Alcohol use disorder (AUD) is a highly heterogeneous disorder, meaning affected individuals differ in their drinking patterns, motivations for drinking, and clinical signs and symptoms, as well as the neurobiological, genetic, and environmental factors that contribute to alcohol misuse. For example, while some people may have trouble moderating their drinking because of increased sensitivity to stress, others may be driven more by an inability to experience pleasure from typically rewarding experiences, or by poor decision-making due to impaired cognitive function, or some combination of these or other factors.

Neurobiological and genetic differences may help explain why current behavioral and pharmacological treatments for AUD are not effective for all individuals who seek treatment. However, most methods for AUD diagnosis currently used in clinical practice focus on behavioral symptoms and consequences, and do not account for such individual differences although they may, in fact, underlie AUD.

Researchers believe that a deeper understanding of individual differences could enable more precise diagnosis of the specific deficits or other drivers that underlie a particular individual’s AUD. More precise diagnosis could, in turn, be used to target behavioral and/or pharmacological therapy to a person’s specific problem(s), thereby increasing AUD treatment effectiveness.

Efforts are underway to develop a framework for assessing and classifying individual differences in AUD based on a person’s neurobiological and behavioral characteristics. Called the Addictions Neuroclinical Assessment (ANA), a team of NIAAA scientists described it in a recent article in the journal *Biological Psychiatry*.

“We currently approach addiction diagnosis as a ‘yes or no’ proposition,” says first author Laura E. Kwako, Ph.D., Clinical Research Psychologist, Office of the NIAAA Clinical Director. “The ANA leverages current knowledge of the neuroscience of addiction to more precisely identify different subtypes of addictive disorders.”

“The framework that we describe capitalizes on decades of neuroscience advances from animal models and human studies,” says NIAAA Director George F. Koob, Ph.D., article coauthor.

*Continued on page 3*
MULTISITE CLINICAL TRIAL OF PROMISING DRUG TREATMENT FOR AUD HIGHLIGHTS EFFORTS OF NIAAA’S DIVISION OF MEDICATIONS DEVELOPMENT

A new medication called ABT-436 that targets the brain’s stress systems may help reduce alcohol use in people with alcohol use disorder (AUD), according to a recent study led by researchers in NIAAA’s extramural Division of Medications Development (DMD).

“Medications have become an important tool for treating AUD, but current medications are not effective for all people who seek treatment,” notes NIAAA Director George F. Koob, Ph.D. “Through our intramural and extramural research programs, NIAAA is committed to developing a wider variety of safe and effective pharmacotherapies and giving clinicians a menu of options for individualized AUD treatment.”

The NIAAA DMD, which oversees NIAAA-supported extramural research on pharmacotherapy for AUD, helps to advance promising medications through the drug development pipeline. This is done using a broad array of efforts aimed at bridging the gap between preclinical research and clinical trials. These efforts include, for example, providing assistance to small businesses to conduct studies of early-stage compounds, and supporting Phase I human studies to ensure the safety, tolerability, and proper dosing of compounds approved for experimental use in people.

As exemplified by the recent study of ABT-436, DMD also oversees the NIAAA Clinical Investigations Group, a network of clinical sites established to efficiently test the safety and effectiveness of promising medications in Phase II clinical trials. As reported online in the journal *Neuropsychopharmacology*, researchers led by Raye Litten, Ph.D., Acting Director of DMD, conducted a randomized Phase II clinical trial of the new compound, which was designed to block the effects of vasopressin, a stress hormone produced in the hypothalamus of the brain.

“Vasopressin helps to regulate brain circuits involved in emotion,” explains Dr. Litten. “As such, it plays a role in regulating stress and anxiety, and their interaction with AUD.”

Dr. Litten; first author Megan Ryan, M.B.A., Clinical Project Manager in DMD; and their NIAAA colleagues worked with the NIAAA Clinical Investigations Group to recruit 144 alcohol-dependent adult men and women for the 12-week study. During the 28-day period prior to the study, female participants consumed at least 28 drinks per week, while male participants consumed at least 35 drinks per week. Participants were then randomized to receive either placebo tablets or ones containing the ABT-436 compound. Researchers monitored participants’ alcohol consumption, as well as their mood changes and smoking habits, as these are known to covary with alcohol consumption.

Researchers found that participants receiving ABT-436 experienced more days of alcohol abstinence than those receiving the placebo. In particular, participants who reported high levels of stress appeared to respond better to ABT-436, in that both the frequency of their drinking and the number of heavy-drinking days they experienced decreased.

“Our findings suggest that future AUD studies with compounds that target vasopressin should focus on individuals who report high levels of stress,” says Ryan.

Smokers may be another population that could benefit from ABT-436. In addition to its effects on alcohol consumption, study participants receiving the new compound experienced a reduction in smoking. The researchers suspect that ABT-436 may be targeting areas in the brain that influence both tobacco use and AUD. Additional research is needed to determine if that is the case.

Reference:
"We are heartened to now know enough to advance research on a diagnostic system which may ultimately help us treat people more effectively."

The ANA will be organized around the three stages of the addiction cycle (see above), which is used as a model for understanding the neurobiological processes underlying AUD. These stages involve: 1) a loss of control over alcohol intake (binge/intoxication stage), 2) the experience of a negative emotional state in the absence of alcohol (withdrawal/negative-affect stage), and 3) a compulsion to seek out and consume alcohol (preoccupation/anticipation stage). People may vary in how they progress through the cycle, the intensity with which they experience each of the stages, and the nature of the disruptions to the underlying neurobiological circuits.

The ANA will assess the key neurobiological domains within each stage of the addiction cycle using a multidimensional battery of tests, including genetics, neuroimaging, and cognitive and behavioral assessments. The results will be used to identify clinically relevant AUD measures and could ultimately guide the provision of individually tailored AUD treatment strategies.

In describing the potential usefulness of the ANA, the authors draw a comparison to how clinicians combine cellular, genetic, molecular, and imaging information with clinical history to make cancer diagnoses. They note that, by integrating this information, cancer clinicians have been able to tailor the treatment of certain cancers to the specific characteristics that an individual with cancer may have.

“Although addiction treatment options exist, and indeed continue to expand, their effectiveness is limited by the significant heterogeneity of AUD and an inability, thus far, to define addictive disorders by their underlying neurobiology,” notes Dr. Koob. “The comprehensive measures of the ANA will facilitate enhanced understanding of the specific causes of addiction at a biological level and pave the way for new treatment strategies.”

The ANA and Precision Medicine

Precision medicine is an emerging approach for preventing and treating disease that considers individual variability in genes, environment, and lifestyle. It is a major initiative of the National Institutes of Health and a guiding framework for NIAAA’s work to treat alcohol misuse and AUD. NIAAA’s Addictions Neuroclinical Assessment (ANA) could provide a framework for diagnosing AUD based on neurobiological, cognitive, behavioral, and genetic characteristics and traits that correspond to an individual’s disorder. Dr. Laura E. Kwako of the NIAAA Division of Intramural Clinical and Biological Research stresses that the ANA is very much a research framework, with more research necessary before it becomes clinically informative.

Also relevant to precision medicine, NIAAA supports research to identify patient cohorts most likely to benefit from existing treatments and to develop new interventions based on the unique characteristics of a person’s disease. For example, because relapse is frequently triggered by stress, NIAAA is evaluating compounds that target brain stress systems as treatments for people who are particularly susceptible to stress-related drinking. Researchers are also investigating whether patterns of brain activation can be used to identify people who are likely to relapse when exposed to certain stimuli, as well as whether particular AUD treatments are more effective in people with certain gene variants.

Reference:
NIAAA PUBLISHES NEW STRATEGIC PLAN

The National Institute on Alcohol Abuse and Alcoholism Strategic Plan, 2017–2021, was released in spring 2017. The plan serves as a roadmap for optimizing the allocation of the Institute’s resources to areas of alcohol research most likely to benefit from additional support, translating scientific discoveries for the benefit of the public, and continuing to build on NIAAA’s position as the nation’s key source of evidence-based information on alcohol and health.

“This strategic plan spotlights significant gains achieved through NIAAA-supported research and articulates a vision for capitalizing on emerging opportunities across the spectrum of alcohol research,” says NIAAA Director George F. Koob, Ph.D. “I want to thank our Advisory Council, the scientific community, and the many public stakeholders that we heard from as we developed this plan.”

The plan focuses on five overarching goals:

1. Identify Mechanisms of Alcohol Action, Alcohol-Related Pathology, and Recovery
2. Improve Diagnosis and Tracking of Alcohol Misuse, Alcohol Use Disorder, and Alcohol-Related Consequences
3. Develop and Improve Strategies To Prevent Alcohol Misuse, Alcohol Use Disorder, and Alcohol-Related Consequences
4. Develop and Improve Treatments for Alcohol Misuse, Alcohol Use Disorder, Co-Occurring Conditions, and Alcohol-Related Consequences
5. Enhance the Public Health Impact of NIAAA-Supported Research

Along with these goals, several cross-cutting research themes are woven throughout the strategic plan:

• Address Alcohol Misuse Across the Lifespan
• Address Co-Occurring Conditions
• Reduce Health Disparities
• Advance Precision Medicine
• Strengthen the Biomedical Research Workforce
• Serve as a Responsible Steward of Our Nation’s Research Resources

To view or download the NIAAA Strategic Plan, please visit the NIAAA website at: https://www.niaaa.nih.gov/about-niaaa/our-work/strategic-plan.

NEW ADDICTION MEDICINE CERTIFICATION AVAILABLE FOR PHYSICIANS

Beginning in fall 2017, physicians will have the opportunity to become certified in the subspecialty of addiction medicine. To help integrate addiction medicine into routine medical practice, the American Board of Preventive Medicine (ABPM) is sponsoring and administering the certification through an examination and clinical experience requirements.

NIAAA strongly supports integrating alcohol and drug screening, prevention, and treatment into primary care and preventive medicine training. In fact, NIAAA, in collaboration with the National Institute on Drug Abuse, has worked to improve physician training in these areas by supporting the accreditation of addiction medicine fellowship training programs. They are also engaging with medical education groups in the design and implementation of national standards for training in addiction medicine for medical students and residents. These objectives are included in National Institute on Alcohol Abuse and Alcoholism Strategic Plan, 2017–2021.

Peggy Murray, Ph.D., Director of the Global Alcohol Research Program at NIAAA, has been central in NIAAA’s efforts to promote addiction medicine across the continuum of medical training. She sees a variety of benefits to the new ABPM certification, including helping to bridge the gap between patients who need and receive treatment.

“In the United States, about 16 million people have alcohol use disorder. Less

Continued on page 8
DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is a type of magnetic resonance imaging, or MRI, that is used to map white-matter pathways in a living brain. White matter is composed of axons, the threadlike nerve fibers that carry signals between neurons, and myelin, the insulating sheath that forms around these nerve fibers and gives white matter its color. DTI takes advantage of freely moving water molecules in the brain. When the movement, or diffusion, of water molecules is restricted by cell membranes or other brain microstructures, the diffusion follows the boundaries of the structure. In the case of axons, water molecule diffusion follows their linear orientation, so DTI scans provide a picture of the connections that axons make in the brain. The figure to the right compares DTI scans of an adult male without alcohol use disorder (AUD) and another with AUD.

POTENTIAL BARCODE IDENTIFIED FOR A FORM OF ALCOHOLIC LIVER DISEASE

NIAAA–supported researchers have discovered that extracellular vesicles (EVs) released by liver cells in a mouse model of alcoholic steatohepatitis (ASH) contain a micro ribonucleic acid (miRNA) signature detectable in the blood. ASH is a form of liver disease and the miRNA may serve as a “barcode” to help diagnose early-stage ASH in humans. EVs are small membrane structures that are released by active or damaged cells. EVs contain many different molecules, including miRNAs, which regulate cell responses and provide clues about the EV’s cell of origin.

In the study, researchers continuously administered ethanol to mice with incremental increases every two days. A control group received a liquid diet matched in caloric content with the alcohol group. At two weeks and four weeks, the researchers isolated and cultured hepatocytes (liver cells) and characterized the EVs released by these cells using standard laboratory techniques. After four weeks, the mice developed features of early-stage ASH and had increased levels of EVs in the blood compared to controls. Analysis of the miRNA suggests that hepatocytes were the primary source of these EVs.

Building on this research, the team analyzed the miRNA profiles of the EVs in the blood of the ASH mice and three other mouse models of chronic liver injury, as well as hepatocytes exposed directly to ethanol. They identified three miRNAs—let7f, mrR-29a, mrR-340—whose levels increased in the blood EVs of ASH mice, but not in the blood EVs of the other liver disease models. The researchers also conducted a small pilot study in humans with ambulatory mild alcoholic liver disease and found that the levels of EVs and miRNAs also had increased in these patients’ blood compared to individuals without alcoholic liver disease.

Nearly half of all liver disease deaths in the United States each year are attributed to alcohol misuse. Early detection of alcohol-induced liver disease is key to preventing progression to more serious disease. Taken together, these findings suggest that ASH-associated EVs and their miRNA “barcode” can be used to distinguish ASH from other types of liver disease, and potentially serve as novel biomarkers and therapeutic targets for ASH.

Reference:
CARDIAC ORIENTING RESPONSE IN INFANTS CAN INDICATE ALCOHOL-RELATED DEVELOPMENTAL DELAY

A relatively simple and inexpensive test based on heart rate patterns has been shown to effectively identify infants at risk of developmental delay due to prenatal alcohol exposure (PAE). Researchers supported by NIAAA found that cardiac orienting response (COR), a measure of heart rate decrease after being exposed to novel stimuli, in infants was a better predictor of developmental delay by 1 year of age than a widely used developmental test (the Bayley Scales of Infant Development-II).

When used to assess 6-month-old infants whose mothers drank during pregnancy, COR had a positive predictive value of 66 percent, meaning that two-thirds of infants identified by the test were confirmed to be developmentally delayed at 1 year of age. By comparison, only 44 percent of 6-month-old infants who tested positive for developmental delay using the Bayley Scales were found to be developmentally delayed at age 1. COR had a negative predictive value of 85 percent compared to 77 percent for the Bayley Scales. In other words, 85 percent of infants found not to be developmentally delayed at 6 months using COR were not when assessed at age 1. The findings suggest that COR is a useful screening tool for identifying infants with neurodevelopmental impairments caused by PAE and is less labor intensive than existing neurobehavioral tests.

COR is the result of the heart controlling oxygen sent to the central nervous system. Animal studies suggest that it may be an early sign of how efficient the prefrontal cortex is in directing energy resources between attention and arousal systems.

Ultimately, it is important to identify children affected by prenatal alcohol exposure as early as possible so they can receive interventions at a young age. Interventions are more effective early on because neural plasticity—the brain’s ability to modify its structure and function as a result of experience—is enhanced in the developing brain. However, it can be challenging to identify children with PAE because neurobehavioral deficits can be subtle until later in childhood. Many children

INTERVENTIONS EFFECTIVE IN PREVENTING ALCOHOL USE AMONG AMERICAN INDIAN AND RURAL YOUTH

Community-based and individual-level prevention strategies are effective in reducing alcohol use among American Indian and other youth living in rural communities, an NIAAA-supported study reports. This study, one of the largest alcohol prevention trials conducted with an American Indian population, is also one of the first to demonstrate that screening and brief intervention with motivational interviewing significantly reduces youth alcohol use at a community level.

The researchers, led by Kelli Komro, Ph.D., at Emory University in Atlanta, Georgia, worked with the Cherokee Nation to implement a trial of two evidence-based strategies to reduce underage drinking and its consequences. The first, Communities Mobilizing for Change on Alcohol (CMCA), is a community-organizing intervention that develops citizen action teams to push for implementation of policies and practices to reduce youth access to alcohol through social and commercial sources. The second intervention, CONNECT, implements individually delivered screenings and brief interventions where a school social worker conducts one-on-one health consultations with students each semester to encourage healthy behaviors. Students who report high-risk drinking attend follow-up sessions and are referred to specialty treatment when appropriate.

Six communities within the Cherokee Nation in northeastern Oklahoma were randomly assigned to receive CMCA,
NIAAA Spectrum

5 QUESTIONS WITH . . .

LAURA E. KWAKO, PH.D.
Clinical Research Psychologist

1 You are a Clinical Research Psychologist in the Office of the Clinical Director (OCD). How does OCD’s clinical work contribute to the overall research program at NIAAA?

The OCD makes a substantial contribution to the NIAAA intramural research program (IRP) by both actively conducting research and fostering studies conducted by other NIAAA IRP investigators. OCD staff serve as the principal and lead associate investigators on a large screening and natural history study protocol, which functions as a platform for recruiting study participants for most of the NIAAA IRP. It is important to note that this protocol obtains comprehensive phenotypic information on our research participants and captures genetic data, as well. These efforts promote translational research, all the way from the bench to the bedside and back again.

2 What are some of the biggest challenges you face as a clinical researcher, particularly in the area of alcohol research?

Recruitment of study participants is probably the biggest challenge we face as clinical researchers, particularly for inpatient studies. Identifying individuals who are willing and able to make the time commitment needed for our studies is difficult. In addition, the significant physical and psychiatric comorbidities that often accompany alcohol use disorder (AUD), particularly in its later stages, further complicate recruitment efforts.

3 Your biggest project is the Addictions Neuroclinical Assessment (ANA). What excites you most about the potential of this diagnostic framework?

I think the ANA has the potential to fundamentally alter the way we think about alcohol and drug addiction and treatment. Using the (mostly) objective measures included within the ANA, in conjunction with the rich data collected from patient interviews, could really help us better understand the heterogeneity of AUD and more effectively tailor treatments to an individual. As a clinical psychologist, I think that psychiatric illnesses in general, and alcohol and drug addiction in particular, face ongoing stigma and other barriers to treatment. I’m hopeful that the ANA might help us move past some of those challenges and lead to a paradigm shift in how we approach addiction.

4 What are your hopes for addiction assessments a decade from now? What may become part of routine screenings and assessments in 10 years?

I think a few key changes in addiction assessments could make a big difference, such as moving beyond brief questions of weekly consumption to those concerning consumption patterns, changes in patterns, and motives to consume alcohol. For example, asking people whether they consume more alcohol when feeling stressed would be useful. I also hope that brief assessments organized around the neurobiological domains measured in the ANA could be done in the clinic and would hopefully provide a more thorough assessment than is currently done.

5 Can you tell us something that might surprise us to learn about you?

When I was growing up, my family spent five summers in Oxford, United Kingdom, for a study-abroad program my father was teaching. I returned and spent several months there before starting graduate school, during which I read more than 20 books, including a dozen on linguistics—maybe that would have been my alternate career path.
NOTEWORTHY: Addiction Medicine Certification . . . Continued from page 4

than 10 percent of them receive any treatment. Expanding the physician workforce in addiction medicine is critical to meeting this treatment gap,” says Dr. Murray.

To be eligible to take this new certification examination, physicians must be certified by another Member Board of the American Board of Medical Specialties and have experience with addiction medicine. For the next five years, this certification will not require completing a fellowship.

Dr. Murray notes, “Broad representation of addiction medicine subspecialists among the 24 medical specialties recognized by the American Board of Medical Specialties, which this exam allows, will go a long way toward reducing stigma and increasing recognition of the need to address these disorders in mainstream medicine.”

For more information on the exam and related certification requirements, please visit the ABPM website at: http://www.theabpm.org.

NEWS FROM THE FIELD: Cardiac Orienting Response . . . Continued from page 6

with PAE are not diagnosed until they begin to struggle in school, so a simple, effective early screening tool would be invaluable.

The research, published in the November 2016 issue of Alcoholism: Clinical & Experimental Research, was conducted in Ukraine and included 124 infants. It was supported by the Collaborative Initiative on Fetal Alcohol Spectrum Disorders, an NIAAA-funded consortium working to improve fetal alcohol spectrum disorder clinical case recognition and develop interventions for affected individuals.

Reference:

NEWS FROM THE FIELD: Interventions Effective . . . Continued from page 6

CONNECT, a combination of both interventions, or neither intervention. Students were first surveyed in 9th or 10th grade and were followed through 11th or 12th grade, respectively. The student population was nearly 50 percent American Indian, but also included other racial/ethnic minorities and Whites.

The researchers found that self-reports of the prevalence of any alcohol use and heavy drinking episodes (five or more drinks on at least one occasion) in the past 30 days were significantly reduced among students receiving either one or both interventions, compared with students in the control communities. These findings indicate that CMCA and CONNECT can be effective approaches for addressing teen drinking in these diverse communities.

Reference:

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.

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
https://www.spectrum.niaaa.nih.gov

https://www.spectrum.niaaa.nih.gov