Alcohol and Cannabis Use Disorders

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This issue of the *Journal* is focused on providing a deeper understanding of the factors underlying alcohol and cannabis use and misuse in relation to the development of substance use disorders and interactions with other psychiatric illnesses. The prevalence of alcohol use disorder in the United States is high. Data from 2019 suggest that 14.5 million individuals age 12 or older suffered with alcohol use disorder (1). It is important to note that alcohol misuse substantially contributes to premature death, which is largely due to alcohol-related accidents, suicides, and medical illnesses. According to the World Health Organization, 5.3% of all deaths worldwide in 2016 were related to alcohol use (2). Cannabis use in the United States is also very common and, notwithstanding federal regulations, numerous states have legalized its recreational and medical use. In 2018, it was estimated that 11.8 million adolescents and young adults used cannabis in the past year (3). Frequent, chronic, and heavy cannabis use can lead to cannabis use disorder, which can be associated with psychosocial dysfunction, effects on cognition and memory, reduced motivation, and alterations in mood and anxiety regulation.

The centerpiece of this issue is an overview on cannabis use, authored by Dr. Margaret Haney from Columbia University, that reviews cannabinoid substances and the endogenous cannabinoid system in relation to cannabinoid abuse and its treatment (4). This overview sets the stage for the accompanying original research papers that examine cannabis use in U.S. veterans, the relation between cannabis use and psychotic disorders, and interactions between cannabis and alcohol use and eating disorders. In addition to the editorials commenting on these papers, we include a piece in which the *Journal*'s Editors highlight papers published in 2021 that they found to be particularly impactful (5).

Cannabis Use and Cannabis Use Disorders in U.S. Veterans

With numerous states legalizing cannabis for medical and recreational use, cannabis use will almost certainly continue to increase in the United States, which is why it is important to better understand the factors associated with the development of cannabis use disorder. Browne et al. (6) focus on cannabis use in U.S. veterans and, by using data from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions–III (NESARC-III), provide insights into the risk of developing cannabis use disorder. The medical use of cannabis was first legalized in California in 1996 and now exists in many states. However, it was not until 2012 when Washington and Colorado first legalized cannabis for recreational use. Therefore, the timing of the collection of the data used in this study is relevant to understanding risk-related factors prior to the legalization of selling cannabis for recreational use. Data from 3,119 veterans were used to understand the relation between the nonmedical use of cannabis and cannabis use disorder. The findings from this sample of veterans demonstrated that the 12-month prevalence of past cannabis use was 7.3% and of cannabis use disorder was 1.8%, and the lifetime prevalence for cannabis use and cannabis use disorder was 32.5% and 5.7%, respectively. When selectively considering nonmedical cannabis users, the lifetime prevalence of cannabis use disorder was estimated to be 17.4%. Factors associated with greater prevalence of cannabis use and cannabis use disorder included male gender, being single, younger age, lower income, and living in a state in which the medical use of cannabis was legalized. Other substance use disorders, as well as psychiatric disorders, were also associated with increased cannabis use and cannabis use disorder. In their editorial, Dr. Catherine Striley and Carolin Hoeflich from the University of Florida discuss this study in more detail and emphasize the findings linking cannabis use and cannabis use disorder to psychopathology, especially posttraumatic stress disorder and opioid use disorder (7).

The papers in this issue of the *Journal* provide insights into the factors underlying alcohol and cannabis use and misuse and also address their interactions with other psychiatric illnesses.

Cannabis Use and Self-Reported Psychotic Disorders

The goal of Livne et al. in their study (8) was to determine the relation between the nonmedical use of cannabis and psychotic disorders. They also used NESARC-III data, in this case from the general adult U.S. population, and analyses were performed with data from two different time periods, 2001–2002 (N=43,093) and 2012–2013 (N=36,309). This approach allowed for two separate assessments of the relation between cannabis use and psychotic disorders, as well as an assessment of the possible change across these periods in the relation between cannabis use and psychosis. When assessing the past-year prevalence of self-reported

psychotic disorders, a significant increase was observed from the 2001–2002 period (0.33%) to the 2012–2013 period (0.80%). At both time points, the data revealed that psychotic disorders during the past 12 months were more likely to occur in past-year cannabis users (nonmedical) compared with nonusers. At the 2001–2003 time point, the prevalence difference for psychotic disorders between nonmedical cannabis users and nonusers was 1.38%, and at the 2012–2013 time point it was 1.21%. In relation to cannabis use disorder, at both time points it was established that individuals with past-year cannabis use disorder, compared with individuals who were nonusers, were more likely to report a psychotic disorder (2001–2002 prevalence difference: 2.28%; 2012–2013 prevalence difference: 2.70%). No significant differences in the associations between cannabis use and psychotic disorders were found when comparing data from the two time points. While these data link cannabis use to psychotic disorders, it is important to keep in mind that the reported findings are associational and do not provide direct evidence for a causal relation between cannabis use or use disorder and psychotic disorders. In their editorial, Drs. Suhas Ganesh and Cyril D'Souza discuss this theme in depth, providing a basis for understanding how to think about causality in relation to epidemiological, population health, and genetic data (9).

Increased Mortality in Patients With Eating Disorders and Substance Abuse

Eating disorders are associated with high levels of morbidity and mortality, and anorexia nervosa is considered to have the highest mortality risk of all psychiatric disorders. Reduced life span in eating disorder patients is due both to a high suicide rate and to the debilitating physiological consequences of dysregulated eating, poor nutrition, and cachexia. Eating disorders are highly comorbid with other psychiatric disorders, including anxiety disorders, depression, and substance use disorders. The data presented by Mellentin et al. (10) address the extent to which comorbid substance use disorders further increase the risk of premature mortality in patients with eating disorders. Eating disorder patients (N=20,7590) were retrospectively identified from a Danish nationwide registry, as were matched control subjects without eating disorders (N=83,036). At entry, 90% of participants were under 30 years of age, and participants were followed on average for approximately 11 years; drugs of abuse were classified into alcohol, cannabis, and hard drugs (e.g., opioids, sedative-hypnotics, cocaine, hallucinogens, volatile solvents). Mortality was considered to be due to either external causes (i.e., suicide, accident, or murder) or internal causes (i.e., related to substance use disorder, eating disorder, other psychiatric disorder, or a somatic disorder). The authors found that eating disorder patients, compared with control subjects, were approximately 4 times more likely to have a substance use disorder. Eating disorder patients without a substance use disorder had a 2.85 hazard ratio for all-cause mortality compared with controls. A marked increase in mortality was found for eating disorder patients with comorbid substance use disorders (e.g., a hazard ratio of 11.84 for alcohol use disorder comorbid with eating disorders). For these individuals the hazard ratio for deaths related to external causes was 13.87 and for internal causes was 11.87. The greatest risk for mortality was observed in eating disorder patients who had all three types of substance use disorders, with a mortality hazard ratio of 22.99. More specifically, in relation to anorexia nervosa and bulimia nervosa, the hazard ratio for all-cause mortality with comorbid alcohol or cannabis use disorder was 11.28, and 5.86, respectively. Taken together, these findings underscore clinically important issues relevant to the assessment and treatment of patients with eating disorders. In their editorial, Drs. Compton Wilson and Beth Han from the National Institute on Drug Abuse comment on the significance of these findings, suggest other questions that are raised by these data, and emphasize that to achieve optimal outcomes in treating eating disorder patients it is critical to assess, and equally value, the treatment of coexisting substance use disorders (11).

Large Genome-Wide Association Study (GWAS) Relevant to Alcohol Consumption, Problems, and Dependence

Numerous GWASs have attempted to uncover genes associated with alcohol use and alcohol use disorder, with results pointing to specific genes. The study by Mallard et al. (12) represents the largest GWAS to date and is also notable because it takes a dimensional approach to understanding the genetics underlying alcohol use. The authors also use the data to examine the genetic relatedness of alcohol consumption with problematic alcohol use. The study relies on the Alcohol Use Disorders Identification Test (AUDIT) for phenotyping, a 10-item survey with two subscales that assess alcohol consumption (AUDIT-C) and alcohol-related problems (AUDIT-P). The large sample used data from 160,824 individuals assembled from three different sources (UK Biobank, Netherlands Twin Register, and Avon Longitudinal Study of Parents and Children), all of whom were AUDIT phenotyped. The researchers also used a novel analytic approach called genomic structural equation modeling. This statistical method enables an understanding of the genetic architecture and shared genetic underpinnings of complex phenotypic traits and also the involvement of specific single-nucleotide polymorphisms (SNPs) in accounting for the variance shared between related traits. Using a latent factor approach with the AUDIT data, the authors identified a "consumption" factor and a "problems" factor that

together demonstrated a high degree of phenotypic and genetic correlation. They also found that these two factors were highly genetically correlated with alcohol dependence and that the "problems" factor was more robustly genetically correlated with psychopathology. When using polygenic risk scores (PGRs) in independent analyses of the three different subsamples, the authors found that the PGR for "consumption" was associated with alcohol use disorder phenotypes. In relation to specific genes, some differences were uncovered for "consumption" compared with "problems." For example, the gene for corticotropin-releasing hormone receptor 1 (CRHR1) was found to be selectively associated with "consumption." This is a potentially important finding because the CRH system plays a prominent role in integrating the hormonal, autonomic, and behavioral responses to stress, and alterations in this system have been implicated in stress-related psychopathology. Numerous other interesting SNP findings are detailed in the paper. Taken together, this work strongly supports AUDIT as a phenotypic measure of importance for linking genetic variation to alcohol use from both a dimensional and a disease-related perspective and sheds new light on specific genes that may contribute to the risk for alcohol consumption and misuse. In their editorial, Drs. Henry Kranzler, Hang Zhou, and Rachel Kember review other GWASs related to alcohol use and discuss in more detail the sociodemographic and medical factors that may confound studies regarding GWAS findings in relation to alcohol-related phenotypes (13).

Conclusions

Alcohol and cannabis are among the most commonly used psychoactive substances that, when misused, can lead to addiction, interference with functioning, disability, and medical and psychiatric comorbidities. The habitual use of alcohol or cannabis during critical developmental phases such as adolescence can be particularly deleterious, interfering with developmental trajectories underlying the maturation of cognitive, emotional, and social capacities that are essential for success during adulthood. The papers in this issue of the *Journal* provide insights into the factors underlying alcohol and cannabis use and misuse and also address their interactions with other psychiatric illnesses. A summary of the findings includes 1) the prevalence of cannabis use and cannabis use disorder in veterans and the factors contributing to use and misuse in this population; 2) an association between cannabis use or cannabis use disorder and self-reported psychotic disorders, as well as an estimate of the magnitude of the increased prevalence of psychotic disorders conferred by cannabis use; 3) a marked increase in premature mortality in patients with eating disorders who also have substance use disorders; and 4) how alcohol consumption and alcohol-related problems share genetic underpinnings with each other and with alcohol dependence (distinct genes associated with these different components of alcohol use were also identified). The findings presented in this issue of the *Journal* relevant to understanding the genetic and nongenetic factors associated with the development of alcohol and cannabis use disorder are derived from human samples. At a preclinical level, considerable work using animal models has elucidated neural circuits and molecular mechanisms underlying the habitual use of these substances (14, 15). New treatment development will benefit from translational cross-species efforts that continue to advance the understanding of causal mechanisms underlying alcohol and cannabis misuse.

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