

NIAAA SPECTRUM

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

FEATURE

LOOKING AHEAD—NIAAA'S VISION FOR ALCOHOL RESEARCH



Through an integrated and multidisciplinary research program, NIAAA has been at the forefront of cutting-edge alcohol science for more than 45 years. In the alcohol prevention and treatment fields, there are more life-saving tools available today than ever before—thanks largely to the determined and uncompromising efforts of NIAAA-supported scientists.

As science has advanced and technology evolved, NIAAA has played an integral role in supporting the most innovative alcohol research advances, including recent developments such as biomarkers, personalized medicine, and integrated treatment strategies. From this strong foundation, NIAAA is now poised to capitalize on new technologies, new research opportunities, and a growing knowledge base—and is looking to an exciting future of alcohol research by expanding current projects and developing new efforts.

NIAAA will articulate its vision in an upcoming strategic plan, which will outline broad Institute priorities and the major initiatives that will help achieve them.

“We’re building on a strong foundation that was already put in place in our last strategic plan. But we’re also now putting new energy into certain areas,” says Dr. George Koob, NIAAA Director. “It’s not just business as usual.”

NIAAA’s vision for the next 5 years emphasizes basic and translational research in a variety of areas, particularly in the development and implementation of effective prevention and treatment strategies, and will reflect the priorities of Dr. Koob and the NIAAA senior staff, the NIAAA Advisory Council, and NIH. The NIAAA strategic planning effort coincides with NIH’s own process of developing a strategic plan, and the final Institute priorities will align with it.

NIAAA’s top focus areas include:

- Understanding and preventing alcohol misuse and alcohol use disorder (AUD), including research on the effects of alcohol on the developing adolescent brain
- Expanding AUD treatment and recovery research, including advancement of precision medicine
- Developing AUD medications
- Understanding, preventing, and treating co-occurring AUD and PTSD

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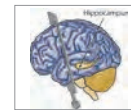
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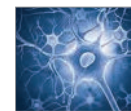


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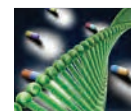
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FEATURE

HOW eHEALTH TECHNOLOGY IS CHANGING ALCOHOL RESEARCH



From social media to wearable fitness trackers, new technology is changing the way we live, work, and conduct research. Advances in electronic health (eHealth) technologies are transforming our approach to the prevention and treatment of alcohol use disorder (AUD). A recent issue of NIAAA's *Alcohol Research: Current Reviews* explores what this transformation means for alcohol research.

Prevention

Researchers can track and measure alcohol use more precisely than ever before using computerized assessments, sensors that continuously track

alcohol use, and smartphone apps that prompt study participants to respond to questions about their drinking in real time. Accurately tracking alcohol use patterns is an important first step in designing better interventions to prevent alcohol use problems. Once researchers more clearly understand the contexts that often lead to drinking problems, they can design prevention efforts with those contexts in mind. For example, we will be able to answer questions about how social media usage can predict whether an adolescent might engage in risky drinking. In addition, mobile technology can offer easily accessible screening and brief interventions that can help to identify harmful drinking patterns and prevent progression to AUD.

Treatment

Web-based and mobile AUD therapies hold the promise of less-expensive access to treatment for underserved populations. Millions of people with AUD who now go untreated might be reached by making treatment more convenient and accessible than it is through traditional methods.

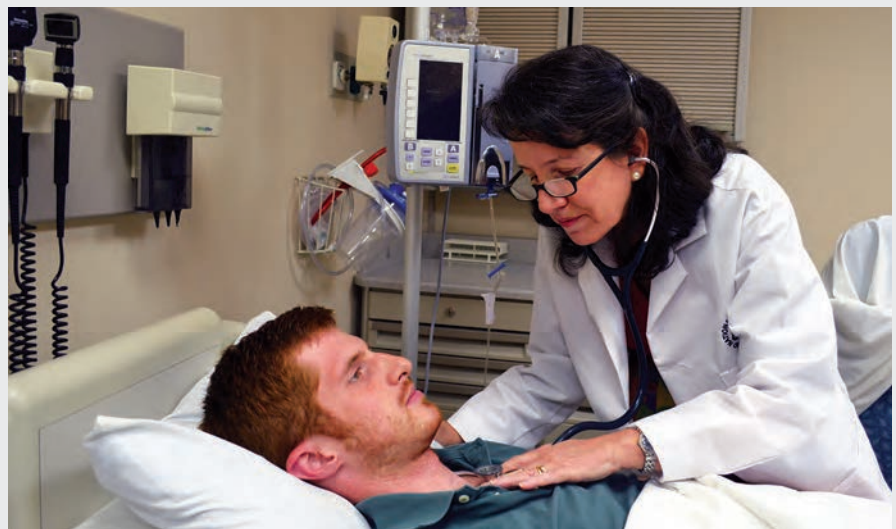
Researchers are exploring how electronic cognitive-behavioral therapy and other treatment apps may enhance traditional treatment, or potentially serve as a stand-alone therapy for some. These tools have the potential to deliver follow-up and "just-in-time" interventions for patients who have left residential treatment programs or who are trying to remain sober between treatment center visits. New technology is also making it easier to schedule appointments and complete intake forms for traditional treatment. While there is much promise in eHealth treatment tools, experts note that they may work best in conjunction with face-to-face treatment methods, particularly for people with more severe alcohol use problems.

NIH believes that eHealth will become a core component of personalized medicine. To this end, NIAAA researchers are working to understand how evolving eHealth technology can best be used to prevent and treat AUD. For more information, see *Alcohol Research: Current Reviews*, Vol. 36, No. 1, and *Alcohol Alert*, No. 88.

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A VISIT TO THE CPN LAB

Dr. Mary Lee, Staff Clinician in the NIAAA/NIDA Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology (CPN), taking vital signs and administering an intravenous study drug via an infusion pump. The CPN Lab strives to improve the clinical treatment of alcoholism by identifying innovative pharmacological approaches to address alcohol use disorder.



FEATURE: NIAAA's Vision. . .Continued from page 1

- Addressing the effects of alcohol on aging populations
- Preventing, diagnosing, and treating fetal alcohol spectrum disorder (FASD)
- Preventing, diagnosing, and treating alcoholic liver disease
- Reducing the spread of HIV and improving health outcomes for HIV-positive individuals by addressing alcohol misuse

“We want to build on our success in these areas and most importantly translate what we know from research into practice,” says Patricia Powell, Ph.D., Associate Director for Scientific Initiatives, who is leading the strategic planning process at NIAAA.

Cross-cutting themes include alcohol across the lifespan, precision medicine, health disparities, genetics, enhanced technology, and communications and education. NIAAA is also concentrating on specific populations, including underage and college drinkers, members of the military, and senior citizens. These priority areas dovetail with several Presidential Executive Orders that NIAAA is contributing to, including the Precision Medicine Initiative; the National Research Action Plan to Improve Access to Mental Health Services to Veterans, Service Members, and Military Families; and the Presidential Task Force to Protect Students From Sexual Assault.

One of several areas that is receiving increased emphasis is the development of medications to treat AUD. “We’re taking advantage of how NCIG [the NIH Clinical Investigations Group] tests compounds more quickly. We’re getting closer and testing smarter,” explains Dr. Koob.

NIAAA anticipates creating a new medications division for the Institute. The proposed new division, which is still awaiting official approval from NIH, will develop and standardize

preclinical and clinical laboratory screening models to test promising medications, and advance precision medicine objectives by predicting which subpopulations are more likely to show favorable responses to specific medications. The division will also oversee NIAAA’s extramural grant portfolio on medications development.

The development of new medications is an important component of NIAAA’s commitment to broaden the range of treatment options for people with AUD. The new division would be created using existing resources within the Institute, and so the change will advance NIAAA’s capabilities without affecting the budget.

“We have set lofty goals. But it’s where we want to be.”

—Dr. George Koob
NIAAA Director

Another major research focus is how alcohol affects the developing brain. One initiative that supports this focus is the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), a multisite longitudinal study to address alcohol’s potential effects on normal brain development. Another is the Adolescent Brain Cognitive Development Study (ABCD), a joint effort of NIAAA, the National Institute on Drug Abuse, and the National Cancer Institute through the Collaborative Research on Addiction at NIH (CRAN) initiative.

Both efforts will assess the short- and long-term impact of substance abuse on brain development and will use advanced brain imaging as well as

psychological and behavioral research tools to evaluate brain structure and function. ABCD will also examine the effects of multiple substances used alone and in combination. The studies will provide a continual source of information that will ultimately help underage drinkers better understand how alcohol affects their brains.

NIAAA is also reaching out to specific audiences with targeted messaging about alcohol use. For example, NIAAA plans to raise physician awareness about alcohol issues by helping medical schools expand their curricula to include the etiology, prevention, and treatment of AUD.

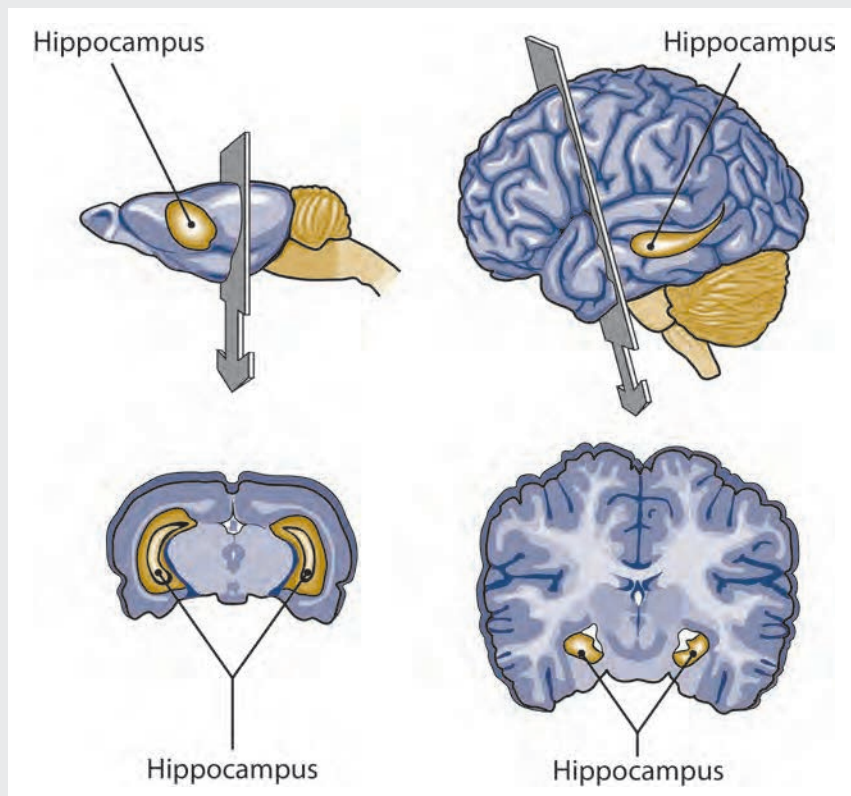
Another outreach focal point will be NIAAA’s *CollegeAIM*, a family of products NIAAA developed in direct response to requests from college presidents and administrators. *CollegeAIM* includes a user-friendly, matrix-based tool, guide, and Web site to help university officials choose wisely among the many potential interventions to address harmful and underage college student drinking. It rates nearly 60 interventions for estimated relative effectiveness, anticipated costs, barriers to implementation, and other factors, and its findings represent a consensus of many of the leading researchers in the field.

NIAAA is also venturing into the latest advances in technology by sponsoring a competition to develop a wearable alcohol biosensor and supporting research to improve imaging for faster liver disease diagnosis.

Overall, there’s an excitement at NIAAA about the vision and new directions. And Dr. Koob embraces the challenge: “We have set lofty goals. But it’s where we want to be.”

FROM THE FIELD

ADOLESCENT ALCOHOL USE AFFECTS BRAIN STRUCTURE AND FUNCTION IN ADULTHOOD



Location of the hippocampus, an area of the brain that appears to be particularly vulnerable to alcohol's effects. It sits below the surface of the neocortex in the rat brain (left) and the human brain (right).

Source: Adapted from Hiller-Sturmhoefel, S., and Swartzwelder, H.S. Alcohol's effects on the adolescent brain—what can be learned from animal models. *Alcohol Research & Health* 28(4):213–221, 2004/2005.

Repeated exposure to alcohol during adolescence can cause structural and functional abnormalities in the brain that last into adulthood, according to a study published in June in the journal *Alcoholism: Clinical and Experimental Research*. Scientists have long known that human adolescence is a crucial time for brain growth and maturation, and have noted that chronic excessive alcohol use during adolescence is associated with memory problems and other cognitive deficits in adulthood. Thus, many have hypothesized that alcohol abuse, which is common during adolescence, might have long-term harmful effects on brain development and function.

To test this hypothesis, researchers, led by Drs. Mary-Louise Risher and Scott Swartzwelder of the Duke University and Durham Veterans Affairs Medical Centers, exposed adolescent rats to alcohol in a way that modeled the intermittent, high-dose alcohol use typically seen among adolescent humans. After the rats reached adulthood, the researchers used a variety of laboratory techniques to measure the rats' brain development and function. Previously, the Duke researchers had reported that animals exposed to alcohol during adolescence grew up to be more vulnerable to memory disruption than animals that were not exposed to alcohol. However, they did

not know how the hippocampus, a region of the brain associated with memory and learning, was affected. So in their new study, they focused on hippocampal area CA1, which plays an important role in learning and memory during both adolescence and adulthood.

The researchers found that, compared with control animals, brains of adult rats that had been exposed to alcohol during adolescence had a number of structural and neurochemical abnormalities in hippocampal area CA1. In particular, they found that a cellular mechanism known as long-term potentiation (LTP) was increased among the alcohol-exposed animals. Although LTP is the mechanism that helps strengthen connections between brain cells as they learn and remember new things, the researchers note that the increased LTP seen among alcohol-exposed animals is not a good thing, as excessive LTP would lead to poorer memory and slower learning, and can be toxic to brain cells. The researchers also found that dendritic spines, brain cell structures that are vital for cell-to-cell communication, appeared immature in the alcohol-exposed animals.

Taken together, the researchers say their findings demonstrate that the adolescent hippocampus is vulnerable to alcohol-induced damage, with pathological changes that impair memory-related brain function into adulthood.

Source:

Risher, M.L.; Fleming, R.L.; Risher, W.C.; Miller, K.M.; Klein, R.C.; Wills, T.; Acheson, S.K.; Moore, S.D.; Wilson, W.A.; Eroglu, C.; and Swartzwelder, H.S. Adolescent intermittent alcohol exposure: Persistence of structural and functional hippocampal abnormalities into adulthood. *Alcoholism: Clinical and Experimental Research* 39(6):989–997, 2015. PMID: 25916839

FROM THE FIELD

THE KNOCK-IN MOUSE: NIAAA-FUNDED STUDY IDENTIFIES GENE VARIANT LINKED TO COMPULSIVE DRINKING



According to the results of a recent NIAAA-funded animal study, carrying a gene variant that affects the release of a specific brain protein may increase the risk of developing an alcohol use disorder. The protein, brain-derived

neurotrophic factor (BDNF), affects the survival of existing neurons and the growth of new neurons and synapses, the junctures through which cell-to-cell communication occurs.

In the study, researchers tested the role of BDNF in alcohol addiction by creating a “knock-in” mouse carrying a gene that reduces activity-dependent BDNF release. These “knock-in” mice drank more alcohol, even when the alcohol was treated with bitter-tasting quinine. This suggests carriers of the variant gene compulsively drink alcohol despite negative results. The effect of the genetic mutation seemed to be specific to alcohol consumption because the mice’s consumption of other fluids did not change, nor was there any difference in their levels of anxiety or compulsive behaviors.

By increasing levels of BDNF in the ventromedial portion of the prefrontal

cortex, a brain region involved in compulsive drug and alcohol seeking, the researchers were able to return the mice to moderate levels of alcohol intake. In addition, by administering a pharmaceutical compound (LM22A-4) developed to mimic the action of BDNF, researchers were able to put a stop to compulsive drinking behaviors. LM22A-4 appears to reduce compulsive alcohol-drinking without a generalized effect on motivation and may have potential as a therapeutic for humans.

Source:

Warnault, V.; Darcq, E.; Morisot, N.; Phamluong, K.; Wilbrecht, L.; Massa, S.M.; Longo, F.M.; and Ron, D. The BDNF valine 68 to methionine polymorphism increases compulsive alcohol drinking in mice that is reversed by tropomyosin receptor kinase B activation. *Biological Psychiatry*, June 12, 2015. [Epub ahead of print]. PMID 26204799

SPOTLIGHT

NIAAA DEBUTS NEW WEB SITE FOR ARCR JOURNAL

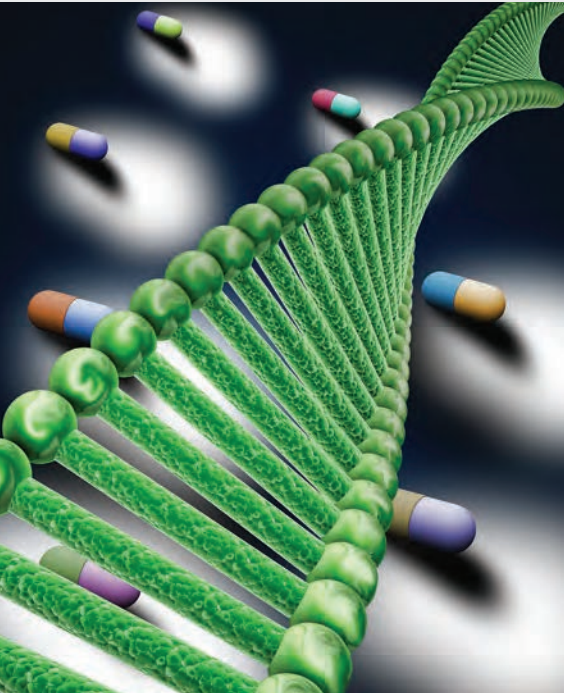
NIAAA’s peer-reviewed journal, *Alcohol Research: Current Reviews* (ARCR) and the accompanying *Alcohol Alert* are now showcased on a new landing page (www.arcr.niaaa.nih.gov), housed on the NIAAA Web site. The landing page features the latest content, an alcohol research topic index, archived issues, and helpful links for contributors. In addition, all ARCR issues from 2007 to the present can now be found in PubMed Central, the main repository for biomedical and life sciences journal literature at NIH’s National Library of Medicine. Published twice per year, each issue of ARCR provides a comprehensive review of an important topic in the alcohol research field and includes in-depth articles spanning the translational science continuum, from basic to clinical to implementation research.

Sign up to receive e-mail notifications when new issues of ARCR, *Alcohol Alert*, and other NIAAA publications become available. You can also subscribe to receive the printed ARCR journal by mail.



FROM THE FIELD

ADVANCING PERSONALIZED TREATMENT OF AUD



In a commentary published in April in the journal *Alcoholism: Clinical and Experimental Research*, Raye Litten, Ph.D., and other NIAAA scientists describe the evolution of our understanding of the heterogeneity of alcohol use disorder (AUD), and outline new treatment and research regimes that follow from the recognition that alcohol problems are manifested along a continuum of severity, ranging from the occasional binge drinker to the chronic relapsing heavy drinker.

“Each patient develops an AUD based on his or her unique neurobiological makeup and lifetime experiences—a complex interaction of underlying genetic and environmental mechanisms,” write Dr. Litten and his colleagues. “This heterogeneity can be understood as a number of subphenotypes, each having its own unique profile of drinking pattern, motivation for drinking, alcohol-related consequences, and neurobiological underpinnings.”

“Not surprisingly,” they note, “a wide variety of clinically acceptable treatment outcomes are possible with AUD, including not only abstinence, but also low-risk drinking, and even some less-conservative forms of moderate drinking.”

A menu of effective treatment options is available today, including three FDA-approved medications to treat alcohol dependence—disulfiram, oral and injectable naltrexone, and acamprosate. A variety of behavioral therapies have also been shown to be effective. However, the authors note that due to the complex heterogeneity of AUD, no single treatment will work for every person with AUD. However, ongoing research progress in both the neurobiology and pharmacogenetics of AUD holds the promise of identifying biologically based AUD subtypes and the selection of treatments to target those subtypes.

“Neurobiological researchers have identified more than 30 molecular targets that appear to alter people’s craving or drinking behaviors,” they write, “and emerging knowledge of the neurobiology and neurocircuitry of AUD provides a framework for organizing targets.”

Dr. Litten and his colleagues say that current evidence allows alcohol addiction, in general, to be broken down into a three-stage cycle: binge–intoxication, withdrawal–negative affect, and preoccupation–anticipation.

“These three stages interact with and build on one another, becoming more intense, and ultimately leading to the pathological state known as addiction. Within this concept, AUD can be conceptualized as a disorder that involves elements of both impulsivity and compulsivity. As an individual moves from impulsivity to compulsivity,

a shift occurs from positive reinforcement to negative reinforcement driving the motivated behavior.”

To promote systematic research discovery efforts based on current knowledge, the NIAAA scientists propose a new framework, called Alcohol Addiction Research Domain Criteria, modeled after a program in use at the National Institute of Mental Health (NIMH). Such a system, they say, enables researchers to “drill down” to the core mechanisms underlying dysfunction, and link behavior and mood to their brain function, neural circuitry, neurotransmitters, and genes.

“The development of an alcohol addiction domain criteria-based framework to conceptualize research on AUD that probes the sources of the disorder could serve to organize and advance our understanding of alcohol addiction,” the authors conclude. “Identifying the major domains underlying AUD and how the profile of vulnerability to each domain varies among individuals, and over time, not only will be vital to understand the heterogeneity of the disorder, but will also enable us to tailor treatment effectively to the individual. This will substantially advance the field of personalized medicine, and foster the translation of findings from basic research into practical, clinical applications.”

Source:

Litten, R.Z.; Ryan, M.L.; Falk, D.E.; Reilly, M.; Fertig, J.B.; and Koob, G.F. Heterogeneity of alcohol use disorder: Understanding mechanisms to advance personalized treatment. *Alcoholism: Clinical and Experimental Research* 39(4):579–584, 2015. PMID: 25833016

5 QUESTIONS WITH . . .

SALLY ANDERSON, PH.D.,

Coordinator, Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders, NIAAA



1 Can you describe the origins of the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD) and its mission?

In 1996, following recommendations from the Institute of Medicine, Congress charged NIAAA to chair ICCFASD. You might call it an outreach program to build bridges across the many diverse agencies and programs involved with the broad array of issues—medical, social, educational and legal—pertaining to fetal alcohol spectrum disorders (FASD). The NIAAA Deputy Director, currently Dr. Kenneth Warren, serves as the ICCFASD Chair.

ICCFASD’s mission is to stimulate communication, coordination, and collaboration among Federal agencies that have an interest in FASD-related activities. Our partners focus on a wide number of fronts, which can be seen from our organizational structure (online at www.niaaa.nih.gov/about-niaaa/our-work/ICCFASD/organization).

2 What is your role as the ICCFASD coordinator?

Broadly speaking, my role is to serve the overarching interests of the interagency committee as a whole. That encompasses many cross-cutting tasks. I coordinate with our Chair and Executive Committee on strategic plans

to develop timely, relevant implementation projects. I also oversee a constant flow of information-sharing across the various agencies as well as organize numerous meetings and workshops each year. I underscore that I don’t come to ICCFASD as another representative of NIAAA but instead work for the entire group. For example, I recently served as an advisor to Canada on both ICCFASD-related projects and the Institute’s research programs to help that country improve its public health plans to address FASD.

3 What are some examples of recent ICCFASD projects?

I can illustrate one of our recent contributions to the field by referring to the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM–5)*, published in 2013. Some members of the American Psychiatric Association’s (APA’s) DSM–5 revision team were exploring the inclusion of a new diagnostic category related to FASD. ICCFASD formed an FASD expert subcommittee to assist APA’s advisory group during the revision process. The result was the addition, as seen in the DSM–5 appendix, of “Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure, or ND-PAE.”

Inclusion in the DSM–5 is a major milestone. Understanding the damaging effects of fetal alcohol exposure will now be part of the educational program for psychiatrists and other mental health care providers. In addition, it will now be easier for mental health care providers to be reimbursed for FASD-related services. Think how that can impact families seeking help for a child with this disorder. And we’re also seeing the emergence of new FASD-related training programs as well, thanks to the inclusion of ND-PAE in the APA’s recent revision of DSM–5.

Other examples include ICCFASD’s collaboration with the American Bar Association to help educate legal professionals about FASD, and working with the nonprofit National Organization on Fetal Alcohol Syndrome on prevention and awareness issues.

4 Looking ahead, what are some of the other projects on the horizon?

Some of our members are working in concert with the American Academy of Pediatrics (AAP). In fact, the AAP is expected to publish new guidelines on identification, diagnosis, and management of ND-PAE soon. That will have huge benefits for infants, children, and adolescents with FASD and their families.

We continue to conduct important outreach, including efforts to educate judges about FASD-related matters. We’ve also had discussions with educators about issues related to these children with special needs.

Closer to home, NIAAA continues to support new research and supplement existing grants that are helping to expand research. These programs will enable us to derive data from diverse populations. That in turn will help future efforts with groups like the APA, AAP, and others involved with formulating improved diagnostic criteria and new interventions.

5 Outside of your work, what hobbies do you enjoy?

My husband and I find travel to be very enriching. We’ve had wonderful experiences seeing new places. We loved the Galapagos Islands, visiting the Great Wall of China, and exploring the coast of Southeastern Alaska, and someday we’d love to hike the Milford Track in New Zealand.

New From NIAAA CollegeAIM Guide and Web Site



Available September 22, 2015, at www.collegedrinkingprevention.gov

What is CollegeAIM?

CollegeAIM is a new resource to help schools address harmful and underage student drinking. Developed with leading college alcohol researchers and staff, CollegeAIM is an **easy-to-use** and **comprehensive** tool to identify effective alcohol interventions.

Why is CollegeAIM needed?

High-risk drinking remains a persistent problem on U.S. campuses. While college officials have numerous options for addressing alcohol issues, they are not all equally effective. CollegeAIM can help inform decisions and guide college staff to evidence-based strategies.

CollegeAIM can help schools **choose interventions wisely**—boosting their chances for success and helping them improve the health and safety of their students.

How can schools use CollegeAIM?

With the help of CollegeAIM, school officials can:

- Review the **individual-** and **environmental-level** strategies to learn how their current strategies compare to other alternatives.
- Discover new evidence-based options.
- **Use the interactive strategy planning worksheet** to help select a combination of approaches that meets the needs of their campus and their budget.

How is CollegeAIM different?

CollegeAIM is distinctive because of the breadth of its research and analysis, the expertise of its contributors, and its user-friendly format:

- Extensive review of decades of scientific literature
- Multi-year collaboration with dozens of developers and reviewers
- Nearly 60 interventions rated for effectiveness, costs, and other criteria
- Two **accessible** and **user-friendly** matrices and other resources

“This new matrix-based instrument is one of the most thoroughly vetted and user-friendly summaries of intervention strategies I have seen in decades.”

—Jonathan Gibraltar, Ph.D.
President, Wells College

ABOUT US

NIAAA Spectrum is NIAAA’s 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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