



Relapse is often triggered by stress and exposure to events or places that the individual associates with alcohol. Studies suggest that most people in recovery from alcoholism relapse at least once before they successfully quit drinking.

Using functional magnetic resonance imaging (fMRI), scientists compared patterns of brain activity in 45 patients who were about to successfully complete an inpatient treatment program for alcoholism to those of 30 people with no history of alcoholism. Participants were asked to imagine relaxing situations, such as sunning on a beach, as well as recent stressful situations. Patients were followed for 90 days after leaving treatment to determine how many had returned to drinking.

"Reducing the high rate of relapse among people treated for alcohol dependence is a fundamental research issue," said NIAAA acting director Kenneth R. Warren, Ph.D. "Improving our understanding of the neural mechanisms that underlie relapse will help us identify susceptible individuals and could inform the development of other prevention strategies."

Source:

Seo D, Lacadie CM, Tuit K, Hong K-I, Constable RT, Sinha R. Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry*. 2013 May 1. [Epub ahead of print]

NEWS FROM THE FIELD

CHILDREN OF MILITARY FAMILIES AT INCREASED RISK FOR SUBSTANCE USE

In a paper published in the journal *Addiction*, researchers report that children of military families have a higher risk for alcohol and other substance use than do their peers in nonmilitary families. On the basis of their findings, the researchers suggest that schools and health care providers consider parental military deployment as an opportunity to provide early intervention and screening for substance abuse for young people in military families.

For this study, researchers analyzed data from the 2010 Iowa Youth Survey, which is administered to 6th, 8th, and 11th graders in Iowa public schools. The survey included questions on military status of families (currently deployed military parent, recently returned military parent, and nonmilitary parent). Additionally, the survey included questions about whether students drink alcohol (including binge drinking, defined as five or more drinks in a row within a couple of hours), whether they use marijuana and other illegal drugs, and whether they misuse prescription drugs.

The researchers' data indicated that substance use overall was higher among those in the currently deployed or recently returned groups than in the nonmilitary group. Deployment often means that children were not living with a parent—which is itself a risk factor for substance use. They found that "substance use was accentuated by the disrupted living arrangements, with the largest effect seen in children with a deployed parent who were not living with a parent or relative."

The authors suggest that children in families with a parent deployed with the military be considered at higher risk for substance abuse than those in nonmilitary families. Because of this, the time of deployment can be a "critical time for intervention with military children who likely experience reduced parental support and increased stressful home environments."

The article abstract can be found here:
Increased Risk of Alcohol and Drug Use Among Children From Deployed Military Families
http://www.ncbi.nlm.nih.gov/pubmed/23441867

NEWS FROM THE FIELD

HOW DOES DRINKING ALCOHOL AFFECT FOOD CHOICES?

A recent NIAAA study shows that people—particularly men—tend to have less healthy diets on days that they drink. On days when alcohol was consumed, men took in an extra 433 calories. While most came from alcohol, about one-third came from food. Food choices on drinking days tended to be less healthy—the men consumed more meat and fat and less fruit and milk.

Women also took in more calories on the days they drank, but almost all came from alcohol. However, like men, they also made poorer food choices. They consumed more fat and less milk.

The study also looked at nutrient intakes. Particularly concerning was that both men and women had higher intakes of total fat on days they drank. Men also had higher intakes of saturated fat, a "bad" fat linked to increased disease risk. Foods high in saturated fat include red meat and butter.

This finding supports previous laboratory studies showing that moderate drinking is associated with increased same-day food intake.

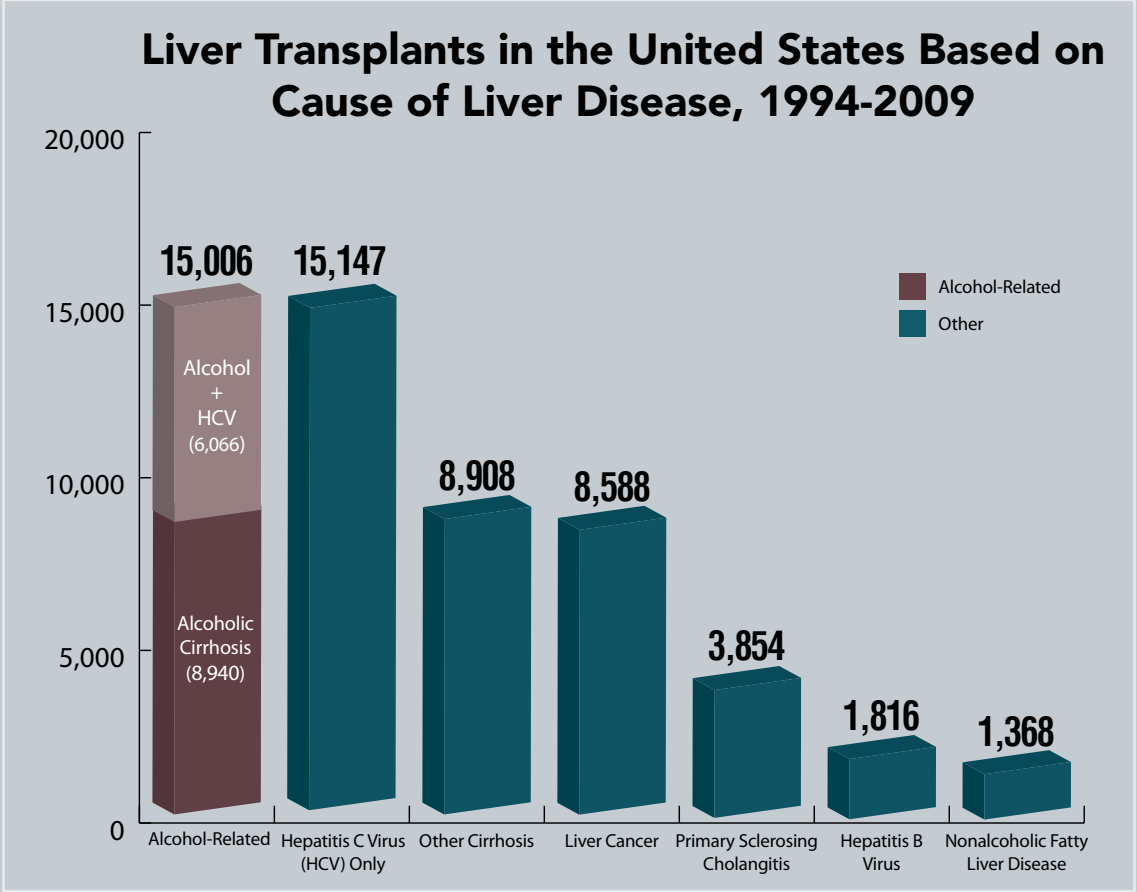
More than 1,800 adults who currently drank took part in the study in which they were asked to recall what they ate over 24 hours on a drinking day and a nondrinking day. The information was collected as part of the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES).

With the high prevalence of obesity in the United States, "understanding the associations between alcohol and diet could be useful targets for public health efforts to improve dietary intake," wrote the study's authors.

The article abstract can be found here:
Diets of Drinkers on Drinking and Nondrinking Days: NHANES 2003-2008
http://www.ncbi.nlm.nih.gov/pubmed/23535109

BY THE NUMBERS

EXCESSIVE ALCOHOL USE AND LIVER DISEASE



Excessive alcohol consumption can have toxic effects on the liver, with deadly consequences. Cirrhosis claimed 31,522 lives in the United States in 2009 alone. More than 48 percent of those cases were alcohol related. In that same year, doctors performed more than 4,000 liver transplants: Alcoholic liver disease was the primary cause of almost one in five of those cases.

That year was no anomaly. An analysis of data from the United Network for Organ Sharing (UNOS) found that 54,687 liver transplants took place in the United States between 1994 and 2009. Of those, 15,006 were attributed to alcohol-related causes (see chart for details).

The economic cost is considerable. A second review of UNOS records revealed that the estimated billed charges per liver transplant in the United States in 2011 averaged $577,000.

Liver disease specialist Scott Friedman, M.D., says, "The data underscore the critical importance of research to develop treatment strategies to prevent or reverse liver damage due to alcohol." Dr. Friedman is Fishberg Professor of Medicine, chief of the Division of Liver Diseases, and dean for Therapeutic Discovery at the Icahn School of Medicine at Mount Sinai in New York City.

Source:

Singal AK et al. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation.* 2013 Mar 15;95(5): 755-60.

FEATURE: *Antismoking Medication Shows Promise . . .* *Continued from page 1*

drinking at least 4 and 5 drinks, respectively, on most drinking days.

Compared with placebo, varenicline significantly reduced measures of alcohol use, including the percentage of heavy drinking days, the number of drinks per day, and the number of drinks per drinking day. The researchers noted that varenicline's effects were comparable to those seen in studies of naltrexone and acamprosate, two of the medications already approved by FDA for the treatment of alcohol dependence. The average treatment effect on alcohol use was similar for smokers and nonsmokers. Alcohol craving also was significantly reduced in people treated with varenicline.

Dr. Litten and colleagues reported that the most common side effects of varenicline in the study were nausea, abnormal dreams, and constipation and that those effects generally were mild. On the basis of their findings, the researchers concluded that longer treatment with varenicline and followup assessments to determine if the effects are sustained would be valuable next steps in the development of this medication for alcohol problems.

NEWS FROM THE FIELD

FRESHMAN-YEAR SPIKE IN ALCOHOL MAY CHANGE CONNECTIONS IN THE BRAIN

Many students increase their drinking dramatically during their first year in college. This increase in alcohol consumption can result in a variety of negative consequences, including possible interference with healthy brain development.

In a new longitudinal study, researchers at the Pennsylvania State University investigated if and how seeing cues about alcohol influenced performance on a task as students progressed through their first year of college. The research team showed images of alcoholic and nonalcoholic beverages to a group of 11 students. Students were told to click a button when either alcohol pictures were shown or nonalcohol pictures were shown. As the students responded, the team mapped the regions of the brain associated with both emotional and cognitive processing using fMRI. The group participated in these sessions three times—once right before starting college, once during the first semester, and once during the second semester.

The researchers analyzed the data collected using the effective connectivity mapping technique. The analyses showed changes in the connectivity between the areas of the brain associated with emotional and cognitive processing during the first year of college. Specifically, connectivity increased between the summer before college and the first semester along with the abrupt, sharp increase in exposure to alcohol and to alcohol cues. It then decreased between the first and second semesters, when exposure to alcohol plateaued, as measured by responses to alcohol cues.

Adriene Beltz, the Penn State graduate student who led the research team, explained that this change in connectivity led her team to conclude "that changes in alcohol use and cue exposure—not absolute levels—were

reflected by the underlying neural processes." This study indicates the potential for future longitudinal mapping of brain connectivity to help explain the brain processes associated with underage drinking and behavior.

The article abstract can be found here:

Changes in Alcohol-Related Brain Networks across the First Year of College: A Prospective Pilot Study Using fMRI Effective Connectivity Mapping

http://www.ncbi.nlm.nih.gov/pubmed/23395930

NEWS FROM THE FIELD

BRAIN IMAGES USED TO STUDY IMPACT OF AEROBIC EXERCISE IN HEAVY DRINKERS

An exploratory study in a small group of volunteers showed that heavy alcohol consumption was associated with greater damage to the brain's white matter in people who do not regularly engage in aerobic exercise. The study appeared online in the April 2 edition of *Alcoholism: Clinical & Experimental Research.*

A research team at the University of Colorado at Boulder surveyed 60 people about their drinking patterns and amount of aerobic exercise. The scientists also conducted brain scans with diffusion tensor imaging (DTI). DTI allows researchers to pinpoint changes in white matter.

White matter, consisting of bundles of nerves that crisscross the brain, is essential for transmitting communications. Evidence from previous studies indicates that for alcohol-dependent people, heavy drinking is associated with a loss of white matter.

The new findings showed that heavy alcohol consumption was associated with damage to white matter in two specific areas—the superior longitudinal fasciculus and the capsule—in participants who did not get regular aerobic exercise. On the other hand, with respect to heavy drinkers who exercised more, the team found no relationship between alcohol consumption and white matter.

The authors concluded that, despite a number of limitations of this study, these results provide a solid foundation for the exploration of the potential of aerobic exercise to mitigate or reverse the damaging effects of heavy alcohol use on the brain.

The research abstract can be found here:

Aerobic Exercise Moderates the Effect of Heavy Alcohol Consumption on White Matter Damage

http://www.ncbi.nlm.nih.gov/pubmed/23551199

A CLOSER LOOK

ANIMAL MODELS FOR ALCOHOL RESEARCH

For decades, scientists have relied on research with animals to study alcohol's effects on biology and behavior and to devise strategies to prevent and treat alcohol-related disorders in humans. Different animal models serve different purposes, specialized to the research question at hand. Lower order animals such as fruit flies and nematodes (a type of worm), for example, allow elegant studies of single genes associated with alcohol sensitivity and tolerance. Small, see-through zebra fish permit exploration of developing embryos, the liver, nerve cells, and simple behaviors. For more complex studies in which it's important to mimic closely the human condition, dozens of mammalian models, primarily mice and rats, permit scientists to examine just about every imaginable interaction among alcohol, biology, and behavior.

Why are animal models essential to alcohol research? We just can't use humans to answer many pressing questions about alcohol and health. It would be unethical, for example, to promote binge drinking, alcohol dependence, or liver disease in a human subject. Also, it would not be possible to control a person's genetic makeup or alcohol exposure history. With animal models, scientists can control both genes and the environment. This allows researchers to view, manipulate, and better understand alcohol's basic mechanisms of action and, from those understandings, to devise new ways to reduce alcohol-related harm in humans.

One of the most far-reaching alcohol research breakthroughs depended vitally on animal studies. Despite clinical and epidemiologic evidence in the early 1970s that heavy alcohol use in pregnancy could cause birth defects, skeptics held that the mother's malnutrition or her "deviant lifestyle" was to blame. Through controlled experiments, scientists showed that alcohol-exposed offspring of rodents and other mammals displayed physical and mental defects similar to those in children born to women with alcohol use disorders. By the late 1970s, the case was closed: Alcohol was labeled a "teratogen," which is an agent or factor that causes birth defects.

Looking ahead, an area of great promise is the use of animal models to find new medications to treat alcohol dependence.

In a recent advance, NIAAA scientists developed a new mouse model that approximates alcoholic liver disease more closely than any existing method. The model simulates drinking patterns and resulting liver injuries seen in alcoholic hepatitis patients. It should provide new insights into how heavy drinking can also damage the heart, lungs, kidneys, pancreas, and central nervous system.

Looking ahead, an area of great promise is the use of animal models to find new medications to treat alcohol dependence. Currently, two major NIAAA initiatives are using rodent models of alcohol dependence to identify neurobiological targets for medication development and to test candidate medications before proceeding to clinical trials. These and other exciting programs, and the hope they offer for new treatments, would not be possible without animal research.

Sources:

Litten RZ, Egli M, Heilig M, Cui C, Fertig JB, Ryan ML, Falk DE, Moss H, Huebner R, Noronha A. Medications development to treat alcohol dependence: A vision for the next decade. *Addiction Biology*. 2012 May;17(3):513-27.

National Institute on Alcohol Abuse and Alcoholism (NIAAA) News Release. NIH develops improved mouse model of alcoholic liver disease. 2013 Feb 28.

Thomas JD, Warren KR, Hewitt BG. *Fetal alcohol spectrum disorders: From research to policy. Alcohol Research and Health.* 2010;33(1):118-26.

5 QUESTIONS WITH . . .

TED GEORGE, M.D.

Dr. George is a senior scientist with NIAAA's Division of Intramural Clinical and Biological Research.

1 Why are clinical trials such an important part of alcohol research?

Clinical research plays an extremely important role in bridging the gap between the laboratory and the physician's office. In clinical studies, we take lessons learned from basic science and apply them to real situations with real-life patients. Basic neuroscience, for example, has improved our understanding of mechanisms through which heavy alcohol use leads to addiction. But only well-designed clinical trials can determine which among those many mechanisms will actually translate into effective treatments. One important recent insight is that few, if any, treatments are likely to be highly successful for all patients. Instead, treatments will need to be personalized.

This is a very exciting time for alcohol research because we're increasingly able to use tools and approaches from different scientific disciplines to match treatments to patients and to get insights into the effects of various medications in the brain. For example, we are currently using brain imaging technologies (such as fMRI and PET [positron emission tomography] scans), our increasing understanding of human genetics, and studies using animal models to design targeted clinical trials that offer hope for personalized treatments to individuals suffering from alcoholism and other addictions. There will never be a magic bullet, but with each successive advance we move closer to our goal of offering health providers effective diagnostic tools and personalized treatment and recovery strategies. In fact, the range of effective treatment options available today—from medications to counseling strategies—are the direct result of collaborative efforts among basic and clinical researchers.

2 What are some of the challenges you face in conducting clinical research?

Finding participants that fulfill carefully defined inclusion and exclusion criteria for our clinical trials is our biggest challenge, but it is crucial for meaningful results. Additionally, protecting the safety of potential research participants is our highest priority. Once patients are enrolled in a clinical study, our goals are to collect research data using rigid, unbiased, and objective approaches—but not at the expense of patient safety and privacy. Also, we must fulfill our responsibility to provide world-class patient care. These are all elements of our challenging and unique mission: to help our patients and advance the science.

But getting back to recruitment—since the NIAAA Clinical Program has grown over the past year with the addition of new principal investigators and their corresponding research programs, recruiting enough subjects for the various ongoing in-patient and out-patient studies has become even more of a challenge. As the need to enroll patients increases, we are working hard to implement new recruitment strategies and coordinate recruitment across the entire clinical program. We have made a major investment in the program by adding a clinical research coordinator to our staff.

A final challenge looks toward the future: The increasing sophistication and multidisciplinary nature of alcohol research create a need for a new generation of physician scientists willing and able to make contributions in this important area.

3 What have some of your trials taught us about alcohol and human health?

We've learned that any one treatment is unlikely to work for everyone. We also know that genetic makeup, environment, and other factors will affect patient responses to treatment. For instance, the results of our clinical trials are profoundly affected by individual differences among patients, such as a history of child abuse or comorbid post-traumatic stress disorder. For example, we have known for quite some time that alcoholic patients respond quite differently to naltrexone, one of the few approved therapies for alcoholism. Thanks to recent clinical research, we now know that this is because different people carry different versions of the gene for the receptor targeted by naltrexone, the *mu*-opioid receptor, and so the receptor will look different in different individuals. Other medication-related factors are also critical. For instance, even if a biological mechanism is promising, for a medication we are investigating to actually work, it needs to reach the brain and act at the specific receptors we want to target. These are complicated processes, and we're learning more about them all the time.

4 What are your current trials investigating, and what types of participants are you recruiting for them?

The clinical trials currently conducted by NIAAA are focused on improving our understanding of the changes in brain function that occur as people develop alcoholism and using that understanding to develop new pharmacological treatments for alcoholism. Because stress is a major relapse factor, we have a strong interest in medications that can dampen emotional stress reactions that get out of hand in addiction. As a result, we are evaluating blockers of the main receptor for corticotropin-releasing hormone (CRH), a master switch for physiologic and emotional stress responses. We are also studying the role of several appetite-regulating hormones, such as ghrelin (a hormone produced by the stomach that acts on

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the brain to regulate appetite and food intake) in alcohol craving and use. Another promising area is based on recent insights that alcohol may drive brain changes by initiating low-level inflammation in the brain, and so we are studying pioglitazone, an approved diabetes medication that has been found to reduce inflammation in several other conditions.

5 What is the most satisfying part of your job?

The thought of changing the course of a disease process is exhilarating, even though the work is fraught with emotional highs and lows. For example, I am currently very excited about a joint clinical trial between the National Institute on Neurological Disorders and Stroke and NIAAA using deep brain stimulation to treat patients with alcoholism that is unresponsive to treatment. This is just one example of our innovative research, which offers promise as an efficacious treatment as well as an avenue to study the complex neuropathways of addiction.

NIAAA—Your One-Stop Resource for Information on Alcohol's Effects Across the Lifespan

- Public Education Materials
- Resources for Professionals
- Underage and College Drinking Prevention
- Addressing Health Disparities

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, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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