Cannabis and Alcohol: From Basic Science to Public Policy

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Overview

The emergence of state-level approval of cannabis for both medical and recreational use is likely to increase the already prevalent co-use of alcohol and cannabis (Yurasek et al., 2017) and raise many important health and social concerns (National Academies of Sciences, 2017). Cannabis research has lagged behind that of alcohol research, but important studies are emerging on the interactions between alcohol and cannabinoids. In this Virtual Issue, *Cannabis and Alcohol: From Basic Science to Public Policy*, we present nine leading-edge research publications spanning preclinical and epidemiological studies, as well as a critical review on the potential therapeutic use of cannabidiol (CBD) in the treatment of alcohol use disorder (AUD) (Turna et al., 2019), which recently appeared in *Alcoholism: Clinical and Experimental Research*.

The Virtual Issue addresses the potential risks and benefits of alcohol and cannabis co-use, which may depend on the particular subgroup of individuals, and whether these drugs are used simultaneously (i.e., drug effects overlap) (Pakula et al., 2009) or concurrently (i.e., drug effects do not overlap in time) (Subbaraman et al., 2019). Simultaneous drug use may be perceived as a means to complement or enhance the effects of each substance (Patrick et al., 2018), despite some individuals reporting negative effects (Lee et al., 2017). The positive perception of complementary drug effects is concerning given the greater health risks associated with simultaneous use (Volkow et al., 2014, Yurasek et al., 2017). Another pattern of use has also developed that substitutes cannabis for alcohol use, particularly in individuals who are making efforts to reduce alcohol intake (Subbaraman, 2016). As summarized in the sections below, this Virtual Issue provides a current assessment of cannabis-alcohol interactions and shows patterns of drug use and risk profiles that may impact the prevalence of co-use and dependence.

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Conflict of interest

The authors have no conflicts of interest to declare.

Endocannabinoids, Exocannabinoids, and Alcohol Actions

Complex cannabinoid signaling systems are found throughout the body and are particularly important for brain, immune, and inflammatory signaling. Endogenous cannabinoids (endocannabinoids) shape neural circuits and affect many behaviors, including reward-driven behaviors such as addiction (Augustin and Lovinger, 2018). Unlike vesicle-secreted neurotransmitters, endocannabinoids are synthesized directly from plasma membrane phospholipids and their transient production generally follows a use-dependent signaling mechanism (Augustin and Lovinger, 2018). Tight control of this system depends heavily on specific enzymes to regulate synthesis and degradation (Friedman et al., 2019), and distinct metabolic processes in brain suggest differential mechanisms are in place for finely-tuned synaptic signaling (Augustin and Lovinger, 2018). The two main endocannabinoids (N-arachidonoylethanolamine and 2-arachidonoylglycerol) bind cannabinoid type 1 and 2 (CB1 and CB2) receptors and have additional targets, such as peroxisome proliferator-activated receptors, transient receptor potential cation channels, and other ligand- and voltage-gated ion channels (Friedman et al., 2019). Exocannabinoids such as CBD also act on CB1 and CB2 receptors and other endocannabinoid targets.

In general, chronic alcohol exposure increases endocannabinoid production, which may in turn downregulate CB1 receptor signaling in rodent models and perhaps also in human alcoholic brain as shown by positron emission tomography (Henderson-Redmond et al., 2016). The overall reduction in these signaling pathways after chronic alcohol consumption may contribute to anxiety and relapse drinking (Henderson-Redmond et al., 2016, Serrano et al., 2018). In most preclinical studies, downregulation of CB1 signaling (e.g., by genetic deletion of CB1) reduced voluntary alcohol consumption and reward (conditioned place preference), whereas activation of cannabinoid signaling (e.g., by inhibition of fatty acid amino hydrolase, an enzyme that degrades endocannabinoids) increased alcohol consumption (Henderson-Redmond et al., 2016). The cannabinoid signaling components and metabolic pathways offer multiple targets for regulating this complex system. It's possible that compensatory cannabinoid-alcohol mechanisms could be used in the future to balance responses to mimic the favorable effects of cannabinoids while protecting against the deleterious effects of alcohol.

Chronic alcohol exposure is known to inhibit adult hippocampal neurogenesis, and in this Virtual Issue Khatri and colleagues used a rat binge-drinking model to show that acute alcohol inhibition of neurogenesis depends on activation of CB1 receptors and is exacerbated by further activation of these receptors (Khatri et al., 2018). This model suggests that acute activation of endocannabinoid signaling by alcohol is an important step in impairment of hippocampal neurogenesis. The acute and chronic effects of alcohol on CB1 receptor signaling indicate that the endocannabinoid system may be a viable target for alcohol-related behaviors or pathologies.

Epidemiology: Prevalence and Developmental Course of Alcohol and Cannabis Use

As cannabis use is increasing worldwide (Degenhardt et al., 2018), there is an immediate need for universal guidelines to diagnose substance use disorders (SUD). The International Classification of Diseases, 11th edition (ICD-11) (World Health Organization, 2018) was recently ratified by the 72nd World Health Assembly, and will go into effect on January 1, 2022. Despite attempts to bring the two main classification systems, ICD and the Diagnostic and Statistical Manual For Mental Disorders (DSM) (American Psychiatric Association, 2013) into closer alignment (Sartorius, 2010), differences between the diagnostic systems remain. These differences highlight ongoing issues in conceptualizing SUD. In this Virtual Issue, a cross-sectional study of adolescents in addiction treatment (N = 339, ages 14–18) found a significantly higher prevalence of diagnoses of alcohol and cannabis dependence using the ICD-11 classification compared to the DSM-IV, DSM-5, and ICD-10 systems (Chung et al., 2017). This is likely due to the radically simplified set of three dependence criteria (physical dependence, priority of substance use, and impaired control over substance use) found in ICD-11, only two of which need to be met for a diagnosis of dependence to be made. Notably, adolescents with an ICD-11 dependence diagnosis usually met only the criteria of tolerance and priority of substance use (e.g., much time spent using or recovering from the substance), rather than the criterion of impaired control over substance use. The absence of reports of impaired control, a hallmark of dependence, raises questions regarding the ICD-11 dependence algorithm when applied to alcohol and cannabis, particularly in adolescents. Field testing of ICD-11 in community and treatment samples internationally is underway (personal communication, J. B. Saunders, University of Queensland, Australia).

Beyond establishing the prevalence of AUD and cannabis use disorder (CUD), risk factors influencing the developmental course of use need to be identified to effectively guide substance use prevention efforts. In this regard, the role of lifetime cannabis use in elevating the risk for increasing alcohol use was examined in this Virtual Issue in adolescents and young adults from 901 high-risk families (Bucholz et al., 2017). For each of four transitions leading to AUD (time to first drink, first drink to first alcohol-related problem, first drink to AUD onset, and first alcohol-related problem to AUD onset), lifetime cannabis use consistently elevated the likelihood of each transition, independent of externalizing psychopathology, which also predicted each transition. These results highlight the role of cannabis use as a consistent risk factor across multiple transitions in the development of AUD, although the underlying mechanisms remain to be determined.

Risks Associated with Co-use of Alcohol and Cannabis

In the United States, the effect of state-level laws on the prevalence of and attitudes toward cannabis use among adolescents is mixed (Blevins et al., 2018, Mason et al., 2016). In this issue, a cross-sectional online survey (White et al., 2019) compared college students (N = 1389) from three states with different cannabis laws (i.e., criminalized, decriminalized, and recreational cannabis use for ages 21+) on the prevalence, negative consequences, and perceived norms associated with simultaneous alcohol and cannabis use. Three-quarters of

the students reported simultaneous use at least once in the past year. Contrary to expectation, students in the state with decriminalized use reported higher rates of simultaneous use, compared with states with legalized or criminalized use. This may be a reflection of a perceived norm for simultaneous use among their peers by students in the decriminalized state, compared with students at the other two colleges. In support of this interpretation, a student's own simultaneous use was positively associated with perceptions of simultaneous use among peers (which were higher in the decriminalized state relative to the other two states). Furthermore, greater simultaneous use was found in Greek members and in non-varsity sports club athletes, suggesting the potential utility of targeted interventions for specific subgroups to reduce risk of simultaneous use (White et al., 2019).

Among adults with AUD, a study in this Virtual Issue by Subbaraman et al. (2019) replicated an intriguing result obtained from secondary analyses of the COMBINE study (Subbaraman et al., 2017), which found that, during alcohol treatment, "midlevel" cannabis use (i.e., average 1–2 times per month), compared with non-use, was associated with worse alcohol outcome (e.g., lower percent days abstinent), while there was no such association with "low" and "high" levels of cannabis use. In their follow-up study in this Virtual Issue, Subbaraman and colleagues (2019) selected adults from the U.S. National Alcohol Surveys who reported prior AUD treatment, and created four comparison groups: no cannabis use in the past year, light cannabis use ("less than monthly"), midlevel use ("more than monthly/ less than weekly"), and heavy use ("weekly or more"). The cross-sectional analyses found, as in the prior COMBINE study, that only the midlevel cannabis use group (not the light or heavy use groups) significantly differed on alcohol outcomes from the group that reported no cannabis use in the past year, with the midlevel use group showing worse alcohol outcomes (e.g., average frequency of 5+ drinks, greater risk for alcohol-related harm). The authors speculate that the association between midlevel cannabis use and worse alcohol outcomes, particularly in the absence of an association between heavy cannabis use and worse alcohol outcomes, might be due to different motives and contexts of use for midlevel versus heavy cannabis use groups. For example, midlevel cannabis use might involve recreational motives, with intoxication as the main reason for use (e.g., significant associations with frequency of 5+ drinks), whereas high frequency cannabis consumption might involve medicinal use, or use of cannabis as a harm reduction substitute for alcohol use (Subbaraman et al., 2019). The authors' interpretations remain speculative, however, since data on cannabis quantity, medicinal use of cannabis, simultaneous use of alcohol and cannabis (i.e., timing of using both substances within a day), and the motives and context of substance use were not collected.

Similar to the Subbaraman et al. (2019) report, a retrospective event-level study (Metrik et al., 2018) in this Virtual Issue found less frequent heavy drinking (defined as > 4 and 5 drinks per occasion for females and males, respectively) among those with heavier (more frequent) cannabis use. This study, which examined daily patterns of alcohol and cannabis use among veterans based on Timeline Followback data, found that heavy drinking occurred on days when cannabis was consumed, and that this association was particularly strong among veterans with both AUD and CUD, or only AUD, but not among veterans with only CUD. The results were interpreted as support for possible complementary effects of alcohol and cannabis use, such that simultaneous use enhances the effects of each substance (Pakula

et al., 2009). In contrast, veterans with only CUD were more likely to drink at moderate, not heavy, levels when using cannabis. The authors surmise that this might reflect a possible substitution effect, for example, in which medical marijuana replaces alcohol use among veterans with CUD only. In support of this possibility, daily or near daily medical marijuana use has been associated with a previous history of alcohol-related problems, but with a lower severity of current alcohol problems, compared with recreational cannabis use (Lin et al., 2016). The study by Metrik and colleagues, however, did not assess medical use, cannabis quantity, or the timing of cannabis and alcohol use on a daily level. Among veterans with CUD only, the extent to which medical marijuana represents an effective harm reduction strategy as a potential substitute for alcohol remains to be determined (Metrik et al., 2018).

Possible Benefits of Co-use of Alcohol with Cannabis or Cannabidiol

Excessive alcohol consumption activates neuroimmune and inflammatory signaling and this contributes to organ damage and may promote further escalation of consumption (Erickson et al., 2019). In contrast, cannabis produces anti-inflammatory actions (Nair et al., 2015), and it is of great interest to determine if any of the detrimental effects of alcohol can be ameliorated by exo- or endo-cannabinoids. As discussed in this Virtual Issue, studies in animal models report protective effects of CBD on alcohol-induced neurodegeneration and alcohol-induced liver steatosis, and human studies suggest a relationship between co-use of cannabis and alcohol on immune function and inflammation (Karoly et al., 2018; Turna et al., 2019). To further examine cannabis-alcohol interactions in humans, Karoly and colleagues determined if plasma levels of proinflammatory cytokines were associated with alcohol and cannabis use (Karoly et al., 2018). They found a positive association for interleukin 6 and alcohol use, and the association was stronger in cannabis non-use groups compared with use groups. Their findings suggest that cannabis use might blunt some of the adverse inflammatory consequences of alcohol abuse. Although certain peripheral cytokines may have the ability to penetrate the blood-brain barrier, this study did not directly measure neuroinflammation and more research is needed to determine the role of inflammatory responses in the periphery and the brain in cannabis and alcohol use groups. Considering the overall opposing effects of alcohol and cannabinoids on inflammatory responses and the effects of cannabinoids on alcohol-mediated inflammation, cannabinoid receptors are attractive anti-inflammatory targets for AUD (Nair et al., 2015).

As reported in two studies in this Virtual Issue, mining of large hospital datasets provides evidence that cannabis use reduces risk of alcoholic pancreatitis and gastritis (Adejumo et al., 2019a, Adejumo et al., 2019b). The authors discussed the possibility that the anti-inflammatory actions of cannabis may lessen the inflammatory effects of these alcohol-associated conditions. It will be of interest to determine which components of cannabis are most important and if the non-psychoactive CBD component may also be beneficial. Although such cross-sectional studies have limitations, they show the power of using large databases to detect potentially important alcohol-cannabis interactions.

CBD has become widely available in many forms from a rapidly increasing number of online and retail suppliers. Preclinical studies reviewed by Turna and colleagues (2019) in this Virtual Issue report diverse beneficial effects of CBD, such as neuroprotection from

adverse alcohol effects in the hippocampus and reduced alcohol-mediated liver damage, as well as reduced alcohol-dependent phenotypes (e.g., alcohol self-administration, craving, acute withdrawal). While only a few studies have examined the effects of CBD and alcohol in humans, the clinical evidence indicates that CBD was well tolerated and did not interact with the subjective effects of alcohol (Turna et al., 2019).

Although not directly assessed, two studies in this issue (Subbaraman et al., 2019, Metrik et al., 2018) suggest that frequent cannabis use in some subgroups may be related to medical marijuana use and might represent a possible harm reduction strategy to substitute marijuana for alcohol (Lin et al., 2016). The effectiveness of medical marijuana as a harm reduction strategy for AUD is not known, but in light of the beneficial evidence that is emerging for some alcohol-cannabis interactions, this is an intriguing area of research.

Conclusions

The articles presented in this Virtual Issue provide an important advance in understanding the combined effects of alcohol and cannabis use. They, however, also highlight significant gaps in research, particularly in humans, that need to be considered in the future. Information is lacking on the actions (molecular, physiological, behavioral) of specific cannabis-derived compounds and how they may be used for specific health conditions (National Academies of Sciences, 2017). This is particularly true of CBD, which is now in popular use despite little information about its mechanism of action or therapeutic effects (Friedman et al., 2019). An attractive anti-inflammatory treatment approach is to amplify endocannabinoid signaling to mimic the favorable actions of exocannabinoids and perhaps correct problems caused by reduced endocannabinoid signaling, such as is observed following chronic alcohol exposure. The considerable interest in fatty acid amino hydrolase inhibitors has not yet led to therapeutic advances, but a successful strategy to harness endocannabinoid pathways may be realized in the future.

Other gaps in our knowledge include understanding the effects of the quantity of cannabis consumed, route of administration (e.g., smoke, vapor, edible), timing of cannabis and alcohol intake to distinguish simultaneous versus concurrent use, cannabis strain (e.g., indica, sativa), tetrahydrocannabinol/cannabidiol (THC/CBD) ratio, use of cannabis for medical purposes, and the impact of state-level cannabis regulatory policies. The article in this Virtual Issue that examined state-level differences in cannabis legislation found limited effects on cannabis use and simultaneous cannabis-alcohol use, relative to perceived peer norms for substance use (White et al., 2019). However, increased implementation of cannabis legislation and continued monitoring of substance use prevalence may have a future impact on patterns of substance co-use and dependence diagnoses.

A key point made in this Virtual Issue is that some of the associations between alcohol and cannabis use were specific to subgroups, such as those diagnosed with SUD (Metrik et al., 2018), particular groups of college students (White et al., 2019), or an individual's frequency of (and possible motives for) cannabis use (Subbaraman et al., 2019). These subgroup-specific associations may explain some of the inconsistencies in previous research findings

and emphasize the importance of identifying more homogeneous populations that demonstrate specific use patterns and risk profiles.

Collectively, the Virtual Issue calls our attention to the paradoxical interactions of cannabis and alcohol found in studies ranging from basic science to epidemiology. This paradox arises because the anti-inflammatory actions of cannabinoids likely ameliorate some actions of alcohol, particularly those where alcohol has an inflammatory component. Yet cannabis and alcohol can interact in other domains to produce enhanced effects (both positive and negative) of both substances. Better understanding of the CBD/THC ratio in relation to anti-inflammatory and psychoactive effects, together with studies of dose, patterns of drug co-use, and other external factors mentioned above will begin to close the research gaps. This Virtual Issue shows the progress in delineating the complex interactions, but also emphasizes that these are early days of cannabinoid-alcohol studies and much remains to be investigated.

Acknowledgements

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