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Alcohol and Cannabis Co-Use: Clinical Correlates, Mechanisms, and Sex Differences

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Alcohol and Cannabis Co-Use: Clinical Correlates, Mechanisms, and Sex Differences

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Psychology

by

Alexandra Susana Venegas

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ABSTRACT OF THE DISSERTATION

Alcohol and Cannabis Co-Use: Clinical Correlates, Mechanisms, and Sex Differences

by

Alexandra Venegas

Doctor of Philosophy in Psychology

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Professor Lara A. Ray, Chair

Cannabis is the most widely used illicit substance across the globe and the most commonly used drug among those who drink alcohol (SAMHSA, 2017). Importantly, alcohol and cannabis co-use has been shown to be associated with an increased risk for a host of negative outcomes (Volkow, Baler, Compton, & Weiss, 2014), including increases in heavy drinking, higher prevalence of alcohol use disorder (AUD) (Blanco et al., 2016; Weinberger, Platt, & Goodwin, 2016), and poorer AUD treatment prognoses (Mojarrad, Samet, Cheng, Winter, & Saitz, 2014; Subbaraman, Metrik, Patterson, & Swift, 2017). However, the detrimental effects of the co-use of alcohol and cannabis have not been uniformly shown in the literature, as some research suggests that alcohol and cannabis may be substitutes for each other, and that cannabis use may be associated with overall lower levels of alcohol consumption (Risso, Boniface, Subbaraman, & Englund, 2020). Taken together, despite the frequent co-use of alcohol and

cannabis, their clinical correlates, underlying mechanisms, and the role of sex differences remain poorly understood.

This dissertation seeks to fill identified gaps within the literature of co-use of alcohol and cannabis by expanding on the literature on sex differences underlying the co-use (Study 1). Next, it probes clinical associations related to varying levels of alcohol and cannabis co-use, identifying relevant factors related to co-use (Study 2). Lastly, Study 3 investigates mechanisms relating substance-induced and cue-induced craving for alcohol and cannabis.

Study 1 (Venegas, Meredith, Green, Cooper, & Ray, 2020) aimed to elucidate the effects of controlled alcohol administration on the urge to use cannabis and considered sex-dependent effects. A community sample of non-treatment-seeking heavy drinkers reporting cannabis use in the past six months completed an intravenous alcohol administration paradigm. Participants rated their urge to use cannabis and drink alcohol, in addition to subjective effects of alcohol, at baseline and at rising levels of breath alcohol concentration (BAC). Results showed that males reported increases in the urge to use cannabis at rising BACs, but females did not. Urge for alcohol significantly predicted urge for cannabis across rising levels of BAC and this relationship was stronger in males than in females. Lastly, stimulation, but not sedation, was positively associated with the urge for cannabis. Overall, these results suggest that the pharmacological effects of alcohol on the urge to use cannabis are sex dependent and that the stimulant effects of alcohol are associated with a greater urge for cannabis.

Study 2 (Venegas, Du, Cooper, & Ray, 2022) examined demographic and clinical correlates of varying levels of cannabis co-use in a large community sample of heavy drinkers. Results revealed that younger age, male gender, and concurrent tobacco were robust predictors of alcohol and cannabis co-use. Further, individuals who reported more frequent cannabis use

also exhibited more problematic drinking profiles, such as more drinking days, more frequent heavy drinking days, and higher levels of tonic alcohol craving. Taken together, this study identified the negative impact of more intense cannabis co-use among heavy drinkers as well as predictors of heavier co-use patterns. Next steps in this line of research suggest the need for tailored intervention strategies among this specific subgroup of drinkers.

Study 3 (Venegas & Ray, 2023) utilized a novel experimental pharmacology paradigm employed remotely via Zoom to test the pharmacological effects of cannabis on craving for alcohol and the pharmacological effects of alcohol on craving for cannabis, both in the absence and presence of drug cues. It employed a crossover design, such that across two counterbalanced and randomized experimental sessions, a community sample of alcohol and cannabis co-users underwent a series of drug administration followed by a cue-reactivity paradigm. Specifically, in one experimental session, participants administered alcohol, followed by a cannabis cue-reactivity paradigm; in another experimental session, they administered cannabis, followed by an alcohol cue-reactivity paradigm. Results revealed that exposure to alcohol/cannabis cues resulted in significant increases in subjective craving, across both experimental sessions. These findings suggest that cue-reactivity robustly increases craving, over and above the pharmacological priming effects of alcohol/cannabis administration. Importantly, the cross-substance effects of alcohol/drug administration and cues were modest.

The successful completion of these projects has provided valuable clinical data as to the nature of the co-use of alcohol and cannabis, including sex differences, risk factors, and mechanisms underlying co-use. An overarching pattern of results indicated that younger, male-identifying, comorbid tobacco users may be an identifiable subgroup of drinkers at heightened risk for co-use and associated negative consequences. Further, it appeared that the stimulating

effects of alcohol were associated with increases in cannabis craving following alcohol administration, whereas the sedative effects of alcohol were not. Alcohol and cannabis co-users were most sensitive to the cue-reactive, as opposed to the pharmacological, effects of alcohol/cannabis on subjective craving. Lastly, the cross-substance effects of alcohol/drug administration and cues were modest. Collectively, results from this series of studies may be used to inform intervention development and further experimental studies for the sizeable group of individuals who co-use alcohol and cannabis.

The dissertation of Alexandra Susana Venegas is approved.

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Dedication

This dissertation is wholeheartedly dedicated to my family.

I want to especially thank my mom and dad, who instilled in me at a young age the value of hard, honest work and the fulfillment that comes from being of service to others. You are my safe space, my home. I don't know where to begin to thank you. To Stevie, my ultimate confidante and cheerleader. My very best friend and forever partner in life. Thank you for never leaving my side. To Cruz and Luna, my babies, for always being sure to remind me to take a break, have a nap, play outside, chase a ball…thank you for grounding me and bringing me so much light and happiness. My life is infinitely better because of the two of you.

Most importantly, thank you to my family for loving me and supporting me unconditionally throughout the challenges of graduate school and life. I love you beyond measure.

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To my participants and clients, thank you for trusting me to be a part of your journey. It has been my unique privilege knowing you, and each of you have made lasting impacts on my life.

Lastly, to Mama, Papa, Grandma, and Pop. I am honored to carry on your legacy. I hope I have made you proud.

I am who I am today because of all of you. From the bottom of my heart, thank you.

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List of Tables, Figures, and Supplementary Materials

List of Acronyms

Alcohol use disorder (AUD)
Breath alcohol concentration (BAC)
Δ^9-tetrahydrocannabinol (THC)
Cannabidiol (CBD)
Cannabis use disorder (CUD)
National Institute of Alcohol Abuse and Alcoholism (NIAAA)
National Institute on Drug Abuse (NIDA)
Cannabis Use Disorders Test – Revised (CUDIT-R)
UCLA Clinical and Translational Research Center (CTRC)
Computerized Alcohol Infusion System (CAIS)
Timeline Follow Back (TLFB)
Structured Clinical Interview for DSM-5 (SCID-5)
Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar)
Alcohol Use Disorders Identification Test (AUDIT)
Alcohol Dependence Scale (ADS)
Penn Alcohol Craving Scale (PACS)
Biphasic Alcohol Effects Scale (BAES)
Urge Form (UF)
Beck Anxiety Inventory (BAI)
Beck Depression Inventory – II (BDI-II)
Fagerström Test for Nicotine Dependence (FTND)
Analysis of variance (ANOVA)
Alcohol by volume (ABV)
Cognitive behavioral therapy (CBT)

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LAR designed the study. AV conducted study analyses, with the assistance of RG. All authors contributed to the conceptualization of the manuscript and the interpretation of the data. AV and LAR drafted the manuscript. All authors revised the manuscript and provided their approval of the current version submitted for publication. All authors agree to be accountable for all aspects of the work, including its accuracy and integrity.

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AV and LAR designed the study, with the assistance of ZDC. AV conducted study analyses, with the assistance of HD. All authors contributed to the conceptualization of the manuscript and the interpretation of the data. AV and LAR drafted the manuscript. All authors revised the manuscript and provided their approval of the current version submitted for publication. All authors agree to be accountable for all aspects of the work, including its accuracy and integrity.

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2. **Venegas, A.,** Du, H., Cooper, Z. D. & Ray, L. A. (2022). Cannabis and alcohol co-use: The effects of intensity of cannabis use among heavy drinkers. *Addictive Behaviors, 135,* 107443.
3. Baskerville, W., Grodin, E. N., **Venegas, A.** & Ray, L. A. (2022). Global sleep quality influences tonic craving, not cue-induced craving. *Addictive Behaviors,* 107372.
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Introduction

Prevalence of Alcohol and Cannabis Co-Use

Cannabis is the most widely used illicit substance across the globe and is the third most used drug of abuse in the United States (U.S.). It is also the most commonly used drug among those who drink alcohol (SAMHSA, 2017); in fact, 20-50% of individuals who abuse alcohol also report cannabis co-use (Petry, 2001). Similarly, among those who use cannabis, over 75% report concurrent alcohol use (Agrawal, Lynskey, Madden, Bucholz, & Heath, 2007; Haas et al., 2015; Hyggen & Hammer, 2014; Midanik, Tam, & Weisner, 2007). It is particularly noteworthy that those who report using both alcohol and cannabis often use them at the same time (i.e., in a single substance use episode) (Midanik et al., 2007; Subbaraman & Kerr, 2015). In fact, it has been suggested that the use of alcohol may predict future cannabis use, as it was recently shown by our group that among alcohol and cannabis co-users, drinking alcohol on a given day was associated with a 2.5-fold increase in the likelihood of same-day cannabis use (Roche et al., 2019).

When characterizing alcohol and cannabis co-use, it is also crucial to consider the broader legislative context. Movements to legalize cannabis have changed the legal and political landscape across the U.S., leading to an increased availability of cannabis, and possibly influencing alcohol, tobacco, and cannabis co- and tri-use patterns. Rates of cannabis use continue to rise across the U.S., potentially due, at least in part, to recent legalization efforts. Specifically, reported use of cannabis within the past year among adults increased from approximately 4% to greater than 9% between 2001–2002 and 2012–2013 (Hasin et al., 2015). To this end, it has been shown that the rise in cannabis use among adults is associated with the increase in states that have either legalized medicinal or recreational cannabis use – or both

(Cerdá, Wall, Keyes, Galea, & Hasin, 2012; Hasin et al., 2015; Mauro et al., 2019; Wen, Hockenberry, & Cummings, 2014). Further, a growing number of women have reported using cannabis for medicinal purposes, and in some cases, they report medicinal use at higher rates than men (Finseth et al., 2015; McConnell, Applegate, Keniston, Kluger, & Maa, 2014 Kluger, & Maa, 2014; Ryan-Ibarra, Induni, & Ewing, 2015).

It is important to note that tobacco is hypothesized to impact alcohol and cannabis co-use patterns across individuals who use these three substances. Alcohol, tobacco, and cannabis are the three substances that are most commonly used among adults in the U.S. (SAMHSA, 2017), and it has been consistently shown that these substances are commonly used concurrently (Prince van Leeuwen et al., 2014; Roche et al., 2019). Alcohol and tobacco co-use is highly prevalent (McKee & Weinberger, 2013; Roche, Ray, Yardley, & King, 2016; Rogers et al., 2020), as it has been estimated that approximately 20% of regular tobacco smokers have also been identified as heavy drinkers (Grant & Dawson, 2000). Similarly, over two-thirds of cannabis users report concurrent use of tobacco (Schauer, Berg, Kegler, Donovan, & Windle, 2015), and the majority of tobacco users report regular cannabis use (Ramo, Liu, & Prochaska, 2012) (SAMHSA, 2017). There is also evidence that tobacco or cannabis use precedes and increases the likelihood of use of the other, in both adults and adolescents, likely within the same day (Humfleet & Haas, 2004) (Patton, Coffey, Carlin, Sawyer, & Lynskey, 2005; Tarter, Vanyukov, Kirisci, Reynolds, & Clark, 2006; Timberlake et al., 2007; Agrawal et al., 2007; Kandel & Kandel, 2015). Notably, the rate of co-use of cannabis and tobacco among tobacco users has increased in states where cannabis has been legalized (Wang & Cataldo, 2016).

In sum, co-use of alcohol and cannabis in some respects shows some consistency, such that these two substances are widely co-used – at striking rates. Additionally, tobacco appears to

play a role to impact these co-use patterns, as the extent of co-use of alcohol and tobacco, cannabis and tobacco, and their tri-use are also well-documented. Further, the legal context surrounding cannabis use in the U.S. is a complicating factor, as cannabis is becoming more widely available and perhaps impacting co- and tri-use patterns. This dissertation seeks to fill important gaps within the literature on co-use of alcohol and cannabis by elucidating additional sex differences, probing demographic and clinical correlates of varying levels of alcohol and cannabis co-use by utilizing an epidemiological framework, and investigating synergistic effects via experimental psychopharmacology approaches.

Alcohol and Cannabis Co-Use in Addiction Research

It is well documented that individuals with AUD are a rather heterogeneous group with complex clinical presentations (Grant et al., 2015). In clinical trials, however, individuals with many medical and psychiatric comorbidities are often excluded in an effort to increase internal validity, ensure participant safety, and increase the likelihood of treatment success (Humphreys, Weingardt, Horst, Joshi, & Finney, 2005). Efforts to increase representativeness of alcohol-using samples while not compromising internal validity of findings has long been a topic of discussion within the field (Blanco et al., 2008; Hoertel et al., 2014; Humphreys, Weingardt, & Harris, 2007; Humphreys & Weisner, 2000; Maisto, Conigliaro, McNeil, Kraemer, & Kelley, 2001; Moberg & Humphreys, 2017; Storbjörk, 2014; Velasquez, DiClemente, & Addy, 2000). However, efforts to enhance the integrity of research protocols via stringent inclusion/exclusion criteria have been questioned (Van Spall, Toren, Kiss, & Fowler, 2007) and have even been hypothesized to increase the risk of biases in outcome estimates without gains in statistical power (Humphreys, Harris, & Weingardt, 2008). In fact, Humphreys & Williams (2018) provide a compelling summary of the magnitude of exclusion rates across studies of various mental health

conditions, and estimate that investigators exclude approximately 64-96% of those participating in clinical research on substance use disorders (SUDs), including AUD, for various reasons, including the existence of comorbidities. In brief, exclusion criteria in studies to date may lead to groups that are non-generalizable to the broader population we wish to impact.

Alcohol and cannabis are among two of the most commonly co-used substances (SAMHSA, 2017; Petry, 2001; Yurasek, Aston, & Metrik, 2017), and individuals who use both alcohol and cannabis have been shown to exhibit a variety of clinical characteristics, including greater psychiatric severity and greater adverse social consequences (Brière, Fallu, Descheneaux, & Janosz, 2011; Metrik, Gunn, Jackson, Sokolovsky, & Borsari, 2018; Midanik et al., 2007; Staiger, Richardson, Long, Carr, & Marlatt, 2013; Subbaraman et al., 2017; Volkow et al., 2014). As such, given their widespread co-use and unique phenotypes, the exclusion of cannabis users from clinical studies of AUD may result in non-representative samples of drinkers. For example, as tobacco remains the most widely used licit substance among those who drink alcohol (Chou et al., 2016; Grant et al., 2015), tobacco use has become a standard inclusion criterion within alcohol studies. Due to their pattern of frequent co-use, it has been established within the field that excluding tobacco users from these studies would severely bias and limit sample representativeness. Similarly, as the co-use of alcohol and cannabis continues to be highly prevalent, it may be the case that the inclusion of cannabis use in alcohol studies too becomes commonplace, as is the case with tobacco. It is important to consider the implications of adjusting inclusion/exclusion criteria in the context of cannabis use within alcohol research studies in order to reduce selection bias, bolster generalizability of findings, potentially limit unnecessary expenditure of study resources, and narrow the gap between research and clinical practice.

To this end, based on the premise that alcohol researchers should consider allowing cannabis users to enroll in clinical studies of AUD to strengthen the generalizability of the findings, a recent study from our group (Venegas, Meredith, Cooper, Towns, & Ray, 2020) examined how heavy drinking cannabis users differ from non-cannabis using heavy drinkers in terms of demographic and clinical characteristics. Alcohol and cannabis co-users were found to be younger, were more likely to be tobacco smokers, endorse symptoms of depression, and display more severe AUD symptomatology than drinkers who did not report using cannabis.

Taken together, it appears that among drinkers, co-use of cannabis may be the norm as opposed to the exception, as evidenced by the extensive rates of co-use and warranted inclusion in clinical research of AUD. However, data that has shown that cannabis co-use may increase clinical severity of AUD and other psychopathologies. As such, it is important to continue to conduct research to effectively characterize this sizeable subgroup of drinkers, as their identification may inform clinical research and eventual substance abuse treatment development.

Health and Psychological Effects of Alcohol, Cannabis, and Alcohol and Cannabis Co-Use

The detrimental health effects of alcohol are well-documented. Long-term consequences of chronic alcohol use and misuse have been shown to be associated with a variety of medical conditions such as heart disease, liver disease, pancreatitis, digestive problems, various cancers of the head and neck, and a generally weakened immune system (International Agency for Research on Cancer, 2012; Klatsky, 2002; Layer et al., 1994; WHO, 2019; Rehm et al., 2010). Psychological and social consequences attributable to heavy alcohol use include negative alterations in mood, impaired judgment, reductions in memory, various alcohol-induced psychiatric disorders, and worsening of pre-existing psychopathology (Oscar-Berman, Shagrin, Evert, & Epstein, 1997; Shivani, Goldsmith, & Anthenelli, 2002). Further, alcohol has been

shown to negatively impact neurological processes such as temperature regulation, sleep, and muscular coordination (Oscar-Berman et al., 1997). Brain volume loss is also well-documented in AUD. Gray matter reductions have been found in corticostriatal-limbic circuits (Grodin & Momenan, 2017; Li et al., 2019; Xiao et al., 2015; Yang et al., 2016), and have been found to be positively associated with alcohol use factors, such as duration of alcohol dependence and length of lifetime alcohol consumption (Cardenas, Studholme, Gazdzinski, Durazzo, & Meyerhoff, 2007; Yang et al., 2016).

The extent to which the literature has conclusively demonstrated long-term negative effects of cannabis use is rather inconsistent, especially as it relates to the brain. Several negative health effects have been identified, however, such as increased risk for breathing problems (Hashibe et al., 2006; Owen, Sutter, & Albertson, 2014; Polen, Sidney, Tekawa, Sadler, & Friedman, 1993), increased heart rate and blood pressure (Jones, 2002), and a potentially increased risk of suffering a heart attack (Thomas, Kloner, & Rezkalla, 2014). Whether chronic cannabis use causes lung cancer, as cigarette smoking does, remains an open question (Lee et al., 2011; Owen et al., 2014), although it has been shown that cannabis smoke inhalation results in far greater amounts of tar deposition than cigarette smoke does (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). Determining cannabis' exact contribution to lung cancer risk has been difficult to determine; one potential reason is because many cannabis users also smoke combustible tobacco. Further, some animal studies have suggested that Δ^9-tetrahydrocannabinol (THC; one of the primary psychoactive compounds found in cannabis) and cannabidiol (CBD; another prominent compound found in cannabis, although it is not psychoactive) may have antitumor effects, although more research is needed on this topic (Owen et al., 2014). With regard to psychiatric risk, evidence has shown that heavy cannabis use is associated with

temporary hallucinations and paranoia, increased risk for the onset of psychosis, and worsening of symptoms in patients with schizophrenia (Hall & Degenhardt, 2000; Semple, McIntosh, & Lawrie, 2005; Smit, Bolier, & Cuijpers, 2004). Despite purported neuroprotective properties of CBD (Demirakca et al., 2011; Jacobus et al., 2009; Pertwee, 2004; Pertwee, 2008; Wilkinson & Williamson, 2007), heavy cannabis use has been attributed with impairments in brain development and function (Filbey et al., 2014). Specifically, cannabis use has been associated with reductions in gray matter volume in various regions of the brain involved in a broad range of executive functions such as memory, learning, impulse control, and emotional and affective processing (Batalla et al., 2013; Battistella et al., 2014; Cousijn et al., 2012; Filbey et al., 2014; Koenders et al., 2016; Weinstein, Livny, & Weizman, 2016). In brief, the literature on the effects of cannabis on gray matter volume is mixed, as some work has demonstrated increased gray matter volume in various brain regions (Moreno-Alcázar et al., 2018).

The use of both alcohol and cannabis, either concurrently or simultaneously, is particularly concerning, due to the burgeoning literature on the negative mental and physical health consequences of co-use. For example, alcohol and cannabis co-use has been shown to be associated with an increased risk for a host of negative outcomes (Volkow et al., 2014), including comorbid psychiatric disorders, poorer clinical treatment outcomes, increases in risky behaviors including heavy drinking and driving while intoxicated, in addition to other adverse social sequelae (Brière et al., 2011; Metrik et al., 2018; Midanik et al., 2007; Staiger et al., 2013; Subbaraman et al., 2017). Alcohol and cannabis co-users have also been found to display higher levels of psychiatric severity and comorbid tobacco use compared to those who drink alcohol only (Venegas, Meredith, Cooper, et al., 2020). Further, it has been shown that cannabis use is predictive of not only heavy drinking, but also the development and maintenance of AUD

(Blanco et al., 2016; Hayley, Stough, & Downey, 2017; Lopez-Quintero et al., 2011; Weinberger et al., 2016) and poorer prognoses of AUD treatment than those who drink alcohol only (Agrawal et al., 2007; Aharonovich et al., 2005; Mojarrad et al., 2014; WHO, 2014; Subbaraman, 2016). Further, the odds of meeting diagnostic criteria for alcohol dependence have been shown to be substantially higher among those with cannabis dependence (Stinson, Ruan, Pickering, & Grant, 2006). Notably, however, these negative effects are not uniformly found in the literature (Mallett, Turrisi, Trager, Sell, & Linden-Carmichael, 2019).

In short, there are well-documented negative physical, psychological, and social consequences related to alcohol use, cannabis use, and their co-use. Of particular importance are the findings that co-use is believed to be associated with additive negative effects, especially as they relate to increased psychiatric comorbidity, increased heavy drinking, and worse AUD treatment outcomes. One goal of this dissertation is to characterize clinical correlates of varying levels of cannabis co-use in a large sample of heavy drinkers. The identification of these differences may inform targeted intervention development for this particularly high-risk group.

Mechanisms Underlying Alcohol and Cannabis Co-Use

Various mechanisms underlying alcohol and cannabis co-use have been purported, including alcohol- and cannabis-induced analgesia (Davis, Walton, Bohnert, Bourque, & Ilgen, 2018; Hill, Palastro, Johnson, & Ditre, 2017; Zale, Maisto, & Ditre, 2015), substitution effects (i.e., the use of one substance as a substitute for the other), complementary effects (i.e., the use of one substance in conjunction with another, resulting in additive effects) (Subbaraman, 2016), and simply a general vulnerability for substance misuse and addiction, which may serve to underlie co-use. Given the broad scope of mechanisms believed to potentially maintain co-use, this dissertation focuses on two specific mechanisms that have been shown to underlie alcohol and

cannabis co-use: pharmacological effects of alcohol on the urge to use cannabis (and associated sex-dependent effects) (Study1) and complementary effects (i.e., additive, or the use of one substance enhancing the effects of the other) (Study 3).

At the population level, various sex differences have been elucidated regarding cannabis use, in addition to alcohol and cannabis co-use patterns. Epidemiological studies of cannabis have reported that men not only use cannabis more frequently (SAMHSA, 2014; Cooper & Craft, 2018; Venegas, Meredith, Cooper, et al., 2020; Venegas, Meredith, Green, et al., 2020), but also show a quicker disease progression to cannabis use disorder (CUD) (Stinson et al., 2006) and utilize substance abuse treatment for cannabis use more frequently than women do (SAMHSA, 2014). Additionally, a recent study by our group found that alcohol use was associated with a 2.5-fold increased likelihood of same-day cannabis use, and that this relationship was greater for men than women (Roche et al., 2019). However, these effects are not consistently documented within the literature. For example, despite some reported sex differences suggesting that men are at heightened risk for cannabis abuse, it has also been shown that women are overrepresented when it comes to severity, such that women show a steeper trajectory from initiation of cannabis use to eventual cannabis-related problems (i.e., the "telescoping effect") (Ehlers et al., 2010; Hernandez-Avila, Rounsaville, & Kranzler, 2004 2004; Schepis et al., 2011). Specifically, women have been shown to report higher ratings on factors associated with greater abuse liability, such as liking the drug and willingness to take again (Cooper & Haney, 2014), experience greater cannabis withdrawal symptoms (Cooper & Craft, 2018), and display higher levels of cue-induced cannabis craving than males (Fattore, 2013). Further, it has been documented that women with a lifetime diagnosis of CUD are more likely to meet diagnostic criteria for a comorbid AUD (Calakos, Bhatt, Foster, & Cosgrove, 2017). Taken

together, it appears that despite a growing body of literature on sex differences on the intersection of alcohol and cannabis use, the underlying nature of sex-dependent nature of their co-use remains elusive.

Few experimental studies have directly examined the interaction between alcohol and cannabis, leading to a mixed body of literature. Previous studies have demonstrated that plasma alcohol levels decrease and the subjective effects of cannabis are attenuated as a result of co-use; however, THC levels may be enhanced if alcohol is consumed immediately after cannabis (Lukas & Orozco, 2001). On the other hand, other work has demonstrated that a combination of alcohol and cannabis leads to increases in both plasma THC levels and subjective effects of cannabis; further, these effects may be more robust when alcohol is consumed prior to cannabis (Hartman et al., 2015). THC has also been shown to reduce the subjective effects of alcohol in some cases, while also increasing craving for alcohol in others (Ballard & de Wit, 2011). It is important to note that these studies vary regarding cannabis and alcohol dose, in addition to the extent of co-use among participants. As such, controlled experimental studies of alcohol and cannabis co-use in a sample of heavy alcohol and cannabis co-users are necessary to directly elucidate the complex interactions between alcohol and cannabis.

Another open question related to the co-use of alcohol and cannabis is whether individuals who co-use the two substances are at heightened risk compared to those who use either substance in isolation (i.e., whether the effects of alcohol and cannabis are synergistic, or complementary). Much of this research largely comes from studies of driving impairment following intoxication. Some studies have shown that the combination of alcohol and cannabis leads to greater impairment than that from either alone (Bramness, Khiabani, & Mørland, 2010; Downey et al., 2013; Ramaekers, Robbe, & O'Hanlon, 2000; Ronen et al., 2010), while others

have shown no significant differences (Lenné et al., 2010; Liguori, Gatto, & Jarrett, 2002). Thus, some studies have demonstrated that cannabis potentiates the intoxicating and impairing effects of alcohol, while others do not report such synergistic effects. In effect, this literature warrants additional inquiry, potentially via controlled human laboratory paradigms.

As evidence that alcohol and cannabis co-use results in additive, detrimental effects, it is well-documented that alcohol and cannabis co-use confers a host of risk factors in that combined use may lead to heavier substance use compared with the use of either alone (Brière et al., 2011; Magill, Barnett, Apodaca, Rohsenow, & Monti, 2009; Metrik et al., 2018; Midanik et al., 2007; Staiger et al., 2013; Subbaraman et al., 2017). As such, in that their effects are additive, it has been suggested that cannabis and alcohol can be considered complements to each other (Moore, 2010). In fact, the developmental literature suggests that cannabis and alcohol use trajectories are related (Pape, Rossow, & Storvoll, 2009; Schulenberg et al., 2005; Windle & Wiesner, 2004). Whether co-use is best explained by common risk factors or if the use of one precipitates the use of the other remains a debated question, however (Jackson, Sher, & Schulenberg, 2008). Despite these data that indicate that alcohol and cannabis complement each other, a developing body of work suggest that individuals may substitute cannabis in place of alcohol. For example, in studies of medical cannabis patients, large proportions of patients report using cannabis as a substitution for alcohol (Lucas et al., 2013; Reiman, 2000; Reiman, 2009). In fact, cannabis has been examined as a potential harm reduction agent for individuals in treatment for AUD; however, the extent to which this is feasible, effective, cost-efficient, and ethical remain to be seen (Subbaraman, 2014).

In conclusion, the literature on sex differences and the mechanisms underlying alcohol and cannabis co-use is mixed. While some work has shown that men use cannabis at higher rates

than women, it has also been suggested that women may show a quicker progression to cannabis-related problems. Further, some research has shown that their combination leads to increased subjective effects of both alcohol and cannabis, coupled with important work showing that impairment resulting from co-use is greater than that from the use of either substance alone, providing evidence for potential synergistic effects. Conversely, other work has shown the opposite, that co-use is associated with attenuated subjective effects, adding to a burgeoning body of literature has posited that cannabis may be used as a substitute for alcohol instead of as a complement. This dissertation expands upon previous research on sex differences in co-use by elucidating, via a novel human laboratory design, alcohol-induced craving to use cannabis, and vice versa.

Significance of the Dissertation

Cannabis and alcohol co-use is highly prevalent and confers a host of risk factors that outweigh the risks related to the use of either substance alone. Despite well-documented negative consequences, few studies to date have examined the associations between varying levels of co-use and clinical variables, sex differences related to cannabis and alcohol co-use, and mechanisms underlying this co-use. The dissertation studies presented herein combine survey and experimental methods to elucidate the clinical correlates of co-use, sex-dependent effects, and cross-substance craving that may promote and maintain co-use. Dissertation Study 1 consisted of an alcohol administration paradigm in a sample of alcohol and cannabis co-users and demonstrated that at rising levels of BAC, males reported an increased urge for cannabis compared to females, suggesting that the pharmacological effects of alcohol on the urge to use cannabis are sex dependent. Dissertation Study 2 investigated clinical correlates of varying levels of alcohol and cannabis co-use in a large sample ($N = 863$) of heavy drinkers. Finally,

Dissertation Study 3 used a novel experimental pharmacology paradigm employed remotely via Zoom to test the pharmacological effects of cannabis on alcohol craving and the pharmacological effects of alcohol on cannabis craving.

Mechanisms of co-use are examined through Studies 1 (Venegas, Meredith, Green, et al., 2020) and 3, which consider sex-dependent and synergistic effects, respectively. Although it has been well-documented that alcohol and cannabis are often used both concurrently and simultaneously, the motivational processes and sex-dependent nature of their co-use remains poorly understood. Study 1 sought to fill a gap in this literature by examining subjective craving as a putative mechanism by which alcohol and cannabis are co-used and considers sex dependent effects. Although there was not a significant effect of alcohol administration on cannabis craving (p = 0.079), which suggests that alcohol did not significantly alter participants' urge to use cannabis, the results revealed a host of sex-dependent outcomes. Specifically, males reported higher levels of subjective cannabis craving than females at rising BAC levels; this effect remained robust and significant after adjusting for a host of variables including cannabis and alcohol use severity and mood symptomatology. These results suggest that craving may be a unique mechanism by which alcohol use increases the likelihood of simultaneous cannabis use in males, but not females. This study is innovative in that it was the first to directly assess the pharmacological effects of alcohol on the urge to use cannabis, explored the bidirectional nature of alcohol and cannabis craving, and elucidated important sex differences.

Study 3 sought to build upon the findings of Study 1 utilizing a novel human laboratory paradigm employed remotely via Zoom. Specifically, participants were asked to complete a modified cue-reactivity procedure to induce craving for one substance following the consumption of the other. In other words, cue-induced craving for cannabis was assessed after

the consumption of alcohol, and cue-induced craving for alcohol was assessed after the consumption of cannabis. The project utilized a within-subjects counterbalanced design such that all participants were exposed to both conditions (i.e., cannabis cue-reactivity following alcohol administration and alcohol cue-reactivity following cannabis administration). This study is the only study to date which has utilized such a design, allowing for the exploration of the bidirectional nature of alcohol and cannabis craving and use, in a controlled setting. The novelty of this study is furthered by executing a human laboratory paradigm within an ecologically valid setting (i.e., one's home). Given that the most common form of alcohol consumption is oral ingestion, administration via oral ingestion provides strengths regarding external validity over alcohol infusion paradigms. Further, conducting this study in a naturalistic setting allows for the examination of behaviors and experiences which approximate real-life scenarios (Cyders et al., 2020).

Taken together, findings elucidate sex dependent variables related to co-use, reveal clinically targetable characteristics of co-users, and uncover mechanisms relating substance-induced and cue-induced craving for alcohol and cannabis. These studies provide much-needed scientific evidence that can inform clinical best-practices for individuals who co-use cannabis and alcohol and highlight the importance of considering the effects of one substance on treatment for the other (Gunn, Jackson, Borsari, & Metrik, 2019).

Sex-Dependent Effects of Alcohol Administration on the Urge to Use Cannabis

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ABSTRACT

Alcohol and cannabis co-use is highly prevalent and associated with various negative consequences. The likelihood of same day co-use is high, especially among men, however, underlying mechanisms to their co-use and its sex-dependent nature remain poorly understood. This study aims to elucidate the effects of controlled alcohol administration on the urge to use cannabis and considers sex-dependent effects. A community sample of non-treatment-seeking heavy drinkers (N = 37, 46% female) reporting cannabis use in the past six months completed an alcohol administration paradigm. Participants rated their urge to use cannabis and drink alcohol at baseline and at rising levels of BAC. Mixed model analyses examined the effects of BAC, sex, and their interaction on craving for cannabis. The relationships across urge for cannabis, urge for alcohol, and subjective responses to alcohol were also tested. There was a significant BAC × sex interaction on the urge to use cannabis, such that males reported increases in the urge to use cannabis at rising BACs but females did not. Urge for alcohol significantly predicted urge for cannabis across rising levels of BAC and this relationship was stronger in males than in females. Lastly, stimulation, but not sedation, during alcohol administration was positively associated with the urge for cannabis. Overall, these results suggest that the pharmacological effects of alcohol on the urge to use cannabis are sex dependent and that the stimulant effects of alcohol are associated with a higher urge for cannabis.

Keywords: alcohol, cannabis, co-use, sex differences, craving

Public Significance Statement: Despite their frequent co-use, the underlying mechanisms and sex-dependent nature of alcohol and cannabis co-use remain poorly understood. In a sample of non-treatment-seeking heavy drinkers, males reported an increased urge for cannabis at rising BACs, whereas females did not. This may imply that the pharmacological effects of alcohol on the urge for cannabis are sex dependent, suggesting a possible mechanism by which males in particular report alcohol and cannabis co-use.

INTRODUCTION

Concurrent use of alcohol and cannabis is highly prevalent (Hasin et al., 2015) and associated with a host of negative consequences, including greater psychiatric comorbidity, increased risk-taking behavior, heavier alcohol use, and poorer mental health treatment outcomes (Brière et al., 2011; Metrik et al., 2018; Midanik et al., 2007; Staiger et al., 2013; Subbaraman et al., 2017; Volkow et al., 2014). It is estimated that 68% of individuals with a current DSM-5 CUD diagnosis and over 86% of those with a lifetime CUD diagnosis will also meet diagnostic criteria for a lifetime AUD (Agrawal et al., 2007; WHO, 2014). Further, it has been shown that individuals who report regularly using alcohol and cannabis frequently consume these two substances at the same time (i.e., in a single episode) (Midanik et al., 2007; Subbaraman & Kerr, 2015). In fact, a recent study by our group found that drinking alcohol on a given day was associated with a 2.5-fold increase in the likelihood of same-day cannabis use (Roche et al., 2019). Notably, in this study, the observed effect of alcohol on the increased likelihood of same-day cannabis use was greater for men than for women.

Epidemiological studies consistently report that men tend to use cannabis more frequently (SAMHSA, 2014), are at a greater risk for developing a CUD (Stinson et al., 2006), and seek treatment for CUD at higher rates than women do (SAMHSA, 2014). Despite these findings, it has also been shown that women show a quicker progression from initiation of cannabis use to the development of cannabis-related problems, than men do (i.e., the "telescoping effect") (Ehlers et al., 2010; Hernandez-Avila et al., 2004; Schepis et al., 2011). Additionally, recent studies found that a growing number of women have reported using cannabis for medicinal purposes, compared to men (Finseth et al., 2015; McConnell et al., 2014; Ryan-Ibarra et al., 2015). A recent review by Cooper and Craft examined sex differences in

cannabis research at the both preclinical and clinical levels of analyses (Cooper & Craft, 2018) and found that women exhibit higher withdrawal symptoms, while men use cannabis at higher rates. Females have also been found to exhibit higher levels of cue-induced cannabis craving than males (Fattore, 2013) and it has been documented that women with a lifetime diagnosis of CUD are more likely than men to have a comorbid AUD (Calakos et al., 2017); however, the intersection between cannabis and alcohol remains poorly understood.

In sum, while alcohol and cannabis are often used concurrently, and alcohol may precipitate the use of simultaneous cannabis use, the underlying mechanisms to their co-use and its sex-dependent nature remain poorly understood. An early study by Chait and Perry (Chait & Perry, 1994) provided little evidence that acute alcohol ingestion increases cannabis use overall; however, the authors did find considerable individual differences between subjects in the effects of alcohol on cannabis consumption. In a more recent study by Ballard and de Wit (Ballard & de Wit, 2011), which examined the separate and combined effects of acute low-dose alcohol and THC ingestion on subjective drug effects, it was found that THC alone did not impact ratings for wanting more of the drug. Instead, THC was found to attenuate the increased ratings observed after alcohol was administered. It is possible that within both of these studies, subjective craving may be a putative mechanism by which alcohol and cannabis are co-used – perhaps synergistically.

To fill this gap in the literature, the present study assessed the effects of controlled alcohol administration on the urge to use cannabis, a factor that is hypothesized to impact subsequent cannabis use and considers sex-dependent effects. Specifically, our aims were to test: (a) the effects of controlled alcohol administration on craving for cannabis, (b) whether alcohol's effect on cannabis craving is moderated by sex, and (c) explore the association between

measures of subjective response to alcohol, namely stimulation and sedation, and the urge to use cannabis during the alcohol administration. Given the finding that drinking alcohol on a given day was associated with a 2.5-fold increase in the likelihood of same-day cannabis use (Roche et al., 2019), especially in men, we hypothesized that alcohol administration would be associated with an increased craving for cannabis across both males and females and that this relationship would be greater in men than in women.

METHODS

Participants

All study procedures were approved by the University of California, Los Angeles Institutional Review Board; the protocol number is 14-000501 and the title is "Modeling alcohol reward and reinforcement in the human laboratory." A community sample of non-treatment-seeking heavy drinkers was recruited via online and print advertisements. Preliminary eligibility screening was conducted through online and telephone surveys followed by an in-person screening/assessment visit. After providing written informed consent and receiving a full explanation of the study procedures, participants were breathalyzed, provided a urine sample for urine toxicology testing, and completed a series of self-report questionnaires and semi-structured interviews on substance use and related individual differences.

All participants were required to: (i) have a BAC of 0.000 g/dl (i.e., 0mg%) at the time of the study visit; (ii) test negative for all drugs (except cannabis) on a urine toxicology screen; (iii) test negative on a urine pregnancy test (if female); (iv) be between the ages of 21 and 45; (v) be current heavy drinkers based on National Institute of Alcohol Abuse and Alcoholism (NIAAA) recommendations (i.e., ≥ 14 drinks per week for men or ≥ 7 drinks per week for women); (vi) be non-treatment-seeking for AUD; (vii) not be experiencing significant withdrawal from alcohol;

and (viii) not meet current (i.e., past 3-month) DSM-5 diagnostic criteria for any SUD other than nicotine or alcohol. Participants were not required to test positive for cannabis on the urine toxicology screen. Current (i.e., past 3-month) DSM-5 CUD was an exclusionary criterion for the current study, whereas lifetime CUD was not. Following the in-person screening visit, a physical examination ensured medical eligibility. For the purposes of the present study, participants who endorsed any cannabis use in the past six months per the Cannabis Use Disorders Identification Test – Revised (CUDIT) (Adamson et al., 2010) at the time of the initial in-person screening visit were selected for the analyses presented herein.

Alcohol Administration Procedure

The alcohol administration procedure was conducted at the UCLA Clinical and Translational Research Center (CTRC) and comprehensive methodology is discussed elsewhere (Bujarski et al., 2018). Briefly, participants' height, weight, and vital signs were collected, and intravenous (IV) lines were placed by a nurse prior to beginning the alcohol administration procedure. All participants also completed baseline assessment measures prior to alcohol infusion, at a BAC of 0.00 g/dl.

Alcohol was then administered IV (6% ethanol v/v in saline) using the Computerized Alcohol Infusion System (CAIS) (Plawecki, Han, Doerschuk, Ramchandani, & O'Connor, 2008; Zimmermann et al., 2008; Zimmermann, O'Connor, & Ramchandani, 2011). Throughout the alcohol challenge, participants were administered IV alcohol in amounts designed to reach target BACs of 0.02, 0.04, and 0.06 g/dl, each over 15 minutes. After reaching each target BAC, BAC level was clamped by pausing the alcohol infusion for approximately 5 minutes to allow participants to complete various self-report questionnaires.

Measures

Substance Use Measures. All of the following measures were completed at the initial in-person screening visit, with the exception of the Timeline Follow-Back (TLFB) (Sobell & Sobell, 1992), which was administered both at the screening visit and at the time of the alcohol infusion. The Structured Clinical Interview for DSM-5 (SCID-5) (adapted from First, Williams, Karg, & Spitzer, 2015) assessed for current (i.e., past 3-month) AUD and CUD. The Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989) measured the presence and severity of alcohol withdrawal. The TLFB measured past-month alcohol and cannabis use quantity and frequency. The Alcohol Use Disorders Identification Test (AUDIT) (Allen, Litten, Fertig, & Babor, 1997) and the Alcohol Dependence Scale (ADS) (Skinner & Allen, 1982) assessed alcohol dependence severity. The CUDIT (Adamson et al., 2010) measured problems associated with cannabis use. The Penn Alcohol Craving Scale (PACS) (Flannery, Volpicelli, & Pettinati, 1999) measured tonic levels of alcohol craving. The Biphasic Alcohol Effects Scale (BAES) (Martin, Earleywine, Musty, Perrine, & Swift, 1993) and the Urge Form (UF) (Ray et al., 2007) were administered during the alcohol administration only. The BAES captures alcohol-induced feelings of stimulation and sedation (i.e., via distinct subscales) at baseline and across rising levels of BAC. The UF was the primary outcome of the present analyses; it measured "state levels" of craving for cannabis at baseline and across rising BAC levels. At each BAC level, participants were asked to rate their urge to use both alcohol and cannabis as responses to the following questions: "How strong is your urge to drink right now?" and "How strong is your urge to smoke marijuana right now?" on a scale from 0 ("no urge at all to drink/smoke") to 11 ("very strong urge to drink/smoke").

Anxiety and Depression Measures. Anxious and depressive symptomatology were assessed during the in-person screening visit using the Beck Anxiety Inventory (BAI) (Beck, Epstein, Brown, & Steer, 1988) and the Beck Depression Inventory – II (BDI-II) (Beck, Steer, & Brown, 1996), respectively.

Data Analysis Plan

Analyses were conducted using a multilevel mixed model in SAS Version 9.4 using PROC MIXED. The analyses examined the effects of BAC, a four-level within-subjects factor (0.00, 0.02, 0.04, and 0.06 g/dl, coded 1 – 4), and sex (i.e., male vs. female, coded 0 and 1, respectively), and their interaction on craving for cannabis during the alcohol administration. Urge for cannabis was predicted as a function of BAC, sex, and their interaction, adjusting for craving for alcohol measured at each BAC level via the UF. Other relevant covariates (i.e., AUDIT, CUDIT, BAI and BDI-II scores) were entered into the models to probe for the robustness of the findings. Multilevel mixed models were also used to examine the relationships across subjective response to alcohol, urge for alcohol, and urge for cannabis during the alcohol administration. These mixed models also account for the effect of BAC level and for sex differences. In all models, a random intercept approach was used along with an unstructured covariance matrix.

RESULTS

Sample Characteristics

Thirty-seven (45.9% female) non-treatment-seeking heavy drinkers who reported cannabis use in the past six months were included in the present analyses. Sample characteristics are presented in **Table 1.** This sample consisted of heavy drinkers (i.e., average AUDIT score of 12.90 (*SD* = 4.91)) with sub-hazardous levels of cannabis use (i.e., average CUDIT score of 4.32

(*SD* = 2.84)). A series of independent-samples t-tests were performed to examine differences between males and females on aforementioned individual differences and substance use variables. Results indicated no significant group differences on any mood or substance use variable (*p's* > 0.07). The only exception to that was the BAI score, in which females, on average, reported higher anxiety symptomatology than males ($t(35) = -2.25$, $p < 0.05$).

Effects of Alcohol on Urge for Cannabis

Across both males and females there was a non-significant effect of breath alcohol concentration on the urge to use cannabis [$F(3,108) = 2.32$, $p = 0.079$]. However, once Sex and BAC × Sex were entered into the model, there was a significant BAC × sex interaction on the urge to use cannabis [$F(3,104) = 2.99$, $p < 0.05$], while adjusting for the urge to use alcohol [$F(1,104) = 22.92$, $p < 0.0001$]. As shown in **Figure 1** and confirmed through simple effects tests, these results suggest that male participants reported increases in the urge to use cannabis across rising BAC levels [$F(3,144) = 3.24$, $p < 0.05$] while female participants did not [$F(3,124) = 0.68$, $p = 0.57$]; in fact, they show reductions in their craving for cannabis across rising BAC levels, although those reductions were not statistically significant. In sum, craving for cannabis across rising BAC levels is going in different directions for males and females, with males having a significant increase and females having a nonsignificant decrease in craving.

To further probe these effects, we re-ran the mixed models adjusting for scores on the AUDIT, CUDIT, BAI, and BDI-II (each covariate tested separately), given their putative role as third variables of interest. Results of the BAC × sex interaction on the urge for cannabis remained significant in all models. Notably, none of the covariates were statistically significant in these models, with only CUDIT score having a marginal effect on the urge for cannabis [$F(1,104) = 3.77$, $p = 0.055$]. The results also remained robust when removing the urge for

alcohol variable as a covariate. Together, these findings suggest that males experienced greater increases in the urge to use cannabis across rising BAC levels than females, and that this sex-dependent effect was not accounted for by differences in alcohol use severity, severity of hazardous cannabis use, depression, or anxiety symptomatology.

Relationship between Urge for Alcohol and Urge for Cannabis

We examined the association between ratings of urge to drink and urge to use cannabis at baseline and at rising levels of BAC using a multilevel modeling approach, in which alcohol urge ratings predicted cannabis urge ratings. The relationship between the urge for alcohol and the urge for cannabis across levels of BAC was robust and statistically significant [$t(110) = 5.38$, $p < 0.0001$, $B = 0.27$, $SE = 0.05$]. There was no significant effect of BAC [$F(3,104) = 0.12$, $p = 0.95$] or BAC × urge for alcohol [$F(3,104) = 0.26$, $p = 0.86$] in predicting the urge for cannabis. This suggests that the association between urge for alcohol and urge for cannabis was relatively stable across BAC levels.

A test of sex effects on the relationship between urge for alcohol and urge for cannabis, found a significant sex × urge for alcohol interaction in predicting the urge for cannabis [$t(109) = -2.14$, $p < 0.05$, $B = -0.21$, $SE = 0.10$]. When probing for this interaction by testing simple effects in males and females separately, we found a stronger relationship between urge for alcohol and urge for cannabis during the alcohol administration in males [$t(59) = 4.85$, $p < 0.0001$, $B = 0.34$, $SE = 0.07$], and a smaller, yet statistically significant effect, of urge for alcohol on urge for cannabis in females [$t(50) = 2.05$, $p < 0.05$, $B = 0.13$, $SE = 0.06$]. As with the models for the effects of alcohol, we probed for these effects by adjusting for scores on the AUDIT, CUDIT, BAI, and BDI-II (each covariate tested separately). The sex × urge for alcohol in predicting the urge for cannabis remained significant in all models. CUDIT score was the only covariate found

to have effect on the urge for cannabis [$F(1,109) = 4.63$, $p < 0.05$]. These results indicate that the relationship between urge for alcohol and urge for cannabis during alcohol administration was stronger for males than for females, and that this effect was not accounted for by differences in alcohol use severity, cannabis use severity, depression, or anxiety.

Relationship between Subjective Response to Alcohol and Urge for Cannabis

We examined the association between alcohol-induced stimulation (measured by the BAES) and urge to use cannabis at baseline and at rising levels of BAC using a multilevel modeling approach, in which ratings of stimulation predicted cannabis urge ratings. The relationship between stimulation and the urge for cannabis across levels of BAC was positive and statistically significant [$t(110) = 2.32$, $p < 0.05$, $B = 0.03$, $SE = 0.01$]. When BAC was added to the model, we found a significant effect of BAC [$F(3,104) = 4.03$, $p < 0.01$] and BAC × stimulation interaction [$F(3,104) = 7.52$, $p < 0.001$] in predicting the urge for cannabis. Probing for this interaction revealed that the association between stimulation and urge for cannabis was not significant at baseline (BAC = 0.00 g/dl) [$t(65) = -0.44$, $p = 0.66$], but became significant at BAC = 0.02 g/dl [$t(65) = 2.71$, $p < 0.01$], and remained significant at BAC = 0.04 g/dl [$t(65) = 2.62$, $p < 0.05$] and BAC = 0.06 g/dl [$t(65) = 2.40$, $p < 0.05$]. In other words, stimulation was positively associated with urge for cannabis once alcohol was administered, but not at baseline. The association between stimulation and urge for cannabis was not moderated by gender [$t(109) = -1.74$, $p = 0.09$].

Contrary to the findings for stimulation, the effects for alcohol-induced sedation (measured by the BAES) on urge to use cannabis was generally non-significant. There was no significant relationship between sedation and the urge for cannabis [$t(110) = 0.06$, $p = 0.95$] nor a BAC × sedation [$F(3,104) = 0.11$, $p = 0.74$] effect in predicting the urge for cannabis. The

association between sedation and urge for cannabis was not moderated by gender [$t(109) = 0.35$, $p = 0.73$].

DISCUSSION

This study examined the pharmacological effects of alcohol on craving for cannabis. Specifically, we predicted that urge to use cannabis would increase with rising levels of BAC, and given the previous literature implicating sex differences in same day co-use of alcohol and cannabis (Roche et al., 2019), we expected that this relationship would be stronger for males than females. Contrary to our hypothesis, there was not a significant effect of alcohol (i.e., rising BAC) on cannabis craving ($p = 0.079$), suggesting that across both males and females, alcohol administration did not significantly modulate participants' urge to use cannabis. Instead, our results implicated a host of sex-dependent effects on the relationship between alcohol administration and craving for cannabis. Specifically, males reported significantly higher levels of cannabis craving than females at rising BAC levels. This sex-dependent effect remained robust after considering a host of potential confounds, such as cannabis and alcohol use severity and mood symptomatology. The stronger association between alcohol and cannabis craving in males is consistent with previous work from our laboratory (Roche et al., 2019); in a separate and large sample ($N = 551$), we found that alcohol use was more strongly related to same-day cannabis use in males than females. Given the literature suggesting that higher levels of alcohol craving is associated with increased likelihood of subsequent alcohol use (McHugh, Fitzmaurice, Griffin, Anton, & Weiss, 2016) and that alcohol use is likely to be met with concurrent cannabis use (Midanik et al., 2007; Subbaraman & Kerr, 2015), craving may be a mechanism through which alcohol use increases the likelihood of simultaneous cannabis use in males, but not females. Additional analyses of the association between alcohol and cannabis craving during

alcohol administration suggested that the two are more strongly linked in males, as compared to females, in this study. While it is speculated that in co-users, the use of one substance triggers craving for another (Metrik et al., 2018), this is the first study to provide data on the direct pharmacological effects of alcohol on the urge for cannabis and to explore the interplay between alcohol craving and cannabis craving. The extent to which these effects are sex-dependent add to a growing body of literature in the field of cannabis research suggesting differential behavioral and clinical responses as a function of sex (Cooper & Craft, 2018).

Another interesting finding from this controlled experimental paradigm has to do with the association between the stimulant effects of alcohol and the urge for cannabis in this sample. Interestingly, across males and females, higher levels of alcohol-induced stimulation were associated with a higher urge for cannabis. This effect was not present at baseline (i.e., BAC = 0.00 g/dl) but reached significance and remained significant when alcohol was on board (i.e., BACs of 0.02, 0.04, and 0.06 g/dl). This finding suggests that the stimulant effects of alcohol may underlie the association between drinking alcohol and having an increased urge for cannabis. Perhaps the stimulant effects of alcohol may increase the urge for the mostly sedative and anxiolytic effects of cannabis. Drug co-use is often influenced by stimulant/sedative properties of alcohol and drugs of abuse.

These results must be interpreted in light of the study's strengths and limitations. A strength of the study is that males and females in the sample did not differ on age, mood, or substance use variables, aside from anxiety symptomatology, allowing for an adequate comparison between groups. Another strength of this study includes the use of controlled alcohol administration as a function of BAC level. While the intravenous mode of alcohol administration lacks ecological relevance, the model results in precise blood alcohol levels and assesses

behavioral outcomes as a function of dose. As the current design lacks a matched placebo condition, we were not able to speak to the extent to which the findings are related to rising blood alcohol levels over the course of the session or whether craving increases simply as a function of session duration (i.e., time). A future direction for research might include the comparison between alcohol and placebo (i.e., saline) administration so as to more clearly elucidate the pharmacological effect of alcohol on cannabis craving. Furthermore, additional opportunities for future research includes testing whether the effects of alcohol on urge to use cannabis predicts the decision to use cannabis by assessing the impact of alcohol exposure on cannabis self-administration. In brief, experimental paradigms that manipulate the exposure to both alcohol and cannabis cues and/or administration are needed to fully elucidate these cross-substance effects.

However, the present study has a number of limitations, such as the relatively small sample size, the lack of a placebo-alcohol condition, the limited overlapping co-use in the sample, the focus on smoking cannabis (i.e., instead of other routes of administration), and the overall low subjective craving ratings. Additionally, given that inclusion in the present study was based on report of any cannabis use in the past six months, these analyses were limited by a sample of participants reporting relatively light to modest levels of cannabis use frequency and severity, on average. For instance, only 18.9% of the sample (n = 7) tested positive for THC at the time of the in-person screening visit, indicating a lack of recency of use. Further, 18.9% (n = 7) also denied any cannabis use in the past month. As such, these findings may not be generalizable to heavier cannabis users and additional studies with heavy drinking and heavy cannabis use samples are needed to extend the present findings. Furthermore, the pharmacological effects of alcohol on the urge for cannabis among heavy cannabis users, a

population that is at greatest risk for the negative effects of alcohol-cannabis co-use, remains unknown. Lastly, given that the present analyses were limited to BAC levels that peaked at 0.06 g/dl, future research might consider the examination of participants' urge to use cannabis at higher levels of BAC approaching the binge-intoxication cycle.

In conclusion, alcohol administration increased the urge to use cannabis in male but not female heavy drinkers who also report cannabis use. There was a positive relationship between urge for alcohol and urge for cannabis across rising levels of BAC; however, this relationship was stronger among males. This formative work suggests a possible mechanism by which males in particular report alcohol and cannabis co-use. Given that females reported higher levels of anxiety than males, on average, in this sample, a potential future direction is to examine the role of anxiety in alcohol and cannabis co-use. This line of inquiry might be especially relevant for females given the baseline differences in this sample, as it has been shown that anxiety and stress symptomatology are common precipitants of cannabis consumption (Temple, Driver, & Brown, 2014). Further research on the alcohol and cannabis relationship, its sex-dependent effects, and associated clinical implications is needed, especially as cannabis use becomes increasingly frequent as a result of public policy changes.

Table 1. Sample Characteristics.

Variable[a]	Males (n = 20)	Females (n = 17)	Test for Difference
Age	27.70 (5.86)	27.06 (4.39)	$t(35) = 0.37$, $p = 0.71$
AUDIT[b]	12.90 (3.88)	13.12 (6.03)	$t(35) = -0.13$, $p = 0.90$
ADS[c]	11.55 (4.72)	9.88 (4.83)	$t(35) = 1.06$, $p = 0.30$
PACS[d]	8.15 (3.88)	9.41 (5.40)	$t(35) = -0.82$, $p = 0.42$
CUDIT[e]	4.45 (2.68)	4.18 (3.09)	$t(35) = 0.29$, $p = 0.77$
Cannabis use days[f]	1.70 (1.42)	3.24 (3.03)	$t(21.87) = -1.92$, $p = 0.07$
Drinking days[f]	19.90 (6.22)	16.06 (5.90)	$t(35) = 1.92$, $p = 0.06$
DPDD[g, f]	5.44 (1.87)	4.38 (1.63)	$t(35) = 1.81$, $p = 0.08$
Alcohol and cannabis co-use days[f]	1.30 (1.42)	1.59 (1.62)	$t(35) = -0.58$, $p = 0.57$
Tobacco use days[f]	7.95 (12.38)	4.47 (9.23)	$t(35) = 0.95$, $p = 0.35$
BDI-II[h]	6.75 (6.62)	11.18 (9.74)	$t(35) = 1.64$, $p = 0.11$
BAI[i]	4.55 (4.30)	8.29 (5.80)	$t(35) = -2.25$, $p < 0.05$*

[a] Standard deviations appear within parentheses for continuous variables.
[b] Alcohol Use Disorders Identification Test (AUDIT).
[c] Alcohol Dependence Scale (ADS).
[d] Penn Alcohol Craving Scale (PACS).
[e] Cannabis Use Disorders Identification Test – Revised (CUDIT).
[f] Assessed by the Timeline Follow Back (TLFB) interview for the past 30 days.
[g] Drinks per drinking day (DPDD).
[h] Beck Depression Inventory – II (BDI-II).
[i] Beck Anxiety Inventory (BAI).
* Single asterisks denote group differences.

Table 2. Urges for alcohol and cannabis at baseline and across rising BAC level.

Variable[a]	Males (n = 20)	Females (n = 17)	Test for Difference
Urge for alcohol (0.00 g/dl)[b]	2.10 (2.00)	1.18 (2.16)	$t(35) = 1.35$, $p = 0.19$
Urge for alcohol (0.02 g/dl)[b]	3.35 (2.72)	2.41 (2.81)	$t(35) = 1.03$, $p = 0.31$
Urge for alcohol (0.04 g/dl)[b]	3.80 (2.55)	2.76 (3.01)	$t(35) = 1.13$, $p = 0.27$
Urge for alcohol (0.06 g/dl)[b]	4.25 (2.67)	3.29 (2.73)	$t(35) = 1.07$, $p = 0.29$
Urge for cannabis (0.00 g/dl)[b]	1.10 (1.62)	0.65 (1.41)	$t(35) = 0.90$, $p = 0.38$
Urge for cannabis (0.02 g/dl)[b]	1.75 (2.34)	0.29 (1.21)	$t(29.44) = 2.43$, $p = 0.02$*
Urge for cannabis (0.04 g/dl)[b]	1.40 (2.23)	0.65 (1.37)	$t(32.04) = 1.26$, $p = 0.22$
Urge for cannabis (0.06 g/dl)[b]	2.25 (3.01)	0.65 (1.41)	$t(27.90) = 2.13$, $p = 0.04$*

[b] Assessed by the Urge Form (UF).

* Single asterisks denote group differences.

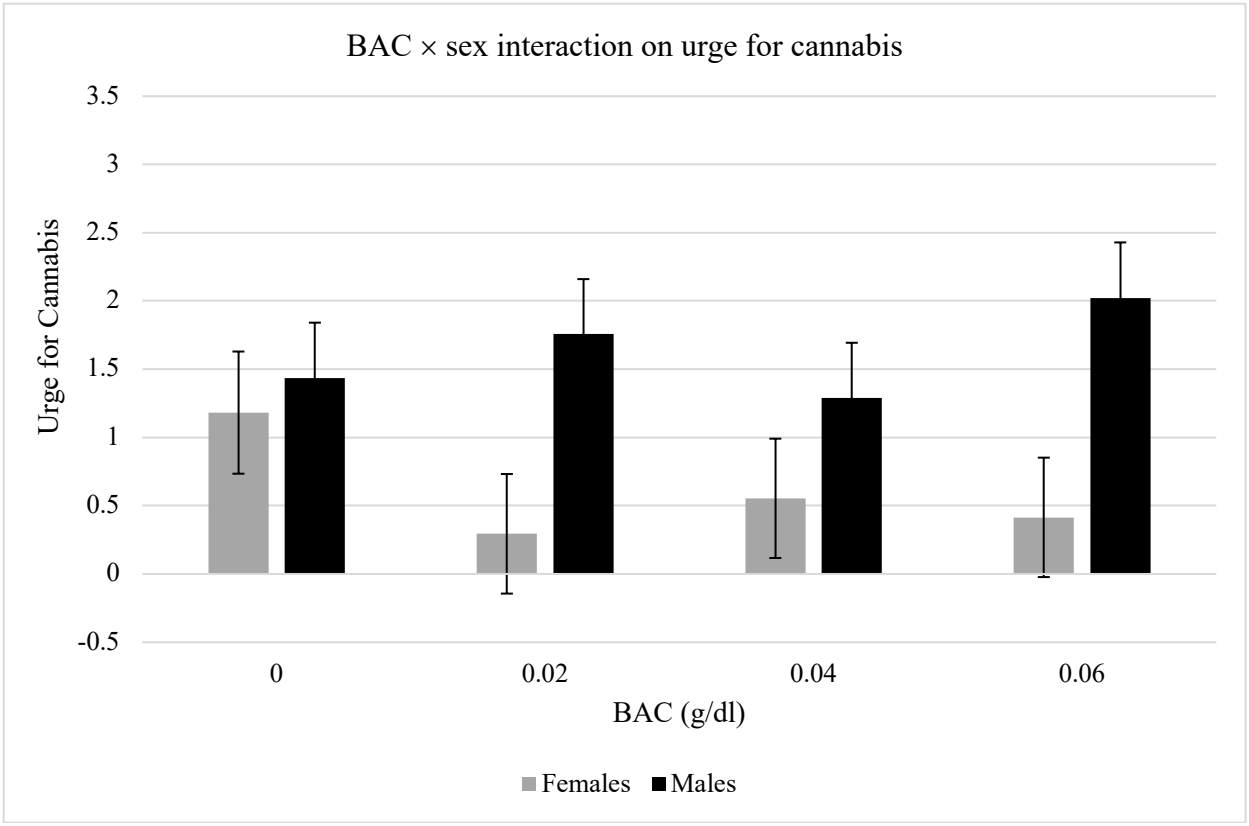

Figure 1. Predicted values of urge to use cannabis across rising BAC levels by sex, adjusting for urge to drink alcohol.

Cannabis and Alcohol Co-Use: The Effects of Intensity of Cannabis Use Among Heavy Drinkers

Alexandra Venegas, M.A., Han Du, Ph.D., Ziva D. Cooper, Ph.D. & Lara A. Ray, Ph.D.

ABSTRACT

Objective: Cannabis and alcohol co-use is highly prevalent and confers a host of risk factors that outweigh those related to the use of either substance alone. However, few studies have examined associations between varying levels of co-use intensity (i.e., frequency) and clinical variables. The present study characterizes the effects of co-use across varying levels of cannabis use frequency in a large sample of heavy drinkers.

Methods: Comparisons among co-use groups (i.e., no, light-to-moderate, and moderate-to-heavy cannabis use; $N = 863$; 33.95% female) on demographic and clinical variables consisted of one-way analyses of variance for continuous outcomes or Chi-Square tests for dichotomous outcomes. Multinomial logistic regression modeling was used to examine the relationship between demographic and clinical variables and co-use group membership. Multiple linear regression was used to explore associations among variables of interest and cannabis use days.

Results: Despite relatively low levels of cannabis use overall in the present sample, younger age, identification with male gender, treatment seeking for AUD, and concurrent tobacco use were robust predictors of co-use. Individuals reporting more frequent cannabis use also reported increased levels of alcohol craving and more heavy drinking days, as compared to those who reported fewer or no cannabis use days. Drinking days and treatment seeking for AUD significantly predicted increases in cannabis use days.

Conclusion: In clinical practice, younger age, male gender, and comorbid tobacco use represent identifiable risk factors for cannabis and alcohol co-use. While in treatment for AUD, reducing drinking days may be an intervention target to mitigate co-use.

Keywords: alcohol, cannabis, co-use, risk factors

INTRODUCTION

Cannabis is the most widely used illicit substance across the globe and the third most used drug in the United States (U.S.). It is also the most commonly used drug among those who drink alcohol (SAMHSA, 2017); in fact, 20-50% of individuals who misuse alcohol also report cannabis co-use (Petry, 2001). Similarly, among those who use cannabis, over 75% report concurrent alcohol use (Agrawal et al., 2007; Haas et al., 2015; Hyggen & Hammer, 2014; Midanik et al., 2007). It is noteworthy that those who report using both alcohol and cannabis often use them at the same time (i.e., in a single substance use episode) (Midanik et al., 2007; Roche et al., 2019; Subbaraman & Kerr, 2015).

Individuals who use both alcohol and cannabis report greater psychiatric severity and adverse social consequences (Brière et al., 2011; Metrik et al., 2018; Midanik et al., 2007; Staiger et al., 2013; Subbaraman et al., 2017; Volkow et al., 2014). For example, co-use is associated with an increased risk for a host of negative outcomes (Volkow et al., 2014), including comorbid psychiatric disorders, poorer clinical treatment outcomes, increases in risky drinking behaviors, and heightened risk for prescription drug misuse (Brière et al., 2011; Linden-Carmichael, Allen, Masters, Ansell, & Lanza, 2021; Metrik et al., 2018; Midanik et al., 2007; Staiger et al., 2013; Subbaraman et al., 2017; Wardell, Egerton, & Read, 2020). Individuals who co-use alcohol and cannabis report higher levels of psychiatric severity and comorbid tobacco use compared to those who drink alcohol only (Venegas, Meredith, Cooper, et al., 2020). Further, the extant literature has largely shown that cannabis use is predictive of not only heavy drinking, but also the development and maintenance of alcohol use disorder (AUD) (Blanco et al., 2016; Hayley et al., 2017; Lopez-Quintero et al., 2011; Weinberger et al., 2016) and poorer prognoses of AUD treatment (Subbaraman et al., 2017; Wardell et al., 2020). Further, the odds

of meeting diagnostic criteria for alcohol dependence is substantially higher among those with DSM-IV cannabis dependence (Stinson et al., 2006). However, despite this well-documented evidence, additive detrimental effects of co-use are not uniformly shown in the literature. In fact, a growing body of research suggests that alcohol and cannabis may act as substitutes for each other, and that the use of cannabis may be associated with overall lower levels of alcohol consumption (Risso et al., 2020).

Movements to regulate cannabis have changed the legal and political landscape of cannabis use across the U.S., leading to an increased availability of cannabis, and possibly influencing alcohol and cannabis co-use patterns. Rates of cannabis use continue to rise across the U.S., potentially due to recent legalization efforts. Specifically, past-year cannabis use among adults increased from approximately 4% to greater than 18% between 2001–2002 and 2019–2020 (SAMHSA, 2021). The rise in cannabis use among adults has been observed in states that have either regulated medicinal or adult-use cannabis – or both (Cerdá et al., 2012; Hasin et al., 2015; Mauro et al., 2019; Wen et al., 2014). As such, it is critical to characterize those who co-use alcohol and cannabis, as rates of co-use will likely continue to rise as cannabis becomes increasingly available across the U.S.

Cannabis and alcohol co-use is highly prevalent and confers a host of risk factors that outweigh the risks related to the use of either substance alone. Despite well-documented negative consequences, few studies have examined the associations between varying levels of cannabis-alcohol co-use and clinical variables. Instead, co-use is often characterized in binary terms, yet understanding the underlying intensity of cannabis use in conjunction with alcohol use is most representative of the clinical landscape. Specifically, individuals who use cannabis less frequently may be less impacted by the adverse consequences associated with alcohol and

cannabis co-use, while more frequent cannabis users may be more likely to experience negative outcomes. The nuanced understanding of co-use can inform clinical and research practices. To that end, this study hypothesizes a cannabis use frequency response for clinical correlates in a large sample of heavy drinkers (N = 863). Consistent with our previous work (Venegas, Meredith, Cooper, et al., 2020; Venegas, Meredith, Green, et al., 2020), we predict that more frequent cannabis use will be associated with male gender, younger age, comorbid tobacco use, and more problematic drinking (i.e., heavier drinking and more alcohol-related problems), as compared to light-to-moderate and non-co-use. In other words, we hypothesize a dose-response pattern whereby more frequent cannabis use among heavy drinkers will be associated with greater likelihood of male gender, younger age, heavy/problematic drinking, and cigarette smoking.

METHODS

Participants

The current sample is a combination of six separate human laboratory studies and randomized clinical trials with similar inclusion criteria and recruitment methods conducted at the University of California, Los Angeles (UCLA). All studies recruited community samples of both treatment seeking and non-treatment seeking heavy drinkers from the greater Los Angeles Area. Four of these studies examined pharmacotherapies for alcohol use: naltrexone (n = 199, comprised of non-treatment seekers) (Ray et al., 2018), combination naltrexone and varenicline (n = 175, comprised of treatment seekers) (Ray et al., 2021) and two studies of ibudilast (n = 183 and n = 128, comprised of non-treatment seekers) (Grodin et al., 2021; Ray et al., 2017). One study was an alcohol self-administration study (n = 140, comprised of non-treatment seekers) (Bujarski et al., 2018), and the final study examined the effects of a brief drinking intervention (n

= 38, comprised of non-treatment seekers) (Grodin, Ray, MacKillop, Lim, & Karno, 2019). The combination of these subsamples resulted in a final sample size for the present study of 863. Participation in multiple studies was not allowed. Data used in the present analyses were collected before the delivery of any pharmacotherapy and/or brief interventions.

All participants met criteria for heavy drinking. This definition varied by study; four studies defined heavy drinking as reporting consumption of greater than 14 drinks per week for men and greater than 7 drinks per week for women over the past month, one study's definition was reporting consumption of greater than or equal to 48 drinks in the past month, and one study defined it as reporting a binge drinking episode (i.e., greater than or equal to 5 drinks in one sitting for men and greater than or equal to 4 drinks in one sitting for women) at least four times in the past month.

Screening Procedures

All study procedures were approved by the UCLA Institutional Review Board, and all participants provided written informed consent after receiving a full explanation of the study procedures. Participants were recruited via online and print advertisements. Interested individuals called the laboratory and completed a telephone interview to determine preliminary eligibility.

All studies generally employed the following exclusion criteria: (i) current involvement in treatment programs for alcohol use or have received treatment in the prior 30 days to study participation (aside from the study which recruited participants treatment seeking for AUD); (ii) use of non-prescription psychoactive drugs or use of prescription medications for recreational purposes, except for cannabis; (iii) self-reported lifetime and/or current history of severe mental illness (e.g., bipolar disorder or psychotic disorders); (iv) current use of antidepressants, mood

stabilizers, sedatives, anti-anxiety medications, seizure medications, or prescription painkillers; and (v) self-reported contraindicated medical conditions (e.g., chronic liver disease, cardiac disease).

Participants who were deemed eligible after completing the telephone interview were assessed for further exclusionary criteria as part of an in-person assessment as follows: (i) pregnancy among females (as verified by a urine sample), nursing, or planning to get pregnant in the next 6 months or refusal to use a reliable method of birth control; (ii) blood alcohol concentration (BAC) greater than 0.000 g/dl as measured by the Dräger Inc. Alcotest® 6510; and (iii) a positive urine toxicology screen for any drug (other than cannabis), as measured by a Medimpex United Inc. 10 panel drug test. A full summary of inclusion/exclusion criteria for all studies is provided in **Supplemental Table 1.**

Measures

At the in-person assessment visit, participants completed a comprehensive battery of individual differences, clinical, and substance use measures. The following measures were shared across all studies, resulting in the largest number of viable observations: (i) the Timeline Follow-Back (TLFB) (Sobell & Sobell, 1992) interview for the past 30 days measured frequency and quantity of alcohol, cannabis, and tobacco use; (ii) the Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999) measured tonic levels of alcohol craving; and (iii) the Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) was used to determine tobacco smoking status and nicotine dependence severity. Of note, participants who endorsed greater than or equal to 10 days of cannabis use per month in the past three months underwent the current (i.e., past-year) cannabis use disorder (CUD) module of the Structured Clinical Interview for DSM-5 (SCID-5) (adapted from First et al., 2015). Following the in-

person assessment visit, those who met diagnostic criteria for a current moderate or severe CUD were excluded from subsequent participation in the parent studies. Participants who did not meet this use threshold were not administered the current CUD module of the SCID-5. However, all participants' data, regardless of current CUD diagnosis (i.e., current CUD module not administered, no current CUD, current mild CUD, current moderate CUD, and current severe CUD) were included in the present analyses.

Cannabis and alcohol co-use groups were classified as the following: (i) non-cannabis users (i.e., no reported cannabis use in the past 30 days on the TLFB); (ii) light-to-moderate cannabis users (i.e., 1-15 days of cannabis use on the TLFB); and (iii) moderate-to-heavy cannabis users (i.e., 16-30 days of cannabis use on the TLFB). These groups were well-validated by comparisons on a measure of cannabis use disorder severity (i.e., the Cannabis Use Disorders Identification Test – Revised (CUDIT-R)) (Adamson et al., 2010), as those in the moderate-to-heavy cannabis use group displayed the highest CUDIT-R scores, followed by those in the light-to-moderate group, with those in the non-cannabis use group with the lowest CUDIT-R scores. However, not all studies included data on the CUDIT-R; in fact, only three out of six studies provided data on this measure. As such, CUDIT-R scores were not included in the subsequent analyses.

Data Analysis Plan

Comparisons among alcohol and cannabis co-use groups (i.e., no cannabis use, light-to-moderate cannabis use, and moderate-to-heavy cannabis use) consisted of one-way analyses of variance (ANOVAs) for continuous outcomes or Chi-Square tests for dichotomous outcomes using R version 3.5.0 (R Core Team, 2017), using the base package.

To examine the relationship between demographic and clinical variables of interest described above and alcohol and cannabis co-use group membership (i.e., light-to-moderate cannabis use and moderate-to-heavy cannabis use), we utilized multinomial logistic regression modeling conducted in R, using the packages 'foreign' (R Core Team et al., 2020) and 'nnet' (Venables & Ripley, 2002). For this analysis, we modeled the likelihood of being classified as a light-to-moderate cannabis user or a moderate-to-heavy cannabis user versus being classified as a non-cannabis user. The predictors included were age, gender, tonic alcohol craving assessed via the PACS, drinking days, drinks per drinking day, percent heavy drinking days, AUD treatment seeking status, nicotine dependence severity via the FTND, and cigarette use days. In order to account for differences among the studies from which these data were culled, we included a categorical study source variable as a covariate. All model predictors and the covariate were entered into the model simultaneously.

Exploratory Analyses

We also sought to explore relationships among the aforementioned variables of interest and a continuous measure of cannabis use days, among those reporting any cannabis use in the past month per the TLFB (i.e., non-cannabis users were excluded from exploratory analyses). To do so, we conducted a multiple linear regression in R using the base package (R Core Team, 2017). We predicted cannabis use days from the following predictor variables: age, gender, tonic alcohol craving via the PACS, drinking days, drinks per drinking day, percent heavy drinking days, AUD treatment seeking status, nicotine dependence severity via the FTND, and cigarette use days. This analysis also controlled for study source. All model predictors and the covariate were entered into the model simultaneously.

RESULTS

Sample Characteristics

A full description of the sample, including cannabis use group comparisons, is shown in **Table 1**. For the subset of the sample that completed the CUDIT, we found that the three-group distinction based on the proposed cut-off pertaining to reported days of cannabis use was robust. Specifically, when comparing groups on the CUDIT-R, all groups significantly differed from each other ($F(2) = 296.1$, $p < 0.001$). Specifically, those reporting no cannabis use displayed the lowest scores on the CUDIT-R ($M = 0.93$, $SD = 2.10$), followed by those reporting light-to-moderate cannabis use ($M = 6.40$, $SD = 4.96$); those reporting moderate-to-heavy cannabis use, on the other hand, displayed the highest CUDIT-R scores ($M = 14.60$, $SD = 6.37$).

To test differences among co-use groups on various clinical and demographic characteristics, separate one-way ANOVAs revealed significant differences among the non-cannabis use and light-to-moderate cannabis use groups with regard to age ($F(2) = 7.89$, $p < 0.001$). Specifically, light-to-moderate cannabis users ($M = 30.71$, $SD = 10.03$) were younger than non-cannabis users ($M = 34.05$, $SD = 11.01$). A Chi-Square test indicated that both cannabis-using groups were more likely to identify as male than female ($\chi^2(2) = 10.79$, $p = 0.005$).

Regarding alcohol use, separate one-way ANOVAs revealed significant differences among the alcohol and cannabis co-use groups on various outcome variables, including tonic alcohol craving via the PACS ($F(2) = 6.22$, $p = 0.002$), drinking days ($F(2) = 6.21$, $p = 0.002$) percent heavy drinking days per the TLFB ($F(2) = 3.41$, $p = 0.034$), and treatment seeking status for AUD ($\chi^2(2) = 37.46$, $p < 0.001$). More specifically, moderate-to-heavy cannabis users reported significantly higher levels of tonic alcohol craving ($M = 12.66$, $SD = 7.19$) than both

the light-to-moderate cannabis users (M = 10.38, SD = 6.31) and the non-cannabis users (M = 10.16, SD = 7.16). Moderate-to-heavy cannabis users reported significantly more drinking days (M = 19.12, SD = 8.30) than both the light-to-moderate (M = 16.37, SD = 7.66) and non-cannabis users (M = 16.43, SD = 8.08). Further, moderate-to-heavy cannabis users reported a significantly greater percentage of heavy drinking days (M = 60.05, SD = 34.96) than non-cannabis users (M = 52.02, SD = 34.70). Lastly, moderate-to-heavy cannabis users were more likely to be treatment seeking for AUD (39.84% treatment seeking) than both light-to-moderate (14.29% treatment seeking) and non-cannabis users (18.46% treatment seeking).

With regard to co-occurring cigarette use, one-way ANOVAs revealed additional group differences on cigarette use days ($F(2) = 27.50$, $p < 0.001$) and nicotine dependence severity ($F(2) = 10.06$, $p < 0.001$). Non-cannabis users reported the fewest number of cigarette use days (M = 9.81, SD = 13.20), with light-to-moderate cannabis users reporting the greatest number of cigarette use days (M = 18.88, SD = 13.57). Lastly, while there were no significant differences in nicotine dependence severity between non-cannabis users and light-to-moderate cannabis users, moderate-to-heavy cannabis users displayed significantly higher levels of nicotine dependence severity (M = 2.80, SD = 2.62) than both non-cannabis users (M = 1.75, SD = 2.42) and light-to-moderate cannabis users (M = 1.84, SD = 2.20).

Multinomial Logistic Regression

A multinomial logistic regression was used to test the relationships between demographic and clinical variables of interest and co-use group membership (i.e., light-to-moderate cannabis use and moderate-to-heavy cannabis use). Specifically, the model estimated the odds of being classified as either a light-to-moderate cannabis user or a moderate-to-heavy cannabis user, versus being classified as a non-cannabis user, as a function of age, gender, tonic alcohol

craving, drinking days, drinks per drinking day, percent heavy drinking days, treatment seeking status for AUD, nicotine dependence severity, and cigarette use days, controlling for study source. The results of the multinomial logistic regression analysis are shown in **Table 3.**

With regard to the odds of being classified as a light-to-moderate cannabis user versus a non-cannabis user, age and cigarette use days were significantly associated with the odds of being a light-to-moderate cannabis user. Specifically, a one-year increase in age was associated with a decrease in the log odds of being a light-to-moderate cannabis user versus a non-cannabis user in the amount of 0.049 ($p < 0.001$). A one-day increase in cigarette use days was associated with an increase in the log odds of being a light-to-moderate cannabis user versus a non-cannabis user in the amount of 0.040 ($p < 0.001$). In other words, younger age and a higher number of cigarette use days were associated with a larger log odds of being classified as a light-to-moderate cannabis user, versus a non-cannabis user.

With regard to the odds of being classified as a moderate-to-heavy cannabis user versus a non-cannabis user, age, gender, drinking days, and cigarette use days were significantly associated with the odds of being a moderate-to-heavy cannabis user. Specifically, a one-year increase in age was associated with a decrease in the log odds of being a moderate-to-heavy cannabis user versus a non-cannabis user in the amount of 0.068 ($p < 0.001$). The log odds of being a moderate-to-heavy cannabis user versus a non-cannabis user differed by 0.69, depending on gender, such that males were more likely than females to be classified as a moderate-to-heavy cannabis user ($p = 0.0079$). The log odds of being a moderate-to-heavy cannabis user versus a non-cannabis user also differed by 1.54, depending on treatment seeking status for AUD, such that treatment seekers were more likely than non-treatment seekers to be classified as a moderate-to-heavy cannabis user ($p < 0.001$). Lastly, a one-day increase in cigarette use days

was associated with a decrease in the log odds of being a moderate-to-heavy cannabis user versus a non-cannabis user in the amount of 0.040 ($p < 0.001$). In other words, younger age, male gender, a greater number of cigarette use days, and treatment seeking for AUD were associated with a larger log odds of being classified as a moderate-to-heavy cannabis user, versus a non-cannabis user.

Exploratory Analyses

A multiple linear regression was used to examine the relationships between the aforementioned demographic and clinical variables of interest and reported number of cannabis use days in the past 30 per the TLFB, among those reporting any cannabis use. Specifically, the model predicted cannabis use days as a function of of age, gender, tonic alcohol craving, drinking days, drinks per drinking day, percent heavy drinking days, treatment seeking status for AUD, nicotine dependence severity, and cigarette use days, controlling for study source. The results of the exploratory multiple linear regression analysis are shown in **Supplemental Table 2.**

A significant regression equation was found ($F(10, 375) = 6.39$, $p < 0.001$), with an R^2 of 0.15. Drinking days in the past 30 days and treatment seeking for AUD were revealed as significant predictors of cannabis use days in the past 30 days. Specifically, cannabis use days increased by 0.15 days for each one-day increase in drinking days ($p = 0.048$), and those who were seeking treatment for AUD reported 8.41 more days of cannabis use in the past 30 than those who were not seeking treatment ($p < 0.001$).

DISCUSSION

Co-use of alcohol and cannabis is becoming increasingly common across the U.S. and has been largely associated with greater negative consequences as compared to those associated

with the use of either substance alone. To date, few studies have compared the relationships between varying levels of alcohol and cannabis co-use and clinical associations as opposed to a binary definition of co-use. As such, the present study sought to characterize demographic and clinical effects of co-use across varying levels of cannabis co-use frequency within a large sample of heavy drinkers. We hypothesized that more frequent cannabis use would be associated with male gender, younger age, comorbid tobacco use, and more problematic drinking, as compared to light-to-moderate and non-cannabis use.

Consistent with our hypotheses, light-to-moderate cannabis users were younger in age than non-cannabis users, and any level of cannabis co-use was more prevalent among those identifying as male. Critically, we also observed a frequency-response effect of cannabis co-use on alcohol outcomes, such that moderate-to-heavy cannabis users reported higher levels of tonic alcohol craving and more drinking days, in addition to a higher likelihood of treatment seeking for AUD, than both the light-to-moderate and non-cannabis users. Further, moderate-to-heavy cannabis users reported more heavy drinking days than non-cannabis users. With regard to co-occurring tobacco use, non-cannabis users reported the fewest amount of cigarette use days, with light-to-moderate cannabis users reporting the greatest number of cigarette use days. Lastly, moderate-to-heavy cannabis users displayed significantly higher levels of nicotine dependence severity than both non-cannabis users and light-to-moderate cannabis users. In other words, there was evidence of a linear effect of cannabis use frequency among heavy drinkers such that heavier cannabis users who were also heavy drinkers were more likely to identify as male, be younger in age, report cigarette smoking, display more severe drinking profiles, and be treatment seeking for AUD.

With regard to the multinomial logistic regression analyses, younger age and comorbid tobacco use were significant predictors when comparing the likelihood of being classified as a light-to-moderate cannabis user as compared to a non-cannabis user. In other words, those who were younger in age and reported a greater number of cigarette use days were more likely to be classified as light-to-moderate cannabis users as compared to non-cannabis users. Relatedly, younger age, male gender, drinking days, treatment seeking for AUD, and cigarette use were also significant predictors of being classified as a moderate-to-heavy cannabis user as compared to a non-cannabis user, such that those who were younger in age, male-identifying, who reported a greater number of both alcohol and cigarette use days, and were treatment seeking for AUD were more likely to be classified as moderate-to-heavy cannabis users as compared to non-cannabis users. These findings are in line with both our previous work (Roche et al., 2019; Venegas, Meredith, Cooper, et al., 2020; Venegas, Meredith, Green, et al., 2020) and the larger literature which suggest that those who identify as male and who are younger in age represent a subgroup at heightened risk for cannabis and alcohol co-use (SAMHSA, 2014; Cooper & Craft, 2018; Yurasek et al., 2017), and that co-use is associated with a more severe course of AUD (Blanco et al., 2016; Hayley et al., 2017; Lopez-Quintero et al., 2011; Weinberger et al., 2016). These results are generally consistent with the ANOVA and exploratory findings reported herein.

The finding that concurrent tobacco use was associated with being classified as an individual who reported any cannabis co-use is also supported by the literature, as tobacco is hypothesized to impact alcohol and cannabis co-use patterns. Alcohol, tobacco, and cannabis are the three substances that are most commonly used among adults in the U.S. (SAMHSA, 2017), and it has been consistently shown that these substances are commonly used concurrently (Prince van Leeuwen et al., 2014; Roche et al., 2019). Alcohol and tobacco co-use is highly prevalent

(McKee & Weinberger, 2013; Roche et al., 2016; Rogers et al., 2020), as it has been estimated that approximately 20% of regular tobacco smokers are heavy drinkers (Grant & Dawson, 2000). Similarly, over two-thirds of cannabis users report concurrent tobacco use (Schauer et al., 2015), and the majority of tobacco users report regular cannabis use (SAMHSA, 2017; Ramo et al., 2012). There is also evidence that tobacco or cannabis use increases the likelihood of use of the other, likely within the same day (Humfleet & Haas, 2004; Patton et al., 2005; Tarter et al., 2006; Timberlake et al., 2007; Agrawal et al., 2007; Kandel & Kandel, 2015). Notably, the rate of co-use of cannabis and tobacco among tobacco users has increased in states where cannabis has been legalized (Wang & Cataldo, 2016). Taken together, it is clear that alcohol, cannabis, and tobacco co- and tri-use patterns are robust and that the use of one or more of these substances likely leads to the use of the others. Further, given that the current sample consisted of heavy drinkers, these findings provide useful information as to the role of cannabis and tobacco use in a population reporting high-risk levels of drinking. Although the entire sample was not comprised of treatment seekers for AUD, a sizeable proportion of the sample was treatment seeking (n = 175); for these individuals, the current results may be indicative of what is expected with regard to alcohol, cannabis and tobacco co- and tri-use patterns in clinical settings for AUD. This is supported by the finding that treatment seeking status for AUD was associated with greater odds of heavier cannabis co-use, and that increases in drinking days were associated with increases in cannabis use days.

These results must be interpreted in light of the study's strengths and limitations. A strength of the study is the large sample size which allows for an adequately powered analysis to detect differences among the cannabis co-use groups and accurate predictions of co-use group classification. In a similar vein, this study uniquely adds to the literature on alcohol and cannabis

co-use as it extends the typical binary classification of co-use versus non-co-use and provides rich data on the differential effects of severity of co-use. Another strength of the study is that all participants were heavy drinkers; as such, it is probable that their presentation may be representative of what is seen in clinical practice, providing useful information that may be used to guide clinical decision-making. A limitation of the study is that there was relatively low levels of cannabis co-use overall, with approximately half of the sample reporting zero cannabis use days in the past 30. Therefore, it is likely that the results observed in this study are approximating what might be expected of cannabis and alcohol co-use, as opposed to formal diagnoses of comorbid AUD and CUD. As such, future directions for research would include comparing varying frequencies of co-use among individuals with more regular cannabis use, including those reporting high-risk or problematic cannabis use. Another limitation is the failure to capture nuance in cannabis use frequency and potency. Given that we identified cannabis use as any amount of use on a given day, we do not have insight into the amount of cannabis that was consumed on a given day and relatedly do not have information regarding THC potency or formulation that was consumed. Although our measurement of cannabis use is defined as across routes of administration, there are potentials for future inquiry into varying cannabis dose quantity, potency, and route of administration, and their differential associations among alcohol-related outcomes.

CONCLUSIONS

In conclusion, younger age, identification with male gender, treatment seeking for AUD, and concurrent tobacco use appear to be robust predictors of alcohol and cannabis co-use. Individuals who reported more frequent cannabis use days also exhibited more problematic drinking profiles, and those reporting greater amounts of alcohol use and who were treatment

seeking for AUD were more likely to engage in heavier cannabis co-use. This pattern of results holds important implications for both prevention and intervention efforts. Large-scale prevention programs have demonstrated efficacy in reducing alcohol and cannabis use separately (Champion et al., 2016; Newton, Andrews, Teesson, & Vogl, 2009), although no studies to date have examined the impact of such strategies on co-use. As such, future efforts may consider targeted programming towards younger, male-identifying, tobacco users to mitigate risk for co-use. At the intervention level, these variables represent identifiable risk factors of which treating clinicians must be mindful, as these factors may place their clients at a greater risk for co-use and associated adverse consequences (Brière et al., 2011; Metrik et al., 2018). Regarding alcohol use specifically, given that cannabis co-use among alcohol drinkers negatively impacts alcohol treatment prognosis (Subbaraman et al., 2017; Wardell et al., 2020), the current findings suggest that these associations may eventually lead to more challenging and complex alcohol treatment planning, highlighting the need for tailored intervention among this specific subgroup of drinkers. Lastly, while in treatment for AUD, targeting drinking reduction specifically may lead to reductions in cannabis use and co-use overall.

Table 1. Sample Characteristics.

Variable[a]	Non-cannabis users (*n* = 452)	Light-to-moderate cannabis users (*n* = 283)	Moderate-to-heavy cannabis users (*n* = 128)	Statistic	*p*
Age[c]	34.05 (11.01)	30.71 (10.03)	33.18 (10.67)	$F(2) = 7.89$	< 0.001*
Gender[c,d]					
Female (%)	173 (38.86)	90 (31.80)	30 (23.44)	$\chi^2(2) = 10.79$	0.005*
PACS[d,e]	10.16 (7.16)	10.38 (6.31)	12.66 (7.19)	$F(2) = 6.22$	0.002*
Drinking days[d,e]	16.43 (8.08)	16.37 (7.66)	19.12 (8.30)	$F(2) = 6.21$	0.002*
DPDD[b]	5.31 (3.26)	5.60 (3.12)	6.00 (3.66)	$F(2) = 2.25$	0.11
PHDD[b,d]	52.02 (34.70)	56.43 (71.78)	60.05 (34.96)	$F(2) = 3.41$	0.034*
AUD treatment seeking status[d]					
Treatment seeking (%)	84 (18.46)	40 (14.29)	51 (39.84)	$\chi^2(2) = 37.46$	< 0.001*
FTND[d,e]	1.75 (2.42)	1.84 (2.20)	2.80 (2.62)	$F(2) = 12.83$	< 0.001*
Cigarette use days[b,c,d,e]	9.81 (13.20)	12.71 (13.16)	18.88 (13.57)	$F(2) = 27.50$	< 0.001*

[a] Standard deviations appear within parentheses for continuous variables.
[b] Assessed by the Timeline Follow Back (TLFB) interview for the past 30 days.
[c] Non-use and light-to-moderate use groups differ.
[d] Non-use and moderate-to-heavy use groups differ.
[e] Light-to-moderate and moderate-to-heavy use groups differ.
* $p < 0.05$.

Table 2. Correlations Among Predictor Variables.

Variable	1	2	3	4	5	6	7	8	9
1. Age	1.00								
2. Gender	0.14***	1.00							
3. PACS	0.17***	0.092**	1.00						
4. Drinking days	0.26***	0.097**	0.49***	1.00					
5. DPDD	0.084*	0.19***	0.41***	0.22***	1.00				
6. PHDD	0.092**	0.052	0.33***	0.16***	0.75***	1.00			
7. AUD treatment seeking status	0.50***	0.039	0.13***	0.093*	0.020	0.032	1.00		
8. FTND	0.39***	0.080*	0.20***	0.16***	0.22***	0.19***	0.64***	1.00	
9. Cigarette use days	0.42***	0.13***	0.20***	0.20***	0.19***	0.16***	0.63***	0.74***	1.00

* $p < 0.05$;
** $p < 0.01$;
*** $p < 0.001$.

Table 3. Multinomial Logistic Regression Model Predicting Level of Cannabis Co-Use (i.e., Non-Co-Use Versus Light-to-Moderate Co-Use and Non-Co-Use Versus Moderate-to-Heavy Co-Use), Controlling for Study Source.

	Light-to-Moderate Cannabis Users		**Moderate-to-Heavy Cannabis Users**	
Predictor[a]	***B*(*SE*)**	***p***	***B*(*SE*)**	***p***
Intercept	-0.10 (0.34)	< 0.001*	-2.38 (0.53)	< 0.001*
Age	-0.049 (0.0098)	< 0.001*	-0.068 (0.012)	< 0.001*
Gender (Female = 0)	0.33 (0.18)	0.066	0.69 (0.26)	0.0079*
PACS	-0.012 (0.015)	0.42	0.0056 (0.018)	0.77
Drinking days	0.010 (0.012)	0.43	0.030 (0.019)	0.021*
DPDD	-0.029 (0.041)	0.48	-0.040 (0.050)	0.44
PHDD	0.61 (0.38)	0.10	0.69 (0.48)	0.15
AUD treatment seeking status (Non-treatment seeking = 0)	-0.22 (0.32)	0.49	1.54 (0.400)	< 0.001*
FTND	-0.023 (0.055)	0.67	-0.037 (0.066)	0.58
Cigarette days	0.040 (0.0095)	< 0.001*	0.049 (0.013)	< 0.001*
Study source	0.11 (0.052)	0.031*	0.29 (0.082)	< 0.001*

[a] Reference group is non-cannabis use.
* $p < 0.05$.

Supplemental Table 1. Inclusion and Exclusion Criteria for Individual Studies.

Study	Inclusion Criteria	Exclusion Criteria	Sample Size (*n*)
Ray et al., 2018	1. Age between 21-55 2. Score of ≥ 8 on the AUDIT[a] 3. East Asian ethnicity (i.e., Chinese, Korean, Japanese, or Taiwanese)	1. Non-treatment seeking for AUD 2. Current major depressive disorder with suicidal ideation 3. Lifetime history of a bipolar or psychotic disorder 4. Lifetime (i.e., past-year) DSM-5 diagnosis of a substance use disorder other than alcohol, nicotine, or cannabis 5. Score of ≥ 10 on the CIWA-Ar[b], indicating clinically significant alcohol withdrawal requiring medical management 6. If female, pregnancy, nursing, or a refusal to use a reliable method of birth control 7. Blood alcohol concentration (BAC) of 0.000 g/dl at the time of the study visit	199
Ray et al., 2021	1. Age between 21-65 2. Treatment seeking for smoking cessation and expressing a desire to reduce or quit drinking 3. Reported use of ≥ 5 cigarettes per day[c] 4. Breath carbon monoxide (CO) reading of ≥ 4 ppm or score of ≥ 3 (100-200 ng/mL) on a cotinine test 5. Reported consumption of > 14 drinks/week or ≥ 5 drinks/occasion at	1. Lifetime history of a bipolar or psychotic disorder 2. Score of ≥ 10 on the CIWA-Ar[b] 3. Current (i.e., past-year) DSM-5 diagnosis of a substance use disorder other than alcohol or nicotine 4. Current major depressive disorder with suicidal ideation	175

	least once per month over the past 12 months for men, or > 7 drinks/week or ≥ 4 drinks/occasion at least once per month over the past 12 months for women[c]	5. If female, pregnancy, nursing, or a refusal to use a reliable method of birth control 6. Current medical condition thought to interfere with safe participation 7. BAC of 0.000 g/dl at the time of the study visit	
Grodin et al., 2021	1. Age between 21-50 2. Meet current (i.e., past-year) DSM-5 diagnostic criteria for AUD 3. Report consumption of ≥14 drinks/week for men or ≥ 7 drinks/week for women, in the month prior to enrollment[c]	1. Currently in treatment for AUD or treatment seeking 2. Current (i.e., past-year) DSM-5 diagnosis of a substance use disorder other than alcohol or nicotine 3. Nonremovable ferromagnetic objects in body 4. Claustrophobia 5. Serious head injury or prolonged period of unconsciousness (i.e., > 30 minutes) 6. Current medical condition thought to interfere with safe participation 7. Reported recent use of medications contraindicated with ibudilast 8. If female, pregnancy, nursing, or a refusal to use a reliable method of birth control 9. BAC of 0.000 g/dl at the time of the study visit	183
Ray et al., 2017	1. Age between 21-65 2. Meet current (i.e., past-month) DSM-5 diagnostic criteria for AUD	1. Currently in treatment for AUD or history of treatment in the 30 days before enrollment, or treatment seeking	128

		2. DSM-IV diagnosis of dependence on any psychoactive substances other than alcohol and nicotine in the past 12 months 3. Lifetime history of a bipolar or psychotic disorder 4. A positive urine toxicology screen for any drug other than cannabis 5. Score of ≥ 10 on the CIWA-Ar[b] 6. If female, pregnancy, nursing, or a refusal to use a reliable method of birth control 7. A medical condition that may interfere with safe study participation (e.g., unstable cardiac, renal, or liver disease) 8. AST, ALT, or GCT ≥ 3 times upper normal limit 9. BAC of 0.000 g/dl at the time of the study visit	
Bujarski et al., 2018	1. Age between 21-45 2. White ethnicity (due to an exploratory genetic aim not reported here) 3. Fluency in English 4. Report consumption of ≥14 drinks/week for men or ≥ 7 drinks/week for women, in the month prior to enrollment[c] 5. If female, not pregnant or lactating, and using a reliable method of birth control 6. Body weight of less than 265 lbs.	1. Treatment seeking for AUD 2. Current diagnosis of a substance use disorder other than nicotine or alcohol 3. Lifetime diagnosis of moderate-to-severe substance use disorder other than nicotine, alcohol, or cannabis 4. Lifetime history of a bipolar or psychotic disorder 5. Current suicidal ideation 6. Current use of psychoactive drugs other than cannabis	140

		7. Use of cannabis more than twice weekly 8. Clinically significant abnormalities as indicated by physical examination and liver functioning labs 9. History of chronic medical conditions 10. Current use of any psychoactive medications 11. Score of ≥ 10 on the CIWA-Ar[b] 12. Fear of, or adverse reactions to needle puncture 13. BAC of 0.000 g/dl at the time of the study visit	
Grodin et al., 2019	1. Age ≥ 21 2. Report consumption of ≥ 5 drinks/occasion for men or ≥ 4 drinks/occasion for women ≥ 4 times in the month prior to enrollment[c]; or a total score of ≥ 8 on the AUDIT[a]	1. Currently receiving treatment for alcohol problems, or history of treatment in the 30 days prior to enrollment, or currently seeking treatment 2. A positive urine toxicology screen for any drug other than cannabis 3. Lifetime history of a bipolar or psychotic disorder 4. Score of ≥ 10 on the CIWA-Ar[b] 5. History of epilepsy, seizures, or severe head trauma 6. Nonremovable ferromagnetic objects in body 7. Claustrophobia 8. If female, pregnancy 9. BAC of 0.000 g/dl at the time of the study visit	38

[a] Alcohol Use Disorders Identification Test (AUDIT)
[b] Clinical Institute Withdrawal Assessment for Alcohol – Revised (CIWA-Ar)
[c] Assessed by the Timeline Follow-Back (TLFB)

Supplemental Table 2. Linear Regression Model Predicting Cannabis Use Days, Controlling for Study Source.

Predictor	***B*(*SE*)**	***p***
Intercept	3.76 (2.35)	0.11
Age	-0.083 (0.061)	0.17
Gender (Female = 0)	1.54 (1.20)	0.20
PACS	0.089 (0.099)	0.43
Drinking days	0.15 (0.076)	0.048*
DPDD	-0.15 (0.26)	0.56
PHDD	0.60 (2.41)	0.80
AUD treatment seeking status (Non-treatment seeking = 0)	8.41 (1.87)	< 0.001*
FTND	0.29 (0.32)	0.37
Cigarette days	0.046 (0.057)	0.42
Study source	0.97 (0.35)	0.0051*

* $p < 0.05$.

Cross-Substance Primed and Cue-Induced Craving Among Alcohol and Cannabis Co-Users: An Experimental Psychopharmacology Approach

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ABSTRACT

Co-use of alcohol and cannabis is highly prevalent and often problematic. However, mechanisms underlying their co-use remain unclear. This randomized and crossover study tests cross-substance subjective craving for alcohol and cannabis. A community sample of non-treatment-seeking alcohol and cannabis co-users (N=30 completers, 40% female) reporting high-risk levels of alcohol and cannabis use completed two experimental sessions in their homes and were monitored remotely using internet meeting technology (i.e., Zoom). The two counterbalanced and randomized sessions were as follows: (i) consumption of a standard alcoholic beverage followed by cannabis cue-exposure, and (ii) consumption (i.e., smoking) of a miniature cannabis cigarette (containing 18-22% tetrahydrocannabinol (THC)), followed by alcohol cue-exposure. Participants rated their subjective craving for both alcohol and cannabis at baseline, following alcohol/cannabis administration, and following the presentation of cross-substance-related cues. Repeated measures analysis of variance (ANOVAs) revealed a statistically significant difference in cannabis craving across time, such that craving for cannabis was significantly higher following cannabis cue-reactivity, compared to baseline and following alcohol administration (p's<0.001). Similarly, there was a statistically significant difference in alcohol craving across time, such that craving for alcohol was significantly higher following alcohol cue-reactivity, compared to baseline and following cannabis administration (p's<0.001). Overall, results suggest that individuals who co-use alcohol and cannabis are most sensitive to the cue-induced, rather than the pharmacologically induced effects, of substance administration on cross-substance craving. This pattern of findings does not support a complementarity model. Conversely, these results may be interpreted as indicative of a substitution model for alcohol and cannabis co-use.

Keywords: alcohol; cannabis; co-use; experimental psychopharmacology; craving

Public Significance Statement: Despite their frequent co-use, mechanisms underlying alcohol and cannabis co-use remain poorly understood. In a sample of non-treatment-seeking individuals reporting high-risk levels of alcohol and cannabis use, participants were most sensitive to the cue-reactive over pharmacological effects on subjective craving. Notably, there were no significant cross-substance effects on subjective craving.

INTRODUCTION

Co-use of alcohol and cannabis is increasingly common, with the prevalence rate of co-use rising from approximately 16% in 2002 to 23-24% in 2018 (McCabe et al., 2021). In a recent analysis of the National Survey of Drug Use and Health (NSDUH), among those who identify as primary alcohol users, 27% reported cannabis co-use, and among those who identify as primary cannabis users, 91% reported concurrent alcohol use (Waddell, 2021). It has also been shown that individuals reporting co-use of alcohol and cannabis often use them at the same time, or in a single substance use episode (Midanik et al., 2007; Roche et al., 2019; Subbaraman & Kerr, 2015). Of note, co-use of alcohol and cannabis has been shown to confer a host of associated risks that outweigh those related to the use of either substance alone, including increases in psychiatric comorbidities and poorer clinical treatment outcomes (Metrik et al., 2018; Midanik et al., 2007; Venegas, Meredith, Cooper, et al., 2020; Volkow et al., 2014), the development and maintenance of alcohol use disorder (AUD) (Blanco et al., 2016; Hayley et al., 2017; Weinberger et al., 2016), and poorer prognoses for alcohol treatment (Subbaraman et al., 2017; Wardell et al., 2020).

Definitive mechanisms underlying alcohol and cannabis co-use remain unclear. Two prominent proposed models of co-use include those related to the complementary or additive effects of alcohol and cannabis (i.e., complementarity, resulting in increased use), and those related to the use of one substance as a pharmacological substitute for the other (i.e., substitution, resulting in decreased use) (Subbaraman, 2016). Whether alcohol and cannabis are considered complements to or substitutes for one another remains a widely debated topic, with mixed evidence for both models (Gunn, Aston, & Metrik, 2022; Risso et al., 2020; Subbaraman, 2016). In fact, systematic reviews by Subbaraman (2016) and Risso et al. (2020) have posited that while

the literature tends to generally provide stronger support for substitution over complementarity, effects vary by population (i.e., age and race/ethnicity). An additional review by Gunn and colleagues (2022) also revealed evidence for both models of co-use, suggested that there are nuanced effects across populations, and identified various potential moderators of whether cannabis acts as a substitute for or complement to alcohol (e.g., differing cannabis formulations, variations in age, and motivations for use). As such, more research aimed at providing a clearer understanding of these mechanisms is warranted.

Experimental psychopharmacology can provide insights into these mechanisms. The co-use of alcohol and nicotine has been widely studied under these approaches, providing robust evidence for complementarity (Epstein, Sher, Young, & King, 2007; King, McNamara, Conrad, & Cao, 2009; King, Vena, de Wit, Grant, & Cao, 2022; King & Epstein, 2005). Laboratory-based self-administration paradigms have provided robust evidence that the use of alcohol increases craving to smoke combustible tobacco cigarettes, decreases latency to initiate smoking, and initiates smoking self-administration (Dermody & Hendershot, 2017; Kahler et al., 2014; Verplaetse & McKee, 2017). Similarly, it has been demonstrated that nicotine increases alcohol craving, decreases the subjective effects of alcohol, and increases alcohol consumption (Barrett, Tichauer, Leyton, & Pihl, 2006; Verplaetse & McKee, 2017). Taken together, the literature has largely demonstrated that alcohol and tobacco reciprocally potentiate craving, subjective responses to alcohol and nicotine, and self-administration of these substances (Verplaetse & McKee, 2017). A similar approach is proposed herein whereby co-users experience the administration of one substance and are asked to report on their subjective craving for the other substance. Based on the complementarity model, we would expect that the administration of alcohol would trigger subjective cravings for cannabis and vice-versa.

Studies to date have not sufficiently leveraged experimental psychopharmacology paradigms to elucidate mechanisms underlying the co-use of alcohol and cannabis, including substance-induced and cue-induced craving. Measuring changes in subjective craving represents a promising endpoint in that craving, while biased due to its largely self-reported nature, can provide insight into eventual alcohol and cannabis self-administration behavior (Buckner et al., 2015; Enkema, Hallgren, & Larimer, 2020; Green et al., 2019; McHugh et al., 2016; Schneekloth et al., 2012). To this end, in a recent study by our group, we have shown that alcohol administration increased subjective craving for cannabis among alcohol and cannabis co-users (Venegas, Meredith, Green, et al., 2020). However, these effects were sex dependent, such that males reported an increase in craving for cannabis following alcohol administration, whereas females did not. Further, the aforementioned study did not have a cannabis administration condition, which would allow for tests of cross-substance craving (i.e., alcohol-induced craving for cannabis and cannabis-induced craving for alcohol). Additionally, this study did not include a cue-reactivity paradigm, which is considered a gold standard for the assessment of craving. Therefore, it remains unknown if the use of alcohol/cannabis potentiates craving for the other substance, and if these modulations in subjective craving are affected by substance-related cues. Moreover, the temporal nature of alcohol and cannabis craving, leading to potential co-use (i.e., if alcohol craving and potential use precedes cannabis craving and potential use, or vice versa) remains poorly understood.

The present study seeks to shed light on answers to these questions. It is the first study to test cross-substance subjective craving for alcohol and cannabis in a non-treatment seeking sample of alcohol and cannabis co-users, utilizing well-established human laboratory paradigms of substance administration, paired with cross-substance cue-reactivity. Participants completed

two counterbalanced experimental sessions: (i) one in which they systematically consumed a standard alcoholic beverage followed by a cannabis cue-exposure session, and (ii) one in which they systematically smoked a miniature cannabis cigarette followed by an alcohol cue-exposure session. Both sessions took place in participants' homes and were observed remotely using internet meeting technology (i.e., Zoom). We examined whether the administration of alcohol caused an increase in subjective craving for cannabis, and vice versa. Next, we tested whether the addition of the cross-substance cue-exposure potentiated craving for that substance. Given our previous work which not only has shown that drinking alcohol on a given day increases the likelihood of same-day cannabis use (Roche et al., 2019), but also has revealed a pharmacological effect of alcohol on the urge to use cannabis (Venegas, Meredith, Green, et al., 2020), we hypothesized that the doses of both alcohol and cannabis, in conjunction with the cross-substance cue-exposure paradigms, would have an additive effect on subjective craving, and that increases in subjective craving would be observed for both substances. In other words, we hypothesized that a dose of alcohol would result in an increase in subjective craving for cannabis and that the addition of exposure to cannabis-related cues would result in even higher levels of subjective craving – and vice versa.

METHODS

Participants

A community sample of non-treatment seeking individuals reporting current high-risk levels of both alcohol and cannabis use (i.e., scores of 8 or higher on the Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) and Cannabis Use Disorders Identification Test – Revised (CUDIT-R) (Adamson et al., 2010), respectively) was enrolled in the study. A total of 87 individuals completed a screening interview

over the telephone, of which 35 were deemed preliminarily eligible and completed the virtual screening visit. Of the 35 individuals evaluated via Zoom, all were deemed eligible for the study and provided written informed consent to participate. Following the virtual screening visit, eligible participants completed two virtual experimental sessions, also conducted via Zoom (N = 35). Four individuals were lost to follow-up, two of whom completed one of two experimental sessions. One additional individual withdrew consent, resulting in a final sample of 30 (N = 30) who completed the entire study and are included in the present analyses.

Inclusion criteria for the study were as follows: (i) age 21 years or older; (ii) fluency in the English language; (iii) meet criteria for hazardous drinking (i.e., score of 8 or higher on the AUDIT); (iv) meet criteria for hazardous cannabis use (i.e., score of 8 or higher on the CUDIT-R; (v) report that the preferred route of cannabis administration is by smoking combustible cannabis (i.e., not ingesting edible cannabis or vaporizing cannabis); (vi) test negative for the presence of alcohol at the time of the study visit, as measured by a saliva alcohol test (i.e., Orawell 6-Panel Oral Fluid Drug Tests with Alcohol Panel); and (ix) have a negative toxicology screen for all drugs (except cannabis) at the time of the study visit, as measured by a saliva toxicology test. Saliva alcohol and toxicology screening followed recommended procedures and was supervised by study staff via Zoom. Specifically, participants were first instructed to open the sealed saliva test, remove the cap, place the test in their mouth and swab the inside of each cheek approximately 10 times in a circular motion, and place the tests under their tongues for one minute until saliva traveled up the observation windows. Staff then instructed participants to replace the cap and place the test down on a flat surface in front of them. Finally, staff instructed participants to hold the test up to the video camera for reading approximately 5 minutes later. There were no gaps in observation.

Exclusion criteria were the following: (i) currently be involved in treatment for alcohol or cannabis use or have a history of treatment in the past 30 days prior to study enrollment; (ii) have a current (i.e., past 12-month) DSM-5 diagnosis of a substance use disorder other than alcohol, cannabis, and/or nicotine; (iii) have a lifetime DSM-5 diagnosis of schizophrenia, bipolar disorder, or a psychotic disorder; (iv) report regular use (i.e., once per week) of any psychoactive drug except for alcohol, cannabis, and/or nicotine; (v) report current use of any psychoactive medications; and (vi) score of 10 or higher on the Clinical Institute Withdrawal Assessment for Alcohol Scale – Revised (CIWA-Ar) (Sullivan et al., 1989), suggesting current clinically significant alcohol withdrawal.

At the beginning of each virtual study visit, study staff verified all participants' current locations from which they were calling to participate. Study staff confirmed that each participant was aware of the closest hospital/emergency room in case of medical or psychiatric emergency and received participants' verbal consent to deploy appropriate services in hypothetical cases of emergency. Given the ethical consideration of alcohol and cannabis administration outside of a controlled laboratory environment, it was determined that self-administration periods following the initial priming dose of either alcohol or cannabis would not be adequate for the present study given its remote nature (i.e., unfavorable risk/benefit analysis).

Screening Procedures and Measures

All study procedures were approved by the University of California, Los Angeles Institutional Review Board; the IRB protocol number was 21-000702 and the title was "Probing Craving as a Mechanism Underlying Alcohol and Cannabis Co-Use." Participants were recruited via online and print advertisements. Interested individuals called the laboratory and completed a telephone interview assessing preliminary eligibility. All participants provided written informed

consent after receiving a full explanation of the study procedures. Informed consent was conducted over Zoom. Specifically, study staff utilized the share screen function to review the informed consent form in its entirety with each participant and answered all questions and addressed all concerns. To maintain confidentiality, all participants were instructed to call in to study visits from a private location, in the absence of others who may have been able to overhear study procedures. In cases in which participants cohabitated with others, they were instructed to call in from a private room and use headphones throughout the study to ensure confidentiality. Relatedly, participants were asked to refrain from use of mobile phones and interacting with other types of media (e.g., television) during each study visit.

Following telephone screening procedures, eligible participants completed one virtual screening/assessment visit conducted via Zoom internet conferencing. The screening/assessment visit lasted approximately ninety minutes. This assessment visit was comprised of individual differences measures, including questionnaires designed to assess demographics, past-month alcohol, cannabis, and tobacco use, AUD/cannabis use disorder (CUD) severity, and psychiatric comorbidity. Following saliva test procedures, using the chat function in Zoom, participants were sent a link to a series of questionnaires in Qualtrics to be completed during the assessment visit. The following measures were administered: (i) the *Timeline Follow-Back* (TLFB) (Sobell & Sobell, 1992) assessed naturalistic alcohol, cannabis, and tobacco use over the past 30 days; (ii) the *Penn Alcohol Craving Scale* (PACS) (Flannery et al., 1999) assessed self-report tonic alcohol craving; (iii) the *Marijuana Problems Scale* (MPS) (Stephens, Roffman, & Curtin, 2000) assessed cannabis-related problems; (iv) the *Structured Clinical Interview for DSM-5* (SCID-5) (adapted from First, 2014) assessed for current (i.e., past year) AUD and CUD, in addition to exclusionary psychiatric diagnoses; (v) the *Beck Depression Inventory – II* (BDI-II) (Beck et al.,

1996) measured depression symptomatology; and (vi) the *Beck Anxiety Inventory* (BAI) (Beck et al., 1988) assessed anxiety symptomatology, including physical and cognitive indicators of anxious mood. Saliva alcohol and drug toxicology tests were sent to all participants via mail for use throughout the study.

Experimental Procedures

Experimental sessions were counterbalanced (i.e., order was randomly assigned), and a crossover design was implemented. One experimental session consisted of an alcohol administration procedure, followed by a cannabis cue-reactivity procedure. The other experimental session consisted of a cannabis administration procedure, followed by an alcohol cue-reactivity procedure. Both sessions occurred at the participant's home via Zoom internet conferencing. Following saliva test procedures, using the chat function in Zoom, participants were sent a link to a series of questionnaires in Qualtrics to be completed throughout the experimental visits. At the end of each experimental session, all participants met with a Master's level research coordinator and clinician to debrief. Each experimental session took approximately one hour to complete.

Study participants purchased two standard drinks (e.g., two 12-ounce 5% ABV beers or two 5-ounce 12% ABV glasses of wine) for use throughout the study. One standard drink was used for alcohol administration and one standard drink was used for alcohol cue-reactivity. Participants were also instructed to purchase one miniature (i.e., 0.25-gram) cannabis cigarette, ranging between 18-22% tetrahydrocannabinol (THC), irrespective of cannabis strain (e.g., indica, sativa, or hybrid), from a regulated dispensary with appropriate packaging labels. The miniature cannabis cigarette was used for both cannabis administration and cannabis cue-reactivity. Additional cannabis paraphernalia were required for participation (i.e., a lighter). The

purchased alcoholic drinks and cannabis cigarettes were visually inspected prior to consumption to ensure that they met the study's consumption criteria.

Alcohol and Cannabis Administration Procedures

At the beginning of each experimental session, completed via Zoom, participants verified, via the saliva alcohol and toxicology test, that they had not consumed alcohol, cannabis, or any other illicit substances prior to the session. Next, participants completed the first series of questionnaires. After participants completed the first series of questionnaires, they administered either alcohol or cannabis, under the supervision of a Master's level research coordinator and clinician.

The alcohol/cannabis administration procedure and initial observation were designed to be completed within approximately 30-40 minutes. Specifically, when administering alcohol, participants were given a maximum of 10 minutes to consume a single dose of alcohol (i.e., one standard drink) in the presence of study staff via Zoom. Observation began following a 30-minute alcohol absorption period, as this is when the peak and stimulant effects of alcohol are shown to occur (Monti et al., 1987). Following the 30-minute alcohol absorption period, participants were instructed to return to the Qualtrics link to complete the second series of questionnaires.

Cannabis administration followed a cued-smoking procedure that has been shown to produce reliable increases in plasma THC levels (Cooper & Haney, 2014; Foltin, Brady, Fischman, Emurian, & Dominitz, 1987). Specifically, while being monitored by study staff via Zoom, participants were verbally instructed to "inhale" for 5 seconds, "hold smoke in lungs" for 10 seconds, and "exhale" for 5 seconds. Participants smoked the miniature cannabis cigarette following this procedure with a 40-second interval

between puffs until approximately 50% of it was pyrolyzed, resulting in a single dose of cannabis. Cannabis administration took approximately 5 minutes to complete. Observation began 15 minutes following cannabis administration (Haney et al., 2016). Following the 15-minute drug absorption period, participants were instructed to return to the Qualtrics link to complete the second series of questionnaires.

Participants who self-identified as cigarette smokers took a smoke break 15 minutes prior to and immediately following the alcohol or cannabis administration procedure, prior to the cue-exposure paradigm (i.e., during the 15- or 30-minute drug absorption periods), to avoid the potential confounding effects of nicotine withdrawal on measures of alcohol and cannabis craving. Lastly, the two experimental sessions were conducted at approximately the same time of day (i.e., in the late afternoon to evening) to avoid potential confounds limiting ecological validity.

Alcohol and Cannabis Cue-Reactivity Procedures

Following alcohol/cannabis administration and completion of associated questionnaires, all participants underwent a cross-substance cue-reactivity paradigm, which took approximately 10 minutes to complete. Specifically, following alcohol administration, participants underwent a cannabis cue-reactivity paradigm, and following cannabis administration, participants underwent an alcohol cue-reactivity paradigm. Cue-reactivity followed well-established procedures (Metrik et al., 2016; Monti et al., 1987; Monti et al., 2001). All instructions were presented by audiotape over the Zoom platform. Scripts instructed participants to hold and smell either a glass of their preferred alcoholic beverage or paraphernalia typically used to consume cannabis, found in their homes, while recalling sensory and psychological memories associated with their alcohol or

cannabis use (e.g., how one typically feels right before beginning to drink or use cannabis, one's mood prior to drinking or using cannabis, the location in which one typically drinks or uses cannabis, and with whom one typically drinks or uses cannabis). Following cue-reactivity procedures, participants were instructed to return to the Qualtrics link to complete the third and final series of questionnaires.

Experimental Sessions Measures

The following measures were collected before and after the alcohol or cannabis administration, in addition to after the presentation of either alcohol- or cannabis-related cues during the cue-reactivity procedure, resulting in three series of completed questionnaires:

(i) the *Alcohol Urge Questionnaire* (AUQ) is an 8-item scale in which participants rated their craving for alcohol in the present moment on an 11-point Likert scale ranging from "strongly disagree" to "strongly agree." The AUQ has demonstrated high internal consistency in human laboratory studies of alcohol (Drummond & Phillips, 2002).

(ii) the *Marijuana Urge Questionnaire* (MUQ) was adapted from the AUQ to assess acute cannabis craving. This adaptation has shown to be effective in measuring cannabis craving in cannabis cue-reactivity studies (Henry, Kaye, Bryan, Hutchison, & Ito, 2014).

Data Analysis Plan

Within-subjects repeated measures ANOVAs were conducted in SAS version 9.4 using PROC GLM (Institute Inc, 2013). Analyses examined: (i) the effects of alcohol administration on alcohol craving and cue-induced cannabis craving and (ii) the effects of cannabis

administration on cannabis craving and cue-induced alcohol craving. Given previous work revealing sex differences in alcohol-induced cannabis craving following alcohol administration in alcohol and cannabis co-users (Venegas, Meredith, Cooper, et al., 2020; Venegas, Meredith, Green, et al., 2020), sex was examined as both a potential predictor and moderator in the present analyses. Sex was not a significant predictor or moderator in any of the present ANOVA models; as such, these models do not account for sex. Post hoc analyses with a Bonferroni adjustment were used to probe differences between individual timepoints (Park, Cho, & Ki, 2009). Study materials and analytic code may be available upon request.

RESULTS

Sample Characteristics

Thirty participants who completed the entire study were included in the statistical analyses reported herein. Sample characteristics are reported in **Table 1,** including demographics, past-month alcohol and cannabis use quantity and frequency, AUD/CUD severity, and psychiatric comorbidities. Briefly, participants had an average age of 32.87 years (*SD* = 9.18) and 40.00% (*n* = 12) of the sample identified as female. Regarding alcohol use frequency, quantity, and severity, participants reported an average of 12.23 days (*SD* = 6.16) of alcohol use in the past month, reported an average of 3.86 (*SD* = 1.83) drinks per drinking day, and endorsed an average of 2.52 (*SD* = 2.16) symptoms of current (i.e., past year) AUD. Similarly, participants reported an average of 15.97 (*SD* = 10.57) cannabis use days in the past month and endorsed an average of 2.41 (SD = 1.78) symptoms of current (i.e., past year) CUD.

Effects of Alcohol Administration followed by Cannabis Cue-Exposure

Craving for Alcohol

Craving for alcohol was measured via the AUQ across three timepoints: at baseline (i.e., prior to alcohol administration), following alcohol administration, and following cannabis cue-reactivity procedures. A repeated measures ANOVA was performed to compare the effects of alcohol administration and alcohol administration plus cannabis cue-reactivity on alcohol craving. A summary of the results from experimental condition 1 is provided in **Figure 1.** Analyses revealed a trending difference in alcohol craving across time ($F(2) = 3.09$, $p = 0.053$). Specifically, craving for alcohol was significantly higher after alcohol administration compared to baseline ($t(58) = -2.48$, $p = 0.02$). There were no significant differences between alcohol craving at baseline (i.e., prior to alcohol administration) and following cannabis cue-reactivity ($p = 0.24$) or following alcohol administration and following cannabis cue-reactivity ($p = 0.20$). This trending effect was not significantly moderated by sex ($p = 0.96$).

Craving for Cannabis

Craving for cannabis was measured via the MUQ across three timepoints: at baseline (i.e., prior to alcohol administration), following alcohol administration, and following cannabis cue-reactivity procedures. A repeated measures ANOVA was performed to compare the effects of alcohol administration and alcohol administration plus cannabis cue-reactivity on cannabis craving. Analyses revealed a statistically significant difference in cannabis craving across time ($F(2) = 19.15$, $p < 0.001$). Specifically, craving for cannabis was significantly higher following cannabis cue-reactivity, compared to both baseline ($t(58) = -5.76$, $p < 0.001$) and following alcohol administration ($t(58) = -4.84$, $p < 0.001$). There were no significant differences between cannabis craving at baseline and following alcohol administration ($p = 0.36$). This

significant difference in cannabis craving across time was not significantly moderated by sex ($p = 0.87$).

Effects of Cannabis Administration followed by Alcohol Cue-Exposure

Craving for Alcohol

Craving for alcohol was measured via the AUQ across three distinct timepoints: at baseline (i.e., prior to cannabis administration), following cannabis administration, and following alcohol cue-reactivity procedures. A repeated measures ANOVA was performed to compare the effects of cannabis administration and cannabis administration plus alcohol cue-reactivity on alcohol craving. A summary of the results from experimental condition 2 are provided in **Figure 2.** Analyses revealed a statistically significant difference in alcohol craving across time ($F(2) = 16.60$, $p < 0.001$). Specifically, craving for alcohol was significantly higher following alcohol cue-reactivity compared to baseline ($t(58) = -5.23$, $p < 0.001$) and following cannabis administration ($t(58) = -4.71$, $p < 0.001$). There were no significant differences between alcohol craving at baseline and following cannabis administration ($p = 0.60$). This significant difference in alcohol craving across time was not significantly moderated by sex ($p = 0.55$).

Craving for Cannabis

Craving for cannabis was measured via the MUQ across three distinct timepoints: at baseline (i.e., prior to cannabis administration), following cannabis administration, and following alcohol cue-reactivity procedures. A repeated measures ANOVA was performed to compare the effects of cannabis administration and cannabis administration plus alcohol cue-reactivity on cannabis craving. Analyses did not reveal a statistically significant difference in cannabis craving across time ($F(2) = 2.20$, $p = 0.12$). This effect

was not significantly moderated by sex ($p = 0.97$). However, results did reveal a significant decrease in cannabis craving following alcohol cue-reactivity compared to following cannabis administration ($t(58) = 2.02$, $p = 0.048$).

DISCUSSION

Co-use of alcohol and cannabis is increasingly prevalent and associated with heightened risk factors that outweigh the risks related to the use of each substance alone. Although alcohol and cannabis co-use has been well-documented, processes underlying their co-use remain unclear. Two prominent proposed mechanisms of co-use are those of substitution and complementarity; however, whether alcohol and cannabis are considered substitutes for or complements to each other remains an open question, with mixed evidence for both (Risso et al., 2020; Subbaraman, 2016). This study combined two experimental psychopharmacology paradigms, namely alcohol/drug administration and cue exposure, to test primed and cue-induced cross-substance craving among alcohol and cannabis co-users. Novel methods for remote data collection, paired with biomarkers (i.e., saliva alcohol and toxicology tests), resulted in high ecological validity. We hypothesized that the doses of both alcohol and cannabis, in conjunction with the cross-substance cue-exposure paradigms, would have an additive effect on subjective craving, and that increases in subjective craving would be observed for both substances.

Results from the experimental session in which participants first administered a single dose of alcohol, then underwent a cannabis cue-reactivity procedure, revealed that after one dose of alcohol, craving for alcohol significantly increased while craving for cannabis did not significantly change. Further, after the presentation of cannabis-related cues, craving for cannabis increased, whereas craving for alcohol decreased, albeit non-significantly. The other experimental session in which participants first administered a single dose of cannabis then

underwent an alcohol cue-reactivity procedure, yielded similar results. Consistent with our hypotheses, there was a significant difference in alcohol craving over time. While there were no significant differences in alcohol craving before and after cannabis administration, once participants were presented with alcohol-related cues, craving for alcohol significantly increased. Contrary to our hypotheses, there were no significant changes observed in cannabis craving over time. However, after the presentation of alcohol-related cues, cue-induced craving for alcohol significantly increased while craving for cannabis significantly decreased.

These results are an important extension of our previous work which revealed a sex dependent pharmacological effect of alcohol on the urge to use cannabis, such that males reported an increase in craving for cannabis following alcohol administration, whereas females did not. Unlike the previous study, the current study included a cannabis administration condition, allowing for tests of cross-substance craving. Further, the current study also included a cue-reactivity paradigm, allowing for the ability to reliably detect changes in craving. Our findings do not provide evidence that the use of alcohol/cannabis potentiates craving for the other substance; further, these modulations in craving do not appear to be affected by cross-substance-related cues. In other words, these results are not consistent with what would be hypothesized based on a complementary model of alcohol and cannabis co-use.

Overall, the findings suggest that despite having administered the other substance previously, cue-induced craving increased in such a way to suggest a preference for the newly available substance (i.e., the one to which participants were exposed). This may be seen as evidence of substitution, as the use or availability of one substance does not trigger increased craving for the other (Subbaraman, 2016). Additional studies are needed to further test the substitution model, including studies in which self-administration is available to participants. As

noted in our methods, self-administration was not justified in the context of a fully remote study. While pharmacologically induced cross-substance craving was not observed, participants showed a robust cue-reactivity response to the alcohol/cannabis cues presented, at the detriment of cross-substance craving. These findings add to the literature on extant mechanisms of co-use (Gunn et al., 2022; Risso et al., 2020; Subbaraman, 2016). Specifically, they show limited support for a complementarity hypothesis, and instead may provide more evidence for substitution, such that the newly available substance was on average preferable, regardless of prior substance administration. Considering findings that show that those who co-use alcohol and cannabis often use them on the same day or in a single substance use episode (Midanik et al., 2007; Roche et al., 2019; Subbaraman & Kerr, 2015), the present results provide inconclusive evidence that the consumption of either alcohol or cannabis generally leads to increases in subjective craving for the other substance, arguably a precursor to using that other substance. It is possible that motivators for same-day co-use are more closely related to drug availability rather than specific pharmacological effects of one substance on the subjective urge for the other. Conversely, it is also possible that the administered dose of alcohol was sufficient to prime alcohol craving and potentially additional alcohol consumption, but the dose of cannabis may have been large enough to satiate participants' urge for cannabis, resulting in a ceiling effect, thereby limiting additional increases in craving and eventual additional cannabis use. An important next step in this line of research is to incorporate a self-administration model to determine substance-induced and cue-induced effects on actual drinking and smoking behavior (i.e., alcohol and cannabis consumption).

These findings have important treatment implications, especially for those who are treatment-seeking for AUD. The potential of cannabis as a substitute for AUD has been

discussed (Subbaraman, 2014), with the general conclusion that there is insufficient evidence to recommend the use of cannabis in place of alcohol. However, it has been argued that the substitution of cannabis for alcohol with the goal of reducing negative outcomes may fit within the larger harm reduction framework (Reiman, 2009). In fact, in a Canadian sample who reported using cannabis as a substitute for other substances including alcohol, common reasons for substitution were to ameliorate withdrawal, reduce negative side effects, and better manage symptoms related to drug use (Lucas et al., 2013). Further, in a sample of medical cannabis users who reported using cannabis as a substitute for alcohol specifically, all participants reported that cannabis substitution was effective, and ten percent reported being abstinent from alcohol for more than a year. These individuals attributed their success to cannabis substitution, and 21% of patients observed a return of AUD symptoms after ceasing use of cannabis (Mikuriya, 2004). In this experimental study, participants displayed a preference for the newly available substance, over and above that for which was previously administered. This may be seen as preliminary evidence of substitution, whereby cannabis may be suggested as a substitute for alcohol in order to reduce alcohol misuse and related negative outcomes.

Regarding behavioral treatment options for AUD and/or CUD, stimulus control represents a central component of cognitive behavioral therapy (CBT) for AUD/substance use disorders (SUD) (Bickel & Kelly, 1988; McHugh, Hearon, & Otto, 2010). The current study suggests that cue-induced craving, rather than the pharmacological effects of alcohol and cannabis, is primarily responsible for the differences in subjective craving for both alcohol and cannabis observed over time. Stimulus control seeks to eliminate stimuli, or triggers, that provoke craving and eventual substance use or misuse. As such, these results provide indirect

support for stimulus control as a critical intervention in CBT for AUD/SUD to mitigate cue-induced craving and problematic substance use.

These results must be interpreted in light of the study's strengths and limitations. A strength of the study is the experimental psychopharmacology design in a naturalistic setting. This is the first clinical study combining both alcohol and cannabis administration in conjunction with a cross-substance cue-reactivity paradigm, and the first study to do so in one's natural environment, yielding high levels of ecological validity. Further, the within-subjects crossover design allows for detecting robust differences in craving over time, controlling for the effects of various individual differences on craving outcomes. Another strength is the sample of individuals who report high-risk levels of both alcohol and cannabis use, resulting in a sample of co-users with relatively well-matched frequency and severity of alcohol and cannabis use. A limitation of the study is that while participants enrolled reported high-risk levels of alcohol and cannabis use, on average, participants met diagnostic criteria for current mild AUD and CUD (i.e., reported an average of 2.52 symptoms of current AUD and 2.41 symptoms of current CUD). As such, the current sample is likely more representative of co-users in general, rather than representing a comorbid sample with moderate or severe AUD and CUD, which is more representative of clinical practice (i.e., treatment seeking samples). To this end, an important next step in this line of research may be to enroll participants at various stages of the AUD and CUD severity spectrum to examine complementarity/substitution hypotheses. Another limitation is the modest potential for subjective intoxication from the doses of alcohol and cannabis. This is due to the fact that participants reported high-risk levels of both alcohol and cannabis use, and the doses of alcohol and cannabis were relatively low. Relatedly, although participants were instructed to purchase their own miniature cannabis cigarettes, it is possible that the purchased

cannabis cigarettes contained inaccurate levels of THC, as work has shown that even regulated cannabis dispensaries do not always accurately label THC, cannabidiol (CBD), or other cannabinoid constituents (Bonn-Miller et al., 2017; Gilman et al., 2021; Vandrey et al., 2015). Next steps in this line of research involve more stringent control over levels of alcohol and THC concentration to probe the effects of cross-substance cue-induced craving at varying levels of both alcohol and cannabis intoxication. Additionally, this study lacked a placebo control condition, limiting our ability to determine whether the current findings are related to substance-specific cue-reactivity or if modulations in craving were a function of session duration (i.e., time) or simply substance availability. Lastly, while craving has been purported as an important outcome measure in treatment research (Tiffany, Friedman, Greenfield, Hasin, & Jackson, 2012), and has been demonstrated to be positively associated with subsequent use of both alcohol (McHugh et al., 2016; Schneekloth et al., 2012) and cannabis (Buckner et al., 2015; Enkema et al., 2020), it is important to emphasize that craving and eventual drug use are fundamentally different aspects of the substance use process. Therefore, care should be taken to not conflate drug craving with drug taking.

In conclusion, results suggest that individuals who co-use alcohol and cannabis are most sensitive to the cue-reactive over pharmacological effects and that the cross-substance effects on subjective craving were limited. These findings are most consistent with a substitution, rather than a complementarity, hypothesis of co-use of alcohol and cannabis. Most notably, cue-exposure was a more robust manipulation of subjective craving, compared to alcohol/drug administration. Treatment implications and future directions are multiple and include the potential for cannabis (and/or cannabis products and pharmaceuticals) as a harm reduction agent and/or therapeutic for AUD.

Table 1. Sample Characteristics.

Variable	Mean	SD
Demographic characteristics		
Age	32.87	9.18
Gender identity (No., %)		
Male	17 (56.67%)	--
Female	12 (40.00%)	--
Other	1 (3.33%)	--
Race/Ethnicity (No., %)		
White	15 (50.00%)	--
Black/African American	6 (20.00%)	--
American Indian/Alaskan Native	1 (3.33%)	--
Asian/Asian American	2 (6.67%)	--
Mixed race	2 (6.67%)	--
Other	4 (13.33%)	--
Hispanic/Latino (No., %)		
Yes	12 (40.00%)	--
No	18 (60.00%)	--
Education (No., %)		
High school/GED equivalent	8 (26.67%)	--
2-year college (i.e., Associate's degree)	7 (23.33%)	--
4-year college (i.e., Bachelor's degree)	12 (40.00%)	--
Master's degree	3 (10.00%)	--
Employment (No., %)		
Unemployed, disabled, retired, or other	4 (13.33%)	--
Part-time, odd jobs, full-time student, or housewife	13 (43.33%)	--
Full-time	13 (43.33%)	--
Drinking characteristics		
Drinking days[a]	12.23	6.16
DPDD[a]	3.86	1.83
PHDD[a]	13.11%	14.83%
AUD symptom count[b]	2.52	2.16
AUDIT[c]	13.07	5.97
PACS[d]	8.20	6.38
Cannabis use characteristics		
Cannabis use days[a]	15.97	10.57
CUD symptom count[b]	2.41	1.78
CUDIT-R[e]	17.70	7.69
MPS[f]	2.73	3.31
Tobacco use characteristics		
Cigarette smoker		
Yes (No., %)	10 (33.33%)	--
No (No., %)	20 (66.67%)	--
Cigarette use days[a]	6.30	10.90

Psychiatric characteristics		
BDI-II[h]	8.33	8.51
BAI[i]	6.13	8.50

[a] Assessed by the Timeline Follow Back (TLFB) interview for the past 30 days.
[b] Assessed by the Structured Clinical Interview for DSM-5 (SCID-5).
[c] Alcohol Use Disorders Identification Test (AUDIT).
[d] Penn Alcohol Craving Scale (PACS).
[e] Cannabis Use Disorders Identification Test – Revised (CUDIT-R).
[f] Marijuana Problems Scale (MPS).
[g] Fagerström Test for Nicotine Dependence (FTND).
[h] Beck Depression Inventory – II (BDI-II).
[i] Beck Anxiety Inventory (BAI).

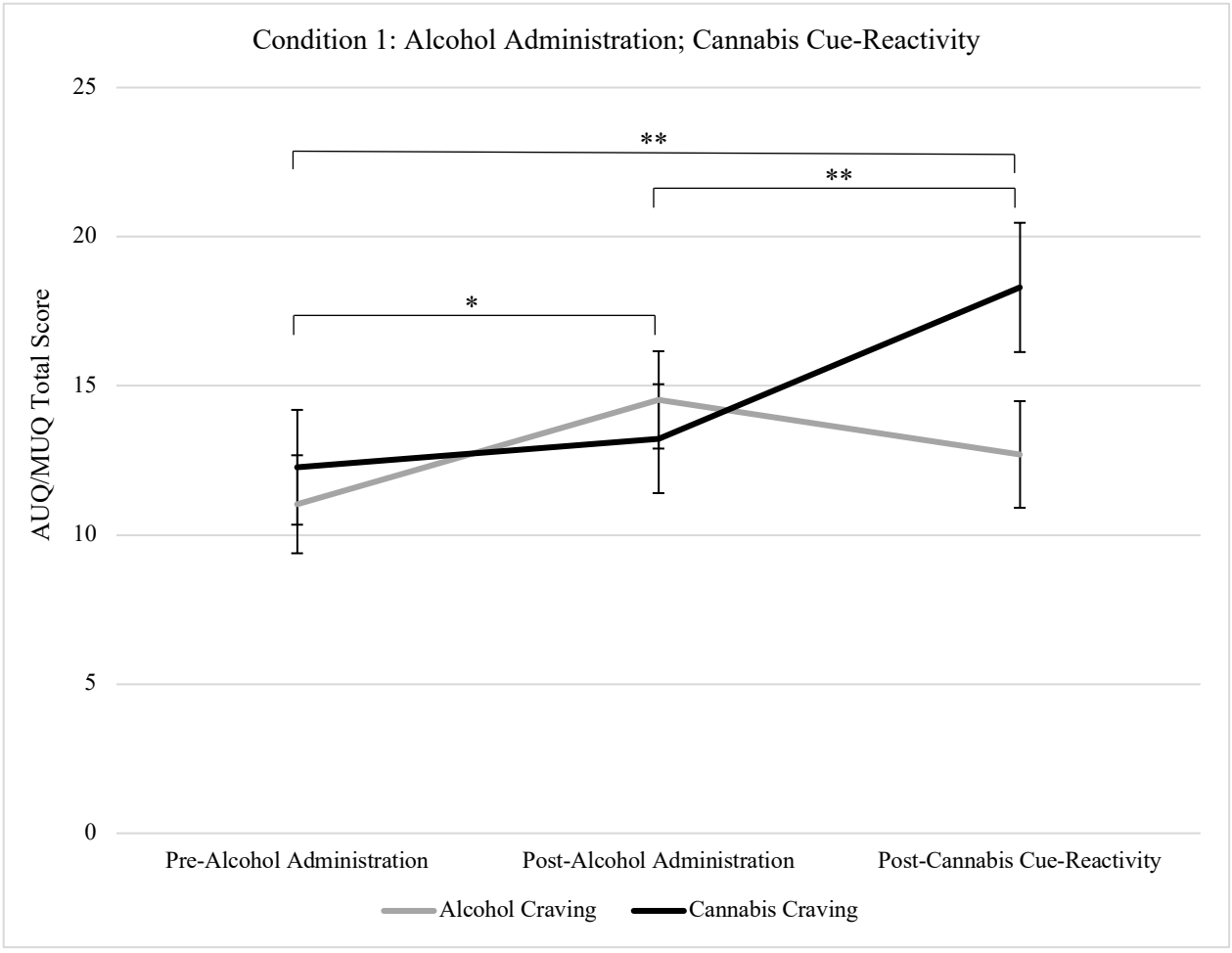

Figure 1. Subjective alcohol (Alcohol Urge Questionnaire; AUQ) and cannabis (Marijuana Urge Questionnaire; MUQ) craving total scores, presented with standard errors, prior to alcohol administration, following alcohol administration, and following cannabis cue-reactivity procedures. The single asterisk denotes a significant increase in alcohol craving following alcohol administration as compared to baseline ($p = 0.016$). Double asterisks denote a significant main effect of time on cannabis craving ($p < 0.001$), such that cannabis cue-reactivity potentiated cannabis craving, over and above levels of craving prior to and following alcohol administration (p's < 0.001).

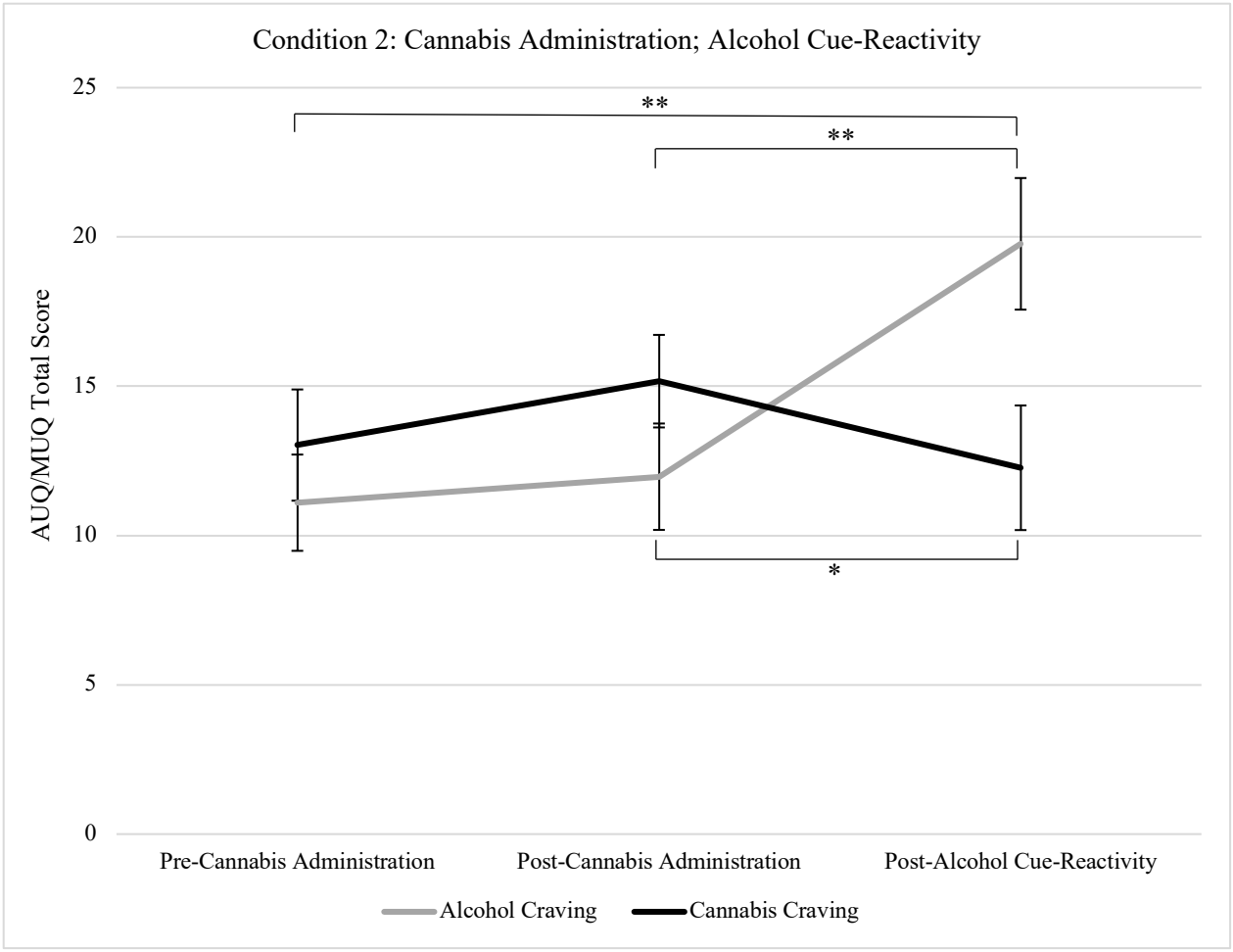

Figure 2. Subjective alcohol (Alcohol Urge Questionnaire; AUQ) and cannabis (Marijuana Urge Questionnaire; MUQ) craving total scores, presented with standard errors, prior to cannabis administration, following cannabis administration, and following alcohol cue-reactivity procedures. The single asterisk denotes a significant decrease in cannabis craving following alcohol cue-reactivity as compared to following alcohol administration ($p = 0.048$). Double asterisks denote a significant main effect of time on alcohol craving ($p < 0.001$), such that alcohol cue-reactivity potentiated alcohol craving, over and above levels of craving prior to and following cannabis administration (p's < 0.001).

DISSERTATION CONCLUSIONS

Cannabis and alcohol co-use is highly prevalent and confers a host of risk factors that outweigh the risks related to the use of either substance alone (Volkow, Baler, Compton, & Weiss, 2014). Of notable importance is that co-use has been associated with increases in heavy drinking, the development and maintenance of AUD (Blanco et al., 2016; Weinberger, Platt, & Goodwin, 2016), and poorer AUD treatment outcomes (Mojarrad et al., 2014; Subbaraman et al., 2017). However, these additive detrimental effects have not been uniformly shown in the literature, as other research suggests that alcohol and cannabis may be substitutes for each other, and that cannabis use may be associated with overall lower levels of alcohol consumption (Risso, Boniface, Subbaraman, & Englund, 2020). Despite their frequent co-use and a large empirical base suggesting a variety of associated negative consequences, few studies to date have examined the associations between varying levels of co-use and demographic (e.g., age, gender) and clinical variables (e.g., anxiety, depression, comorbid substance use), sex differences related to co-use, and mechanisms underlying co-use. The dissertation studies presented herein combine survey and experimental methods to elucidate the clinical associations, sex-dependent effects, and cross-substance craving that may promote and maintain co-use.

Study 1 (Venegas, Meredith, Green, Cooper, & Ray, 2020) consisted of an intravenous alcohol administration paradigm in a sample of alcohol and cannabis co-users. At baseline (i.e., prior to alcohol administration) and at rising levels of BAC, participants provided ratings of subjective craving for alcohol and cannabis, in addition to the subjective effects of alcohol. Results demonstrated that at rising levels of BAC, males reported an increased urge for cannabis compared to females. Further, across sex, the stimulating effects of alcohol, as opposed to the sedative effects, were found to be positively associated with increases in craving for cannabis.

These results suggest that the pharmacological effects of alcohol on the urge to use cannabis are sex dependent, and that the stimulating effects of alcohol are associated with a greater urge for cannabis.

Study 2 (Venegas et al., 2022) investigated clinical correlates among several demographic and clinical factors and varying levels of alcohol and cannabis co-use in a large community sample of heavy drinkers ($N = 863$). Results revealed readily identifiable risk factors for co-use: younger age, male gender, and concurrent tobacco use. These variables were robustly predictive of increases in cannabis co-use frequencies. Further, individuals who reported more frequent cannabis use also exhibited more severe drinking profiles, as evidenced by a greater reported number of drinking days, increases in heavy drinking, and higher levels of tonic alcohol craving.

Finally, Study 3 (Venegas & Ray, 2023) utilized a novel experimental pharmacology paradigm employed remotely via Zoom to test the pharmacological effects of cannabis on alcohol craving and the pharmacological effects of alcohol on cannabis craving. Across two counterbalanced and randomized experimental sessions, a community sample of individuals reporting high risk levels of both alcohol and cannabis use underwent a series of drug administration followed by a cross-substance cue-reactivity paradigm. In other words, in one session, participants administered alcohol, followed by a cannabis cue-reactivity paradigm, and in the other session, participants administered cannabis, followed by an alcohol cue-reactivity paradigm. Results revealed that, across both experimental sessions, exposure to cross-substance cues resulted in significant increases in subjective craving, over and above the effects of drug administration. Importantly, the cross-substance effects of alcohol/drug administration and cues were modest.

This series of dissertation studies should be interpreted in light of its strengths and limitations. Strengths of Study 1 include the well-matched sample of males and females on measures of age, mood, and substance use, in addition to the use of controlled intravenous alcohol administration. On the other hand, this study lacked a matched placebo condition, impeding the ability to clearly elucidate the pharmacological effect of alcohol on cannabis craving. Strengths of Study 2 include the large sample size and the extension beyond the typical binary classification of co-use versus non-co-use. However, a limitation of the study is that on average, participants reported relatively low levels of cannabis use, limiting generalizability to more severe or frequent cannabis users. Strengths of Study 3 include the experimental psychopharmacology design in a naturalistic setting; further, it is the first study to date to combine alcohol/cannabis administration in conjunction with a cross-substance cue-reactivity paradigm, in one's home environment, yielding high levels of ecological validity (Cyders et al., 2020). A possible limitation of this study is the limited potential for intoxication from priming doses of alcohol and cannabis.

There are a variety of potential directions for future research utilizing these dissertation data, especially as it pertains to Study 3. First, given that Study 3 is the first to combine the human laboratory paradigms of substance administration and cue-reactivity in alcohol and cannabis co-use, and the first to do so from participants' natural environments (i.e., their homes), harnessing internet meeting technology, we are awaiting reviewers' comments on the methods employed, especially regarding remote data collection. Feedback from reviewers may inform future data collection efforts. Second, upon further replication of this study, it would be important to include the assessment of subjective cross-substance craving at varying levels of alcohol/cannabis intoxication. Third, a natural follow-up to the present analyses of Study 3 is to

probe the subjective response data collected. A study from our group (Green et al., 2019) showed that subjective ratings of alcohol craving represent a more proximal indicator of alcohol self-administration than measures of alcohol-induced stimulation. As such, it would be beneficial to probe the interplay of subjective response and cross-substance subjective craving for alcohol/cannabis. Further, an interesting future direction would also be to probe potential sex by subjective response interactive effects to this end. Lastly, it has been shown by our group that those who co-use alcohol and cannabis are likely to use them on the same day (Roche et al., 2019). However, a limitation of this study were the relatively low levels of reported cannabis use in the sample. Given that Study 3 specifically recruited a sample of participants reporting high-risk alcohol and cannabis use, we plan to replicate this study to determine if increases in alcohol and cannabis co-use severity, as indexed by increases in cannabis use overall, may result in differences in the temporal nature of alcohol and cannabis use and co-use on a given substance-using day.

Taken together, findings from these studies elucidated sex-dependent variables related to co-use, revealed clinically targetable characteristics of co-users, and uncovered mechanisms relating substance-induced and cue-induced craving for alcohol and cannabis. Specifically, a key pattern of results suggests that younger, male-identifying, comorbid tobacco users may be an identifiable subgroup of drinkers at risk for co-use of cannabis and related sequelae. Second, the stimulating effects of alcohol may serve as an important driver of cannabis craving among co-users. Third, alcohol and cannabis co-users appear to be more sensitive to the cue-reactive, as opposed to the pharmacological, effects of alcohol/cannabis on subjective craving. Finally, the cross-substance effects of alcohol/drug administration and cues were modest. In conclusion,

these studies provided much-needed scientific evidence that may inform clinical best-practices for individuals who co-use alcohol and cannabis.

APPENDICES

APPENDIX A: Study 1 – Urge Form (UF)

SUBJECT ID.
_ _ _ _ _

DATE OF ASSESSMENT
_ _ Month _ _ Day _ _ _ _ Year

Urge Form

Please circle the number below each question that best fits how you feel:

1. How strong is your urge to drink right now?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to drink — very strong urge to drink

2. What was the highest urge to drink that you felt during the time that the alcohol was present?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to drink — very strong urge to drink

3. How strong is your urge to smoke a cigarette right now?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to smoke — very strong urge to smoke

4. What was the highest urge to smoke a cigarette that you felt during the time that the alcohol was present?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to smoke — very strong urge to smoke

5. How strong is your urge to smoke marijuana right now?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to smoke — very strong urge to smoke

6. What was the highest urge to smoke marijuana that you felt during the time that the alcohol was present?

1 2 3 4 5 6 7 8 9 10 11
no urge at all to smoke — very strong urge to smoke

APPENDIX B: Study 3 – Study Procedures and Assessment Schedule

Telephone Screen	Behavioral Visit	Experimental Visit 1	Experimental Visit 2
Pre-screen: 1. Study synopsis 2. Telephone consent **Screening measures:** 1. Alcohol Use Disorders Identification Test (AUDIT) 2. Cannabis Use Disorders Identification Test – Revised (CUDIT-R) **Inclusion/exclusion criteria:** 1. Non-treatment-seeking 2. Age 21 or older 3. Fluency in the English language 4. Meet criteria for hazardous drinking (i.e., AUDIT score ≥ 8) 5. Meet criteria for hazardous cannabis use (i.e., CUDIT-R score ≥ 8) 6. No regular use of any psychoactive drug (i.e., 1x/week) except for cannabis 7. No lifetime diagnosis of a psychiatric disorder (except AUD and/or CUD) 8. No aversion to smoking combustible cannabis or drinking light beer	**Pre-visit:** 1. Informed consent 2. Alcohol test strip 3. Toxicology strip **Interview measures:** 1. Structured Clinical Interview for DSM-5 (SCID-5) 2. 30-day Timeline Follow Back (TLFB; alcohol, cannabis, tobacco) 3. Clinical Institute Withdrawal Assessment for Alcohol – Revised (CIWA-Ar) 4. Marijuana Withdrawal Checklist Diary **Qualtrics measures:** 1. Demographics 2. Barratt Impulsivity Scale (BIS) 3. Beck Depression Inventory – II (BDI-II) 4. Beck Anxiety Inventory (BAI) 5. Pittsburgh Sleep Quality Index (PSQI) 6. Graded Chronic Pain Scale (GCPS) 7. Drug Use Questionnaire (DUQ) 8. Fagerström Test for Nicotine Dependence (FTND) 9. Marijuana Consumption Questionnaire (MCQ) 10. Marijuana Effect Expectancy Questionnaire (MEEQ) 11. Alcohol Consumption Questionnaire (ACQ) 12. Alcohol Effects Questionnaire (AEQ) 13. Penn Alcohol Craving Scale (PACS) 14. The Impact of Beverage Impact on Behavior (ImBIBE) 15. Reward Relief Drinking Scale (RRDS) **Post-visit:** 1. Confirm no SI per BDI-II 2. Schedule experimental visit 1 3. Compensation	**Pre-visit:** 1. Informed consent 2. Alcohol test strip 3. Toxicology strip 4. TLFB **Baseline, pre-administration:** 1. <u>Alcohol craving:</u> Alcohol Urge Questionnaire (AUQ) 2. <u>Cannabis craving:</u> Marijuana Urge Questionnaire (MUQ) 3. <u>Subjective response to alcohol:</u> Profile of Mood States (POMS) Biphasic Effects of Alcohol Scale (BAES) **Alcohol administration (~10-15 minutes)** **30-minute break** **Cigarette if smoker** **Baseline, post-alcohol administration:** 1. <u>Alcohol craving:</u> AUQ 2. <u>Cannabis craving:</u> MUQ 3. <u>Subjective response to alcohol:</u> POMS BAES **Adapted cannabis cue-reactivity (~8-10 minutes)** **Post-alcohol administration + cannabis cue:** 1. <u>Alcohol craving:</u> AUQ 2. <u>Cannabis craving:</u> MUQ 3. <u>Subjective response to alcohol:</u> POMS BAES **Post-visit:** 1. Debrief 2. Schedule experimental session 2 3. Compensation	**Pre-visit:** 1. Informed consent 2. Alcohol test strip 3. Toxicology strip 4. TLFB **Baseline, pre-administration:** 1. <u>Alcohol craving:</u> AUQ 2. <u>Cannabis craving:</u> MUQ 3. <u>Subjective response to cannabis:</u> POMS Addiction Research Center Inventory (ARCI) **Cannabis administration (~5-10 minutes)** **15-minute break** **Cigarette if smoker** **Baseline, post-cannabis administration:** 1. <u>Alcohol craving:</u> AUQ 2. <u>Cannabis craving:</u> MUQ 3. <u>Subjective response to cannabis:</u> POMS ARCI **Adapted alcohol cue-reactivity (~8-10 minutes)** **Post-cannabis administration + alcohol cue:** 1. <u>Alcohol craving:</u> AUQ 2. <u>Cannabis craving:</u> MUQ 3. <u>Subjective response to cannabis:</u> POMS ARCI **Post-visit:** 1. Session wrap-up 2. Compensation

APPENDIX C: Study 3 – Alcohol Urge Questionnaire (AUQ)

SUBJECT ID.
__ __ __ __

DATE OF ASSESSMENT
__ __ (Month) __ __ (Day) __ __ __ __ (Year)

Alcohol Urge Questionnaire (AUQ)

Listed below are questions that ask about your feelings about drinking. The words "drinking" and "have a drink" refer to having a drink containing alcohol, such as beer, wine, or liquor. Please indicate how much you agree or disagree with each of the following statements by placing a checkmark (like this: X). The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling right now as you are filling out the questionnaire.

1. All I want to do now is have a drink.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

2. I do not need to have a drink now.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

3. It would be difficult to turn down a drink at this minute.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

4. Having a drink now would make things seem just perfect.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

5. I want a drink so bad I can almost taste it.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

6. Nothing would be better than having a drink right now.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

7. If I had a chance to have a drink, I don't think I would drink it.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

8. I crave a drink right now.

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

APPENDIX D: Study 3 – Marijuana Urge Questionnaire (MUQ)

SUBJECT ID.
— — — —

DATE OF ASSESSMENT
__ __ __ __ __ __ __ __
Month Day Year

Marijuana Urge Questionnaire (MUQ)

Listed below are questions that ask about your feelings about smoking marijuana. Please indicate how much you agree or disagree with each of the following statements by placing a checkmark (like this: ×). The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling right now as you are filling out the questionnaire.

1. **All I want to do now is smoke marijuana.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

2. **I do not need to smoke marijuana right now.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

3. **It would be difficult to turn down marijuana at this minute.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

4. **Smoking marijuana now would make things seem just perfect.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

5. **I want to smoke so bad I can almost taste it.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

6. **Nothing would be better than smoking marijuana right now.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

7. **If I had a chance to smoke marijuana, I don't think I would smoke it.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

8. **I crave marijuana right now.**

STRONGLY DISAGREE:_____:_____:_____:_____:_____:_____:_____:STRONGLY AGREE

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