Alcohol Alert

National Institute on Alcohol Abuse and Alcoholism

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Improving Health Through Translational Alcohol Research

Alcohol misuse has profound effects on the health and well-being of individuals, families, and communities. In the United States, nearly 88,000 people—approximately 62,000 men and 26,000 women—die from alcohol-related causes each year.[1] Alcohol misuse not only increases the risk for alcohol use disorder (AUD),[a] which affects nearly 17 million people in the United States, but it contributes to a wide range of adverse social, vocational, and health conditions. These include traffic fatalities, injuries, poor academic performance, alcoholic liver disease, alcoholic pancreatitis, certain cancers, and fetal alcohol spectrum disorders, among many others.[2] Over the past several decades, scientists have made great strides in illuminating the biological and behavioral underpinnings of alcohol misuse and "translating" this knowledge into effective preventive and treatment interventions for AUD and other substance use disorders.

Translational research is the process of turning observations made in the laboratory, clinic, and community into interventions that improve health—from diagnostics and therapeutics to medical procedures and behavior change.[3] Although translational research has long been a goal of the National Institutes of Health (NIH), in recent years, NIH has expanded its focus on this research area. Translation occurs at multiple points along the scientific research continuum, including from basic to clinical research, from clinical research to clinical practice, and from clinical practice to the implementation of public health interventions (see figure). For example, translational alcohol researchers may seek to demonstrate how alcohol's effects on the brain and on behavior at the fundamental level (e.g., in cells or animals) are relevant to humans. Others seek to translate our understanding of the mechanisms by which alcohol affects human health and well-being into interventions for preventing or treating those effects.

Translation does not stop there, however. Interventions that prove effective in people must then be adopted into healthcare practice. Translational researchers working at this stage of the continuum may study how to increase the adoption of healthy drinking behaviors or increase clinician use of alcohol screening or pharmacotherapies. They may also conduct research to understand how interventions that have been adopted into clinical practice affect health at the population level. Importantly, translation does not proceed in one direction. Just as basic research informs clinical studies and clinical practice, observations made in studies with people and by clinicians at the frontlines of patient care can drive new basic and clinical research questions. Such "reverse" translation is also important for validating basic research models for preventing, diagnosing, and treating disease.

This *Alert* addresses an active area of translational research—the neurobiology of AUD. Drawing on human and animal research, it offers a brief overview of the changes in the brain that underlie the

[a] The *Diagnostic and Statistical Manual of Mental Disorders* (DSM–5) describes AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress. AUD may be categorized as mild, moderate, or severe depending on the number of diagnostic criteria that a patient meets. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.).* Washington, DC: APA, 2013.

development and progression of AUD—from moderate to excessive to compulsive drinking—and how our understanding of these changes is informing—or being translated into—the development of interventions to help people reduce or abstain from alcohol use altogether.

Alcohol's Influence on the Brain

Scientists have long understood that our brains are adaptable. One type of adaptation occurs through "synaptic plasticity," a process through which connections among brain cells, called synapses, transform over time. When positive, these changes, or neuroadaptations, can enhance the efficiency of brain functioning, such as when learning a new task. But plasticity also can be harmful, causing disruptions in brain circuitry, as can occur with chronic, excessive drinking.

"A growing body of evidence indicates that neuroadaptations in these brain regions drive the development and progression of AUD."

Research has demonstrated that chronic alcohol misuse produces negative changes in three regions of the brain, each associated with one of the three stages of the AUD cycle:[4]

- The *basal ganglia*, which is involved in the *binge/intoxication* stage of AUD. This is the stage at which an individual consumes alcohol and experiences its rewarding or pleasurable effects.
- The *extended amygdala*, which is involved in the negative emotional state that individuals with AUD experience in the absence of alcohol during the *withdrawal/negative* affect stage.
- The *prefrontal cortex*, which is involved in behavioral control and decisionmaking, underlies the "preoccupation/anticipation" stage of AUD during which individuals experience a compulsion to drink.

A growing body of evidence indicates that neuroadaptations in these brain regions drive the development and progression of AUD.[5–8] On the hopeful side, reversing these neuroadaptations may help individuals with AUD maintain sobriety or return to low-risk drinking.

Basal Ganglia: The basal ganglia include two subregions that are particularly important in substance use disorders: the nucleus accumbens, which is involved in motivation and the experience of reward, and the striatum, which is involved in habit formation and other routine behaviors. Repeated activation of the reward system of the nucleus accumbens by alcohol can trigger changes in the striatum, leading to the development of habitual or compulsive alcohol seeking. In addition, the stimuli that are present when people drink—including people, places, and even their own internal mood states—can become associated with the pleasurable effects of alcohol. Over time, these cues may acquire the ability to activate the brain's reward systems even in the absence of alcohol. This helps explain the intense craving and compulsive alcohol seeking that occurs when some people with AUD are exposed to stimuli they have come to associate with drinking.

Evidence for the role of the basal ganglia in AUD comes from research conducted with animals and humans. For example, animal studies show that chronic alcohol consumption disrupts communication between cells within the basal ganglia and in circuits connecting the cortex to the basal ganglia. This abnormal communication is linked to alterations in how animals respond to alcohol and to alcohol-associated cues, such as its smell.[5] Animal studies also show that alterations in the striatum are associated with habitual alcohol seeking and drinking behaviors similar to those observed in people with AUD.[5] Using functional magnetic resonance imaging (fMRI), a noninvasive neuroimaging technique that measures brain activity, researchers found that activity in the striatum increases when heavy[b] drinkers[8] and people with AUD drink or are exposed

[b] Participants in this study reported drinking an average of 11.8 times per month and an average of 5.53 drinks per drinking occasion. The Substance Abuse and Mental Health Services Administration defines heavy drinking as drinking 5 or more drinks on the same occasion on each of 5 or more days in the past 30 days.

to alcohol-associated cues.[6] This activity is highly correlated with alcohol craving. Even patients with a history of AUD who have stopped drinking show alterations in how they process stimuli associated with reward. For example, compared with people who lack a history of AUD, detoxified AUD patients showed greater activity in the striatum when presented with cues associated with alcohol, but less activation in that area of the brain when expecting a monetary reward. Together, these and other studies suggest that repeated alcohol use alters the reward and habit pathways in the brain, making individuals more sensitive to environmental stimuli associated with alcohol and increasing alcohol craving, seeking, and drinking.[8]

Extended Amygdala: AUD is associated with heightened stress sensitivity, anxiety, and depressive symptoms, and individuals with severe AUD often experience these symptoms when they stop drinking.[8] These negative feelings are thought to stem from disruptions in the brain's reward circuits, as well as activation of the brain's stress systems in the extended amygdala. Studies with animals have found that short- and long-term alcohol use disrupts synaptic plasticity in the extended amygdala. They have also found associations between altered neuronal responses in the extended amygdala and stress-triggered drug use. Moreover, stress neurotransmitters—chemical messengers that relay information throughout the nervous system—are activated in the extended amygdala during alcohol withdrawal. Blocking the activation of these chemical messengers has been shown to reduce alcohol consumption both in animal models of AUD and in people with AUD.[9] Additional evidence for a role of the extended amygdala in AUD comes from brain-imaging studies: researchers have found that the volume of the amygdala is smaller in individuals with AUD compared with those without the disorder, and smaller amygdala volume is associated with increased alcohol craving and relapse.[8]

Prefrontal Cortex: The prefrontal cortex (PFC) aids in organizing thoughts, controlling behavior, and making decisions, a set of skills known as "executive function." Executive function is necessary for making appropriate choices about whether or not to drink and for overriding strong urges to drink that people with AUD may experience, particularly when faced with stress or alcohol cues as described above. Brain-imaging studies consistently show that people with severe AUD have structural and functional abnormalities in the PFC.[7]

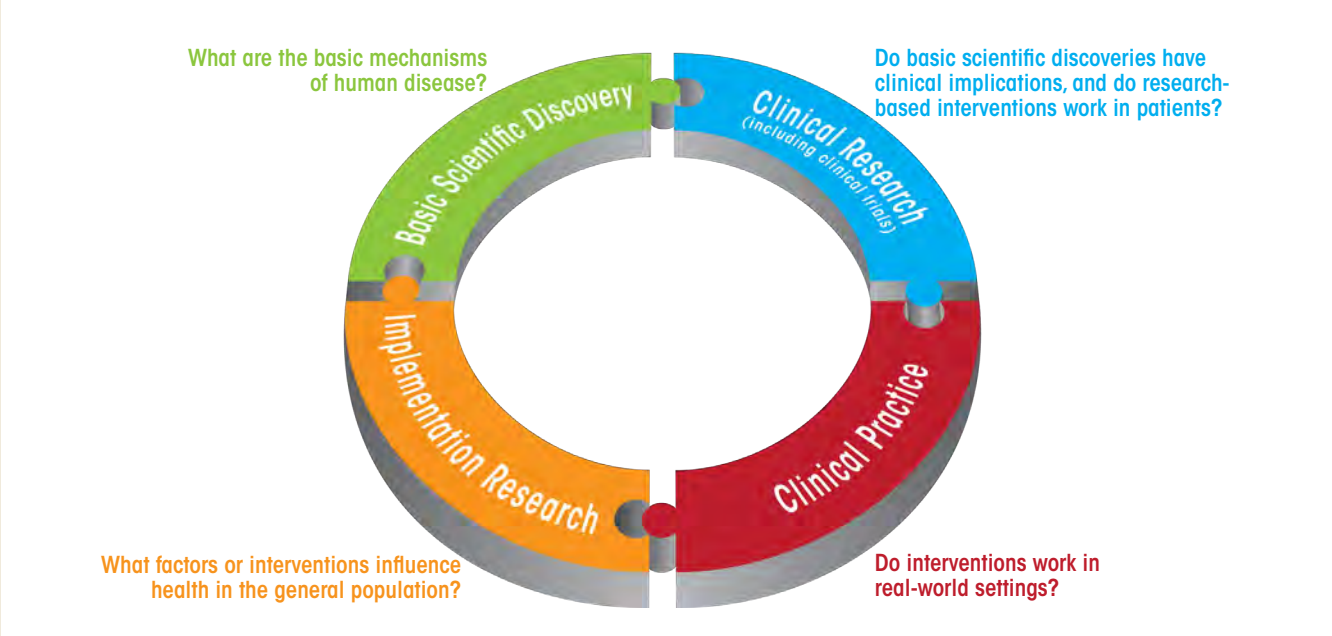

Figure Translational research is the process of transforming discoveries made in the laboratory and clinic into interventions that improve public health. Translation occurs at multiple points along the scientific research continuum, including from basic to clinical research, from clinical research to clinical practice, and from clinical practice to the implementation and dissemination of public health interventions.

They generally have less activity in executive function networks responsible for decisionmaking and impulse control, and higher activity in the areas involved in the rewarding or pleasurable effects of alcohol and other drugs.[6] This pattern is opposite in people who succeed in maintaining abstinence. Moreover, compared with people without a history of substance misuse, people with or recovering from AUD appear to need to marshal more regions of the brain to perform as well on certain cognitive tasks. Recruitment of additional brain regions may be a way of compensating for the compromise of function in brain circuits that normally would be responsible for carrying out such tasks.

Another study found that smaller prefrontal cortex volume predicted a shorter time to relapse in abstinent individuals with AUD. Studies of individuals with damage to the PFC also suggest a role for this brain region in AUD. Using an experimental gambling task, researchers have found that both people with AUD and people with PFC damage tend to make impulsive choices that result in immediate monetary rewards, even if those choices lead to greater future losses.[10] This behavior is similar to the behavior observed in some people with AUD and other substance use disorders who may compulsively use drugs or alcohol in spite of the potential negative consequences.[7] These data suggest that alcohol-induced disruptions in PFC function may underlie the executive function deficits exhibited by individuals with AUD.

From Brain Circuits to Targeted Therapy

As a whole, studies find that brain circuits linking the basal ganglia, extended amygdala, and prefrontal cortex play a pivotal role in the reinforcing effects of alcohol (i.e., those effects that make a person want to continue drinking), habitual alcohol use, stress, and decisionmaking throughout the course of AUD.[8] An ongoing challenge for scientists is to translate these findings into interventions for preventing and treating the disorder. Two of the three medications currently approved by the U.S. Food and Drug Administration for the treatment of AUD appear to work by targeting the processes described above. Naltrexone, for example, helps to reduce heavy drinking by diminishing alcohol's rewarding effects. Acamprosate, in contrast, reduces the negative experiences associated with alcohol withdrawal, and some studies show that it also diminishes craving, making it easier for people to maintain abstinence. Researchers are currently investigating numerous other compounds as potential treatments for AUD, including those that target brain–stress systems. Recognizing that no one AUD treatment is likely to be effective for all people, scientists are studying genetic variants that might help to predict how well a person with AUD will respond to a particular medication.[11] Like developing new AUD treatments, identifying the individuals most likely to benefit from a particular treatment is an important goal of translational alcohol research that will help clinicians tailor treatment strategies to the needs of their patients.

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In addition to continuing to develop medications, alcohol researchers are exploring exciting nonpharmacological AUD treatment approaches based on what we have learned about alcohol's effects on brain circuits. One area of investigation involves examining how patterns of brain activity may be used to predict treatment outcomes. For example, using functional magnetic resonance imaging (fMRI), researchers have found that individuals with AUD who maintain abstinence have less synchrony in brain–reward networks and greater synchrony in behavioral control networks than individuals without a history of substance use disorder.[6] fMRI studies have also found that greater activity in the prefrontal cortex and striatum during the performance of tasks designed to measure cognitive control is associated with better outcomes in substance use disorder treatment.[12] Another study found that behavioral therapy resulted in a decrease in the quantity and frequency of adolescent drinking, and these changes were correlated with brain-activation patterns in response to the language the therapist used (i.e., asking youth open-ended vs. "yes"/"no" questions about their substance use).[13]

Researchers are also investigating whether altering the activity of brain networks involved in AUD can influence drinking.[14] One research team found that using transcranial magnetic stimulation (TMS)—a procedure that stimulates the brain using a magnetic coil placed near the scalp—to increase PFC activation made it easier for people to exert control over their alcohol craving.[6] Other investigators are exploring the use of electroencephalography (EEG), a technique that measures patterns of electrical activity in the brain using electrodes attached to the scalp, to treat AUD.[6,8,15] Scientists have found that individuals with AUD have abnormal EEG patterns. Training them to manipulate these signals—a technique called neurofeedback—may hold promise for treating AUD. Studies of EEG neurofeedback as a treatment for substance use disorders are not new. In fact, they date back to the 1970s. Relatively recent advances in the field, however, are allowing researchers to measure EEG activity in *specific* areas of the brain. That, coupled with an improved understanding of the brain regions involved in alcohol and other substance use disorders, may lead to more effective use of this technique.[6]

Conclusion

Alcohol use disorder is an extraordinarily complex and formidable public health problem. Nearly 30 percent of the U.S. population has experienced AUD at some point in their lives.[16] Basic neurobiological and behavioral research has laid the foundation for the development of a host of effective AUD treatments and continues to drive progress in the field. However, the vast majority of people in the United States who have experienced AUD have not received treatment or help. Moreover, existing behavioral and pharmacological interventions, although effective, work better for some people than they do for others. This underscores the need for continued research aimed at further illuminating the mechanisms through which alcohol contributes to disease and disability, translating this knowledge into a broader array of effective interventions, and ensuring that these interventions are delivered to and used by the people who will benefit from them.

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Resources

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Through translational research, scientists are turning discoveries made in basic and clinical research laboratories into new and improved applications in health and medicine. Moreover, the information gained through clinical research and practice is stimulating new directions in basic science. This issue of *Alcohol Research: Current Reviews* highlights the bidirectional nature of translational alcohol research and explores how today's investigations are setting the stage for tomorrow's interventions to prevent and treat alcohol misuse and alcohol use disorder.

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