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NIAAA 50th ANNIVERSARY FESTSCHRIFT

NIAAA 50th Anniversary Festschrift: From the Editor

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Publisher's Note
This article addresses the presentations delivered at the NIAAA 50th Anniversary Science Symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," held on November 30–December 1, 2020. Links to the videocast are available on the NIAAA 50th Anniversary Science Symposium agenda webpage.

In 2020, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) celebrated its 50th anniversary. In honor of this important milestone, the Institute organized a 2-day scientific symposium, entitled "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," that featured presentations by leading researchers who discussed research advances across many domains of alcohol research. The articles in this Festschrift topic series are based on these presentations.

A Look Back

NIAAA's 50th anniversary is truly a highlight in the history of public health. More than 5 decades ago, a group of researchers, advocates, and elected officials made a farsighted decision when they pushed for the creation of a federal institution dedicated to research that improves the lives of millions of Americans and their families devastated by alcohol misuse. As a result, on December 31, 1970, President Richard Nixon signed the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970.

The Act launched NIAAA, authorizing the new agency to develop and conduct comprehensive health, education, training, research, and planning programs for the prevention and treatment of alcohol-related problems.[1] The creation of NIAAA set the stage for a trusted, federally funded agency to plan and support advances in a variety of domains, ranging from alcohol's effects on the developing adolescent brain to alcohol-associated liver disease and from fetal alcohol spectrum disorder to the treatment of alcohol use disorder (AUD).

The Institute also helped change the way we view alcohol misuse and AUD. It provided evidence that AUD is a chronic health condition, not a moral failing. AUD is now conceptualized as a preventable and treatable brain disorder with symptoms that vary across the life span and by individual.

Thanks to innovative research funded by NIAAA, we have a better understanding of how alcohol affects the brain and other organs across the life span. We have also developed evidence-based interventions to prevent and treat alcohol misuse and AUD. Progress has been made in numerous areas, from decreasing underage drinking to understanding fetal alcohol spectrum disorder and to stimulating medications development for treatment of AUD.

The presentations at the 50th Anniversary Symposium represented a small sample of these crucial advances.

A Look Ahead

NIAAA today is the world's largest funder of alcohol research, with a mission of improving the diagnosis, prevention, and treatment of AUD and other alcohol-related problems across the life span. With its broad research portfolio, NIAAA's work focuses on health topics that touch the lives of almost every family and community across the United States.

Yet, despite our progress, many challenges remain. The scope of alcohol misuse and the associated problems place a significant and growing burden on public health and our health care system. Alcohol-related deaths number more than 140,000 per year, making alcohol a leading cause of preventable death in the United States.[2] Alcohol misuse is also associated with an increased risk of injuries, chronic illnesses such as liver and heart disease, and cancer.[3] Overall, substantially more individuals suffer from AUD (14,504,000 people, or 5.3% of the population)[4] than from opioid use disorder (2,060,000 people, or 0.8% of the population).[4] I often say that "AUD is the addiction that everyone knows about, but nobody wants to talk about."

A significant challenge is the co-occurrence of alcohol misuse and AUD with other disorders, and how to best help affected individuals recover from both conditions. For example, many individuals with AUD also suffer from other mental health conditions and may use alcohol to cope with these conditions. Additionally, these disorders frequently exacerbate each other. Pain also often co-occurs with alcohol misuse. Although acute alcohol consumption at binge-drinking levels may lead to a temporary reduction of pain, chronic alcohol use and alcohol withdrawal in fact increase pain sensitivity.[5] Perhaps even more problematic, chronic alcohol use and alcohol withdrawal increase emotional pain, termed hyperkatifeia.[6] Finally, alcohol misuse, and particularly abstinence after chronic use, can result in persistent sleep problems that promote relapse and thus are a major impediment to recovery from AUD.[7]

In coming years, researchers will need to pay close attention to emerging trends in alcohol use in the U.S. population. Research shows that gender gaps are narrowing for numerous alcohol-related parameters, and that overall prevalence of drinking, prevalence of early-onset drinking, frequency and intensity of drinking, prevalence of AUD, and many negative consequences of alcohol misuse are increasing in women.[8] Similarly, alcohol use is increasing among adults age 65 and older, and 1 in 10 individuals in this age group engages in binge drinking.[9] Given that the older population is growing at an unprecedented rate,[10] this is an important public health concern.

Another major challenge is closing the persistent treatment gap. In 2019, fewer than 8% of people with AUD in the United States received any form of treatment.[4] Routine health care visits present a unique opportunity for prevention, early intervention, and treatment of AUD, yet many health care providers do not perform alcohol screening, are not aware of evidence-based treatments, or do not know where to refer patients for treatment.[11] Therefore, it remains essential to improve health care provider training in substance misuse prevention and treatment at all levels and to integrate prevention, early intervention, and treatment into routine health care. To address this need, NIAAA developed the Healthcare Professional's Core Resource that provides health care providers—from pharmacists, nurse practitioners, physician assistants, clinical psychologists, and primary care physicians to board-certified addiction specialists—all the information they should know about alcohol.

The 50th Anniversary Scientific Symposium: Festschrift Topic Series

The articles in this Festschrift topic series of *Alcohol Research: Current Reviews* highlight some of the key discoveries made possible over the last 50 years through NIAAA funding to grantees and support to the Institute's intramural researchers. Epidemiological research has enabled us to track progress and challenges associated with alcohol misuse in the U.S. population overall as well as in various subpopulations. Some of these findings are reviewed in Dr. Keyes' article, "Age, Period, and Cohort Effects in Alcohol Use in the 20th and 21st Centuries: Implications for the Coming Decades."[12]

Significant advances also have been made in understanding the genetic basis of AUD and the identification of relevant genes. Dr. Schuckit's article, "AUD Risk, Diagnoses, and Course in a Prospective Study Across Two Generations: Implications for Prevention," describes some of these findings, as well as their implications for prevention of alcohol misuse and AUD and for potential precision medicine approaches to the treatment of AUD.[13]

Research also has established that the adolescent brain is uniquely vulnerable to the effects of alcohol. As described by Dr. Tapert and Dr. Eberson-Shumate in the article, "Alcohol and the Adolescent Brain: What We've Learned and Where the Data Are Taking Us," longitudinal studies that assess predictors and consequences of adolescent alcohol consumption continue to inform prevention and treatment strategies aimed at this age group.[14]

Another important topic is recovery from AUD, as many individuals will eventually suffer a relapse to alcohol use, often even after extended periods of abstinence. Dr. Sinha's article, "Alcohol's Negative Emotional Side: The Role of Stress Neurobiology in Alcohol Use Disorder," reviews the current understanding of the role of stress neurobiology in alcohol misuse and its implications for the risk of, and recovery from, AUD.[15]

Decades of research have paved the way for behavioral interventions and medications to help people recover from AUD. Dr. Mason's article, "Looking Back, Looking Forward: Current Medications and Innovative Potential Medications to Treat Alcohol Use Disorder," reviews the state of knowledge of the three medications currently approved by the U.S. Food and Drug Administration for the treatment of AUD, as well as introduces other medications with potential for treating AUD that are on the horizon.[16]

The developing fetus is uniquely sensitive to alcohol exposure. Research on understanding how prenatal alcohol exposure affects development as well as on the prevention and mitigation of the effects of prenatal alcohol exposure have been a long-standing research priority for NIAAA since the recognition of fetal alcohol syndrome in the early 1970s. Dr. Charness summarizes research demonstrating advances in our understanding in "Fetal Alcohol Spectrum Disorders: Awareness to Insight in Just 50 Years."[17]

Finally, Dr. Ramkissoon and Dr. Shah review the current state of knowledge for one of the most common consequences of alcohol misuse, alcohol-associated liver disease, in "Alcohol Use Disorder and Alcohol-Associated Liver Disease." Alcohol-associated liver disease is a major contributor to alcohol-related mortality, and its treatment remains an unmet clinical need.[18]

Despite the broad range of topics they cover, these articles represent only a snapshot of the full spectrum of research that NIAAA-funded investigators have conducted over the last 50 years and will continue to explore in the coming decades (https://www.niaaa.nih.gov/).

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Alcohol Use Disorder and Alcohol-Associated Liver Disease

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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Shah's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; alcohol-associated liver disease; screening; prevention; mortality; patient readmission; policy; liver diseases

Alcohol use disorder (AUD) is prevalent worldwide, and the burden of heavy alcohol consumption has been increasing over time. An important complication of prolonged, heavy alcohol use is alcohol-associated liver disease (ALD), which can progress from liver steatosis to fibrosis and cirrhosis and frequently involves alcohol-associated hepatitis. In particular, cirrhosis—the most severe type of ALD—can be associated with fatal and resource-intensive complications and impose a significant social and financial burden on families, hospitals, and communities.

This article summarizes the epidemiology of alcohol use and ALD and describes the outcomes and mortality associated with ALD. This is followed by a review of screening and prevention approaches for AUD and ALD, as well as of current treatment strategies for both conditions, including integrated treatment approaches. Policy measures to mitigate the impact of alcohol misuse are also discussed.

Epidemiology of Alcohol Use and ALD

There is currently a very high burden of alcohol use and misuse globally. In 2016, an estimated 2.4 billion people worldwide consumed alcohol, including 1.5 billion men and 900 million women.[1] Furthermore, nearly 40% of people who consume alcohol reported heavy, episodic drinking in 2016 (defined as 60 or more grams of pure alcohol on at least one single occasion at least once per month).[2]

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, AUD is a maladaptive pattern of alcohol use characterized by two or more from a list of symptoms, such as increasing alcohol use despite negative consequences; persistent, unsuccessful attempts to quit drinking; craving; tolerance; or withdrawal.[3] The estimated global prevalence of AUD is currently 9% and continues to rise.[4] Of note, psychiatric comorbidities are often present in individuals with AUD and may precede the onset of heavy alcohol use.[5]

ALD is a common complication associated with long-term alcohol misuse and AUD, and clinicians may encounter a spectrum of ALD in practice (Figure 1). Hepatic steatosis occurs in 90% to 95% of patients with chronic, heavy alcohol use. Steatosis causes inflammation of the liver, known as steatohepatitis, and progression to liver fibrosis occurs in 20% to 40% of patients. Liver fibrosis can continue to progress and result in cirrhosis in 8% to 20% of patients. Hepatocellular carcinoma is a primary liver neoplasm that is a complication of cirrhosis, occurring in 3% to 10% of these patients.[6] Alcohol-associated hepatitis is a specific clinical entity that occurs with long-term heavy alcohol use and may occur anywhere along the spectrum of ALD. There are several risk factors for progression of ALD, which include female sex, obesity, dietary factors, genetic polymorphisms, harmful patterns of alcohol consumption, and smoking. Clinicians should also consider and treat comorbidities that may contribute to disease progression, such as viral hepatitis, hemochromatosis, and human immunodeficiency virus (HIV).[6]

Cirrhosis is associated with chronic alcohol use, which accounts for 21% of physiologically compensated cirrhosis around the world. The global prevalence of alcohol-related, compensated cirrhosis remained relatively unchanged from 1990 (290/100,000 people) to 2017 (288/100,000 people). However, the global prevalence of decompensated cirrhosis rose from 1.1 million individuals in 1990 to 2.5 million individuals in 2017, with the greatest increases found in Western and Central Europe. Furthermore, ALD is the underlying cause of 30% of hepatocellular carcinoma cases.[7] The overall burden of ALD is expected to increase over time. This prediction is based on multiple variables, including socioeconomic factors, changes in drinking patterns, and the rising prevalence of obesity and fatty liver disease.[5]

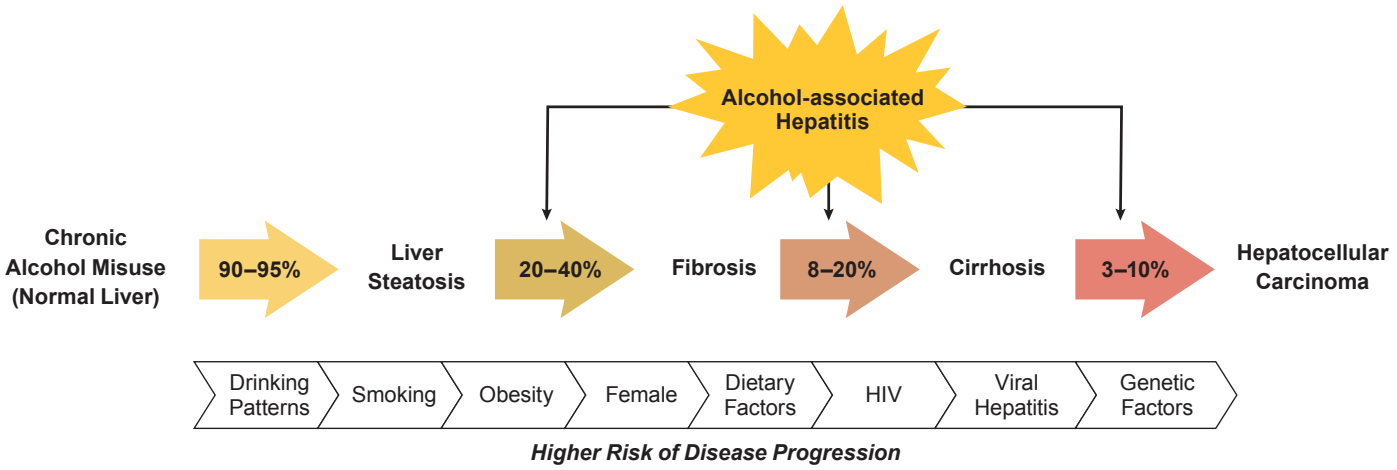

Figure 1. The spectrum of alcohol-associated liver disease, from steatosis to cirrhosis complicated by hepatocellular carcinoma. Alcohol-associated hepatitis can occur at any stage of disease. Numerous risk factors and comorbidities contribute to the risk of disease progression.[6] Note: HIV, human immunodeficiency virus.

Mortality and Outcomes Associated With ALD

The incidence of cirrhosis is expected to triple by the year 2030 due to the rising prevalence of ALD as well as non-alcoholic fatty liver disease (NAFLD). Cirrhosis is associated with fatal complications, such as gastrointestinal hemorrhage, renal failure, and hepatocellular carcinoma, which impose significant social and financial burdens on families, hospitals, and communities. Mortality rates from cirrhosis have risen in the United States from 2009 to 2016, with the greatest relative increase observed in young people (ages 25 to 34).[8] This trend parallels increased mortality due to AUD. Compared with women, men had a higher age-adjusted mortality due to cirrhosis (2:1) and hepatocellular carcinoma (4:1). However, women experienced a more rapid increase in cirrhosis-related mortality than did men; the annual percentage increase in mortality was highest in women ages 25 to 34.[8] Among different racial/ethnic groups in the United States, Native Americans and white Americans had the highest mortality due to cirrhosis, whereas Asians and Pacific Islanders had the highest mortality due to hepatocellular carcinoma. Furthermore, Hispanic individuals had a higher mortality from cirrhosis and hepatocellular carcinoma, compared with non-Hispanic individuals.[8]

The development of ALD may also be dependent on other factors related to the patient's health, such as obesity. Dietary guidelines by the U.S. government state that to minimize risks associated with drinking, adults of legal drinking age can choose not to drink or to drink in moderation by limiting intake to two drinks or less per day for men and one drink or less per day for women, on days when alcohol is consumed.[9] However, the American College of Gastroenterology recommends that the obese population should avoid alcohol consumption entirely due to increased risk of hepatic steatosis—a condition characterized by lipid deposits within the liver that is caused by heavy alcohol consumption or metabolic syndrome and can lead to chronic liver disease and cirrhosis.[10] A large cohort study using the Mayo Clinic Biobank examined the impact of alcohol consumption and obesity on the development of hepatic steatosis and mortality.[11] Moderate alcohol consumption (defined in the study as no more than two standard drinks per day) increased the risk of hepatic steatosis and all-cause mortality in obese individuals (body mass index [BMI] > 30 kg/m^2), whereas heavy drinking (defined as more than two standard drinks per day) increased the risk of hepatic steatosis and all-cause mortality in all patients, regardless of BMI.[11] In individuals with a normal BMI (< 25 kg/m^2), moderate alcohol consumption lowered the risk of hepatic steatosis and all-cause mortality. This effect was not observed in overweight individuals (BMI 25 kg/m^2 to 30 kg/m^2).

Screening and Prevention Strategies for AUD and ALD

The key to mitigating the future burden of AUD and ALD is early detection and prevention. Unfortunately, ALD is often detected at a later stage of disease when patients present with decompensated cirrhosis. Improved screening modalities for liver fibrosis are needed to identify affected individuals before irreversible, decompensated liver disease develops. Technologies such as smartphone applications, telemedicine, or electronic medical records can be used to improve population screening for AUD and ALD and may prove useful in linking people with a diagnosis of AUD or ALD to treatment programs or support groups. Such tools have been well received by individuals who drink heavily and those who have cirrhosis.[5]

Not all people with AUD are identified through screening or receive treatment. Barriers to AUD treatment include a shortage of providers, limited insurance reimbursement, and patient attitude toward treatment. Most screening for AUD occurs in health care environments, usually when patients are evaluated for other medical issues. Individuals who have little to no contact with health care systems almost never receive screening.[5]

Accordingly, in-person screening for AUD and ALD should be expanded outside of traditional health care environments to nontraditional settings such as pharmacies, annual employee health screenings, or driver's license renewal appointments.[5] A prime example for this approach is the effectiveness of screening for hypertension at community barbershops.[12]

Treatment of AUD

Once AUD or ALD has been identified, treatment and therapy should be initiated early to prevent disease progression or relapse to alcohol use. Treatment of AUD may involve nonpharmacological and pharmacological approaches.

Nonpharmacological Treatment

Nonpharmacological therapies for AUD, such as patient counseling and motivational interviewing, play a key role in achieving alcohol abstinence. These strategies are used universally and can be employed by any health care provider, including primary care providers.

Motivational interviewing is a form of nonconfrontational counseling that encourages patients to make choices consistent with their long-term goals and health. This technique is especially helpful in patients with heavy alcohol use that does not meet diagnostic criteria for AUD.[13] Providing patients with feedback surrounding changes in liver tests is associated with decreased alcohol use in patients who have, or are at risk of, chronic liver

disease.[14] Motivational interviewing can be used in combination with pharmacotherapy to help patients achieve alcohol abstinence.[15] Other nonpharmacological treatment strategies for AUD include establishing a supportive patient-physician relationship, scheduling follow-up clinic visits, engaging family members for support, referring patients to 12-step programs, developing coping strategies to manage early relapse, and treating psychiatric comorbidities.[15]

Pharmacological Treatment

The U.S. Food and Drug Administration (FDA) has approved three medications to treat AUD; these include disulfiram, naltrexone, and acamprosate. Baclofen is another option for therapy; however, it has not been approved by FDA. Although these medications are well studied for AUD, few studies have examined their effectiveness in patients with cirrhosis. Any medication approved by FDA can be used in patients with mild forms of liver disease; however, the use of disulfiram and naltrexone is cautioned in patients with cirrhosis or any features suggestive of liver dysfunction.[15]

Disulfiram is an acetaldehyde dehydrogenase inhibitor that produces an acetaldehyde syndrome characterized by facial flushing, nausea, vomiting, tachycardia, and hypotension when consumed with alcohol. It is prescribed as a deterrent to alcohol consumption based on this reaction. A meta-analysis showed that disulfiram significantly helped with alcohol abstinence in six out of 11 clinical trials.[16] Disulfiram is most effective in patients who are committed to abstinence or take it in a monitored fashion.[16] Cirrhosis is a known contraindication to disulfiram use due to reported events of liver failure leading to death or liver transplantation. Liver toxicity also has been reported in patients without liver disease.

Naltrexone is an opioid receptor antagonist that affects alcohol use primarily by inhibiting mu-opioid receptors and reducing the rewarding and reinforcing effects of alcohol. Clinical trials have demonstrated that naltrexone therapy is associated with a reduced risk of relapse to alcohol use and longer abstinence compared to placebo.[17] Naltrexone can result in elevated liver enzymes, especially at doses greater than 100 mg per day, and should be avoided in patients with acute hepatitis or acute liver failure. Providers should monitor for injection-site hematomas related to naltrexone injections in patients with coagulopathy of liver disease. Naltrexone is contraindicated in patients who are being treated for opioid use disorder with mu-opioid receptor agonists (i.e., methadone or buprenorphine).

Acamprosate can reduce the symptoms of alcohol craving during prolonged abstinence and reduces alcohol intake in patients with AUD.[18] Its therapeutic effects on AUD are thought to be through antagonizing *N*-methyl-D-aspartate (NMDA) receptors, although it also has been reported that pharmacological effects could modulate gamma-aminobutyric acid type A ($GABA_A$) receptor activity.[15] Acamprosate can be used safely in patients undergoing treatment for opioid use disorder and has no hepatic metabolism. However, its safety and efficacy in patients with advanced liver disease has not been validated. Dose adjustments of acamprosate are required in patients with chronic kidney disease, especially when the creatinine clearance is below 30 mL per minute.

Baclofen is a selective GABA type B ($GABA_B$) receptor antagonist that is typically prescribed for muscle spasticity. Although it is not approved by FDA for treatment of AUD, baclofen is commonly used off-label in other countries. Several clinical trials and open-label studies using baclofen to treat AUD in patients with advanced liver disease have shown mixed results.[19,20] Overall, baclofen use is not associated with liver toxicity and can be used safely in patients with ALD.[15]

Integrated Care of Patients With AUD and ALD

In patients with alcohol-associated hepatitis, the most important predictor of long-term mortality is alcohol relapse. In fact, recurrent episodes of alcohol-associated hepatitis in patients who relapse to alcohol use have a mortality of nearly 60%. Among patients with alcohol-associated hepatitis, 34% to 37% relapse to alcohol use, and approximately 30% are readmitted to hospitals. The most common reasons for readmission are recurrent alcohol-associated hepatitis (19%) and alcohol intoxication and/or alcohol withdrawal (8%).[21]

Integrated treatment that addresses not only the patients' liver disease but also alcohol use can improve outcomes. In patients with alcohol-associated hepatitis, alcohol rehabilitation—defined as residential or outpatient AUD treatment or mutual support group participation—after hospital discharge is associated with a 70% to 84% decrease in 30-day readmission rate, an 89% to 91% decrease in 30-day alcohol relapse, and an 80% reduction in mortality.[21] Furthermore, alcohol rehabilitation plays a particularly important role in therapy of people with AUD and ALD because only a few medications to treat AUD can be used in individuals with recent or active alcohol-associated hepatitis. A large body of evidence suggests that psychosocial interventions, such as cognitive behavioral therapy and motivational interviewing, are effective tools for supporting alcohol abstinence.

Overall, there is a clear need for the implementation of alcohol rehabilitation in preventing undesirable patient outcomes.[21] Currently, only 16% to 20% of patients with alcohol-associated hepatitis attend alcohol rehabilitation. However, patients who were seen by addiction specialists during hospitalization are twice as likely to attend alcohol rehabilitation after discharge.[21] Implementing these strategies for the care

of patients with AUD can reduce the risk of alcohol relapse, recurrent alcohol-associated hepatitis, hospital readmission, and overall mortality. Therefore, it is strongly suggested that health care providers should arrange for alcohol rehabilitation at the index hospitalization, and referral should be used as a quality metric in the management of all patients with alcohol-associated hepatitis. In this manner, implementing quality metrics could lead to improved patient outcomes.[21] Further integrated care can include evaluation of alcohol biomarkers, validated screening tools, appropriate pharmacotherapy, multidisciplinary and telehealth care, as well as appropriate referral for specialty care (Figure 2).

Recent technological advances have improved health care delivery to patients with AUD and ALD. Biomonitoring (using wearable devices) and telehealth have revolutionized patients' access to health care. With these approaches, providers can

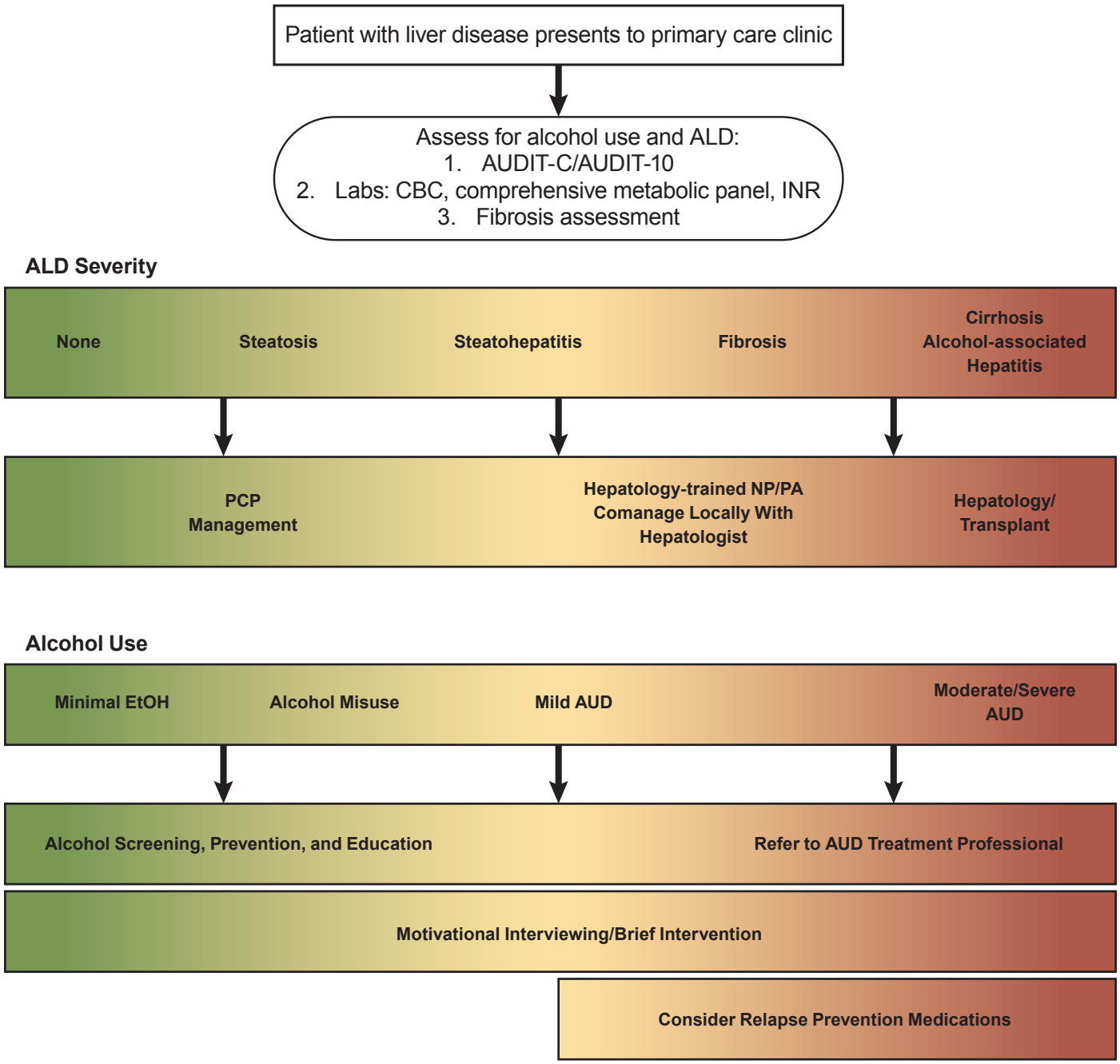

Figure 2. Treatment paradigm for patients with AUD and the spectrum of ALD. Reprinted with permission from Asrani et al., 2021.[5] *Note*: ALD, alcohol-associated liver disease; AUD, alcohol use disorder; AUDIT-10, 10-item Alcohol Use Disorders Identification Test; AUDIT-C, three-item Alcohol Use Disorders Identification Test; CBC, complete blood count; EtOH, ethanol; INR, international normalized ratio; NP, nurse practitioner; PA, physician assistant; PCP, primary care provider.

obtain clinical information, such as blood alcohol levels or vital signs, and respond accordingly through smartphone applications and other technology. This advancement has allowed providers to reach more patients.[22]

Treatment of ALD

The mainstay of treatment for patients with alcohol-associated hepatitis is therapy for AUD, either pharmacologic, nonpharmacologic, or a combination thereof. Alcohol-associated hepatitis is classified as either mild or severe based on the Maddrey discriminant function (mDF) or the model for end-stage liver disease (MELD) scores.[23] Therapy for patients with mild alcohol-associated hepatitis (mDF < 32 or MELD < 20) is centered around supportive care and AUD therapy. Nutritional support is essential as malnutrition and sarcopenia are common complications of ALD and have a negative impact on patient outcomes. Enteral nutrition supplementation, instead of intravenous administration, is preferred due to lower cost, greater safety, and lower risk of infection. Feeding tube insertion is safe in patients with nonbleeding, esophageal varices who have not undergone recent variceal band ligation. Fluid resuscitation, preferably with albumin, is also part of treatment.[10]

For patients with severe alcohol-associated hepatitis (mDF > 32 and MELD > 20), corticosteroids should be considered in addition to supportive therapy. If there are no contraindications to corticosteroids, prednisolone can be initiated to treat severe alcohol-associated hepatitis as its use modestly increases 1-month survival.[24] Corticosteroid use in clinical practice is often limited by concern about adverse reactions and high risk of infection. Once treatment has been started, clinicians should assess patient response using the Lille score, which is a calculated score on treatment day 7 to estimate if a patient is responding to corticosteroid therapy.[25] Clinicians can discontinue corticosteroids in nonresponders and avoid the increased risk of infection associated with their use. There is some indication that the Lille score on day 4 is as accurate as on day 7 in predicting treatment response.[25] There is currently an unmet need for alternative and safe medical therapy for severe alcohol-associated hepatitis.[10]

Liver Transplantation

Liver transplantation is a treatment option for patients with severe ALD, including those with severe alcohol-associated hepatitis that fails to respond to corticosteroids. ALD is the leading indication for liver transplant in the United States, accounting for 15% of liver transplants in the nation, as well as for 20% of liver transplants in Europe.[10,26] The process starts with a referral to a liver transplant center, followed by a formal evaluation and listing for transplant. However, numerous barriers to receiving a liver transplant exist for patients with ALD. For example, physicians may be biased against referral for a formal evaluation based on patient age or race, lack of empathy due to considering AUD a behavior rather than a disease, duration of alcohol use, and geographical area.[27]

Relapse to alcohol use occurs in 17% to 30% of patients on a waiting list for a liver transplant and in 10% to 60% of post-transplant patients.[28] This emphasizes that a liver transplant cures liver disease but not the underlying AUD. Many transplant programs require patients to abstain from alcohol for a minimum of 6 months before considering a liver transplant; however, protracted abstinence is not a reliable predictor of recidivism. Instead, important predictors include age, social support, psychiatric comorbidities, polysubstance abuse, family history, and previous failed rehabilitation attempts. The Psychosocial Assessment of Candidacy for Transplantation scale is widely used to determine a patient's risk of recidivism and need for alcohol rehabilitation prior to liver transplantation.[29] Patients should be screened for recidivism at every clinic visit, as 10-year survival after liver transplantation is 45% to 71% in those with harmful alcohol use versus 75% to 93% in abstinent patients with occasional slips.[30] Self-reported alcohol use may not be reliable, and clinicians should consider using biomarkers to assess for ongoing alcohol consumption.[10]

Liver transplantation for ALD remains a controversial topic and requires careful consideration and expertise. Established criteria for transplant candidacy specify that patients should be presenting with liver disease for the first time, have failed medical therapy, and are without severe medical or psychosocial comorbidities. It is important to avoid liver transplantation in patients who will recover without it and in those with low predicted short-term survival. This will avoid creating a disparity in available liver grafts based on indication and socioeconomic factors. Transplant candidates with ALD should have a high likelihood of long-term abstinence, and treatment of AUD should be incorporated into pre- and post-transplant care.[31]

Recent Advances in ALD and Implications for Treatment

Alcohol-associated hepatitis is characterized by unrelenting inflammation that is a complex response to hepatocellular stress and death. Advancements in understanding the molecular biology of ALD have changed approaches to caring for patients. Heavy, long-term consumption of alcoholic beverages results in damage to hepatocytes, which respond by releasing extracellular vesicles (EVs). The release of EVs results in activation of inflammatory cells (e.g., macrophages), which release inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha), interleukin 1 beta (IL-1-beta), and IL-6.[32] Research is now being conducted to investigate the interplay of other hepatic endothelial cells, hepatic stellate cells, and the patient's inflammatory cascade of lymphocytes. Further research also is needed to determine how alcohol's effects on

the intestine may result in mild intestinal injury, alter intestinal permeability, and affect the gut microbiome, which can result in the progression of ALD.[32]

EV release from hepatocytes, which has been observed with in vitro studies, mouse models, and human subjects in response to liver injury, may be useful as a biomarker for ALD. Sehrawat et al. examined the quantity of EVs released and demonstrated that a high EV count was associated with a worse prognosis for ALD compared to a low EV count, and was predictive of disease severity and mortality.[33] Furthermore, detectable EVs in the blood were liver-specific and could be useful in the diagnosis of ALD and dynamic risk profiling.[33] Magnetic resonance elastography is also under investigation as a possible diagnostic tool for assessing inflammation, hepatic injury, and fibrosis in ALD.[34] This technology could be useful in clinical practice and avoid the need for a liver biopsy and its associated risks.

Enhanced understanding of the molecular biology of ALD has revealed targetable disease mechanisms for drug therapies and promising alternatives to corticosteroid therapy. Some therapies under current investigation include granulocyte colony stimulating factor (G-CSF), the IL-1 receptor antagonist anakinra, IL-22, and high-dose vitamin C. IL-22 therapy is of notable interest as it has already succeeded in a proof-of-concept study.[35] Thus, IL-22 reduced hepatocyte injury, promoted liver regeneration, reduced steatosis and fibrosis, and was not immunosuppressive. Recombinant IL-22 (termed F-652 in clinical trials) has demonstrated safety and efficacy in early, open-label studies with improved MELD scores and Lille scores, as well as reduced inflammatory markers. F-652 administered to patients with moderate to severe alcohol-associated hepatitis was associated with a reduction in patient MELD score at days 28 and 42.[35] Further studies are being conducted to evaluate the real-world efficacy of F-652. Other cytokines, such as TNF-alpha or transcription factor BRD4, also may be targeted to reduce hepatocellular injury.[35]

Policies to Mitigate the Impact of AUD and ALD

The effects of AUD and ALD have major individual and societal impacts. National and regional interventions can help decrease the societal impact and reduce the number of individuals at risk. To lower the overall burden associated with AUD and ALD, medical societies have recommended community-wide alcohol reduction strategies as well as personalized treatment options for these conditions. Various initiatives led by the World Health Organization also aim to decrease the impact of alcohol use, for example, through appropriate taxation of alcohol, restricted alcohol availability, and restricted promotion to vulnerable populations.[5]

One of the strongest approaches to influencing alcohol consumption and, consequently, ALD risk at the population level is regulation of the unit price of alcohol through measures such as alcohol taxation. When alcohol prices increase, alcohol consumption and ALD burden notably decrease. Conversely, reduced alcohol prices are associated with increased alcohol consumption and alcohol-related deaths. However, the impact of these measures varies among population subgroups and is most prominent in groups with the highest amount of alcohol use and those with lower socioeconomic status.[36,37] In addition to taxation, strategies such as adjusting for inflation and income, minimal pricing policies, volumetric taxes, and banning volume discounts can be employed to reduce alcohol consumption.[5]

Reducing availability is another strategy to decrease alcohol consumption and its consequences at the population level. Regulating hours of alcohol sales, controlling liquor licenses, and raising minimum legal purchasing age are examples of strategies to reduce alcohol availability. Educational initiatives also have proved effective in reducing the per-capita alcohol consumption. For example, over a period of 20 years, Iceland was able to reduce alcohol and drug use in young people from 42% to 5% by introducing a wide range of targeted policies involving families, schools, communities, and politicians.[38] Finally, limiting alcohol-related marketing, particularly to vulnerable populations such as youth, is an important strategy to reduce alcohol consumption.[5]

Conclusions

AUD and ALD are prevalent worldwide and are associated with significant morbidity and mortality. Currently, the individuals at highest risk of mortality are young people, women, as well as Native Americans and white Americans. Expanded screening approaches can reach individuals at high risk and those who have little contact with health care systems.

Treatment of the underlying AUD is essential for improving outcomes of patients with ALD. There are several approved medications for AUD; however, their use is cautioned in people with advanced liver disease. Alcohol rehabilitation significantly reduces 30-day hospital readmission, alcohol relapse, and mortality in individuals with ALD. Consulting addiction specialists and setting up alcohol rehabilitation at hospital discharge are quality metrics used when managing hospitalized patients with ALD.

Treatment of alcohol-associated hepatitis is centered around therapy for AUD, as well as supportive medical therapies and nutrition. Corticosteroids improve 1-month survival in alcohol-associated hepatitis, but the potential side effects limit their use. Additionally, liver transplantation is an option for patients with severe alcohol-associated hepatitis and advanced liver disease who have failed other therapies. Listing a patient for

transplant requires a formal evaluation at a liver transplant center; moreover, health care providers should screen for ongoing alcohol use at every clinic visit, both while patients are wait-listed and after liver transplantation. In recent years, several advancements in ALD research have led to improved diagnosis, prognostication, and treatment. For example, recombinant human IL-22 is an emerging therapy that is being tested in clinical trials for the treatment of alcohol-associated hepatitis. Additionally, policy makers have an opportunity to expand regulations to help reduce the burden of heavy alcohol consumption and, consequently, ALD.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Alcohol's Negative Emotional Side: The Role of Stress Neurobiology in Alcohol Use Disorder

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Acknowledgments
This article is a summary of the presentation delivered at the NIAAA 50th Anniversary Science Symposium on December 1, 2020. It serves as a tribute to NIAAA in commemoration of their persistent commitment to developing the science of alcohol effects and associated harm, and to developing novel cutting-edge strategies in support of prevention and treatment of, and recovery from, alcohol use disorder. I was honored to present at this symposium that captured some of the innovative research supported by NIAAA over the years. It is especially personally meaningful as the discoveries presented here would not have been possible without the financial and intellectual support provided by NIAAA and its dedicated staff to my work and lab over the past 25 years. It has been a real privilege to receive this support from NIAAA to conduct this work and to have this opportunity to share the research findings at this important symposium.

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The author declares no competing financial or nonfinancial interests.

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This article was based on a presentation at the NIAAA 50th Anniversary Science Symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," held on November 30–December 1, 2020. Links to the videocast are available on the NIAAA 50th Anniversary Science Symposium agenda webpage. Opinions expressed in contributed articles do not necessarily reflect the views of NIAAA, National Institutes of Health. The U.S. government does not endorse or favor any specific commercial product or commodity. Any trade or proprietary names appearing in *Alcohol Research: Current Reviews* are used only because they are considered essential in the context of the studies reported herein.

This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Sinha's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; distress; craving; relapse; negative emotions; neural activity; glucocorticoids

The word "alcohol" often conjures up positive feelings and associations with fun, socializing, relaxing, and partying. Yet there is another side to drinking alcohol, especially with risky, hazardous levels of consumption. This side is associated with distress and may include anxiety, loneliness, pain, and depressive symptoms.[1] This has been labeled the "dark side," or "negative emotional, stress side," of alcohol intake.[2] These two paradoxical, dialectically opposing alcohol experiences map onto the biphasic drug effects of alcohol, with alcohol being both a stimulant and a depressant drug. They also represent a shift from positive to negative situations that may drive alcohol intake, especially as alcohol intake increases from low or moderate "social" levels of drinking to binge, heavy, and chronic consumption. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines drinking in moderation as an intake of two drinks or less per day for men and one drink or less per day for women. Binge drinking is generally defined as five or more drinks per occasion for men and four or more drinks per occasion for women. Heavy drinking is generally defined as more than four drinks per day or more than 14 drinks per week for men and as more than three drinks per day or more than seven drinks per week for women.[3]

One aspect of the research the author has conducted with the support of NIAAA, and which is the topic of this article, has focused on identifying the physiological and neural effects, as well as the subjective and cognitive effects, of binge and chronic alcohol use. This research also has explored the factors that influence these effects and investigated whether these effects can be reversed or normalized to allow for recovery from any of the long-term changes that occur with binge and chronic alcohol misuse.

The worldwide coronavirus (COVID-19) pandemic is a chronic, ongoing stressor. Research has shown that alcohol consumption has increased significantly during this period, especially among individuals who regularly binge drink or drink heavily.[4,5] While onsite alcohol sales were down as businesses closed, e-commerce profits increased more than 30% during the COVID-19 pandemic.[4,5] Who is most susceptible to increased drinking episodes during COVID-19–related stress? This question highlights the need to understand the well-known bidirectional relationship between stress or trauma and alcohol intake, and why those with binge and chronic alcohol use are most vulnerable to increased alcohol use under high levels of stress and with traumatic exposure.

This article reviews human research investigating neurobiological and psychological changes related to alcohol misuse that are associated with greater distress and stress-related alcohol craving and their role in predicting risk of binge drinking, relapse, and impact on treatment outcomes. The author presents the effects of stress and trauma on brain stress responses and their associations with resilient coping and describes the impact of binge and chronic alcohol use on brain and peripheral stress responses and their role in promoting alcohol craving and relapse risk. Specific clinical and biobehavioral markers of both risk of developing alcohol use disorder (AUD) and relapse are also reviewed. Finally, the article discusses recent findings on treatments that focus on reversing stress and craving disruptions related to chronic alcohol misuse to improve treatment outcomes.

Alcohol and Stress—Shift From Positive to Negative Effects

It is well known that one or two standard alcoholic drinks have a stimulating and physiologically arousing effect; for example, heart rate increases acutely, and blood pressure changes have been documented. These responses are part of the autonomic nervous system readouts that occur with alcohol intake, but also are observed in challenging situations such as when faced with acute stressful life events.[6,7] The arousing response to alcohol is associated with a sense of feeling energized and stimulated as well as increases in sociability.[6] With increasing levels of alcohol intake in one sitting, however, alcohol also stimulates the hypothalamic-pituitary-adrenal (HPA) axis, and increases in cortisol are observed.[8,9] Alcohol also activates brain emotion and stress pathways, including the amygdala, under emotional arousing and stressful states.[10,11] In addition, acute alcohol use stimulates the brain cortico-striatal pathways involved in reward, motivation, and goal-directed behaviors. These include the ventral and dorsal striatum, the orbitofrontal cortex (OFC), and the ventromedial prefrontal cortex (VmPFC).[10-13] The emotion/stress pathway and the reward/motivation pathways closely interact, and such interactions are involved in emotional cue-related drinking motivation.[11,12]

Binge and hazardous alcohol drinking patterns are associated with well-documented changes both in the brain stress and emotion regions, such as the amygdala,[8,12] and in associated brain networks, including the ventral and dorsal striatum as well as the OFC, VmPFC, and dorsolateral prefrontal cortex.[9,12,14,15] These brain changes are associated with blunted autonomic and cortisol responses to stress and to acute alcohol intake,[6,8] as well as with increases in negative emotional and stress responses and greater alcohol craving.[6,9,14-17] Together, these changes are part of the psychobiological adaptations in humans that occur with increasing patterns of binge and hazardous alcohol intake.

Stress, Alcohol Craving, and Binge Alcohol Intake

Acute stress exposure stimulates the autonomic, endocrine, and brain emotion and motivation regions that process and regulate negative emotion and distress responses, and it also activates

stress coping.[6,12,18] Additionally, acute stress exposure increases physiological arousal, including cortisol responses, and activates brain stress pathways involved in emotional arousal, emotional learning, and memory. This activation occurs via circuits involving the hypothalamus, amygdala, hippocampus, insula, and prefrontal regions, including the OFC, VmPFC, and inferior frontal cortices. Also activated is the premotor supplementary motor area, which is involved in behavioral intent, response selection, and action.[6,18,19] Previous studies reported that there are dynamic time-dependent changes in the cortico-striatal regions involving the ventral and dorsal striatum and the VmPFC during stress versus non–stress conditions; these changes were associated with active, goal-directed stress coping.[18] Additionally, greater dynamic responses in these brain stress-reward pathways were associated with lower daily numbers of alcoholic drinks consumed, lower reports of emotional conflicts, and lower emotional eating, whereas blunted ventral striatum and VmPFC responses during stress were associated with greater reports of binge drinking, emotion dysregulation, and emotional eating.[18] Based on these findings, the dynamic neural responses in the striatum and VmPFC are thought to document neurophysiological flexibility during stress, and their associations with behavioral coping suggest that this circuit is part of the resilient stress-coping pathway involved in behavioral control and self-regulation of stress, emotions, and reward impulses.[6,18]

These adaptations to alcohol also vary by sex, as fundamental differences between men and women exist in brain organization, structure, and functional networks[20] as well as in the responses of brain stress, emotion, and reward regions[21] and in patients with cocaine use disorder.[22] Moreover, sex differences in the responses to stress and to alcohol-related stimuli have been documented in people who drink moderately. Unlike in animal studies, males in human studies show greater adrenocorticotropic hormone (ACTH) and cortisol responses to stress,[23] whereas females show higher autonomic physiologic arousal to stress; a greater response to stress cues in the amygdala, insula, OFC, and VmPFC; and greater VmPFC response to alcohol cues.[24-28] This suggests that the psychological and biological responses to alcohol and to stress vary by sex and that although men and women report similar levels of alcohol motivation when matched for recent drinking history, the psychological and neurobiological pathways that facilitate alcohol use are different for men and women who drink moderately.

Regardless of sex, repeated escalated alcohol use induces changes in both peripheral and brain stress systems.[2,12,16] Higher binge levels of alcohol use increase basal cortisol levels and blunt the peripheral stress responses; these changes also predict greater craving and behavioral motivation for alcohol use in people who binge drink or drink heavily (see Figure 1).[8,9] Additionally, changes in the amygdala responses to emotional cues and ventral striatal responses to alcohol have been reported with higher binge levels of alcohol use.[14,29] Along with these neural changes, increased salience of alcohol and greater alcohol craving levels have been observed in response to stress as well as in response to alcohol and to alcohol cues, which then promote increased alcohol intake and escalation to risky drinking.[8,15,17] These brain stress system, physiologic, and behavioral effects of binge drinking history need to be further examined by sex to better understand the recent data on greater escalation of binge drinking in women compared to men.[30]

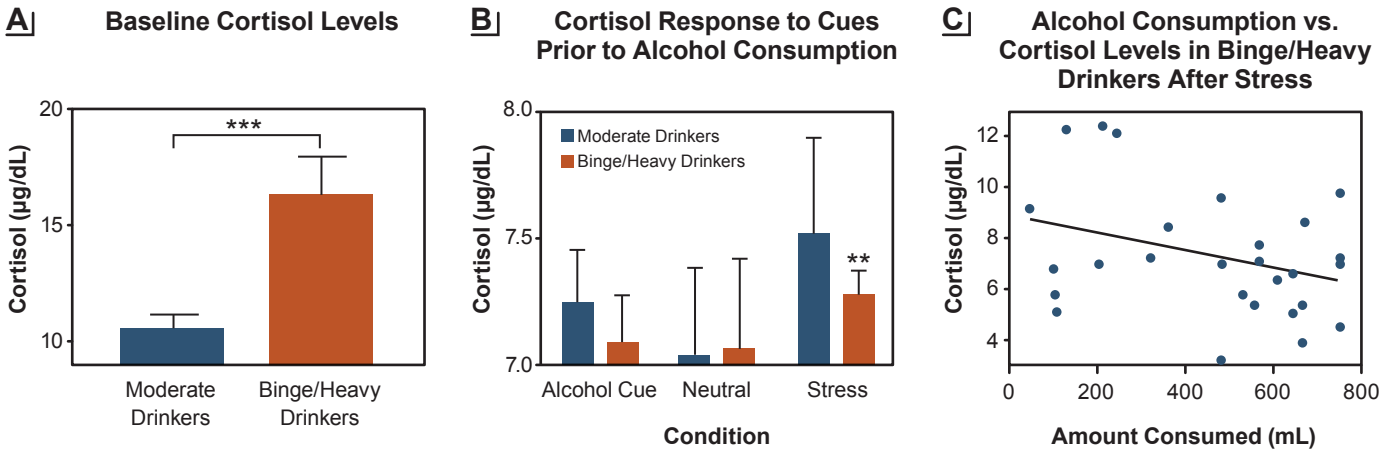

Figure 1. Baseline cortisol levels and responses to stress differ between moderate drinkers and binge/heavy drinkers. (A) Fasting morning plasma levels of cortisol (µg/dL) were higher in binge/heavy drinkers (orange bars) compared to moderate drinkers (blue bars) (***$p < .001$). (B) Cortisol responses to stress and alcohol cues, but not to neutral cues, were blunted in binge/heavy drinkers compared with moderate drinkers (**$p < .01$). (C) In binge/heavy drinkers, the behavioral motivation for alcohol use as reflected in the amount of alcohol consumed post stress in an ad lib drinking task was greater in individuals with a more blunted cortisol response to stress ($r^2 = .11$, $p = .0022$). *Source:* Adapted with permission from Blaine et al. (2019).[8]

Effects of Stress and Trauma on Brain Pathways and AUD Risk

Stress and trauma are associated with greater levels of risky alcohol intake as well as greater severity of AUD.[19] Numerous different types of traumatic stress and life events as well some temperament and individual-level variables relate to risk of binge drinking and developing AUD (see Table 1). Exposure to repeated stress and trauma also contributes to changes in the brain and body's responses to stress and emotions as well as to changes in alcohol motivation and adaptive coping responses.

Greater levels of cumulative adversity, stressful life events, and trauma are associated with lower brain volume and greater negative emotion and subjective stress responses. They also are associated with dysregulated neural and peripheral physiological responses to stress and to alcohol cues in the brain regions involved in stress, emotion, reward regulation, and self-control, including the OFC, VmPFC, supplementary motor area, amygdala, insula, and striatum.[31-33] Furthermore, altered or blunted ACTH and cortisol and autonomic responses to stress and to alcohol and drug cues are observed with greater trauma or stress.[19,33] These stress- and trauma-related brain and peripheral alterations co-occur alongside emotional and behavioral dysregulation and higher alcohol motivation. As a result, people with more risky drinking exposed to stress or trauma are at greater risk of emotion dysregulation as evidenced by more arguments, fights, emotional eating, and higher maximum drinks consumed per occasion (see Figure 2).[18,34]

Several interacting brain networks are activated during stress, including those involved in emotion experiences (e.g., amygdala, insula), emotional memory (e.g., amygdala, hippocampus), reward and motivation regions (e.g., ventral and dorsal striatum), and goal-directed behavior (e.g., OFC, VmPFC).[13,18,19,21,29] These regions form networks and patterns of activation that enable emotional and motivational coping, and both stress and alcohol directly act on these networks to influence active coping, motivation, and flexible control of behavior, such as exercising self-control with drinking. The accumulating evidence shows that stress and trauma exposure alter these emotional and motivational responses involved in adaptive stress coping, such that people become more vulnerable to craving and consuming higher levels of alcohol, which increases risk of hazardous and risky drinking.

The research described above resulted in the development of a model explaining the role of glucocorticoids in drinking behavior on the basis of changes in peripheral cortisol levels and responses across the full spectrum of alcohol consumption levels.[8] At baseline, people who binge drink or drink heavily have higher cortisol levels than those who drink moderately (see Figure 1A), indicating a shift in HPA axis functioning. This also suggests possible changes in brain glucocorticoid pathways in

Table 1. Types of Adverse Life Events, Trauma, Chronic Stressors, and Individual-Level Variables Predictive of Addiction Risk

Adverse Life Events	Childhood and Life Trauma	Chronic Stressors	Stressful Internal States
• Loss of parent • Parental divorce and conflict • Isolation and abandonment • Single-parent family structure • Forced to live apart from parents • Loss of child by death or removal • Unfaithfulness of significant other • Loss of home to natural disaster • Death of significant other or close family member	• Physical neglect • Physical abuse by parent, caretaker, family member, spouse, or significant other • Emotional abuse and neglect • Sexual abuse • Rape • Victim of gun shooting or other violent acts • Observing violent victimization	• Being overwhelmed • Unable to manage life problems • Difficulties with job, living situation • Financial problems • Interpersonal conflicts, loneliness • Unfulfilled desires • Problems with children • Illness of loved ones • Negative emotionality • Poor behavioral control • Poor emotional control	• Hunger or food deprivation • Food insecurity • Extreme thirst • Sleep deprivation or insomnia • Extreme hypothermia or hyperthermia • Excessive drug use • Drug withdrawal states • Chronic illness

Source: Included with permission from Milivojevic & Sinha (2018).[37]

humans that may increase risk of hazardous drinking. As stated earlier, alcohol consumption stimulates cortisol release; however, in response to either stress or alcohol exposure, the increase in cortisol is lower in people who binge drink or drink heavily than in those who drink moderately. Thus, when given one standard alcoholic drink, those drinking at binge levels do not feel its effects as robustly as do people who drink moderately.[8,9] As cortisol is critical for survival, humans have well-preserved neurobehavioral signals with the brain stress system pathways[12] that seek to enhance cortisol release in response to stress. In people with blunted cortisol responses due to heavy drinking, this mechanism may signal greater motivation for alcohol to increase alcohol-related cortisol responses.[9] Thus, there is a neurophysiologic drive to enhance wanting alcohol in order to increase cortisol and HPA axis functioning in people who drink heavily. This disruption in alcohol-related cortisol signaling and the need to drive the homeostatic HPA axis rhythm back to functional levels may be one component of the enhanced motivation for alcohol in those who drink alcohol at binge and heavy levels. This conceptual model suggests that normalizing the brain and body's stress and motivational coping responses may reduce risk of hazardous drinking. Researchers are seeking to develop and evaluate novel strategies to achieve this normalization and to reduce the risk of heavy drinking.

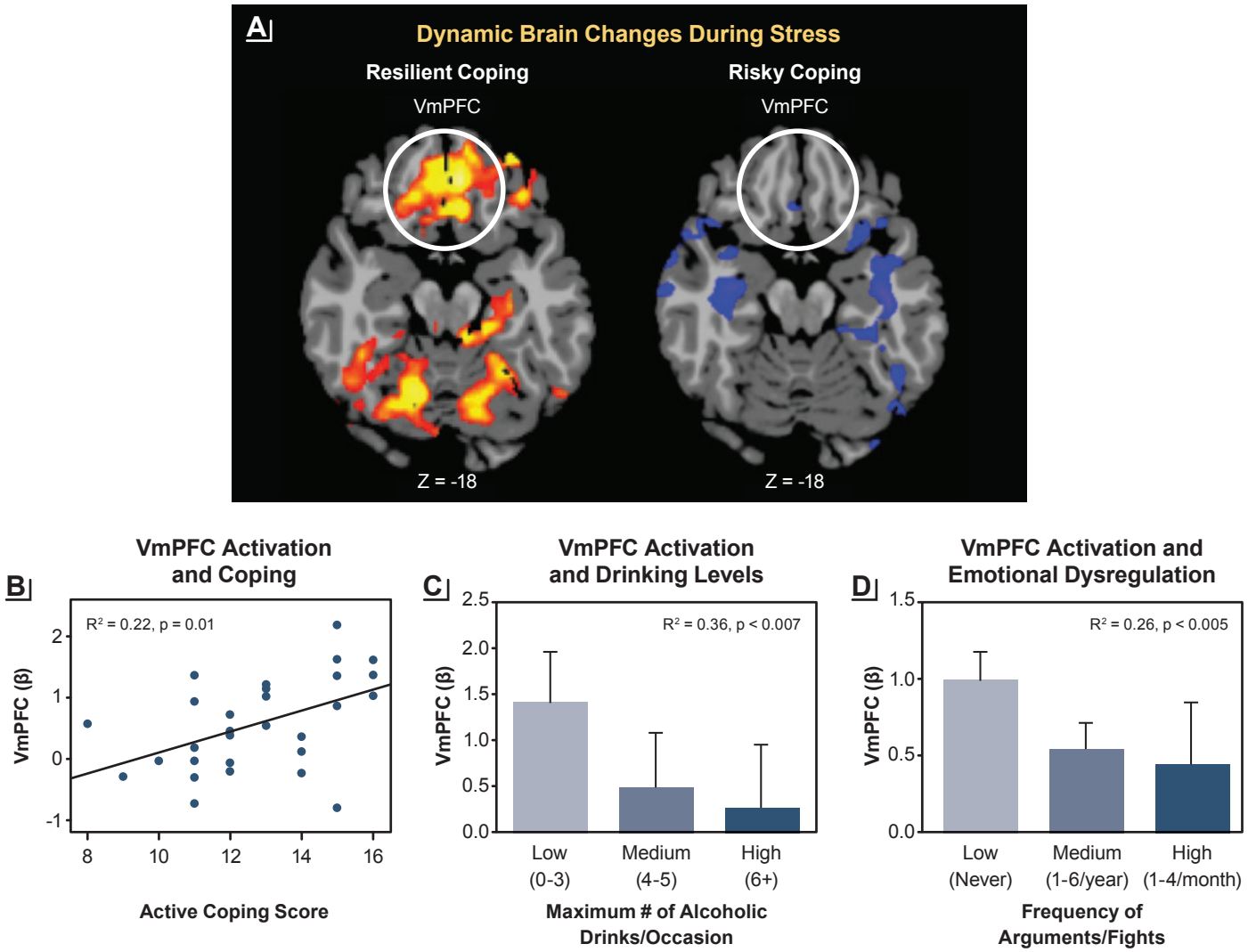

Figure 2. Associations between brain stress responses and resilient coping. (A) Dynamic activation in the ventromedial prefrontal cortex (VmPFC) during stress challenge (represented by red and yellow) was a sign of resilient coping, whereas a lack of dynamic changes in the VmPFC during stress, suggesting inability to mobilize during stress, was a sign of risky coping. (B) Greater dynamic activation of the VmPFC was associated with greater self-reported active coping. (C) Lack of dynamic activation of the VmPFC was more pronounced in binge drinkers. (D) Greater emotional dysregulation (measured by greater frequency of arguments or fights) also was associated with less dynamic activation of the VmPFC. *Source:* Adapted with permission from Sinha et al. (2016).[18]

Effects of Stress and Alcohol Cues in AUD

Researchers also have investigated the role of stress biology and stress responses in people with AUD. Chronic heavy drinking or binge drinking increases the risk of disrupted alcohol-related autonomic and HPA axis responses as described in previous sections. These disruptions contribute to clinical symptoms associated with the negative emotional side of AUD,[15] such as increased levels of anxiety, negative mood, sleep difficulties, emotional reactivity, and impulsivity, along with high levels of craving for alcohol.[1,35] Furthermore, these disruptions increase the risk of relapse and heavy drinking during treatment and posttreatment, thereby jeopardizing long-term recovery.[6,36,37] Alcohol relapse refers to return to heavy drinking (at binge levels) after any period of abstinence, whereas treatment failure refers to maintaining or returning to binge and hazardous drinking levels during or after treatment.[3] These observations have led researchers to investigate which factors contribute to early risk of dropout and recovery failure during treatment.

A series of studies assessed brain and body responses as well as cognitive, emotional, and motivational responses to both stress and alcohol cues in a laboratory study of human participants with AUD who were entering treatment and control participants without AUD. The analyses also included structural and functional magnetic resonance imaging as well as real-world daily assessment of stress and motivational responses using smartphones. These analyses using multiple approaches across different samples of individuals with AUD found that stress exposure increased alcohol craving. This response was accompanied by higher emotional, mood, and anxiety symptoms and lower ability to regulate emotions and control alcohol cravings.[36,37] Furthermore, the biological stress response was significantly disrupted during the early recovery period. Thus, individuals in early recovery exhibited a higher basal heart rate and higher free cortisol levels, but lower levels of endogenous bound cortisol. Additionally, these individuals did not show a significant normal response to stress or alcohol challenge.[6,37] Thus, the biological responses that support emotion and mood regulation are disrupted during this early recovery phase, and the greater these levels of dysfunction, the higher the risk of relapse or heavy drinking. Notably, sex differences in these biological responses have been reported, where women with AUD showed a more blunted ACTH and cortisol level than men with AUD; however, women had much higher basal norepinephrine levels, which in turn affected their response to stress and to alcohol cues.[26,38]

Another series of experiments examined brain correlates of later alcohol relapse and treatment failure. These analyses found that the volume of gray matter cells in the medial prefrontal brain regions—which are involved in regulating emotions, reward, and actions—was lower among individuals entering treatment compared with healthy control participants.[39] Also, individuals with the lowest gray matter volume in the medial prefrontal brain region tended to be most likely to relapse and not do well in treatment.[39] Analyses assessing the function of these brain regions during experimental exposure to stress and to alcohol cues (compared to neutral cues) detected disrupted, hyperactive VmPFC responses to neutral relaxing cues, but blunted, hypoactive VmPFC responses to stress and cue exposure. These observations suggest that the brain pathways that help regulate emotions and desires showed dysfunction and that the greater the VmPFC disruption, the higher the risk of alcohol relapse and heavy drinking.[40,41]

The studies described above have led to the characterization of a risk profile to identify individuals who are most vulnerable for alcohol relapse and heavy drinking during treatment. Thus, risk was determined by specific clinical measures—such as alcohol craving and withdrawal,[42,43] mood, anxiety, and sleep difficulties—and biological markers[37] as well as by additional moderating factors, including childhood maltreatment (see Table 2).[44] Furthermore, this research supported the conceptualization that the effects of binge drinking and chronic alcohol use on stress biology occur along a continuum, with higher levels of alcohol intake associated with more significant chronic stress pathophysiology, which in turn contributes to greater risk of alcohol relapse and treatment failure.[35]

AUD Treatments Targeting Stress, Craving, and Loss of Control of Alcohol Intake

Critical basic science and translational work by Koob and colleagues[45] had focused on stress pathophysiology to develop novel therapeutics for AUD. Similarly, the findings described above motivated additional research to evaluate whether reversal of the chronic alcohol-related disruptions in stress psychobiology that are associated with increased alcohol craving and relapse risk could improve treatment and treatment outcomes for individuals most vulnerable to alcohol-related stress pathophysiology. Previous research by Arnsten had shown that noradrenergic agents such as guanfacine and prazosin could rescue the prefrontal cortex from the toxic effects of high uncontrollable stress.[46] Because the effects of chronic alcohol exposure are similar to those of high chronic stress, it seemed plausible that pharmacologic targets that reduce prefrontal norepinephrine and the toxic effects of stress-related damage also could be of benefit in improving the stress and craving-related pathology associated with AUD. Studies to test these hypotheses have shown positive results. Guanfacine, an alpha-2 adrenergic agonist that reduces brain norepinephrine in the prefrontal cortex, improved prefrontal functioning and reduced alcohol and drug craving.[47,48]

Table 2. Markers and Moderators Associated With Relapse to Alcohol Use and Treatment Failure in Alcohol Use Disorder (AUD)

Clinical and Biological Markers	Moderating Factors
• Increased levels of alcohol craving • High early physical, sexual, emotional abuse and trauma history • High basal beat-by-beat heart rate and blunted autonomic response to stress and cues • Altered bound and free fasting morning cortisol levels, and adrenal sensitivity • Blunted and hypoactive cortisol response to stress • Lower medial prefrontal gray matter volumes in magnetic resonance imaging • Blunted medial prefrontal cortex response to stress and alcohol cues • Hyperactive striatal responses to alcohol cues	• AUD severity, including life span factors of early or late AUD; acute withdrawal symptoms, including anxiety, sleep, and negative mood; alcohol abstinence days • Early physical, sexual, and emotional abuse and lifetime traumas; chronic stress; and trauma-related pathophysiology • Sex differences and gender-related comorbid psychopathology and medical conditions • Genetic and pharmacogenomic effects

Furthermore, guanfacine had some sex-specific effects, with greater benefits in women than in men.[49,50]

Similarly, prazosin—an alpha-1-adrenergic antagonist that had been shown to improve working memory and prefrontal functioning during stress[46] as well as withdrawal-related drinking in laboratory animals[51]—reduced stress-related craving and stress dysfunction in AUD.[52,53] Based on these findings, an NIAAA-supported, 12-week proof-of-concept, double-blind, placebo-controlled, randomized trial of prazosin versus placebo (16 mg/day, three times a day dosing, titrated over 2 weeks) was conducted with 100 individuals with AUD. The study found that alcohol withdrawal symptoms were a moderating factor impacting prazosin efficacy in improving drinking outcomes over 12 weeks; that is, prazosin treatment benefit was determined by the presence of alcohol withdrawal symptoms at treatment entry. Thus, individuals with more severe alcohol withdrawal symptoms at treatment initiation experienced greater reductions in heavy drinking days and drinks per occasion during the 12-week treatment period.[54] In addition, prazosin reduced alcohol craving, anxiety, and negative mood compared with placebo in participants with high alcohol withdrawal symptoms, but had no impact in those with no or low levels of alcohol withdrawal symptoms. Finally, prazosin appeared to reverse VmPFC and dorsal striatal dysfunction, improving medial prefrontal response to stress and reducing dorsal striatal response to alcohol cues in participants treated with prazosin compared with those receiving placebo.[55] These findings support further development of prazosin in the treatment of severe AUD. However, they also underscore the need to pursue further research to identify behavioral and pharmacologic strategies to prevent and treat chronic alcohol effects on stress pathophysiology in AUD.

Conclusions

This article summarizes research by the author's group demonstrating that binge, heavy, and chronic drinking leads to adaptations in brain, biological, and psychological stress responses. These adaptations are associated with alcohol's negative emotional aspects, as evidenced by greater alcohol craving, higher alcohol withdrawal, greater negative mood and anxiety symptoms, as well as sleep difficulties that are commonly reported by individuals with AUD entering treatment. These changes occur in brain stress, reward, and motivation pathways that represent the stress pathophysiology of AUD. This stress pathophysiology directly targets brain circuits that underlie people's ability to cope with stress and day-to-day challenges and are involved in jeopardizing recovery from AUD.

This research also has identified various clinical and biobehavioral markers that are associated with relapse and treatment failure and has allowed for identification of individuals who may be at greatest risk of treatment failure. Additionally, identification of these markers has led to research seeking to develop new strategies to target and reverse the stress pathophysiology of AUD to optimize interventions for AUD. Current and future work is focused on developing and testing specific treatments that can target this particular stress pathophysiology and help individuals who are most vulnerable to jeopardizing their recovery in the early phase of AUD treatment.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Looking Back, Looking Forward: Current Medications and Innovative Potential Medications to Treat Alcohol Use Disorder

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Disclosures
Dr. Mason is on the Scientific Advisory Board for Imbrium Therapeutics and on the Scientific Advisory Board for Awakn Life Sciences.

Publisher's Note
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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Mason's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; alcohol use disorder; treatment; medication; disulfiram; naltrexone; acamprosate

According to national surveys, more than 85% of U.S. adults have consumed alcohol at some point in their lifetime, and about 70% did so in the last year.[1] Most individuals drink responsibly and without adverse effects. However, a substantial proportion of people misuse alcohol.[1,2] Drinking patterns associated with alcohol misuse include binge drinking, heavy drinking, and high-intensity drinking. Binge drinking is typically defined as five or more drinks within a few hours for men and four or more drinks within a few hours for women. Heavy drinking is defined as four or more drinks per day or more than 14 drinks per week for men and more than three drinks per day or more than seven drinks per week for women. High-intensity drinking is defined as two or more times the gender-specific thresholds per day for binge drinking.[3] Moreover, according to the National Survey on Drug Use and Health, nearly 15 million people age 12 and older in the United States, or 5% of this age group, met the criteria for alcohol use disorder (AUD) in 2019.[1] Alcohol misuse and AUD exert a heavy toll on the individual, their families and communities, and society as a whole. Alcohol contributed to about 99,000 deaths in 2020, making it one of the leading preventable causes of death in the United States.[4] Additionally, alcohol misuse imposes a heavy economic burden on the nation.[5] Indeed, in many respects, alcohol misuse and its consequences are a substantially greater societal problem than the current opioid crisis, yet it generally receives less attention.[6-10] Therefore, the development and availability of effective treatments for AUD are of utmost importance.

Various treatment approaches have been identified for AUD, including pharmacological and nonpharmacological approaches. However, only a small proportion of people with AUD receive treatment. In 2019, only about 7% to 8% of these individuals were estimated to receive any treatment for AUD, and less than 2% reported using a medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD.[11] To date, only three medications—disulfiram, naltrexone, and acamprosate—have been approved by FDA for the treatment of AUD. Development of additional medications has largely been ignored by the pharmaceutical industry and instead is being driven by grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to academic scientists, as well as by work conducted by NIAAA's Clinical Investigations Group and Intramural Research Program. Numerous potential medications—including those currently used for other indications as well as newly developed medications—are being investigated and will hopefully help to increase the number of treatment options available to people with AUD and their health care providers. This article describes the characteristics, benefits, and risks of the FDA-approved medications for AUD; evaluates the benefits and risks of novel drugs repurposed for the treatment of AUD; and appraises novel drug targets that are in the pipeline.

FDA-Approved Medications

The three FDA-approved drugs to treat AUD have very different mechanisms of action, but they share some key characteristics:

- For AUD medications, the pivotal clinical trials conducted to gain FDA approval involved behavioral counseling for all the participants—both those receiving the active drug and those receiving placebo. In these pivotal trials, drinking outcomes were better for participants who received the medication plus counseling than for those who received placebo plus counseling, demonstrating an incremental benefit of using evidence-based medications combined with counseling beyond that shown by counseling alone.[12,13]
- All three medications are not to be used as a stand-alone treatment but as part of a comprehensive treatment plan based on a chronic care model, as suggested in the 2016 *Surgeon General's Report on Alcohol, Drugs, and Health*.[14] This comprehensive model includes medications and additional components such as behavioral therapies and recovery support services.
- Like behavioral counseling and other therapeutic approaches, the medications are a treatment for AUD but are not a cure. Moreover, they are not a treatment for alcohol withdrawal, which requires its own special type of medication.
- The medications do not substitute for alcohol—such as methadone does for opioids in the treatment of opioid use disorder—and they do not induce euphoria. Moreover, the drugs are not addictive; people taking them long term do not develop tolerance or experience withdrawal upon treatment discontinuation. Accordingly, these medications have no street value as illicit drugs.[15]

To obtain FDA approval for a medication to treat AUD, manufacturers must assemble a safety dossier that includes studies demonstrating that the medication itself has no misuse potential and does not harmfully interact with alcohol, for example, by further impairing awareness or coordination if a person consumes alcohol while taking the drug. Additionally, the medication must demonstrate efficacy in typically two pivotal trials—defined as randomized, double-blind, placebo-controlled, multicenter trials that ideally represent the four quadrants of the United States and have adequate representation of women and minority participants.[16] Pivotal trials typically are 6 months in duration, during which the medication is given in conjunction with behavioral counseling. Primary outcome measures used by FDA to determine efficacy generally are rates of days with no drinking or no heavy drinking (i.e., consumption of five or more drinks per day for men and four or more drinks per day for women).[15] To determine these outcomes, a standard "drink" is defined as the beverage volume that contains 0.6 oz. of pure ethanol, which corresponds to approximately 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of distilled spirits.[17]

To determine participants' alcohol consumption in trials submitted for FDA approval, self-report instruments such as the Timeline Follow-back Interview capture the self-reported number of daily drinks consumed.[18] These self-reports are often combined with biochemical measures, such as breathalyzer readings, alcohol glucuronide urine dipsticks, or blood tests for the levels of the liver enzyme gamma-glutamyl transferase (GGT). Breathalyzer analyses only capture alcohol consumption at the time of the study visit whereas the alcohol glucuronide urine dipstick may reflect drinking up to 3 days before the study visit. Blood levels of GGT are an indirect marker of more distant alcohol consumption; they typically rise after heavy alcohol consumption that has continued for several weeks and may have occurred as long as 3 weeks prior to the study visit.[19] Smartphone apps for real-time drinking data collection and noninvasive transdermal wrist alcohol sensors are under development, but have not been used in regulatory studies.

Disulfiram

The first medication to be approved for AUD was disulfiram (Antabuse, now available in generic formulations), which entered the market in 1951—thus preceding even the inception of NIAAA. Its mechanism of action involves inhibition of the enzyme aldehyde dehydrogenase, which plays a central role in alcohol metabolism, converting the alcohol metabolite acetaldehyde into acetate. If an individual consumes alcohol while having disulfiram in their system, the drug will inhibit the acetaldehyde metabolism, resulting in rapid acetaldehyde accumulation that leads to a quick onset of flushing, nausea, palpitations, and other symptoms that can become quite severe and at times life-threatening. This mechanism of action acts as a psychological deterrent to any alcohol use.

Because of the rapid and potentially even fatal consequences of acetaldehyde accumulation after taking disulfiram, the medication should never be given to individuals with acute alcohol intoxication or without their full knowledge.[20] Additionally, individuals should be instructed to abstain from alcohol for at least 12 hours before taking disulfiram and be advised that reactions with alcohol can occur for as long as 14 days after discontinuing the medication. Disulfiram itself is associated with some hepatotoxicity; therefore, the patient's liver function should be measured before and during disulfiram treatment to ensure safety.

Disulfiram can only exert its effects if taken regularly. Studies found that outcomes are better in patients with high medication adherence who are strongly motivated to quit drinking, as well as in those patients who have a partner who is supportive of their recovery and will supervise the daily administration of disulfiram.[21,22]

Naltrexone

FDA originally approved naltrexone in 1984 for opioid addiction; for treatment of AUD, it was approved as an oral medication in 1994 (Revia and generic formulations) and as a long-acting injectable medication in 2006 (Vivitrol).[23-25] Naltrexone is a pure mu-opioid receptor antagonist that binds to the receptor, thereby blocking some of the rewarding effects of alcohol. Blunting the rewarding effects of drinking is thought to reduce alcohol consumption and thereby promote recovery from AUD. Consistent with this hypothesis, meta-analyses of numerous naltrexone studies have shown that, compared to placebo, the medication decreases heavy drinking.[12,13]

As with disulfiram, the efficacy of naltrexone is affected by adherence problems associated with oral dosing. To address these problems, a once-monthly, extended-release, intramuscular injection formulation has been developed.[25] Because naltrexone has such a specific mechanism of action, researchers have attempted to identify genetic predictors to determine which individuals with AUD might be most likely to respond to naltrexone treatment. To date, these investigations have not yielded reliable results; for example, initial findings of an association of different variants of the mu-opioid receptor gene *OPRM1* with response to naltrexone could not be replicated in other clinical trials.[26] However, the investigations into genetic predictors of naltrexone response are still ongoing.

Naltrexone treatment is generally considered safe. But because of the medication's effects on the mu-opioid receptor, it is important to rule out co-occurring illicit or prescribed opiate use prior to initiating treatment for AUD to avoid inducing acute opioid withdrawal. Also, like disulfiram, naltrexone itself is associated with some hepatotoxicity, particularly in higher doses. However, because alcohol itself is a hepatotoxin, naltrexone actually can improve liver functioning by reducing alcohol intake in individuals with AUD.[23]

Acamprosate

Disulfiram and naltrexone both aim to reduce drinking by making alcohol consumption a less pleasant experience, either by causing unpleasant effects after alcohol consumption or by reducing alcohol's stimulation of receptors in the brain's reward system. Acamprosate (Campral) takes a different strategy that is based on the observation that heavy drinking and withdrawal dysregulate the balance between the excitatory (glutamatergic) and inhibitory (primarily gamma-aminobutyric acid [GABA]-ergic) neurotransmitter systems in the brain. In particular, the excitatory system becomes hyperactive during early abstinence, and acamprosate has been shown to restore homeostasis in this system by reestablishing normal *N*-methyl-D-aspartate receptor tone in the glutamate system.[27,28]

Clinical studies lasting up to 1 year found that acamprosate treatment increased rates of abstinence relative to placebo.[12,15] Post-treatment follow-up studies found that these effects persisted for as long as 1 year after the last dose of medication.[12,15,28] Thus, unlike disulfiram and naltrexone, acamprosate seems to restore normal function in aspects of the brain's glutamatergic signaling system that can result in long-term AUD treatment effects. One additional component contributing to acamprosate's effectiveness may be its normalizing influence on alcohol-related sleep disturbances, which can be quite severe in early abstinence and precipitate relapse to drinking.[29,30]

Researchers at the Mayo Clinic have been seeking to identify predictors of patient response to acamprosate. They determined that a patient's serum glutamate concentrations at baseline could serve as a biomarker of treatment outcome, with high serum glutamate levels predicting a good response. Moreover, individuals who showed a response to acamprosate treatment showed the greatest reduction in serum glutamate levels from baseline to the end of treatment.[31]

Unlike disulfiram and naltrexone, acamprosate is not metabolized in the liver. Therefore, it is safe to use in patients with hepatic impairment. However, as acamprosate is excreted through the kidneys, it is important to ensure that patients do not have severe renal impairment. Acamprosate has low bioavailability, which necessitates that the medication be taken three times per day.[15]

U.S. Treatment Guidelines

In 2017, the American Psychiatric Association issued practice guidelines for the pharmacological treatment of patients with moderate to severe AUD.[20] These guidelines recommend use of acamprosate or naltrexone in patients who wish to cut down or quit drinking, who prefer medication or have not responded to nonpharmacological treatments, and who have no medical contraindications to use of these drugs. Disulfiram is not recommended as a first-line treatment for AUD, given (a) the potential risk of severe reactions and physiological consequences of drinking while taking the drug, and (b) the more robust evidence for efficacy in acamprosate and naltrexone. However, it may be used in patients who prefer disulfiram or are intolerant to or have not responded to naltrexone or acamprosate and who understand the risks of alcohol consumption while taking disulfiram.

The guidelines also recommend that antidepressant medications and benzodiazepines should not be used for the treatment of AUD unless the individual has been diagnosed with a concurrent disorder (e.g., depression, anxiety) for which these medications are indicated. Benzodiazepines can be used to manage acute alcohol withdrawal for up to 5 days; beyond that time, there is no support for the use of benzodiazepines in the treatment of AUD, especially because benzodiazepines themselves have misuse potential and are cross-tolerant with alcohol.[20]

Nalmefene—Widely Approved Outside the United States

A fourth medication, nalmefene, has been approved for treatment of AUD throughout the European Union, the United Kingdom, and other countries. In contrast to naltrexone, which mainly binds to the mu opioid receptor, nalmefene acts as a more potent antagonist at the mu, delta, and kappa opioid receptors.[32] Nalmefene's activity at the kappa opioid receptor is of interest because activation of this receptor is associated with increases in anxiety and dysphoria. Consequently, by blocking this array of receptors, nalmefene may diminish both the rewarding effects of alcohol as well as the anxiety and dysphoria associated with not drinking in individuals with AUD.

In contrast to oral naltrexone, disulfiram, and acamprosate, which must be taken daily, nalmefene is only taken 1 to 2 hours prior to anticipated drinking occasions. Follow-up studies of up to 1 year found that nalmefene treatment was associated with decreased drinking relative to placebo.[33-35] The European Medicine Agency based its approval on slightly different treatment outcome criteria than FDA, including a two-level reduction in World Health Organization (WHO) drinking risk levels.[36] (These risk levels—very high, high, medium, and low—are defined based on estimated mean daily ethanol consumption in grams in the previous 12 months.[37]) This level of reduction in alcohol consumption has been shown to be associated with improved mental health, particularly anxiety and depression; improved physical health (liver functioning); and improved overall quality of life.[38] Thus, both the FDA-approved drinking outcomes (i.e., rates of no drinking or no heavy drinking days) and the WHO risk level-based outcomes have broad clinical relevance for individuals with AUD.

Identifying New Medications for AUD

As described above, the currently approved medications for AUD largely focus on reducing the expected positive or rewarding effects of drinking. Disulfiram, naltrexone, and nalmefene all interrupt the binge intoxication phase, either by inducing negative responses after drinking or by reducing alcohol's rewarding effects, whereas acamprosate reduces craving in the preoccupation-anticipation phase in individuals in recovery (see Figure 1). Use of these anti-reward medications is based on the assumption that most people drink due to positive reinforcement—they want to experience alcohol's rewarding effects—and that taking away those effects will thereby discourage further drinking. However, as recent research has uncovered more information on alcohol's effects on the brain and the neurobiology of AUD, it has become clear that many people drink because of negative reinforcement—they want

to avoid the negative effects of not drinking.[39] In people with AUD, drinking cessation acts as a stressor because the brain has become used to the presence of certain alcohol levels. In these individuals, abstinence induces excessive activation of the brain stress systems, particularly in the central nucleus of the extended amygdala. This stress response includes the release of corticotropin-releasing factor (CRF), especially in early abstinence, which prompts symptoms of anxiety, dysphoria, irritability, and sleep disturbance that are characteristic of post-acute or protracted withdrawal.[39] At the same time, the brain's anti-stress systems often are depleted in early abstinence.[39] These observations have launched a new avenue of research in the quest for effective treatments for AUD focusing on the neuropeptides that have been shown to be dysregulated during early abstinence and which are associated with the symptoms of protracted withdrawal as potential drug targets for novel medications. The hope is that such treatments could interrupt the AUD cycle before reaching the craving and relapse/binge intoxication stage. Building on recent discoveries of the neurobiology of AUD—and particularly the role that the stress response has during early abstinence in driving the AUD cycle toward relapse—the goal is to normalize those systems to support recovery in a way that is safe and acceptable to patients.

To develop and study the effects of such medications, researchers, with support from NIAAA, developed parallel animal and human laboratory models of risk factors for relapse in protracted withdrawal.[40] The human model employed techniques already used for other purposes in the field. For example, the investigators used affective priming to induce some of the internal risk factors for relapse, such as the affective states mentioned above, by showing participants images associated with those mood states. Additionally, participants were exposed to external risk factors for relapse through visual and olfactory alcohol cue exposure (i.e., they were asked to view and smell a glass of their favorite alcoholic beverage but not drink it). The studies recruited non-treatment-seeking men and women with AUD who were required to remain abstinent for 3 days prior to testing while taking double-blind study medication. Thus, the volunteers were beginning to exhibit an activated stress response and were highly likely to be responsive to the alcohol beverage cues. The main goal of the experiments was to screen medications aimed at reducing the stress response associated with relapse risk in protracted withdrawal. The study participants were randomly assigned to the medication under investigation or placebo for a relatively short dosing period, based on the period needed to achieve steady-state or

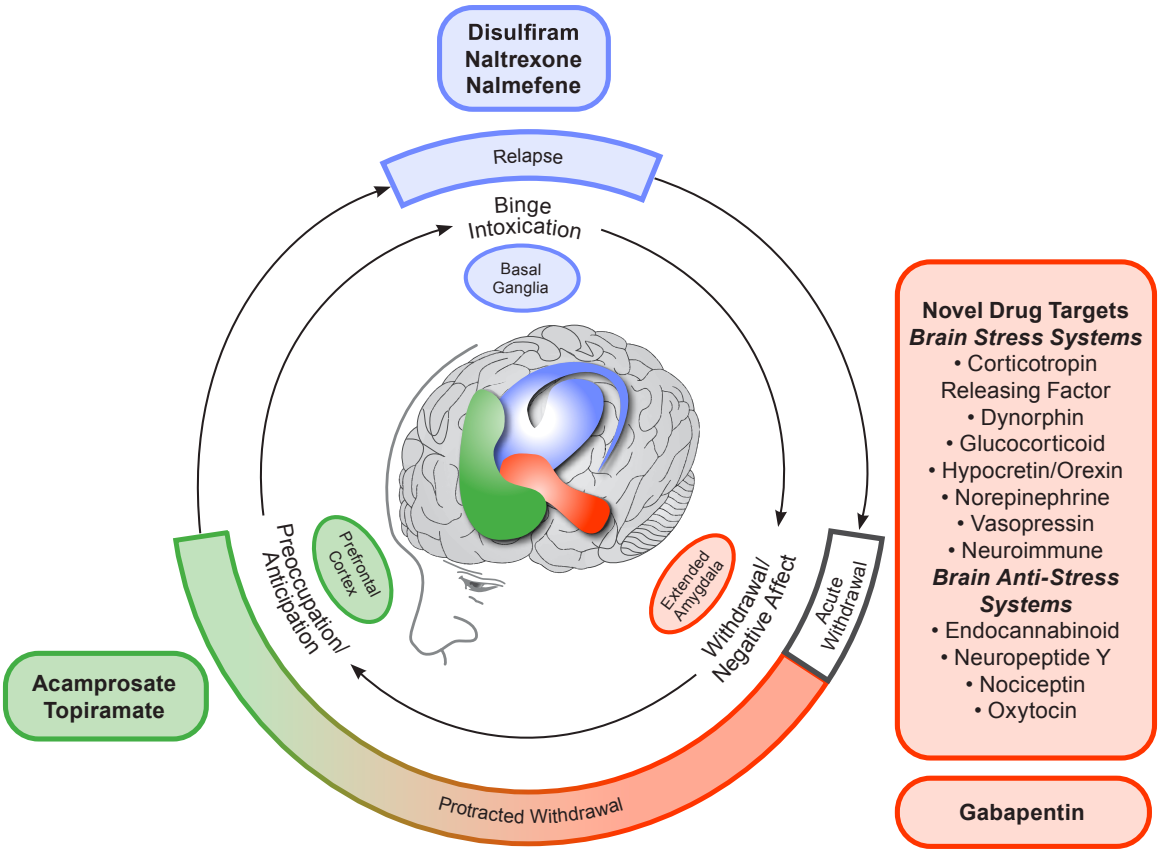

Figure 1. Conceptual framework for the effects of various medications on the three major stages of the alcohol addiction cycle and the clinical stages of alcohol use disorder. The outer ring relates to the clinical stages of alcohol use disorder; the inner ring relates to the three stages of the addiction cycle. *Note:* Adapted by permission from Springer Nature: *Neuropharmacology*, 35(1):217-238. Neurocircuitry of addiction. George F. Koob and Nora D. Volkow, 2010.[59]

maintenance dosing, which is typically between 1 and 2 weeks. Participants were then tested on the last day of dosing, using both subjective and objective measures of responsivity to alcohol as well as extensive analyses to evaluate how well tolerated and safe the studied drug was in individuals with AUD. This approach has been used to evaluate the effectiveness of several medication candidates.

Gabapentin

The first medication studied using this model was gabapentin, an oral anticonvulsant approved by FDA for the treatment of epilepsy and neuropathic pain. It acts by modulating GABAergic activity on voltage-gated calcium channels, which reduces postsynaptic excitability and decreases the release of excitatory neurotransmitters.[41] Because this activity also helps restore homeostasis in brain stress systems that become activated in early abstinence, gabapentin seemed to be a promising candidate for treatment of AUD. Moreover, several off-label clinical studies reported beneficial effects of gabapentin on symptoms associated with post-acute protracted withdrawal and risk of relapse, such as dysphoria, anxiety, and insomnia.[41] In fact, several studies reported that gabapentin was effective for treatment of insomnia, including alcohol-related sleep disturbance, indicating that it decreased stage 1 sleep and arousals while increasing slow-wave sleep and sleep efficiency.[41,42] Like acamprosate, gabapentin is not metabolized in the liver and has an acceptable safety and tolerability profile, further supporting its investigation in the treatment of AUD.[41]

To assess the efficacy of gabapentin in the treatment of AUD, Mason and colleagues conducted a human laboratory study in which they randomly assigned 33 volunteers with AUD to receive either 7 days of gabapentin (1,200 mg/d) or placebo and then tested them on the last day of dosing.[43] These analyses found that participants who were treated with gabapentin had significantly less craving, lower impulse to drink, and less feelings of loss of control over drinking than those who had received placebo. Gabapentin-treated participants also showed benefits compared with placebo across multiple dimensions of sleep, including sleep efficiency, sleep latency, and sleep quality. Moreover, individuals treated with gabapentin did not report next-day dysfunction or somnolence, which often occur after taking sleep medications.

Based on the findings of the initial study, the research team conducted a larger, double-blind, placebo-controlled, dose-ranging clinical trial of gabapentin in 150 outpatients seeking treatment for AUD.[44] Participants were randomized to 12 weeks of treatment with either the highest FDA-approved dose of gabapentin (1,800 mg/d), the lowest FDA-approved dose (900 mg/day), or placebo. All patients also received weekly abstinence-oriented counseling over the treatment period. Outcomes analyzed include rates of complete abstinence and no heavy drinking; drinking quantity and frequency; GGT levels as an objective indicator of recent alcohol use; as well as measures of craving, sleep disturbance, and negative affective symptoms.

Over the 12-week treatment period, participants who had received the highest dose of gabapentin had significantly less relapse to drinking and higher rates of complete abstinence compared with placebo; relapse and abstinence levels for participants treated with the 900 mg dose were intermediate. Similarly, participants receiving the high gabapentin dose had the highest proportion of individuals with no heavy drinking at about half the sample, which was about twice as much as among participants receiving placebo; the rate of heavy drinking in participants receiving the lower dose of gabapentin was again intermediate. Thus, both of these key outcomes showed significant linear dose effects. Similar results also were observed for quantity and frequency measures of drinking.[44]

Treatment with the 1,800 mg gabapentin dose also yielded the greatest effect on symptoms of protracted abstinence. Participants who had received this dose showed the greatest reduction in negative affective symptoms on the Beck Depression Inventory II; in craving as determined using the Alcohol Craving Questionnaire; and in sleep complaints as measured using the Pittsburgh Sleep Quality Index.[44] These results replicated the findings obtained in the earlier laboratory study.[42] Finally, gabapentin treatment was associated with significant reductions in GGT levels, indicating reduced recent alcohol use.[44] Together, the results supported the conclusion that gabapentin dose-dependently and significantly improved various parameters of AUD, including rates of complete abstinence and no heavy drinking; drinking quantity and frequency; as well as protracted withdrawal symptoms such as craving, sleep disturbance, and negative affect.

Gabapentin was well tolerated, with no serious or unexpected drug-related adverse events or evidence of misuse potential.[44] To date, numerous studies conducted in the United States and elsewhere have found no evidence of misuse potential for gabapentin in the treatment of AUD.[41] Bisaga and Evans demonstrated that gabapentin does not interact pharmacokinetically or pharmacodynamically with alcohol.[45] However, there have been reports that gabapentinoids, such as gabapentin and the newer drug pregabalin, have been misused by people with opioid use disorder who are in withdrawal, people who misuse prescription drugs recreationally, and people who are incarcerated, with self-administered doses greatly exceeding recommended doses.[41] Heightened monitoring for gabapentin misuse is warranted in these at-risk populations.

Based on these and other studies supporting the efficacy of gabapentin in treating AUD, the American Psychiatric Association has included gabapentin and another anticonvulsant, topiramate, in its 2017 *Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder.*[20] These guidelines recommend that gabapentin or topiramate be used in patients who have a goal of decreasing or quitting drinking, who prefer

gabapentin or topiramate, who are intolerant to or have not responded to acamprosate or naltrexone, and who have no contraindications to the use of gabapentin or topiramate.

Mifepristone

Mifepristone is a medication approved by FDA for Cushing's syndrome that shows promise as a repurposed medication for the treatment of AUD and acts upon the protracted withdrawal phase of the AUD cycle.[46] Mifepristone is a mixed glucocorticoid/progesterone receptor antagonist that has been hypothesized to normalize the altered activity of the hypothalamic-pituitary-adrenal axis. As previously mentioned, heavy alcohol consumption and subsequent withdrawal have an impact on the body's stress response, with heavy alcohol use blunting activity of the hypothalamic-pituitary-adrenal axis and the stress associated with subsequent abstinence driving CRF release in the amygdala, which contributes to protracted withdrawal symptoms.[47,48] Consequently, administration of mifepristone to people with AUD following acute withdrawal was hypothesized to normalize the individual's stress response and CRF dysregulation, thereby protecting against relapse during protracted withdrawal.

To investigate this hypothesis, Vendruscolo and colleagues evaluated the effects of mifepristone on people with AUD in a laboratory model of risk factors for relapse.[46] Participants were randomly assigned to mifepristone (600 mg/d) or matched placebo for 7 days, with testing conducted on the last day of dosing. The analyses found that participants treated with mifepristone not only exhibited significant reductions in craving and response to alcohol cues, but they also had significantly lower levels of drinking than did those who had received placebo, both during the week of treatment and at 1-week follow-up. Moreover, participants receiving mifepristone showed a significant reduction from baseline in GGT levels, the marker of liver function that is sensitive to alcohol intake, as well as in two other measures of liver function (i.e., aspartate transaminase and alanine transaminase levels).[46]

Looking Ahead in Medication Development for AUD

The clinical studies of both gabapentin and mifepristone showed reductions in craving and alcohol consumption, as well as improvements in liver function tests compared to placebo, suggesting that both medications have therapeutic potential for AUD.[43,44,46] Additionally, both medications were well tolerated and triggered no concerns regarding safety, medication adherence, or misuse potential, including rebound craving or alcohol use after medication discontinuation, in these samples of individuals with AUD. These findings provide clinical validation of earlier preclinical studies of protracted withdrawal, in which the medications reduced reinstatement of ethanol seeking and ethanol intake. They also lend support to the role that medications targeting abstinence-related dysregulation in brain stress systems can play as a novel treatment approach for AUD. Such medications may reduce the negative affect and insomnia associated with early abstinence and thereby both increase medication adherence and reduce the misery of early abstinence.

In addition to these studies, which were largely funded by NIAAA, the institute itself has an active research program. The NIAAA Clinical Investigations Group conducts multicenter trials that have shown positive results for two medications relevant to protracted abstinence—varenicline (Chantix), a partial alpha(4)beta(2) nicotinic acetylcholine receptor agonist that FDA has approved as a treatment for smoking cessation, and an investigational vasopressin antagonist.[49,50] The NIAAA Intramural Research Program also has been active in studying molecules that may be relevant to treating protracted abstinence, including ghrelin receptor antagonists[51] and mineralocorticoid receptor antagonists,[52,53] and a molecule that may show efficacy for both AUD and alcohol-associated liver disease.[54] These are just a few examples of the many hundreds of drugs that have been evaluated, with NIAAA support, for efficacy in the treatment of AUD.

What characteristics should medications to treat AUD have? Ideally, they should be small molecules that can cross the blood-brain barrier and target the brain regions and systems that are dysregulated by chronic heavy alcohol consumption in a way that is relevant to treating AUD. They should not have misuse potential, nor should they interact with alcohol. This is important so that, in case of relapse, the medication does not exacerbate alcohol's effects, such as impaired alertness and motor coordination. Additionally, medication candidates should have a good safety profile, particularly no hepatotoxicity; they should show good tolerability with only mild to moderate adverse events that do not prompt treatment discontinuation; they should have good patient acceptability in terms of the route of administration, which is typically oral; and the dosing regimen should be acceptable to the patients and adaptive to their lifestyle.

Another consideration in developing medications for AUD is the potential for sex differences as well as racial differences in drug metabolism, as exemplified by a greater prevalence of the flushing response in certain East Asian populations. Such differences in drug metabolism may affect drug efficacy or safety. Therefore, it is important to have diversity, equity, and inclusion among participants in clinical trials of medications to treat AUD. Sex differences have not been studied systematically for disulfiram and naltrexone; however, although sex does not affect the pharmacokinetics of the long-acting formulation of naltrexone, only men responded to the medication in the pivotal

trial, whereas women did not.[25] The reasons underlying these differences are not fully understood. Sex differences have been comprehensively analyzed for acamprosate in a meta-analysis of individual records obtained from more than 1,300 women and nearly 4,800 men who participated in 22 acamprosate clinical trials.[55] The meta-analysis found a significant effect of acamprosate relative to placebo on both rates of abstinence and rates of no heavy drinking, and these effect sizes did not differ between men and women. Similarly, the side effect and tolerability profile of acamprosate, including the number, type, and severity of adverse events, did not differ between men and women. Moreover, despite a history of significantly more anxiety, depression, suicide attempts, drug misuse, interpersonal loss, and greater liver impairment at baseline in women than in men, women responded comparably well to acamprosate treatment of AUD.[55]

Another issue to consider in AUD treatment is the age of the patient, as it is never too early (or too late) to treat AUD. In the United States, drinking is illegal for people under age 21, although some in this age group do meet the criteria for AUD. A small, double-blind, placebo-controlled clinical trial of disulfiram conducted in teens found good tolerability and higher rates of abstinence with the medication compared to placebo.[56] At the other end of the age spectrum, some people older than age 65 have been included in some trials of disulfiram,[57] naltrexone,[25] and acamprosate;[58] however, the numbers were not sufficient to analyze differences in safety and efficacy from younger patients. AUD is a serious concern in older adults because some of its common effects may have more serious consequences in this population, such as the increased risk of falls. Closer monitoring with medication treatment may be necessary if an older person is at increased risk for liver, kidney, or cardiac problems, or uses additional medications to treat other disorders; however, unless there is a medical contraindication, medication treatment is indicated in this age group.

Overall, however, it is clear that new medications to treat people with AUD are urgently needed and that the use of the existing medications must be significantly expanded to support people recovering from AUD. Effective treatments for AUD—both pharmacological and nonpharmacological—are available, but they can only help if they are actually being used. The fact that only 7% to 8% of individuals with AUD report receiving any treatment is a clear indication that much remains to be done in this respect. To support both patients and treatment providers in ensuring that people with AUD receive the appropriate care, NIAAA has created the *NIAAA Alcohol Treatment Navigator* (www.alcoholtreatment.niaaa.nih.gov). This online tool outlines the features of evidence-based AUD treatment, describes the varied routes to recovery, and provides a strategy to help people find practitioners in their area that provide evidence-based treatments, whether behavioral or pharmacological, for AUD.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Alcohol and the Adolescent Brain: What We've Learned and Where the Data Are Taking Us

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This article was based on a presentation at the NIAAA 50th Anniversary Science Symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," held on November 30–December 1, 2020. Links to the videocast are available on the NIAAA 50th Anniversary Science Symposium agenda webpage. Opinions expressed in contributed articles do not necessarily reflect the views of the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health. The U.S. government does not endorse or favor any specific commercial product or commodity. Any trade or proprietary names appearing in *Alcohol Research: Current Reviews* are used only because they are considered essential in the context of the studies reported herein.

This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Tapert's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; adolescence; binge drinking; neuroimaging; magnetic resonance imaging; neuropsychological tests; young adults; drinking behavior

The past 50 years of research supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) have resulted in an accumulation of invaluable data to address the multifaceted problems surrounding underage drinking. Youth use of alcohol remains a pervasive social and public health concern in the United States and a leading cause of disability and mortality during adolescence.[1,2] Alcohol use in adolescence has a distinct pattern from adult drinking, whereby adolescents may have fewer drinking occasions but consume relatively high levels per occasion, referred to as binge or heavy episodic drinking and defined as consuming four or more standard ethanol consumption units on an occasion for females and five or more for males.[3-5] Highly prevalent among youth in Western countries is an intermittent pattern of heavy alcohol consumption that typically is associated with social leisure occasions on weekend nights.[6] Moreover, adolescent alcohol use, along with smoking and illicit drug use, has undergone changes in prevalence and patterns in recent decades. For example, alcohol use peaked in the mid-1990s, with approximately 50% of 12th graders reporting past-month alcohol use, followed by a steady long-term decline to 30% in 2018. In 2020, the downward trend reversed course, with 34% of 12th graders reporting past-month alcohol use.[1] Recent reports indicate that prevalence estimates for 2021 will need to account for impacts of the COVID-19 global pandemic on underage substance use behavior and availability.[7]

High-risk alcohol consumption patterns and associated problems alone increase risk for adverse outcomes—such as motor vehicle accidents, high-risk sexual behaviors, other illicit substance use, and mental health challenges—for adolescents who drink. These risks are further compounded by the fact that adolescence is a period of crucial brain development and maturation.[8,9] Neuroimaging studies have provided clear evidence that the brain (a) continues to develop throughout adolescence and into adulthood, and (b) undergoes important structural and functional changes in synaptic plasticity and neural connectivity during adolescence.[10,11] These changes and the enormous plasticity of the teen brain make adolescence a time of both great risk and great opportunity.[11]

This article begins with an overview of typical adolescent brain development, followed by a summary of four key themes in the current understanding of alcohol and the adolescent brain: (1) predictors of underage drinking; (2) consequences of alcohol on adolescent brain structure and function; (3) moderating and confounding factors, including age of onset, sex disparities, family history, co-use of other substances, and mental health comorbidities; and (4) reversibility of and recovery from alcohol misuse. The article concludes with a discussion of where the data lead us to reach the next milestones in NIAAA-supported research.

Typical Adolescent Brain Development

The brain of an adolescent, much like teenage behavior, undergoes significant developmental changes. This neurodevelopment continues after adolescence, typically until around age 25.[12-15] The maturational processes in the brain occur in stages, with more basic functions (e.g., motor and sensory functions) maturing first and areas such as the lateral temporal and frontal lobes, which are responsible for higher cognitive function (e.g., decision-making, attention), developing later in adolescence.[13] The prefrontal cortex is one of the last brain regions to complete its maturation. Its rate of change does not plateau until the third decade of life, in concert with typical developmental trajectories of cognitive abilities, such as decision-making, attention, and cognitive control.[16-18] The late maturation of the prefrontal cortex has been linked to risky behavior during adolescence, particularly if the limbic subcortical system develops earlier.[16]

Executive functioning typically matures during this developmental stage,[19] coincident with gray matter reductions and white matter growth.[20,21] Functional magnetic resonance imaging (fMRI) studies of executive behaviors have demonstrated increasing prefrontal activity and better inhibitory control with adolescent age.[22] Challenges in executive functioning have been observed in adolescents with a family history of alcohol use disorder (AUD),[23] repeated childhood trauma experiences,[24] and poor sleep,[25] all of which also have been identified as risk for adolescent binge drinking and AUD.[17,26,27] Deficits in control circuitry have been linked to impulsivity, sensation seeking, and alcohol use into early adulthood.[28]

One of the studies investigating adolescent alcohol use and its effects is coordinated by the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), which is conducting a multisite longitudinal study supported by funding from NIAAA and other National Institutes of Health partner institutes. Launched in 2012, this five-site consortium recruited a community cohort of 831 diverse adolescents ages 12 to 21 from five U.S. regions (Durham, North Carolina; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California). Half the sample was enriched for key characteristics conveying risk for heavy drinking among adolescents (i.e., family history of substance use disorder, youth externalizing or internalizing symptoms, and having tried alcohol by age 14). Most of the sample (85%) reported very limited alcohol use at project entry; the remaining 15% exceeded typical age thresholds for alcohol at project entry in this cohort-sequential design.[29] At project entry and annually thereafter, participants received neuroimaging (high-

resolution structural, diffusion, and resting-state fMRI scans), neurocognitive testing, detailed substance use and mental health interviews; provided urine samples for drug testing as well as saliva samples for genetics and pubertal hormone assays; and completed various self- and parent reports on personality, behaviors, and environment.[29] NCANDA will continue to examine the interactive effects of typical development as well as adolescent alcohol use and executive dysfunction into early adulthood.

Resting-state fMRI findings from NCANDA and other studies have shown that intrinsic functional networks subserving cognitive control and limbic circuitry develop across adolescence and may be influenced by adolescent heavy drinking.[24,30,31] Moreover, the adverse effects of alcohol may be more prominent in girls than in boys.[32]

Predictors of Underage Drinking

Being able to identify youth at higher risk for alcohol misuse could lead to early intervention and ultimately help reduce the significant personal and public health burden of AUD; however, relatively few studies have explored individual-level precursors of adolescent alcohol use. Prospective longitudinal studies of substance-naïve youth are uniquely positioned to identify factors predating the onset of alcohol use. Squeglia et al. identified several markers of alcohol initiation by age 18 in 137 adolescents.[27] These markers included demographic and behavioral factors (e.g., male sex, higher socioeconomic status, early dating, more externalizing behaviors, positive alcohol expectancies), lower executive functioning, thinner cortices, and less brain activation in diffusely distributed brain regions.

NCANDA seeks to expand on these findings using a greater number of measurements in a large sample to lead to more accurate individual-level forecasting. The consortium is employing machine learning models, which can avoid multiple-comparison correction and reduce measures to a single, individual-level prediction.[33,34] NCANDA developed a model that distinguished youth who drink heavily from those who drink little or no alcohol, based on patterns of macrostructural and microstructural imaging metrics in multiple brain regions.[35] The analyses suggested delayed development of white matter connectivity among the older youth in the sample who drank heavily, as well as increased risk of subsequent heavy drinking in youth with more externalizing symptoms. These findings fit closely with those from the IMAGEN Consortium, which found that variability in personality, cognition, life events, neural functioning, and drinking behavior features predicted Alcohol Use Disorders Identification Test scores at ages 14 and 16.[36]

Neural Consequences of Underage Heavy Drinking

Gray Matter Volume

Unlike white matter, gray matter volume peaks in the primary school-age years, around age 10.[11] Squeglia et al. reported that youth who drank heavily (n = 75) (defined using modified Cahalan quantity x frequency criteria[37,38]) showed accelerated reductions in gray matter volumes in cortical lateral frontal and temporal areas compared to those who drank no or little alcohol (n = 59).[39] These results were largely unchanged with co-use of marijuana and other drugs; also, similar patterns of developmental trajectory abnormalities existed in males and females. This finding was replicated in the NCANDA cohort, which examined the influence of alcohol use on gray matter structure in 483 adolescents ages 12 to 21 both before and 1 to 2 years after the onset of heavy drinking.[13] For youth with no or low alcohol consumption, gray matter volumes declined throughout adolescence, with rates slowing in many brain regions in later adolescence. However, youth who initiated heavy drinking exhibited a steeper decline in frontal gray matter volumes. For both youth with no or low alcohol consumption and those with heavy drinking, cannabis use did not influence gray matter volume trajectories.

These findings were confirmed in a recent analysis spanning five time points in the NCANDA study and using linear mixed-effects models.[40] A greater number of past-year binge drinking episodes was linked to greater decreases in gray matter volumes in 26 of 34 bilateral Desikan-Killiany cortical parcellations tested. The strongest effects were noted in frontal regions as well as among younger adolescents; moreover, the effects largely attenuated in later adolescence. The gray matter volumes decreased most for individuals with greater numbers of binge-drinking episodes and recent binge drinking. These findings provide yet more evidence that adolescent binge drinking is linked to a greater risk of more prominent gray matter reductions during adolescence.[40]

Functional MRI studies further suggested that adolescents with histories of heavy drinking showed aberrant patterns of activation in response to cognitively challenging tasks,[41,42] including tasks of working memory and inhibition. In adolescents with a history of 1 to 2 years of heavy drinking, the aberrant activation was not linked to detectable deficiencies in task performance. However, if heavy drinking persisted longer, reduced task performance was often evident in the adolescents.[43,44] This pattern of results suggested that the brain may be able to compensate for subtle neuronal insults for a period of time, but if drinking patterns persist and become heavier, the brain may no longer be able to compensate and may be vulnerable to the effects of repeated and sustained heavy doses of alcohol.

White Matter Volume and Integrity

Throughout adolescence, white matter volume increases and matures, resulting in myelination that increases speed of neuronal transmission and modulates the timing and synchrony of neuronal firing patterns that convey meaning in the brain.[11] Squeglia et al. reported that adolescents who drank heavily showed attenuated white matter growth of the corpus callosum and pons relative to adolescents who did not drink.[39] Pfefferbaum et al. indicated that among those in the NCANDA sample who consumed no or little alcohol, white matter regions grew at faster rates in younger age groups and slowed toward young adulthood.[13]

To examine the potential for a neurotoxic effect of alcohol use on adolescent development of white matter, Zhao et al. conducted a whole-brain analysis of fractional anisotropy of NCANDA participants ages 12 to 21 at baseline.[45] For 63 adolescents who initiated heavy drinking, the researchers examined white matter quality before and after drinking onset and compared it to the white matter maturation trajectory of 291 adolescents with no or low alcohol consumption. Results showed deterioration of white matter integrity in youth who drank heavily compared with age- and sex-matched controls. Moreover, the slope of this reduction over time corresponded with days of drinking since the study entry.[45] Within-subject analyses contrasted developmental trajectories of youth before and after they initiated heavy drinking. These analyses suggested that drinking onset was associated with, and appeared to precede, disrupted white matter integrity. This disruption was greater in younger adolescents than in older adolescents, and was most pronounced in the genu and body of the corpus callosum.[45] It is possible that these brain structure changes may occur concomitantly with modifications in certain neurotransmitter and hormone secretion systems, which markedly influence the refinement of certain brain areas and neural circuits.[46]

Neurocognition

Along with altered development and maturation of gray and white matter, studies have reported neurocognitive consequences of underage drinking, such as impairments in attention,[47] verbal learning,[48,49] visuospatial processing,[47,50] and memory.[49] Neurocognitive deficits linked to moderate to heavy drinking during this critical developmental period may lead to direct and indirect changes in neuromaturational course, with effects that may extend into adulthood. Squeglia et al. examined neurocognitive function in adolescents who drank heavily, moderately, or not at all, based on the Cahalan classification system.[51] Their findings suggested that initiation of moderate to heavy alcohol use and incurring hangovers during adolescence may adversely influence neurocognitive functioning. For females, more drinking days in the past year predicted a greater reduction in performance on visuospatial tasks, in particular visuospatial memory, from baseline to follow-up. For males, a tendency was seen for more hangover symptoms in the year before follow-up testing to predict a relative worsening of sustained attention.[51]

Alcohol Cue Reactivity

Another set of studies demonstrated that youths who drank heavily exhibited greater brain activation while viewing alcohol advertisements[25,52-54] than while viewing ads for nonalcoholic beverages.[52] Adolescents are exposed to alcohol advertising materials on a daily basis in many countries. As studies in adults with AUD have shown atypical responses to alcohol-related materials,[55] Tapert and colleagues used fMRI analyses to determine whether similar response patterns existed in adolescents who drink.[52] The study included 15 adolescents ages 14 to 17 with AUD and 15 demographically similar adolescents who drank infrequently. The participants were shown pictures of alcoholic and nonalcoholic beverage advertisements during neuroimaging. Adolescents with histories of heavy drinking showed greatly enhanced neural activation while viewing the pictures of alcoholic beverages compared with pictures of nonalcoholic beverages. The extent of alcohol-related activation was greatest for those with the highest levels of monthly alcohol intake (see Figure 1). In contrast, youth with limited drinking histories showed similar levels of activation while viewing the two beverage picture types. These results demonstrated pronounced alcohol cue reactivity in heavy drinking teens, particularly in reaction to alcohol advertising materials.

Factors Contributing to Adolescent Alcohol Use

Age of Onset

Studies examining longer-term impacts of adolescent alcohol misuse have yielded mixed results. Some studies reported a maturing-out without significant consequences in adulthood, while others found ongoing effects on mental health, physical health, and social functioning, as well as higher levels of alcohol use and AUD.[56] Analyses using data from the National Longitudinal Alcohol Epidemiologic Survey determined that 40% of those initiating alcohol use before age 15 were diagnosed with AUD at some point in their lives compared to only 10% of those who delayed the onset of drinking until age 21 or later.[57]

The first study of adolescents (ages 12 to 15 at baseline; $N = 215$) to assess the association between age of adolescent drinking onset and neurocognitive performance found that earlier age of drinking onset predicted poorer performance on tasks requiring psychomotor speed and visual attention. Similarly, an earlier age of onset of regular (weekly) drinking predicted poorer performances on tests of cognitive inhibition and working memory.[58] This study suggested that early onset

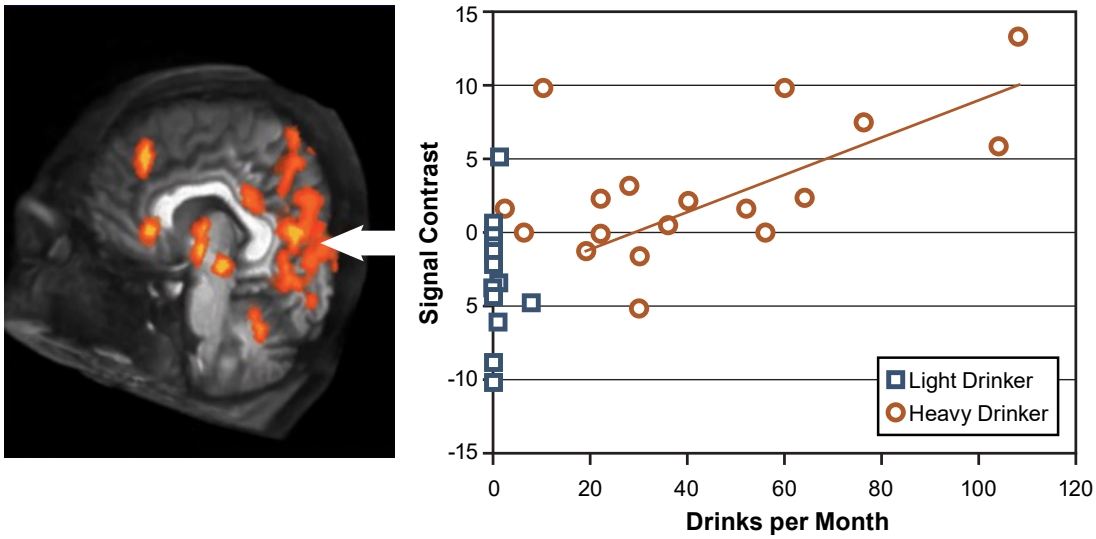

Figure 1. Response to alcohol pictures in youth with heavy versus light drinking. Brains of youths who drank heavily activated strongly in response to seeing alcohol advertisements but showed little brain response to nonalcoholic beverage ads; this difference (i.e., signal contrast) was smaller in youth who drank lightly. The difference in brain response was greatest in adolescents with the highest consumption levels and was especially strong in the left hemisphere (positive affect), limbic, and visual cortex areas. *Source:* Tapert et al., 2003.[52]

of drinking increased risk for subsequent neuropsychological dysfunction.

Sex Disparities

Several studies have reported that the associations between alcohol and brain structure and function differ by sex, especially in adolescents engaging in binge drinking. While not conclusive across the literature, female adolescents who engaged in binge drinking appeared to show effects such as blunted activation in frontal, temporal, and cerebellar cortices compared to females who did not drink, whereas male adolescents who engaged in binge drinking showed the opposite activation pattern.[59] Female adolescents ages 15 to 17 meeting criteria for AUD showed larger prefrontal cortex volumes than female controls, while male adolescents with AUD had smaller prefrontal cortex volumes than male controls.[60] A similar finding was observed for white matter.

Family History of AUD

Having a family member with AUD is associated with almost double the risk of initiating drinking in early adolescence.[57] Using fMRI, Spadoni et al. observed greater neural activity during rest and reduced activity during an active baseline condition were linked to denser family history of AUD.[61]

Mental Health Comorbidities

Adolescence is the peak time for both onset of substance misuse and emergence of mental illness, including anxiety disorders, bipolar disorder, major depression, eating disorders, and psychosis.[10] The National Survey on Drug Use and Health (NSDUH) estimated that 20% of adolescents had a mental illness that persisted into adulthood.[2] Moreover, adolescents with a past-year major depressive episode were more likely to be current binge alcohol users (6% vs. 4%).[2] However, it remains unclear how comorbid mental health problems contribute to and exacerbate the neurobiological effects of alcohol misuse.[4] Frontal and temporal cortical thinning may predict increased vulnerability to development of adolescent depression. In the NCANDA sample of 692 adolescents without a history of depression, the 101 youth who transitioned into depression were found at study baseline to have thinner cortices in the superior frontal cortex, precentral and postcentral regions, and superior temporal cortex, beyond effects attributable to age and sex.[62,63]

Adverse Childhood Events

Childhood trauma and post-traumatic stress symptoms have been shown to confer increased risk for adolescent and adulthood AUD, mental illness, and physical health problems.[64,65] Youth with trauma exposure showed thinner frontal cortices, and those with chronic post-traumatic stress disorder (PTSD) had smaller orbital frontal cortices[66] and less superior posterior cortical and cerebellar gray matter volume.[67] These observations indicate that trauma may be associated with structural brain aberrations.

NCANDA has also examined the relationship between childhood trauma and subsequent adolescent alcohol use.[68] In a sample of 392 NCANDA participants, adverse childhood event history was linked to greater self-reported executive dysfunction spanning four annual follow-ups. Greater childhood trauma also was linked to less connectivity in sensorimotor and cognitive control networks (i.e., the bilateral dorsal anterior cingulate cortex, right anterior insula, right intraparietal sulcus,

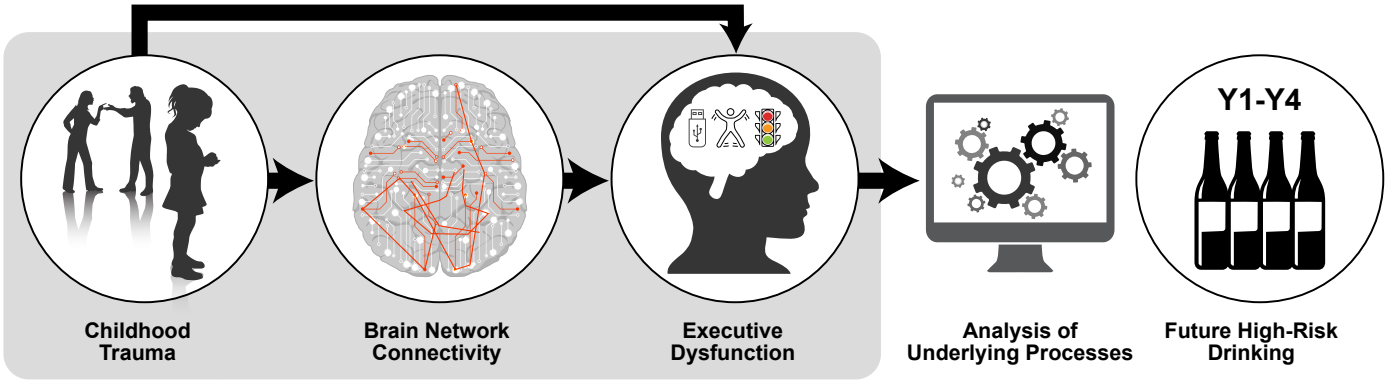

Figure 2. Model depicting how childhood trauma may lead to subsequent high-risk drinking. *Note:* Y1-Y4, Year 1 through Year 4. *Source:* Silveira et al., 2020.[24]

and bilateral pre- and postcentral gyri hub regions) at baseline. This reduced connectivity explained the relationship between executive dyscontrol and subsequent increased frequency of adolescent binge drinking (see Figure 2).[24]

Poor Sleep

Sleep patterns change substantially during adolescence and emerging adulthood.[69] Lack of sleep, going to sleep relatively late, and large weekend-weekday sleep differences all are risk factors for alcohol use in adolescents and young adults.[70] Similarly, in the NCANDA sample, sleep difficulties in adolescence predicted later substance use problems.[71] The reverse has also been seen, with acute and chronic alcohol intake altering sleep structure and electroencephalography patterns[72] in older adolescents[73] and adults.[69] NCANDA will continue to longitudinally examine whether these changes remain evident into adulthood and how alcohol use influences sleep neurobiology.

Use of Other Substances

Co-use of multiple substances may influence the relationship between alcohol use and neural integrity. For example, during a spatial working memory task, adolescents with co-occurring AUD and cannabis use disorder showed less inferior frontal and temporal neural activation but a greater medial frontal response compared to adolescents with AUD alone.[74] Co-use of alcohol with cannabis also may adversely influence executive functioning.[75] Given the high rates of co-occurring alcohol and other substance use during adolescence,[76] future well-powered studies will benefit from detailed analyses of various combinations of substances of abuse on neural and neurocognitive outcomes.

Recovery From Consequences of Adolescent Heavy Drinking

In adults with AUD, improvements in attention and concentration, reaction time, and memory are generally seen after 2 to 8 weeks of abstinence;[77] however, executive functioning, processing speed, visuospatial, and verbal skills appear more resistant to recovery,[78] and spatial processing deficits may persist for years.[79] Younger adults tend to recover more quickly and completely than older adults (i.e., over age 50).[80] As mentioned previously, preliminary evidence suggested that adolescent heavy drinkers showed greater response to alcohol cues,[54] more emotional reactivity and poorer distress tolerance,[81] and poorer visuospatial performance compared with adults.[82] These effects remitted after a month of abstinence, indicating that some deficits are linked to alcohol intake and may be transitory. However, executive dysfunction[81] and negative mood states[83] did not remit within 4 weeks of abstinence, suggesting that these differences may have predated the onset of heavy drinking or may take more time to recover. As reported by Infante et al., cortical gray matter volume decreases were greater in proximity to reported drinking episodes in a dose-response manner, suggesting a causal effect and raising the possibility that normal growth trajectories may recover with alcohol abstinence.[40] However, other studies have suggested that impaired visuospatial functioning following adolescent AUD persisted even after reduced levels of use.[84]

Where Do the Data Lead Next?

Longitudinal studies with large, diverse, representative samples of youth and a range of detailed measures are key to helping understand the behaviors that convey disadvantages to adolescent and young adult development and outcomes. To date, a handful of large-scale multisite studies are being conducted to

gain insight into the consequences of adolescents transitioning into and out of substance use. These include the largest long-term study of brain development in the United States, the Adolescent Brain Cognitive Development (ABCD) Study, which is currently underway; NCANDA; the IMAGEN study in Europe; the Pediatric Imaging, Neurocognition, and Genetics (PING) study; and the Lifespan Human Connectome Project (HCP) study. NCANDA has already been able to confirm impressions from prior smaller studies that adolescent heavy drinking appears linked to accelerated gray matter decline,[40] disrupted functional connectivity,[30] and reduced cognitive performance. Determining the degree to which these effects remit or persist with alcohol abstinence or reduced use will be a key next step in this line of work.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Fetal Alcohol Spectrum Disorders: Awareness to Insight in Just 50 Years

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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Charness' presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: fetal alcohol syndrome; fetal alcohol spectrum disorders; alcohol; brain development; craniofacial dysmorphology

The establishment of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in 1971 was bracketed by three seminal papers that laid the groundwork for the field of fetal alcohol spectrum disorders (FASD) research. In 1968, Lemoine et al.[1] described children with birth defects and neurodevelopmental disorders associated with prenatal alcohol exposure (PAE). This French-language report was not widely appreciated until after the publication in 1973 of two landmark papers in *The Lancet*,[2,3] providing the first English-language description of fetal alcohol syndrome (FAS). The subsequent recognition of the high global prevalence of FASD and FAS highlighted a paradox. If alcohol and PAE have been ubiquitous since antiquity, why was FASD not recognized sooner?

Indeed, there were hints dating back to biblical times that PAE was harmful to the developing fetus (reviewed by Jones and Smith[2] and by Warren[4]). The London gin epidemic from 1690 to 1752 led to a petition by the London College of Physicians to the House of Commons to reimpose a tax on spirits, noting "Spirituous Liquors…[are] too often the cause of weak, feeble, and distempered children who must be instead of an advantage and strength a charge to their country."[4] Their petition implicated distilled spirits, rather than alcohol, per se, and did not impugn beer. Human and animal studies from the early 20th century suggested that PAE adversely affected pregnancy outcomes; however, when NIAAA was first established, the prevailing view was that alcohol was not harmful to the developing fetus, and high-dose, intravenous alcohol continued to be administered to some pregnant women to prevent premature labor. Thus, one of NIAAA's seminal accomplishments was the nurturing of FASD research and the deployment of research findings to alert clinicians, legislators, and the public to the dangers of PAE.

This brief review focuses on selected discoveries of the last half century on the effects of PAE, highlighting the work of NIAAA-funded researchers as well as the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), a research consortium funded by NIAAA from 2003 until the present, for which Dr. Ed Riley has served as principal investigator and the author of this review has served as scientific director. Readers are referred to more comprehensive reviews of FASD for additional information.[5,6]

Fetal Alcohol Syndrome

The major functional disabilities associated with PAE are due to lifelong cognitive and behavioral impairment.[5] Alcohol affects brain development throughout pregnancy, yet the neuropathology is often microscopic and not evident on clinical imaging. What made FAS recognizable to early investigators was not a specific neurodevelopmental syndrome, but rather the associated constellation of prenatal and postnatal growth retardation, small head circumference (microcephaly), and facial and nonfacial dysmorphology in infants or children with PAE.[2,3] Microcephaly and prenatal and postnatal growth retardation are found in numerous neurodevelopmental disorders. However, alcohol exposure during one of the earliest embryonic developmental stages (i.e., gastrulation) induces relatively specific facial dysmorphology that serves as a visible marker for the underlying brain and neurodevelopmental abnormalities that cause functional impairment. This specific facial dysmorphology provided the long-missing link between PAE, abnormal brain development, and neurodevelopmental abnormalities. It is the frequent absence of this specific facial dysmorphology and the difficulty of obtaining a history of PAE that have challenged clinicians and investigators in fully characterizing the neurodevelopmental outcomes associated with alcohol exposure at other stages of gestation.

Diagnosis of FAS and FASD

There is no biological marker or gold standard that identifies a child with FASD. Consequently, as research on FASD progressed over the past half century, diagnostic criteria for FASD, including FAS, evolved and diverged, both within the United States and in other countries.[5,7-10]

All diagnostic systems for FAS require either two or three of three cardinal facial features: short palpebral fissures; smooth nasal philtrum; and thin upper lip vermilion. All diagnostic systems also require structural and/or functional abnormalities of the central nervous system. Prenatal and postnatal growth retardation, although predictive of adverse neurodevelopmental outcomes,[11] are not universally required for diagnosis. FAS may be diagnosed in the absence of a history of PAE, given the relative specificity of the cardinal facial features, particularly after ruling out phenocopies of FAS, including genetic conditions and other teratogenic exposures (see Table 4 in Hoyme et al. [2016][7]).

Absent a gold standard, no diagnostic system can be considered superior, and agreement among diagnostic systems within a single cohort is modest.[8,9] Clearly, clinical care and research on FASD would benefit from the harmonization of these various diagnostic and classification systems. Below is a more detailed description of one representative diagnostic framework, which was developed by the Collaboration on Fetal Alcohol Spectrum Disorders Prevalence (CoFASP), a study funded by NIAAA to investigate the epidemiology of FASD across the United States.[7] According to CoFASP, the umbrella term FASD encompasses any one of four conditions: FAS, partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) (see Table 1).[7]

Table 1. Diagnostic Criteria for Four Conditions Within the FASD Spectrum According to CoFASP.[5]

Diagnostic Criterium	FAS		Partial FAS		ARND	ARBD
Confirmed Prenatal Alcohol Exposure[a]	Yes	No	Yes	No	Yes	Yes
Facial Dysmorphology[b]	Required	Required	Required	Required	Not required	N/A
Growth Deficiency[c]	Required	Required	Not required	Required if brain abnormality is not present	Not required	N/A
Brain Abnormality[d]	Required	Required	Not required	Required if growth deficiency is not present	Not required	N/A
Cognitive or Behavioral Impairment[e]	Required	Required	Required	Required	Required*	N/A
Other Systemic Malformation	Not required	Not required	Not required	Not required	Not required	Required

[a] Defined as ≥ 6 drinks/week for 2 weeks or ≥ 3 drinks on ≥ 2 occasions; documentation of maternal intoxication in records; positive biomarker for alcohol; or evidence of risky maternal drinking on a validated screening tool.

[b] Defined as ≥ 2 of the following: short palpebral fissures, thin vermilion border, and smooth philtrum.

[c] Defined as height and/or weight ≤ 10th centile based on racially/ethnically normed charts.

[d] Defined as head circumference ≤ 10th centile, structural brain anomaly, or recurrent nonfebrile seizures.

[e] Cognitive impairment is defined as global cognitive impairment, verbal or spatial IQ, or individual neurocognitive domain ≥ 1.5 SD below mean. Behavioral impairment is defined as impairment of self-regulation ≥ 1.5 SD below mean. For children under age 3, developmental delay is required.

* ARND requires two behavioral or cognitive deficits if IQ is not ≥ 1.5 SD below the mean.

Note: ARBD, alcohol-related birth defects; ARND, alcohol-related neurodevelopmental disorder; FAS, fetal alcohol syndrome; N/A, not applicable.

Source: Adapted with permission from Wozniak et al.[5]

The CoFASP diagnostic criteria for FAS require abnormalities in four clinical domains: craniofacial anomalies; growth retardation; abnormal brain structure or function; and neurobehavioral impairment.[7] Short palpebral fissures are identified when direct measures are in the 10th centile or below. Smooth philtrum and thin vermilion border are identified by comparing facial features to racially normed lip/philtrum charts. Only two of the three cardinal craniofacial anomalies need be present for an FAS diagnosis. Prenatal and/or postnatal growth deficiency is defined as height and/or weight in the 10th centile or below. Abnormal brain structure or function may include head circumference in the 10th centile or below, structural brain abnormalities, or recurrent nonfebrile seizures.

In the CoFASP framework, neurobehavioral impairment is measured using standardized tests and may include cognitive deficits, such as low full-scale IQ, as well as impairment of executive functioning, learning, memory, visuospatial perception, or behavior, including self-regulation, attention, and impulse control. Most of these impairments are defined based on scores of at least 1.5 standard deviation (SD) below the mean. For children younger than age 3, the criterion for neurobehavioral impairment is met if there is developmental delay of at least 1.5 SD below the mean.[7] Other diagnostic systems set different thresholds for dysmorphology and neurobehavioral impairment. For example, a framework included in the most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)[12] as a condition for further study focuses on three domains of impairment (i.e., neurocognitive, self-regulation, and adaptive function).[13] Mattson and colleagues provide a detailed description of neurobehavioral impairment in FASD.[14]

According to the CoFASP framework, with documented PAE, a diagnosis of PFAS is made when there is cardinal facial dysmorphology and neurobehavioral impairment but no growth retardation and no abnormal brain structure or function; absent evidence of PAE, the diagnosis of PFAS additionally requires growth deficiency or deficient brain growth.[7] ARND is diagnosed when there is neurobehavioral impairment and a history of PAE but no cardinal facial

dysmorphology.[7] Although many children with FASD have a constellation of dysmorphic features affecting the face, limbs, and internal organs, PAE in rare cases causes major malformations without neurobehavioral impairment, structural brain abnormalities, or growth retardation. This condition is referred to as ARBD.[7]

The definition of PAE assumes great importance in clinical diagnosis and research but differs among the different diagnostic systems. CoFASP defines PAE based on one of the followed criteria for maternal alcohol consumption: six or more drinks per week for two or more weeks during pregnancy; three or more drinks on at least two occasions; alcohol-related social or legal problems around the time of pregnancy; documented intoxication during pregnancy; positive testing for biomarkers associated with alcohol exposure; or a positive screen using a validated tool for alcohol use.[7]

Alcohol Is a Teratogen

Many children diagnosed with FASD have been exposed to other drugs, such as nicotine, cannabinoids, opioids, or stimulants; have nutritional deficiency; are raised in chaotic households; and experience numerous adverse childhood events. Separately, each of these insults may cause neurobehavioral impairment. Therefore, not surprisingly, there was initial reluctance to accept that alcohol causes birth defects (i.e., is a teratogen).

Animal models can control for many of these confounding variables and provided the first strong evidence that alcohol was indeed teratogenic. Sulik and colleagues showed that a single alcohol exposure during gastrulation in mice caused microcephaly, growth retardation, and the cardinal facial features of FAS in the absence of nutritional deficiency or other teratogens.[15] This discovery drew a direct connection between alcohol and the constellation of developmental abnormalities described less than a decade earlier in humans with FAS. It allowed the conclusion that alcohol toxicity causes FAS, even though concurrent teratogenic exposures, genetic polymorphisms, nutritional deficiency, and stressors may further impact craniofacial and brain development. Because gastrulation occurs during the third week of human gestation, when many women are unaware of their pregnancies, this seminal work also underscored the potential for binge drinking to cause FAS prior to pregnancy recognition.

Later work from the same laboratory highlighted both the relative specificity and insensitivity of the cardinal facial dysmorphology of FAS as a marker of PAE.[16,17] Whereas alcohol exposure in mice on gestational day 7 (corresponding to gastrulation) reproduced the cardinal facial dysmorphology of FAS, exposure on gestational day 8.5 (corresponding to neurulation) produced different facial anomalies more characteristic of DiGeorge syndrome or retinoic acid embryopathy. Indeed, retinoic acid exposure and alcohol exposure during gastrulation in mice caused similar malformations. Although alcohol and retinoic acid are chemically unrelated, their common potentiation of programmed cell death in selected embryonic cell populations induced similar, stage-dependent, developmental outcomes.[18,19]

These animal studies demonstrated that the presence and pattern of craniofacial malformations were dependent on the timing of teratogen exposure. The cardinal facial dysmorphology that was first and irrevocably associated with FAS proved to be a happenstance of alcohol exposure during gastrulation. These discoveries contributed to the recognition that, at least in some people, neurobehavioral impairment due to PAE could occur in the absence of cardinal facial dysmorphology or any facial dysmorphology at all, as is the case in people with ARND.

The Face Is a Window to the Brain

The first descriptions of FAS identified a variety of craniofacial abnormalities in addition to the cardinal features of short palpebral fissures, smooth nasal philtrum, and thin upper lip vermilion. Some of these malformations, such as maxillary hypoplasia, ptosis, and retrognathia, occur in a host of developmental disorders and are readily recognized by geneticists, dysmorphologists, and developmental pediatricians. Therefore, a major quest for the field has been the discovery of other patterns of facial or nonfacial dysmorphology that might also link neurobehavioral impairment to PAE, even in the absence of a history of PAE.

An equally important goal has been to simplify or automate the detection of any defining facial dysmorphology to facilitate diagnosis for the many patients that lack access to highly specialized clinicians. Astley used computer analysis of two-dimensional facial photographs to evaluate the diagnostic features defined by the FASD 4-Digit Diagnostic Code,[20] whereas CIFASD and other investigators employed automated analysis of three-dimensional (3D) facial images. Suttie and colleagues used dense surface modeling to study facial dysmorphology in 3D images of children from the CIFASD cohort.[21] This method allowed them to quantitate facial shape and to sort facial images based on the degree to which they resembled those of children with FAS or controls. This analysis differentiated children with PAE whose faces did not clearly show the characteristic features (i.e., those who had nonsyndromal faces) from children without PAE with greater than 90% specificity. Importantly, children with PAE who had nonsyndromal facial features also had significantly lower IQ and learning ability than children whose faces more closely resembled controls. Using dense surface modeling,

Muggli and colleagues demonstrated that even mild PAE could affect facial shape.[22]

Technology has evolved to enable the acquisition of 3D images on smartphones, and contour analysis can be automated in the Cloud. Hence, it may be possible to automate the analysis of facial dysmorphology and facilitate the diagnosis of FASD wherever access to internet-connected smartphones is available.

Epidemiology of FASD

FASD is the most common preventable cause of intellectual disability.[23] Using active case ascertainment, CoFASP investigators estimated the prevalence of FASD among first-grade students to be 1% to 5% across four regions of the United States.[24] These conservative estimates of FASD prevalence equal or exceed those for autism spectrum disorder. Among 222 cases identified as FASD within this cohort, 12% were classified as FAS, 47% as PFAS, and 41% as ARND. However, only two of the 222 children (1%) had previously been diagnosed with FASD, highlighting the extent to which FASD is underrecognized or misdiagnosed.[25]

Estimates of FASD prevalence vary across studies, in part because of differences in study methodology and classification definitions. One meta-analysis estimated the global prevalence of FAS at 0.15% and FASD at 0.77%.[26] Prevalence estimates also vary across different countries due to cultural differences in drinking. One of the highest estimates of FASD prevalence has been 14% to 21% in the wine-growing region of the Western Cape Province of South Africa, where weekend binge drinking has been common.[27]

High rates of binge drinking during the childbearing years are an important contributor to the high prevalence of FASD in the United States. Approximately 25% of Americans ages 18 to 44 binge drink, 45% of pregnancies are unintended, and gastrulation often occurs before a woman is aware of her pregnancy.[28,29] Among pregnant women, the prevalence of any alcohol use (10%) and binge drinking (3%) within the past 30 days is also high. The combination of binge drinking and sex without contraception greatly increases the risk of an alcohol-exposed pregnancy.

Whereas binge drinking is a widely accepted risk for FASD, there is less certainty regarding the risk associated with low or moderate levels of alcohol consumption during pregnancy, stemming in part from the inherent challenge of proving safety as opposed to harm. Both human and animal studies have failed to establish a threshold for safe drinking during pregnancy.[30] For example, in cell culture experiments, alcohol concentrations corresponding to those achieved in the blood and fetus after just one drink inhibit cell adhesion mediated by the developmentally critical L1 neural cell adhesion molecule.[31] In humans, intake of less than five to six standard U.S. drinks per week is associated with craniofacial dysmorphology and neurobehavioral impairment.[22,30,32] Research funded by NIAAA has played a major role in informing the advisories from the U.S. Surgeon General that women who are pregnant or trying to conceive should not consume alcoholic beverages.[4]

The Neurodevelopmental Effects of PAE

Early autopsy studies in infants and children with FAS revealed major brain malformations.[33] Among these were microcephaly, agenesis or hypoplasia of the corpus callosum, ventricular enlargement, dysplasia of the anterior lobes of the cerebellum, and neuronoglial heterotopias—findings consistent with major disruption of neurogenesis, neural cell migration, and the premature triggering of programmed cell death. These gross neuropathological abnormalities are not observed in most children with FASD but highlight the mechanisms underlying similar, but milder, abnormalities in grey matter thickness, microstructural white matter abnormalities, decreased brain volume, and neuronal and glial migration defects.[5] Prenatal alcohol exposure also alters the trajectory of grey matter development during childhood.[34] In some studies, facial abnormalities correlated with volume reductions in specific brain regions, reinforcing the concept that face and brain dysmorphology arise concurrently and that the face is a window to the brain.[17,35,36] Clinical imaging in children with FASD is frequently normal, reflecting the microscopic nature of brain developmental abnormalities that underlie typical neurobehavioral impairments related to PAE. Overall, studies found that neurodevelopmental outcomes are related to the quantity, frequency, and timing of alcohol exposure as well as to maternal age, nutritional status, socioeconomic status, and genetic background of both mother and fetus.[5]

Animal studies have shown that alcohol disrupts brain development through a variety of mechanisms. Alcohol causes oxidative injury and programmed cell death in neural crest cells destined to form craniofacial and brain structures.[15,18,37] Alcohol is metabolized to acetaldehyde, a toxic molecule that chemically modifies and damages DNA and cells.[38] Alcohol also produces enduring epigenetic changes[39] that alter DNA transcription and diverse signaling pathways involved in brain development. Moreover, alcohol impairs neurogenesis and diverts differentiation of neural stem cells from neural to nonneural lineages, contributing to brain volume reductions.[38] Early research further identified similarities between FAS and milder phenotypes of syndromes associated with holoprosencephaly,[40] a disorder that affects midline craniofacial and brain

development and is sometimes associated with mutations in the Sonic hedgehog (Shh) gene. Alcohol similarly disrupts the Shh signaling pathway,[41,42] thereby altering the function of primary cilia[43]—cellular organelles that are critical for development.

Alcohol also may disrupt neuronal cell migration and synaptic connections through its interactions with the L1 protein, a developmentally critical neural cell adhesion molecule that guides neuronal cell migration and axon pathfinding. Alcohol inhibits L1-mediated cell adhesion at half maximal concentrations achieved after just one drink.[31] Alcohol blocks L1 adhesion by binding to specific amino acids that regulate the interaction of L1 molecules located on adjacent cells.[44] The nanopeptide NAPVSIPQ potently antagonizes alcohol inhibition of L1 adhesion and prevents alcohol teratogenesis in mouse embryos.[45]

Finally, genetic factors also may influence the development of FAS and alcohol's effects on neurodevelopment. Concordance for FAS is higher in monozygotic than dizygotic twins,[46] and diverse genes have been identified that modulate the effects of alcohol on craniofacial and brain development.[47,48]

Biomarkers of Alcohol Exposure and Adverse Outcome Risk

In many cases, information on an infant's history of PAE is unavailable or unreliable, hampering the clinical diagnosis of FASD and related research. Analyses of early markers of alcohol exposure, such as fatty acid ethyl esters in meconium, can provide relatively sensitive and specific confirmation of PAE in the last two trimesters of pregnancy[49] but are not routinely performed in clinical practice. More recent research from CIFASD has raised hopes that biomarkers of exposure and risk for adverse outcomes may be obtained during the second trimester to identify infants and children requiring early intervention. For example, maternal blood samples from the second trimester of pregnancy showed increased methylation of pro-opiomelanocortin and period 2 genes,[50] unique cytokine signatures,[51] and a unique profile of micro RNAs linked to alcohol exposure and neurodevelopmental delay.[52] Infant plasma micro RNAs also predicted PAE-associated growth restriction and cognitive development.[53]

Some of these biomarkers also may be mediators of biological effects of PAE. Decreased expression of pro-opiomelanocortin was associated with increased levels of cortisol in children with PAE, consistent with disinhibition of the hypothalamic pituitary stress axis.[50] The identified micro RNAs were shown to collectively modulate placental growth and development,[54] and proinflammatory cytokines may predispose to autoimmune and inflammatory conditions later in life.[55,56]

FASD Across the Lifespan

The effects of PAE on morphology and neurobehavior and health are lifelong.[5] As children with FASD mature into adulthood, the cardinal facial dysmorphology may become less pronounced, making diagnosis in adulthood more difficult.[57] More challenging still is the diagnosis of FASD in adults with neurobehavioral disorders who lack both cardinal facial dysmorphology and a history of PAE. The high prevalence of FASD makes it likely that many such individuals are followed in adult medical practices without ever being diagnosed.

A growing area of FASD research concerns the developmental origins of health and disease associated with PAE.[58] Premature death and increased prevalence of metabolic, immune, and cardiovascular disorders have been reported in informal surveys of adults with FASD[56] as well as in epidemiological studies.[55,59] For example, studies in human cohorts and zebrafish indicate that PAE induces elements of metabolic syndrome in adults by modifying developmental programs for hepatic and adipose tissue embryogenesis.[60] Further research will be important to delineate the full range of human diseases associated with PAE to allow for earlier detection and intervention.

The Next 50 Years

What should we hope for from the next 50 years of NIAAA-funded research on FASD? There will never be enough specialized clinics to diagnose and treat the large numbers of children and adults with FASD. Recent advances in remote diagnosis of facial dysmorphology and in neurobehavioral assessment[61] hold promise for broader access to automated, cloud-based screening and diagnostic tools. The identification of more specific markers of PAE and adverse developmental outcomes will greatly aid diagnosis. Treatment is similarly limited by the high prevalence of FASD in relation to the availability of skilled therapists. The refinement of early interventions and their translation to accessible online platforms will be necessary to fully address the public health burden of FASD. App-based approaches show early promise but still require considerable development and refinement.[62] Studies on the postnatal administration of choline to mitigate the neurodevelopmental effects of PAE also have been encouraging.[63-65] Finally, the high prevalence of FASD will most readily be reduced by continued progress in one of NIAAA's primary missions—the development of effective strategies to prevent and treat alcohol use disorder and the patterns of drinking that engender PAE. Equally important will be the reduction in stigma associated with these disorders, so that effective strategies are embraced by those at risk or affected.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Age, Period, and Cohort Effects in Alcohol Use in the United States in the 20th and 21st Centuries

Implications for the Coming Decades

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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Keyes' presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; age-period-cohort; cohort effects; gender; socioeconomic status

Alcohol consumption, including any alcohol use; patterns of high-risk use, including binge drinking; and alcohol use disorder (AUD) incidence and prevalence, differs substantially over time and by life stage. Variation also occurs across demographic groups, and such differences themselves vary across time and place. In the first quarter of the 21st century, changes in incidence and prevalence of alcohol use and alcohol-related health consequences have been accelerating. Understanding the magnitude and direction of these changes informs hypotheses regarding the reasons underlying alcohol consumption changes across time and development, including both long-term historical changes as well as abrupt shifts. It also permits determining the optimal focus of research and targets of services. Such surveillance is informed by science and statistical considerations of variation by age, period, and cohort effects.

Age-, period-, and cohort-effect estimation has proved to be an extraordinarily useful framework for organizing and interpreting data, uncovering patterns, and identifying causes of trends in incidence and prevalence of many health conditions and mortality over time. This article provides an overview of the conceptual basis of such effects as related to alcohol consumption, and reviews recent studies of age-period-cohort variation, especially regarding gender, social class, and specific beverage and drinking patterns.

Age, Period, and Cohort Effects and Their Importance

Age Effects

Age effects refer to the effects of a person's age on their health. They may be caused by the accumulation of exposure or social experiences; critical and sensitive developmental windows; or immunological periods of vulnerability, such as infancy and end of life. Extensive evidence documents that alcohol use is most likely to begin during adolescence or young adulthood, peak during the transition to adulthood, and generally decrease thereafter.[1,2] However, these age patterns are not static; in the United States, for example, the onset and peak of alcohol use has been shifting in recent decades to a later point in development.[3] Because onset and persistence of alcohol use are in part social phenomena and are amenable to policy interventions (e.g., changes in minimum legal drinking age laws),[4] the specific structure and magnitude of age effects are historically variable. However, the general patterns of onset early in adult maturation, and desistence during adulthood, have been largely stable over historical time.

Period Effects

Period effects refer to changes in outcome that affect all individuals alive in a particular period—that is, a year or set of years. Reasons for period effects include changing environmental or social factors that affect incidence and persistence of certain behaviors or disorders, policy or law changes, or other environmental conditions that affect health. For alcohol use, numerous factors have been associated with substantial changes in consumption patterns, including major policy initiatives to restrict access to alcohol, such as U.S. Prohibition from 1920 to 1933, and broad economic factors, such as booms and recessions that affect spending on nonessential goods. The general social climate for heavy drinking has also changed over time as advocacy movements placed the dangers of heavy consumption into stark focus, followed by policies to increase criminal sanctions on impaired driving.[5] However, as detailed below, such policy changes are not simply period effects because they often impact age groups differently; therefore, their effects may manifest as cohort effects.

Cohort Effects

Against the backdrop of age and period effects, cohort effects have also proven to be powerfully predictive of a range of health behavior, including alcohol use. Cohort effects can perhaps be most efficiently conceptualized as age-by-period interactions.[6] For example, a cohort effect would be apparent if historical change across time in a health behavior such as alcohol consumption resulted in increasing overall prevalence (i.e., a period effect), but the increase in prevalence is faster or slower for people in different age groups (i.e., an age by period interaction). Cohort effects can also be conceptualized as a unique rate of an outcome for individuals depending on birth year.[7]

Before reviewing the current literature on cohort effects in alcohol use, it is important to understand that cohort effects are powerfully predictive of many health outcomes, and critical to consider when evaluating trends. There are numerous historical examples of particular birth cohorts with increased rates of disease outcomes and mortality in the United States, including all-cause mortality,[8,9] tuberculosis,[10] peptic ulcer,[11] lung cancer,[12] and other diseases. More recently, the strong influence of generational cohort effects is apparent in the leading U.S. contributors to premature mortality, including obesity, hepatitis C, drug overdose, and suicide.[13–16] Similarly, numerous studies in recent decades have found that alcohol use and health outcomes related to heavy consumption cluster by birth cohort, as well as have exhibited age and period effects at various points in history. Cohort effects have long been documented in substance use,[17,18] including alcohol use and alcohol-related harms,[19] as described in more detail below.

Recent Alcohol Use Time Trends in the United States

Time trends in alcohol use and alcohol-related harms have been dynamic in the United States, especially over the last 2 decades. Among adolescents, the prevalence of alcohol use has declined. Data from two major nationally representative surveys—Monitoring the Future and the National Survey on Drug Use and Health—converge in demonstrating these reductions. Although the specific prevalence of any alcohol use and binge drinking differs between the two surveys, both document substantial, sustained reductions in adolescent drinking over the last 20 years.[20,21] The most recently published data from the Monitoring the Future Study, depicted in Figure 1, show the trend in past 2-week binge drinking among 12th grade adolescents through 2019; as the figure shows, binge drinking declined from a peak in approximately 1982 to less than 20% for both boys and girls in 2019.[22]

In contrast, adult alcohol use and binge drinking has been increasing. A meta-analysis of six national surveys of alcohol use found (Figure 2) that from 2000 to 2016, the overall prevalence of binge drinking increased approximately 7.5% per decade across the 2 decades analyzed.[23] Importantly, however, these increases were primarily concentrated among women, as discussed further below.

The observation that changes over time in alcohol consumption differed by age immediately raises the possibility of cohort effects. Indeed, many studies using different data sources and analytical approaches have documented cohort effects for numerous alcohol-related outcomes. Generally, post-World War II U.S. birth cohorts had higher rates of consumption than earlier cohorts,[19,24,25] driving much of the increase in consumption in the 1970s and 1980s. For many of these studies, however, reliance on retrospective recall is a common limitation. Avoiding this limitation, Kerr et al.[24,26] used the National Alcohol Surveys, which reports current consumption patterns that are less subject to recall issues. These analyses documented that several birth cohorts had higher risks of alcohol consumption and binge drinking throughout the life course, especially men born in the late 1970s and women born in the early 1980s. In contrast, among cohorts born in the 1990s and later, alcohol use has consistently been declining during adolescence and early adulthood. However, those same cohorts have exhibited accelerating drinking after transition to adulthood.[27]

In sum, the cohorts of today's adults who are now in their 30s and 40s were part of the historical shift toward declining alcohol consumption in adolescence. This decline is explained in part by shifts in the minimum legal drinking age across states, especially in the 1980s,[27] yet declines continued thereafter, potentially aided by focused prevention efforts on reducing underage drinking. However, because drinking then accelerated during the transition to adulthood, adult rates of drinking did not benefit from these prevention efforts. Indeed, Patrick et al. (2019) have documented an overarching historical shift in the age effect on binge drinking among recently born cohorts; thus, the peak age of binge drinking in 1996 to 2004 was 2 years later than it was in 1976 to 1985.[3]

In addition to these overall age, period, and cohort effects, additional variation across other levels of dynamic change have implications for prevention, policy, and causal etiology assessments. Three areas of variation that have received substantial attention are gender, socioeconomic status, and beverage type.

Effects of Gender

Men consume more alcohol and are more likely to have AUD compared with women,[1] but the gender gap has been closing for decades in the United States and elsewhere.[19,25] However, the manner in which the gender gap is closing differs by birth cohort. Among today's birth cohorts of adolescents (i.e., those born in and around the same year), the gender gap is closing because for more than 30 years, alcohol consumption and binge drinking have declined among both boys and girls, but the decline is faster for boys than girls (see Figure 1).[28] Conversely, in adults, alcohol consumption and binge drinking have increased, especially in the past 10 years, and those increases have been greater for women than for men (see Figure 2).[23] The recent increases in drinking among women reflect the high-risk cohorts identified by Kerr et al.[26] as they age into middle-adulthood. Interestingly, compared to earlier generations, these cohorts of women progressed through adolescence with lower alcohol use and binge drinking, yet had a faster acceleration of their drinking during the transition to adulthood, resulting in high levels of alcohol use and strong cohort effects in adulthood.[27]

Additional analyses have indicated that the increases in alcohol consumption and binge drinking among women in midlife are concentrated among those with high levels of education,[29] occupational prestige,[30] and income,[29] suggesting that traditional gender norms sanctioning alcohol consumption are shifting among women now occupying traditionally male statuses and spaces. The human costs of these increases in consumption are reflected in alcohol-related mortality rates. These rates have doubled between 1999 and 2016,[31] with the largest increases observed among women and adults emerging into midlife, consistent with alcohol consumption trends.

Effects of Socioeconomic Status

Historically, the role of socioeconomic status has been a critical axis for examining trends over time in alcohol consumption, as exemplified by the higher consumption rates in adult women, who are increasingly occupying high socioeconomic positions. Overall, individuals with a higher socioeconomic status are less likely to fully abstain from alcohol compared to those with a

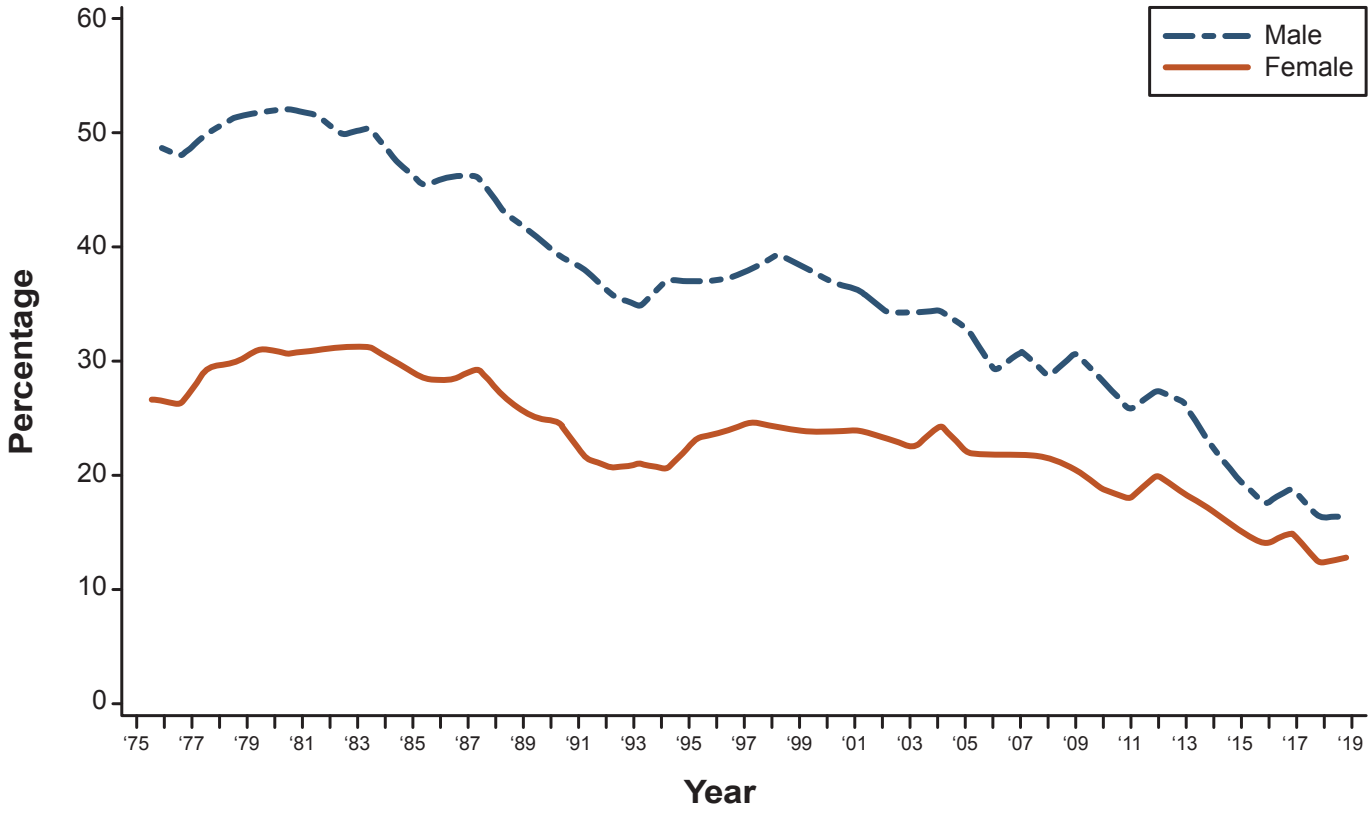

Figure 1. Trends in 2-week prevalence of binge drinking (≥ 5 or more drinks in about 2 hours), by gender. *Source:* Adapted with permission from Johnston et al. (2019).[22]

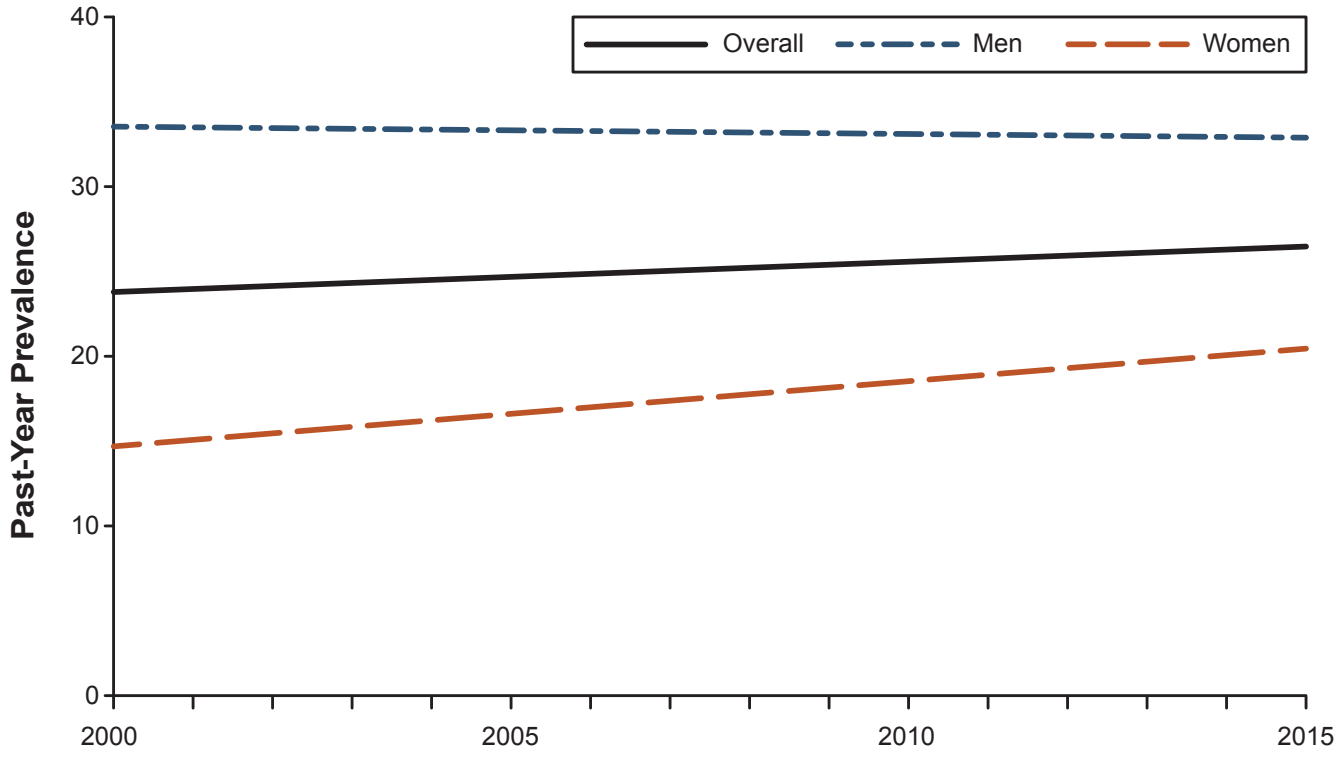

Figure 2. Simulated trend lines for past-year binge drinking prevalence overall and by gender. Results are based on trend estimates from meta-analysis and use of 2002 NSDUH data to establish baseline prevalence. *Source:* Adapted with permission from Grucza et al.[23]

lower status.[32] The relationship between socioeconomic status and binge drinking or AUD, however, is more mixed and depends on the socioeconomic indicator, population, and time period analyzed.[33–35] Further, population distributions of socioeconomic status are an outcome of economic conditions (i.e., income and wealth are functions of times of economic expansions and recessions); therefore, trends in socioeconomic status, and who achieves and maintains high status positions, are important potential drivers of population trends.

Renewed attention to theories of the relationship between social class and health has been prompted by evidence that recent increases in U.S. mortality, including alcohol-related and other substance-related mortality, are concentrated among men with less than a high school education.[36] However, these findings run counter to available data on heavy drinking birth cohorts. The birth cohorts identified by Case and Deaton[36] are different than the birth cohorts emerging into adulthood in the 1970s and 1980s or those of college age in 2002 to 2012, suggesting that the dynamics of alcohol-related harm are likely to substantially change in the decades to come. Indeed, National Alcohol Survey data show that cohort trends in U.S. alcohol consumption are primarily driven by changes in education.[37] As more recent cohorts have entered college at higher rates, drinking and binge drinking have become concentrated in these college-attending young adults. The alcohol consumption cohort effect of those born in the late 1970s and early 1980s is attributable largely to their high rates of college attendance. Conversely, however, there may be signs of emerging socioeconomic differences when considered across gender (more on gendered trends in alcohol consumption below). For example, from 2002 to 2012, binge drinking was largely stable among college-attending young adults, but slightly increased among non-college enrolled women (from 29% to 33%) while decreasing among non-college-enrolled men.[38] Continued surveillance of the role of socioeconomic status within trends in alcohol consumption, and beyond education into other indicators, is warranted.

Effects of Beverage Type

Another important area for research is variation in alcohol consumption dynamics by type of alcoholic beverage. Although all alcoholic beverages are carcinogenic, beverage types vary in ethanol concentration and potential for harm, as well as in their prevalence and popularity across demographic groups. A growing literature indicates that the types of alcoholic beverages that individuals in the United States are consuming are dynamic and may depend on cohort. Kerr et al. (2004)[39] found that pre-1940s cohorts preferred spirits throughout the life course compared with later cohorts. In contrast, cohorts born in the 1940s through 1970s, especially men, tended to prefer beer, and wine has been gaining dominance in beverage preferences among younger cohorts. These changes may be related at least in part to marketing and sales efforts by the alcohol industry to increase profits. For example, the increase in wine consumption, which has been observed in alcohol sales surveillance,[40] is commensurate with the increases in income and education in the United States, as wine is marketed as a prestige product and is often sold at high price points. Additional analyses have found that the alcohol content of beverages is increasing in the United States,[41,42] portending potential further harm and greater rates of AUD.

The dynamics of cohort effects on beverage preferences are particularly salient for the role of alcohol policy and reduction of alcohol-related harms. Sales restrictions and alcohol taxes have a substantial, demonstrable overall impact on population-level consumption and alcohol-related harms,[43] although this varies to some extent by age of consumer, level of consumption, and beverage type.[44] For example, tax variations by beverage type can influence trends in the consumption of particular beverages. Spirit and wine consumption is typically most sensitive to price and tax policy changes,[45] and although consumption of spirits has been increasing in the United States in recent years, there has been little change in tax and price regulations. This suggests that one driver of the increase in spirits consumption is that they are becoming effectively less expensive over time. Beer and wine are also regulated differently in many states; thus, changing dynamics in the popularity of each beverage have implications for how effective beverage-specific alcohol taxes are in reducing sales and, consequently, harm. Regulations related to alcohol sales and consumption that can respond to market changes in beverage preferences (e.g., increased taxes on wine and spirits that reflect their growing share of the alcohol market) may be an important lever for promoting public health in the coming decades.

Differences in Drinking Patterns Among Cohorts

Taken together, the literature on age, period, and cohort effects in alcohol research indicates that different cohorts have different drinking patterns and that socioeconomic and demographic factors are critical to contextualizing the observed trends. Although it is possible to document time and cohort trends with the available data, understanding why alcohol consumption patterns are changing is more challenging.

Certainly, alcohol policies play a fundamental role in determining population-level patterns of consumption, and the way that policies target particular demographic groups (intentionally or unintentionally) creates opportunities for cohort effects to emerge. For example, the adoption of a minimum legal drinking age of 21 across states throughout the 1980s mediates a portion of the decline in alcohol consumption among U.S. adolescents since then.[27] However, consumption

has continued to decline for decades after the increase in drinking age, suggesting that additional factors, such as the public health investment in underage drinking prevention, provided further benefits. Numerous other policies have shifted and impacted population-level alcohol consumption since the U.S. Prohibition, including restrictions on where and when alcohol can be sold, state monopolies on sales, criminal penalties for hazardous use, and others.[46,47] These policies likely have affected different age groups in different ways, depending on their developmental stage when exposed to newly restrictive or permissive alcohol policies.

Of course, alcohol policies are not the only determinant of alcohol consumption and, consequently, of age, period, and cohort effects. Substantial research has evaluated the impact of social norms and social roles, as well as community and societal norms and values on changes in alcohol use over time.[48,49] Social values have an inherent role in the use of alcohol, and the acceptability of drinking and drunkenness within and across social groups at different times and different life stages is potentially a powerful factor influencing population-level consumption. For example, heavy consumption on college campuses, especially within social institutions such as Greek life,[50] is often normative and expected, but norms and values around alcohol use swiftly change as young adults encounter the social norms of early adulthood.[51] Moreover, these normative trajectories and patterns become variable as societal roles and values themselves change. For example, religious attendance and the importance of religion have long been a robust predictor of decreased alcohol consumption.[52] However, the centrality of religion to U.S. adolescents and adults has been declining for more than a decade,[53] and this decline explains a portion of the cohort effects in binge drinking among today's adults.[54] Monitoring these and other broader societal changes is critical to determining the influences that mediate shifts in alcohol consumption over time.

For example, the coming years will be critical to determining the effects of health knowledge regarding alcohol-related risks on population consumption. For decades, low levels of alcohol consumption were considered protective, especially for cardiovascular health.[55] The evidence supporting this hypothesis, however, was subject to substantial confounding,[56] and dissemination of the message of alcohol's protective effects was well-funded by the alcohol industry, which had a clear financial incentive.[55] Recently, studies using large administrative databases and quasi-experimental designs, such as Mendelian randomization, have called into question and refuted the idea that a moderate level of alcohol consumption benefits health.[57,58] The extent to which public health messages shift to reflect this change in scientific consensus may be important in reducing population-level alcohol-related harms. These changes may further manifest as cohort effects, as the dissemination and implementation of health information and guidelines are likely to affect age groups differently as they progress through the life course.

Conclusions

Alcohol consumption continues to be a leading contributor to morbidity and mortality, both in the United States and worldwide. Although significant progress in reducing adolescent and young adult alcohol use has been achieved and sustained for decades, it is offset by increases in drinking during the transition to adulthood. The cohorts currently at midlife, especially women, are increasing alcohol consumption and binge drinking at greater levels than other cohorts, portending health consequences that may persist for decades. Understanding the motivations for consumption, destigmatizing the use of services to reduce consumption, and increasing the availability and accessibility of such services are necessary to improve population health. Moreover, age, period, and cohort effect estimations are critical surveillance tools for epidemiology and population health research. Such assessments have already answered critical questions and uncovered patterns in the data that specifically identify high-risk groups requiring prevention and intervention efforts.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

AUD Risk, Diagnoses, and Course in a Prospective Study Across Two Generations: Implications for Prevention

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Acknowledgments
This paper was developed from my tribute to NIAAA that was delivered as a lecture at the NIAAA 50th Anniversary Science Symposium on November 30, 2020. That meeting was personally meaningful to me because my scientific career began with help from NIAAA's precursor at NIH, and the work presented here was supported by NIAAA over the years. Particularly the San Diego Prospective Study would not have been possible without the institute's support, both financially and intellectually, and their dedicated staff. It has been a privilege for me to have received this support as well to have this opportunity to share some aspects of our program of research supported by NIAAA.
I was introduced to research and the importance of alcohol problems as a medical student at Washington University, St. Louis Medical School through mentoring by Eli and Lee Robins, Sam Guze, George Winokur, and Donald Goodwin. During that experience I received additional important mentorship through interactions with Jack Mendelson and Nancy Mello at the NIH. The work described in this article has been supported by NIAAA since the mid-1970s and was enriched by my interactions with institute directors over the years, especially Enoch Gordis, Ting Kai Li, and George Koob. The data were developed through ongoing interactions with my colleague Tom Smith and could not have been produced without his close collaboration. Whatever I have been able to accomplish is a tribute to these mentors and friends and the NIAAA itself.
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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Schuckit's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; genetics; sensitivity; prevention

A large proportion of the population consume alcoholic beverages at some time in their lives. For most people, alcohol consumption is low to moderate and is not associated with harmful physiological, psychological, or social outcomes. However, for a substantial number of individuals, alcohol consumption increases over time; leads to the development of tolerance and alcohol-related life problems; and, ultimately, results in a diagnosis of alcohol use disorder (AUD). The reasons why some people develop harmful drinking behaviors and AUD are complex and still not entirely understood.

One crucial tool for identifying factors that influence alcohol consumption and its consequences are longitudinal studies that follow individuals over long periods of time, sometimes including evaluating family members over several generations. Among the most important alcohol-related longitudinal studies are the San Diego Prospective Study (SDPS), the Collaborative Study on the Genetics of Alcoholism (COGA) and the Avon Longitudinal Study of Parents and Children (ALSPAC), each of which have been supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). This article briefly summarizes some findings from these studies, particularly the SDPS. After reviewing the contribution of genetic and environmental influences in AUD, it will introduce a low level of response (low LR) to alcohol as a risk factor for AUD. The article will then describe the 40-year SDPS in more detail, as well as its main conclusions regarding the contributions of genes and environment on the low LR and AUD, and summarizes an AUD prevention program based on the low LR.

Genetic and Environmental Influences in AUD

The modern era of genetic studies regarding alcohol and other drug-related problems was built upon many years of observations that these problems cluster in families. Thus, children of parents with AUD have a three to four times higher risk of having AUD themselves than children of parents without AUD.[1,2] However, the presence of a familial influence does not by itself demonstrate whether this familial link relates to shared genes, a shared environment, or their combination. Those distinctions were subsequently addressed in part through twin studies demonstrating that twins of people with AUD were at significantly higher risk to have AUD themselves if they were identical twins, who shared 100% of their genes, than if they were fraternal twins, who shared only 50% of their genes. An identical twin of someone with AUD has about a 60% risk of AUD compared to about a 40% risk for fraternal twins. Therefore, even in identical twins, the risk that the second twin also developed AUD was not 100%, indicating the involvement of additional factors.[3-5]

Additional studies examined if the enhanced risk for alcohol problems observed in children of parents with AUD remained even if the offspring had been separated from that parent early in life. In 1972, analyses of half-siblings from AUD families and control families found that adverse alcohol outcomes in offspring related more closely to presence of an AUD in a biological parent than to alcohol problems in a non-biological parent who raised the child.[6] These data were consistent with subsequent larger and better controlled investigations of adoptees in Scandinavia.[2,7] Overall, these studies supported the conclusion that genes and gene-environment interactions explained between 40% and 60% of the AUD risk.[8-10]

The research also indicated that genetic variants (i.e., mutations) that affect AUD risk operate in complex ways that do not fit into either dominant or recessive models of inheritance. Rather, like diabetes and hypertension, AUD can be considered a complex genetically influenced condition to which numerous genes contribute. In other words, AUD reflects the impact of multiple characteristics that do not by themselves cause the problems with alcohol but contribute to overall risk. Subsequently, research identified several genetically influenced characteristics, or intermediate phenotypes, through which genes impacting AUD risk operate.

One such intermediate phenotype is an intense alcohol-related skin flushing reaction caused by several variants of alcohol-metabolizing enzymes, which were identified in the 1970s. This phenomenon, which has been observed for centuries in people of Japanese, Chinese, or Korean descent who consume alcohol, is associated with a decreased risk for AUD but is unrelated to other types of substance use disorder (SUD).[11] The second intermediate phenotype, which enhances risk for both AUD and other types of SUD, is the long-known association between substance-related problems and impulsive-like or externalizing behaviors.[12,13] The underlying characteristics include elevated levels of sensation seeking and behavioral/physiological disinhibition. These behaviors contribute to what has been referred to as type 2 and type B subtypes of AUD that are associated with an early onset of alcohol and other drug problems and a severe clinical course.[14] A third intermediate group of phenotypes that also is related to increased risks for both AUD and other types of SUD operates through the presence of several additional major psychiatric conditions, such as schizophrenia and bipolar disorders.[15,16] Finally, this abbreviated list of genetically influenced characteristics related to the risk for AUD includes a phenotype characterized by low LR to alcohol, as described in the next section.

Each step of these studies of genetic influences for AUD also demonstrates the importance of the environment as well as gene-environment relationships. One example of data supporting the influence of environment is the finding that identical twins of individuals with AUD have only about a 60% risk for this disorder, not the 100% rate one would expect if genes explained the entire

risk. Thus, it is important to study both genes and environment when looking for characteristics that might be helpful in early identification of the risk for repetitive alcohol problems or might reveal clues of ways to mitigate that risk.

Low LR to Alcohol and Risk of Alcohol Problems

A low LR to alcohol is a genetically influenced characteristic that increases AUD risk but does not significantly impact vulnerability toward other forms of SUD or other psychiatric conditions. This low LR phenotype is most prominent at peak and falling blood alcohol concentrations (BACs).[17,18] The rationale for linking a low LR with heavier drinking relates to a Social Information Processing Model which posits that individuals are likely to consume as many drinks as are needed to achieve the desired effects.[19] According to this model, which is presented in Figure 1, young people begin drinking to achieve an effect, such as intoxication. If they need to consume more alcohol to achieve this effect—for example, because of a low LR—they will increase consumption. The resulting heavier drinking becomes associated with other outcomes, especially in individuals with a family history of AUD (FHalc), such as choosing friends who also drink heavily (Peer) or starting to expect that heavy drinking is the best way to have fun (Expect). As heavy drinking begins to increase life problems and stress, alcohol is increasingly used as a means to cope with the stress (Cope). Thus, the major impact of the low LR is on drinking quantity which then increases the risk for alcohol problems (↑HD & Probs). However, low LR has a less robust relationship with drinking frequency.[20]

The low LR is not the only response-related phenotype linked to adverse alcohol outcomes. Another phenotype is greater stimulation from alcohol, which is observed most prominently at rapidly rising BACs in some research paradigms.[21,22] However, prospective work with low LR beginning in the mid-1970s forms the basis for follow-ups in the ongoing prospective study described below. Therefore, the data presented here focus on the low LR.[23]

The first documentation of the relationship between a low LR and several AUD risk factors, such as a family history of AUD, came from alcohol challenges carried out with alcohol-consuming young adults who did not have AUD but were at higher or lower AUD risk.[24] The study compared participants at a higher risk of AUD because of a positive family history with participants at lower risk because of a negative family history who were closely matched on sex, race, percent body water, and recent drinking histories. The study found that both groups had almost identical BACs during the challenge. However, the family-history–positive group demonstrated lower intensities of response to alcohol than the family-history–negative group as measured by a range of effects, including subjective feelings of intoxication, standing steadiness (body sway), changes in hormones, and/or several electrophysiological measures.[24-27]

Because these alcohol challenge analyses were cost- and labor-intensive, researchers subsequently developed a less expensive and less time-consuming measure of LR that could be used in large numbers of subjects, including younger drinkers. The Self-Report of the Effects of Alcohol (SRE) questionnaire—a simple 12-item retrospective self-report—records a person's perception of the number of standard drinks (10 to 12 grams of ethanol) required to experience up to four subjective effects (to first feel any effect, dizzy or slurred speech, unsteady gait, and unwanted falling asleep) during a typical drinking session.[28] This instrument gathers

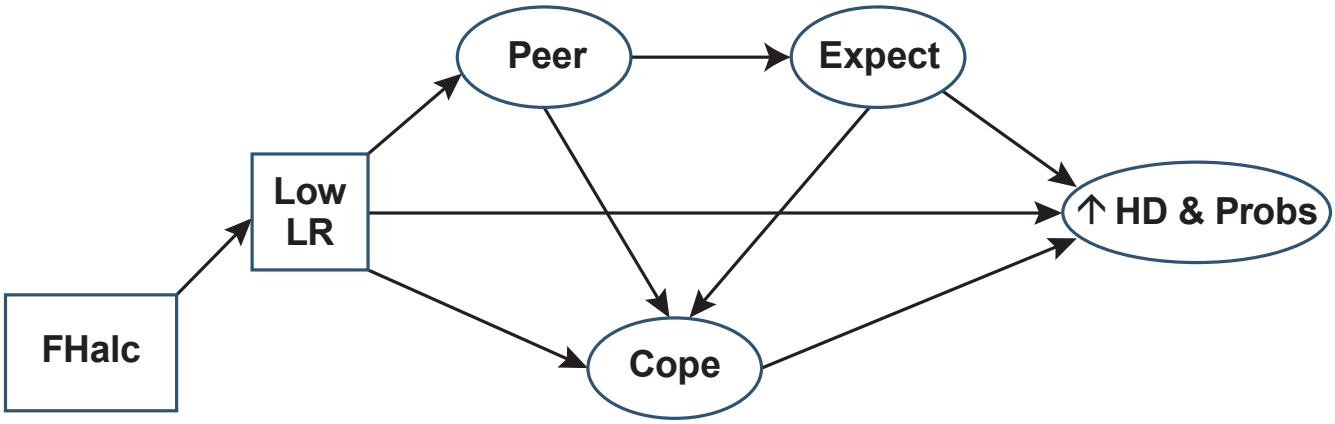

Figure 1. The level of response (LR) model. A low LR to alcohol, which is often associated with a family history of alcohol use disorder (FHalc), increases the risk for heavy drinking and alcohol problems (HD & Probs) both directly and indirectly, through association with heavier-drinking peers (Peer), expectations that heavy drinking is desirable (Expect), and use of alcohol to cope with stress (Cope).[31,37,42] *Source:* Adapted from Schuckit et al. (2004).[19] Reprinted with permission.

data for three timeframes, including the approximate first five times of consuming a full drink (SRE-5), the most recent 3 months of drinking (SRE-3), and the period of heaviest drinking (SRE-H). The score for each timeframe is generated by adding the number of drinks needed for effects that the respondent has experienced and dividing that sum by the number of effects the respondent reported; this calculation yields the average number of drinks needed to achieve effects for that period. SRE values have retest reliabilities and predictive validities regarding drinking quantities and alcohol-related problems of .7 or higher.[28,29] Moreover, multiple studies have documented significant positive correlations between SRE scores (i.e., needing on average higher numbers of drinks for effects or a lower LR per drink) and future heavier alcohol intake and alcohol problems.[30-32]

The retrospective LR measure is not identical to the alcohol challenge in which specific changes in alcohol responses are observed at rising, peak, and falling alcohol blood levels.[18,23] However, laboratory measures of subjective feelings gathered at about the same time as the self-report questionnaire correlated with the SRE at >.3, and SRE ratings overlapped about 60% with alcohol-challenge results in predicting drinking quantities.[28,33]

The SDPS: An Ongoing Prospective Protocol

The study comparing young adult sons of individuals who had a parent with AUD and family history controls described above progressed into the 40-year San Diego Prospective Study (SDPS), each stage of which was approved by the University of California, San Diego (UCSD), Human Research Protections Committee. The study began in 1978 with the recruitment of 453 young men (the original subjects, or probands; average age, 22 years) who were recruited through questionnaires randomly distributed to UCSD students. The participants were 18- to 25-year-old men who consumed alcohol but had never met criteria for AUD.[24] Individuals with lifetime histories of schizophrenia, bipolar disorder, or multiple problems with alcohol or illicit drugs were also excluded.

When entering the study, probands were evaluated for low LR using oral alcohol challenges that resulted in average BACs of 60 mg/dL at 60 minutes.[24,34] Probands then were followed over the next 40 years with personal interviews about every 5 years regarding changes in demography, substance use and problems, as well as major psychiatric disorders. These interviews used questions derived from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) instrument, which has validity, retest reliabilities, and cross-interviewer reliabilities of .7 to .8.[35,36] Over the years, as probands themselves became parents, information about their children's early development was gathered from the probands and the offspring's mothers, and the same interviews used for the probands were also used with their children when they reached age 18 and older.

During the follow-up evaluations, probands and their children gave information on their LR to alcohol using the SRE instrument described above. Beginning with the 15-year follow-up of SDPS families, the investigators also began to record environmental and attitudinal characteristics that might partially mediate the impact of low LR on heavy drinking and alcohol problems.[31,37,38] These mediators included:

- Perception of the maximum number of standard drinks consumed by close peers as assessed using a short version of the Important People and Activities Scale, which is scored from 0 (abstainer) to 4 (> 10 drinks) with retest reliabilities >.85 (noted in Figure 1 as Peer);[39]
- The usual effects a person expects to experience from alcohol as measured by the Social Behavior (e.g., alcohol makes parties more fun) and Increased Arousal (e.g., alcohol helps people stand up to others) subscales of the Alcohol Expectancy Questionnaires (AEQ) that are graded on a 5-point scale with an internal consistency (Cronbach's alphas) of .72 to .92 (noted in Figure 1 as Expect);[40]
- Whether a person uses alcohol to cope with psychological problems as assessed by the Drinking to Cope scale that records how often respondents use alcohol to decrease negative emotions or boredom or to feel more confident; scores range from 1 (almost never) to 4 (almost always), and Cronbach's alpha is .79 (noted in Figure 1 as Cope).[41]

Testing has supported the hypothetical model in Figure 1 regarding how a low LR, which occurs more frequently in individuals with a family history of AUD, increases the risk for heavy drinking and alcohol problems both directly and indirectly through these potential mediators.[31,37,42] The findings suggested that as much as half of the impact of low LR on adverse alcohol outcomes occurs indirectly, through associating with heavier-drinking peers, expectations that getting drunk is rewarding and desirable, and using alcohol to cope with stress. These findings raised the possibility that for individuals with low LR, interventions that decrease the impact of these three mediators on heavier drinking might reduce the risk for higher maximum drinks and alcohol problems later.

Decreasing Risk of Adverse Outcomes in People With Low LR

The findings of the SDPS served as the basis for a subsequent new study in a different population that assessed an intervention to reduce the risk of heavy drinking and alcohol problems in individuals with a low LR. To recruit participants, a questionnaire was distributed to 18-year-old students entering UCSD as freshmen to review their demography, alcohol and drug use, and

related diagnoses.[43] Potential participants also filled out the SRE to measure LR. After excluding nondrinkers and those who had been diagnosed with alcohol or drug problems, schizophrenia, bipolar disorder, or antisocial personality disorder, the researchers used a median split on the SRE to identify individuals with low and high LR, with the two groups matched on sex, ethnicity/race, and recent alcohol consumption quantities and frequencies. More than 80% of eligible students agreed to participate, and the process continued until 250 pairs of high LR and low LR respondents (500 individuals) were enrolled.

These pairs were randomly assigned to one of three conditions: One group watched four 45-minute internet-based videos that taught general ways to avoid heavy drinking and emphasized the importance of low LR (LR-based group), one group watched similar videos with information about how to limit drinking but without an emphasis on LR (state-of-the-art group), and a control group who were followed over the same 55 weeks as the first two groups but who watched no education videos. The education-group participants received $25 for viewing each of the four 45-minute lectures, one each during the first 4 weeks of the study. Students in all three groups were also paid $25 for filling out each of seven 20-minute internet-based questionnaires over the 55 weeks of the study regarding their recent drinking patterns and problems. More than 90% of participants fully participated in the protocol.

The analyses focused mainly on the pattern of drinking quantities (i.e., usual drinks per occasion and maximum drinks per occasion) and alcohol-related problems (i.e., alcohol-related blackouts) over the 55 weeks for the three groups and the differences between the participants with low LR and high LR. Figure 2 illustrates the findings for the average maximum number of drinks; the results for usual drinks per occasion and the number of alcohol-related blackouts were similar. The left side of Figure 2, panel A, gives the average maximum drinks at each of seven timepoints over the 55 weeks for the participants with SRE scores above the median (i.e., had a lower response per drink, or a lower LR). These data are demonstrated separately for controls (in black), for the state-of-the-art group (in orange), and for the LR-based group (in blue). The right side of Figure 2, panel B, gives the results for individuals who had lower SRE scores (i.e., had higher responses per drink, or higher LRs).

The study found that among the participants with low LR, the average maximum number of drinks per occasion increased steadily over the school year, peaking during the period when the university hosted a spring celebration where heavier drinking was more common than usual. Overall, participants in the control

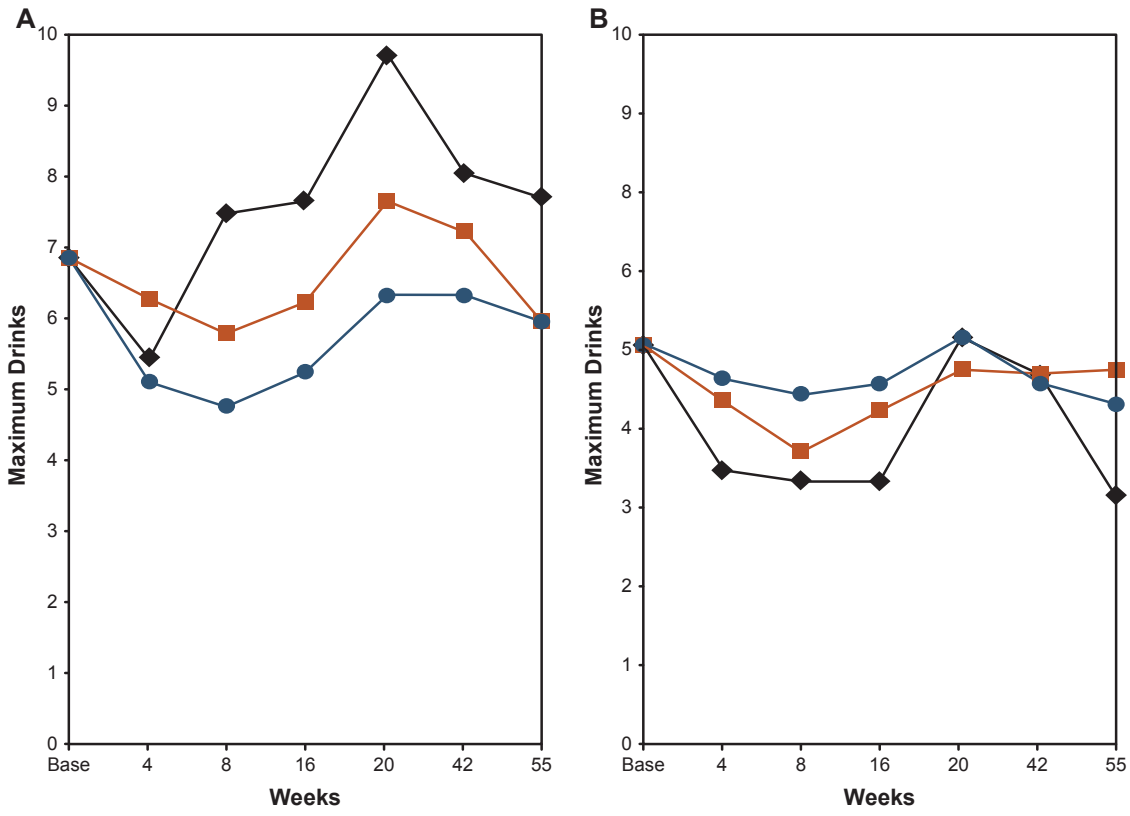

Figure 2. Maximum number of drinks consumed per occasion by students with low (panel A) or high (panel B) level of response (LR) to alcohol over 55 weeks in the San Diego Prevention Study. Blue lines and circle symbols represent students who had watched four videos with LR-based information, orange lines and square symbols represent students who had watched four videos with general alcohol education, and black lines and diamond symbols represent control students who had watched no videos. *Source:* Adapted from Schuckit et al. (2016).[43] Reprinted with permission.

group had the highest maximum number of drinks; the group receiving the standard-of-care intervention had significantly lower maximum numbers of drinks per occasion over the 55-week study period. The greatest reduction in maximum number of drinks, however, was found in the group who had received the LR-based intervention. Among the students who had high LR (i.e., were more sensitive to alcohol's effects), in contrast, there were no significant changes in the maximum number of drinks over time. Moreover, no significant differences existed between the control group, the group receiving the standard-of-care intervention, and the group receiving the LR-based intervention.[43]

This study joins several others[44,45] that underscore the potential importance of targeting a person's specific preexisting vulnerability toward heavy drinking. Imparting knowledge about the genetically influenced risk factor and the mediators that amplify the impact of that risk factor can modify drinking behaviors for extended periods of time.

Conclusions

Long-term prospective studies such as SDPS with its follow-up component provide an opportunity to evaluate problems from a unique perspective compared to other investigations.[31,43,46,47] Such studies are challenging to carry out when funding requires renewal every 3 to 5 years, and they require great effort to ensure consistent participation over time. Thus, such investigations are costly and the number of subjects in the protocol are often limited to several hundred individuals or less, but the data that can be produced by these efforts are unique.

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