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# Cannabis use and subjective response to alcohol in the human laboratory

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## Abstract

**Background:** Cannabis is often used in combination with alcohol; yet, whether cannabis use impacts risk factors for alcohol use disorder (AUD) remains unknown. Subjective response (SR) to alcohol represents a biobehavioral risk factor for subsequent heavy drinking and for developing AUD. Given the high prevalence of alcohol and cannabis co-use, it is plausible to hypothesize that cannabis users differ in SR to alcohol compared to non-cannabis users. The purpose of this study is to examine the influence of past-month cannabis use on subjective response to alcohol in the human laboratory.

**Methods:** This study culled data from multiple alcohol administration trials to test whether cannabis users, compared to non-cannabis users, differed in subjective response to alcohol, comprised of four domains: stimulation, sedation, negative affect, and craving. Non-treatment-seeking heavy drinkers (N=168) completed a battery of self-report scales of mood and alcohol/cigarette/cannabis use and problems. All participants completed an intravenous alcohol administration session wherein SR domains were measured at the following breath alcohol concentrations (BrAC): baseline (i.e., 0), 20, 40, and 60mg%.

**Results:** Multilevel statistical analyses revealed that cannabis users had a greater reduction in negative affect during alcohol administration, compared to non-cannabis users. No significant differences were found for the other SR domains.

**Conclusions:** Using a large sample and advanced data analytic methods, this study extends the literature by suggesting that cannabis users are more sensitive to alcohol-induced reductions in negative affect compared to non-cannabis users. This work extends research on how cannabis use may influence risk factors for AUD, such as subjective response to alcohol.

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**Keywords**

alcohol; alcohol use disorder; cannabis; subjective response; negative affect

## 1. Introduction

Rates of cannabis use are increasing in the United States largely due to the decriminalization and/or legalization of recreational cannabis use (SAMHSA, 2013). While use of cannabis alone can have its own unique problems, cannabis is often used in combination with other substances with about 24% of individuals entering treatment for any substance dependence having a cannabis use disorder (CUD) diagnosis (Cerdá et al., 2012; SAMHSA, 2012). Co-use of alcohol and cannabis is increasingly common, with the prevalence rate of co-use rising from approximately 16% in 2002 to approximately 23-24% in 2018 (McCabe et al., 2021). In a recent analysis of the National Survey on Drug Use and Health data, within primary alcohol users, 26.9% reported cannabis co-use, and within cannabis users, 91.3% reported alcohol co-use (Waddell, 2021). Approximately a quarter of individuals with current (i.e., past-year) AUD report concurrent cannabis use (Falk et al., 2008). Alcohol and cannabis co-use is associated with heavy episodic drinking and more alcohol-related problems compared to using alcohol alone (Black and Casswell, 1992; Midanik et al., 2007; Subbaraman and Kerr, 2015). The odds of AUD are substantially higher among those with CUD (Stinson et al., 2005), suggesting that heavy alcohol drinking may increase as cannabis use increases. Furthermore, epidemiological data show a greater odds of AUD persistence in individuals who use cannabis versus no cannabis use (Stinson et al., 2005). While the field is beginning to recognize the influence of cannabis use on alcohol-related problems (Yurasek et al., 2017), few studies have examined the effects of recent cannabis use on biobehavioral risk factors that predict heavy alcohol drinking and the development of AUD.

Acute subjective response to alcohol is one of the most well-studied risk factors for AUD (Ray et al., 2016). Subjective response to alcohol is typically measured under well-controlled alcohol administration paradigms. Subjective response to alcohol is captured via self-report assessments across several putative domains: stimulation, sedative, negative affect, and alcohol craving (Bujarski et al., 2015; Ray et al., 2009). Decades of research provide support that lower sensitivity to sedative effects of alcohol and greater sensitivity to the stimulating/rewarding effects of alcohol predict subsequent heavy drinking and AUD (King et al., 2021; Schuckit, 1984). Given their costly and time-intensive nature, alcohol administration paradigms tend to have small sample sizes and, as such, have primarily been leveraged to answer focal research questions, such as the effects of candidate AUD medications on subjective response to alcohol. Larger sample sizes allow for greater statistical power to identify moderator variables (i.e., cannabis use) that influence subjective response to alcohol.

Few experimental studies have directly examined the interaction between alcohol and cannabis. These studies show that cannabis availability decreased alcohol self-administration, (Mello et al., 1978) and that $\Delta^9$-tetrahydrocannabinol (THC; one of the primary psychoactive compounds in cannabis) dampened the desire for more alcohol after

alcohol administration in healthy volunteers.(Ballard and de Wit, 2011). A review of this literature found that the combined effects of cannabis and alcohol have the strongest effects on impaired driving tasks, subjective sensations, and physiological measures (Ronen et al., 2010). This may indicate a certain degree of cross-sensitization, wherein cannabis effects can influence certain alcohol effects and vice versa. Research on cannabis effects on subjective response to alcohol are in their infancy and the work in this area has largely focused on simultaneous administration/availability of cannabis and alcohol. To our knowledge, no studies have examined whether individuals who use cannabis differ from non-users on acute subjective response to alcohol in the human laboratory.

At the pharmacokinetic level, cannabis may slow absorption of alcohol thereby reducing alcohol's psychoactive effects (Lukas et al., 1992); however, plasma THC levels can be enhanced if alcohol is consumed immediately after smoking cannabis (Downey et al., 2013; Lukas and Orozco, 2001). Thus, cannabis combined with alcohol can lead to greater impairment than ingestion of either substance alone. It is possible that cannabis use may influence subjective responses to alcohol even outside of simultaneous administration/availability study designs, as work from our laboratory has shown that the stimulant effects of alcohol are associated with higher urge to use cannabis during alcohol administration (Venegas et al., 2020). Furthermore, most of the aforementioned laboratory work in this area has been conducted largely in healthy volunteers, limiting the generalizability and application of the literature to relatively healthy individuals. Thus, experimental studies among heavy drinkers are needed to improve generalizability and further elucidate the complex interactions between alcohol and cannabis.

Given the need for more research on the interaction between alcohol and cannabis, the purpose of the current study was to determine whether cannabis use moderates subjective response to alcohol during alcohol administration in a sample of heavy drinkers. We hypothesized that individuals who use cannabis would have increased sensitivity to alcohol-induced stimulation and alcohol-induced relief of negative affect, as well as decreased sensitivity to alcohol's sedative effects compared to non-users.

## 2. Method

### 2.1. Data source and sample

The current sample (N = 168) is culled from three separate clinical and experimental psychopharmacology studies with similar inclusion criteria and recruitment methods, all conducted in the Addictions Laboratory at the University of California, Los Angeles. Specifically, the sample analyzed herein were drawn from studies examining alcohol self-administration (Bujarski et al., 2018) and medication studies involving naltrexone (Ray et al., 2018) and ibudilast (Ray et al., 2017) as pharmacotherapies for AUD. Although some studies involved pharmacological manipulations, *participants were only included in the current analyses if they were randomized to the placebo condition.* All studies recruited community samples of non-treatment-seeking drinkers from the greater Los Angeles Area. Recruitment procedures were identical across all studies, with more recent studies benefiting more from social media as a recruitment tool. All study procedures were approved by the University of California, Los Angeles Institutional Review Board. All participants provided

written informed consent after receiving a full explanation of the study procedures, with the alcohol administration procedures discussed with a licensed physician. All study procedures were carried out in accordance with the Declaration of Helsinki.

Interested individuals called the laboratory and completed a telephone interview for preliminary eligibility. After providing written informed consent, participants were breathalyzed, provided urine for toxicology screening, and completed a battery of self-report questionnaire and interviews. Heavy drinking was verified through one of the following methods: (i) greater than 48 drinks per month (ibudilast study); (ii) greater than 7 drinks per week for females and greater than 14 drinks per week for males (alcohol self-administration study); or (iii) an Alcohol Use Disorder Identification Test (Saunders et al., 1993) (AUDIT) score of 8 of higher (naltrexone study). Participants were compensated up to $590 depending on the study.

Full exclusion criteria can be found in (Bujarski et al., 2018; Ray et al., 2017; Ray et al., 2018). Briefly, participants were excluded if they were involved in an alcohol treatment program in the past 30 days prior to study participation, self-reported history of serious mental illness, self-reported current use of psychoactive medications, had a breath alcohol concentration (BrAC) of greater than 0.000 g/dl, scored ≥10 on the Clinical Institute Withdrawal Assessment for Alcohol-Revised (Sullivan et al., 1989), had a positive urine toxicology screen for any drug (other than cannabis).

### 2.2. Alcohol administration procedures

Alcohol administration was conducted at the UCLA Clinical and Translational Research Center (CTRC). Detailed alcohol administration methodology can be found in our previous work (Ray et al., 2013). Briefly, at intake, vitals, height, and weight were measured and IV lines were placed by a registered nurse. Participants then completed baseline assessments. Study staff remained in the room to monitor the infusion, breathalyze the participant, take vital signs, administer questionnaires and answer questions but did not significantly engage with participants otherwise. To enable precise control over BrAC and to dissociate biobehavioral responses to alcohol from responses to cues, alcohol was administered IV (5% ethanol v/v in saline) using an established nomogram that considers participants' sex and weight. Infusion rates were: 0.166-ml/minute × weight, in kilograms, for males, and 0.126-ml/minute × weight, for females. During the alcohol challenge, participants were administered alcohol designed to reach target BrACs of 20, 40 and 60 mg%, each over 15-20 minutes. Infusion rates were reduced to half upon reaching each target BrAC, so that BrACs would remain stable while participants completed questionnaires (~5 minutes). All participants were required to have a BrAC ≤ 0.02 g/dl before leaving the laboratory (or a BrAC = 0.00 g/dl if driving).

### 2.3. Measures

Alcohol/cannabis/cigarette use and problems were measured using: (1) The Timeline Follow-Back (Sobell and Sobell, 1992) to measure frequency of alcohol consumption, cannabis, cigarette use in the previous 30 days; (2) the Alcohol Dependence Scale (Skinner et al., 1984) to measure severity of alcohol use problems; (3) the Alcohol Use

Disorder Identification Test (Saunders et al., 1993) to assess hazardous and harmful alcohol consumption; (4) the Penn Alcohol Craving Scale (Flannery et al., 1999) to measure tonic (i.e., unprovoked) alcohol craving; (5) the Fagerström Test for Nicotine Dependence (FTND; (Heatherton et al., 1991)) to determine cigarette smoking status. Cannabis use group was informed by the Timeline Follow-Back. Participants were designated cannabis users if they reported any cannabis use in the past 30 days, and non-users if they did not report any cannabis use in the past 30 days. This resulted in a two-level categorical variable (i.e., users versus non-users) that was used in subsequent analyses.

Depressive symptomatology was assessed using the Beck Depression Inventory-II (Beck et al., 1996).

Subjective responses were captured using the following measures given at baseline and at each target BrAC: (1) The Biphasic Alcohol Effects Scale (BAES) that captures the stimulant and sedative subjective effects of alcohol (Erblich and Earleywine, 1995; Martin et al., 1993); (2) The Subjective High Assessment Scale (SHAS) to capture sedation (Schuckit, 1984); The Alcohol Urge Questionnaire (AUQ) to measure state levels of alcohol craving (Bohn et al., 1995); and (3) The Profile of Mood States (POMS (McNair, 1992)) that was used to record positive and negative mood states. As in our previous work, combined scores were computed within each SR domain by first Z-score transforming each measure across the entire challenge and then summing the scores (Bujarski et al., 2018; Grodin et al., 2019). These methods allow for the incorporation of multiple scales per SR domain. Specifically, the stimulation SR domain included the BAES stimulation subscale and the POMS positive mood and vigor subscales. The sedation SR domain included the BAES sedation subscale and the SHAS. The negative affect SR domain included the POMS negative mood and tension subscales. The alcohol craving SR domain was comprised of the AUQ.

### 2.4. Statistical plan

Group differences between cannabis users and non-users on demographic and clinical variables were assessed using *t* tests, Chi-square tests, and Fisher's exact test when appropriate. Due to the nested data structure, a multilevel model tested whether cannabis use predicted SR during the alcohol challenge across four domains: stimulation, sedation, negative affect, and craving. The nested structure of the data was as follows: repeated SR measurements across the alcohol challenge (Level 1) nested within individuals (Level 2), who were nested within studies (Level 3). These 3-level models were selected to account for any potential between study variability; thus, a categorical study variable was not included as a covariate in analyses because study-related variability is accounted for in the multilevel models. Model fit indices (i.e., AIC) indicated that three-level models were a better fit to the data than two-level models. In each model, SR was predicted by BrAC time point (coded 0-3), cannabis use (categorical; user versus non-user), and their interaction. Age and sex were included as covariates in each model. Intercepts and BrAC slopes were random at Level 2. Sensitivity analyses were conducted including tobacco smoking status (categorical; smoker versus non-smoker determined from the FTND) as a covariate. All analyses were conducted in SAS 9.4 with statistical significance set at $p < 0.05$. The data that support the findings of this study are available from the corresponding author upon reasonable request.

# 3. Results

## 3.1. Sample demographic and clinical characteristics

Demographic and clinical variables are presented in Table 1. Non-cannabis users and cannabis users differed on age, cigarette smoking status, and tonic alcohol craving. Specifically, cannabis users were younger, more likely to be a cigarette smoker, and had lower tonic alcohol craving scores.

## 3.2. Alcohol challenge manipulation check

Stimulation ($B = 0.34$, SE = 0.06, $p < 0.0001$), sedation ($B = 0.57$, SE = 0.04, $p < 0.0001$), and alcohol craving ($B = 0.15$, SE = 0.20, $p < 0.0001$) increased over rising BrAC. Negative affect decreased over rising BrAC ($B = -0.29$, SE = 0.04, $p < 0.0001$). These BrAC effects provide a manipulation check by demonstrating that, as expected, as BrAC increased, so did alcohol craving, stimulation, and sedation, whereas negative affect decreased.

## 3.3. Cannabis use as a SR moderator

Neither cannabis use nor its interaction with BrAC predicted stimulation or sedation (all $p$'s > .05). After adjusting for age and sex, cannabis use predicted greater reductions in negative affect compared to non-cannabis use ($B = -0.58$, SE = 0.28, $p = 0.04$; see Figure 1), such that cannabis users reported a steeper decrease in negative mood compared to non-cannabis users. The cannabis use × BrAC interaction did not reach statistical significance ($p > .05$). The main effect of cannabis use on alcohol craving did not reach statistical significance; however, there was a trend-level cannabis use × BrAC interaction ($B = -0.07$, SE = 0.04, $p = 0.07$) on alcohol craving after adjusting for age and sex, such that cannabis users reported lower alcohol craving relative to non-cannabis users at higher BrACs (0.04 and 0.06).

## 3.4. Sensitivity analyses

Additional multilevel analyses were conducted including cigarette smoking status as a covariate (see supplemental table). The results did not substantially change the main findings reported above.

# 4. DISCUSSION

Given the high prevalence of cannabis and alcohol co-use, the objective of the current study was to determine whether cannabis use (versus non-cannabis use) in the past 30 days influenced subjective responses to alcohol measured during a well-controlled alcohol administration paradigm. Subjective responses to alcohol represent a well characterized biobehavioral risk factor for developing AUD and engaging in heavy drinking. We found that cannabis users reported greater reductions in negative affect during alcohol administration compared to non-cannabis users. Cannabis users also reported lower alcohol craving relative to non-cannabis users as BrACs increased during alcohol administration. Thus, cannabis use is an important moderator of subjective response to alcohol that should be considered in future alcohol administration studies.

In partial support of our hypothesis, alcohol decreased negative affect to a greater extent in cannabis users relative to non-cannabis users. One possible explanation for this finding is that independently, alcohol and cannabis are commonly used as coping mechanisms to relieve some dimension of negative emotionality (e.g., depressive or anxiety symptomatology) and/or pain-related experiences. However, it is likely that co-use over the long term can exacerbate negative affect, which may motivate further co-use. This hypothesis is consistent with findings in adolescent populations, which demonstrated that simultaneous alcohol and cannabis use was associated with more depressive symptoms compared to those who used alcohol only (Brière et al., 2011). National epidemiological studies also found evidence that simultaneous alcohol and cannabis users had greater social consequences and depressive symptoms compared to alcohol-only users (Midanik et al., 2007). Thus, when cannabis and alcohol are used in combination, either simultaneously or concurrently, there may be additive short-term relief of negative emotionality. It may also be the case that alcohol and cannabis alcohol co-users are characterized by negative affect motives. Future work is needed to examine this hypothesis directly.

Subjective responses to alcohol observed in cannabis users may be due, at least in part, to pharmacokinetic factors and cross-sensitization. Smoking cannabis reduces the absorption of alcohol which in turn likely influences subjective experiences with alcohol (Lukas et al., 1992; Ronen et al., 2010). Several studies have shown that cannabis and alcohol co-use have additive effects on measures of impairment (Bramness et al., 2010; Ronen et al., 2010). It might also be the case that cannabis and alcohol co-use may have stronger effects on subjective responses to alcohol relative to other behaviors. In line with this hypothesis, our laboratory found that alcohol-induced stimulation during alcohol administration was associated with greater urge for cannabis among heavy drinkers who self-reported cannabis use in the past 6 months (Venegas et al., 2020). Importantly, it seems to be the case that in simultaneous (cannabis and alcohol used in the same episode) co-use situations, cannabis can dampen alcohol effects; yet, when co-use occurs on separate occasions

Strengths of the current study include a larger than typical sample sizes used in alcohol administration studies, a multifaceted SR structure, and the use of well-validated self-report measures. Notable limitations include the cross-sectional nature of the current study, a lack of descending BrAC limb timepoints to capture peaks in the sedative effects of alcohol, as well as a fine-grained assessment of frequency and quantity of cannabis consumed. Given the experimental nature of our study, our findings may not generalize to heavy drinkers in the general population. Furthermore, we are unable to shed light on how various alcohol and cannabis co-use patterns (simultaneous versus concurrent co-use) may have impacted SR to alcohol. Despite these limitations, our findings extend past work by demonstrating that cannabis use moderates select domains of subjective response to alcohol, a key biobehavioral risk factor for developing AUD. We found that cannabis users self-reported greater reductions in negative affect during alcohol administration compared to non-users. This line of work is important because cannabis and alcohol co-use is highly prevalent and will likely continue to grow as many states in the U.S. legalize and/or decriminalize recreational cannabis use. The influence of cannabis use on alcohol-induced reductions in negative affect, and to a lesser extent alcohol craving, provide a behavioral mechanism by which cannabis use may contribute to developing AUD. Conversely, individuals who

use cannabis may be motivated to use alcohol through mechanisms of negative affect alleviation, which may be subserving the co-use of cannabis and alcohol. In regard to clinical implications of the proposed work, there are several substance use preventive and treatment interventions that teach prosocial, non-substance-related coping skills that promote health and well-being in the long run that may be beneficial for individuals who co-use alcohol and cannabis for relief of negative emotionality.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## References

Ballard ME, de Wit H, 2011. Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers. Pharmacol Biochem Behav 97(4), 627–631. [PubMed: 21110996]

Beck AT, Steer RA, Brown GK, 1996. BDI-II, Beck depression inventory : manual.

Black S, Casswell S, 1992. User reports of problems associated with alcohol and marijuana. British journal of addiction 87(9), 1275–1280. [PubMed: 1392551]

Bohn MJ, Krahn DD, Staehler BA, 1995. Development and initial validation of a measure of drinking urges in abstinent alcoholics. Alcohol Clin Exp Res 19(3), 600–606. [PubMed: 7573780]

Bramness JG, Khiabani HZ, Mørland J, 2010. Impairment due to cannabis and ethanol: clinical signs and additive effects. Addiction 105(6), 1080–1087. [PubMed: 20331551]

Brière FN, Fallu JS, Descheneaux A, Janosz M, 2011. Predictors and consequences of simultaneous alcohol and cannabis use in adolescents. Addict Behav 36(7), 785–788. [PubMed: 21429672]

Bujarski S, Hutchison KE, Roche DJ, Ray LA, 2015. Factor Structure of Subjective Responses to Alcohol in Light and Heavy Drinkers. Alcohol Clin Exp Res 39(7), 1193–1202. [PubMed: 26010049]

Bujarski S, Jentsch JD, Roche DJO, Ramchandani VA, Miotto K, Ray LA, 2018. Differences in the subjective and motivational properties of alcohol across alcohol use severity: application of a novel translational human laboratory paradigm. Neuropsychopharmacology 43(9), 1891–1899. [PubMed: 29802367]

Cerdá M, Wall M, Keyes KM, Galea S, Hasin D, 2012. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. Drug Alcohol Depend 120(1-3), 22–27. [PubMed: 22099393]

Downey LA, King R, Papafotiou K, Swann P, Ogden E, Boorman M, Stough C, 2013. The effects of cannabis and alcohol on simulated driving: Influences of dose and experience. Accid Anal Prev 50, 879–886. [PubMed: 22871272]

Erblich J, Earleywine M, 1995. Distraction does not impair memory during intoxication: support for the attention-allocation model. J Stud Alcohol 56(4), 444–448. [PubMed: 7674680]

Falk D, Yi HY, Hiller-Sturmhöfel S, 2008. An epidemiologic analysis of co-occurring alcohol and drug use and disorders: findings from the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC). Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism 31(2), 100–110. [PubMed: 23584812]

Flannery BA, Volpicelli JR, Pettinati HM, 1999. Psychometric properties of the Penn Alcohol Craving Scale. Alcohol Clin Exp Res 23(8), 1289–1295. [PubMed: 10470970]

Grodin EN, Bujarski S, Venegas A, Baskerville WA, Nieto SJ, Jentsch JD, Ray LA, 2019. Reward, Relief and Habit Drinking: Initial Validation of a Brief Assessment Tool. Alcohol Alcohol 54(6), 574–583. [PubMed: 31557278]

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO, 1991. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. British journal of addiction 86(9), 1119–1127. [PubMed: 1932883]

King A, Vena A, Hasin DS, deWit H, O'Connor SJ, Cao D, 2021. Subjective Responses to Alcohol in the Development and Maintenance of Alcohol Use Disorder. American Journal of Psychiatry, appi.ajp.2020.20030247.

Lukas SE, Benedikt R, Mendelson JH, Kouri E, Sholar M, Amass L, 1992. Marihuana attenuates the rise in plasma ethanol levels in human subjects. Neuropsychopharmacology 7(1), 77–81. [PubMed: 1326277]

Lukas SE, Orozco S, 2001. Ethanol increases plasma Delta(9)-tetrahydrocannabinol (THC) levels and subjective effects after marihuana smoking in human volunteers. Drug Alcohol Depend 64(2), 143–149. [PubMed: 11543984]

Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM, 1993. Development and validation of the Biphasic Alcohol Effects Scale. Alcohol Clin Exp Res 17(1), 140–146. [PubMed: 8452195]

McCabe SE, Arterberry BJ, Dickinson K, Evans-Polce RJ, Ford JA, Ryan JE, Schepis TS, 2021. Assessment of Changes in Alcohol and Marijuana Abstinence, Co-Use, and Use Disorders Among US Young Adults From 2002 to 2018. JAMA Pediatr 175(1), 64–72. [PubMed: 33044552]

McNair DM, 1992. Profile of mood states. Educational and industrial testing service.

Mello NK, Mendelson JH, Kuehnle JC, Sellers ML, 1978. Human polydrug use: marihuana and alcohol. J Pharmacol Exp Ther 207(3), 922–935. [PubMed: 731440]

Midanik LT, Tam TW, Weisner C, 2007. Concurrent and simultaneous drug and alcohol use: results of the 2000 National Alcohol Survey. Drug Alcohol Depend 90(1), 72–80. [PubMed: 17446013]

Ray LA, Bujarski S, MacKillop J, Courtney KE, Monti PM, Miotto K, 2013. Subjective response to alcohol among alcohol-dependent individuals: effects of the μ-opioid receptor (OPRM1) gene and alcoholism severity. Alcoholism, clinical and experimental research 37 Suppl 1(Suppl 1), E116–E124. [PubMed: 23240711]

Ray LA, Bujarski S, Roche DJO, 2016. Subjective Response to Alcohol as a Research Domain Criterion. Alcoholism: Clinical and Experimental Research 40(1), 6–17. [PubMed: 26727518]

Ray LA, Bujarski S, Shoptaw S, Roche DJ, Heinzerling K, Miotto K, 2017. Development of the Neuroimmune Modulator Ibudilast for the Treatment of Alcoholism: A Randomized, Placebo-Controlled, Human Laboratory Trial. Neuropsychopharmacology 42(9), 1776–1788. [PubMed: 28091532]

Ray LA, Green R, Roche DJO, Bujarski S, Hartwell EE, Lim AC, Rohrbaugh T, Ghahremani D, Hutchison K, Miotto K, 2018. Pharmacogenetic Effects of Naltrexone in Individuals of East Asian Descent: Human Laboratory Findings from a Randomized Trial. Alcohol Clin Exp Res 42(3), 613–623. [PubMed: 29265379]

Ray LA, MacKillop J, Leventhal A, Hutchison KE, 2009. Catching the alcohol buzz: an examination of the latent factor structure of subjective intoxication. Alcohol Clin Exp Res 33(12), 2154–2161. [PubMed: 19764932]

Ronen A, Chassidim HS, Gershon P, Parmet Y, Rabinovich A, Bar-Hamburger R, Cassuto Y, Shinar D, 2010. The effect of alcohol, THC and their combination on perceived effects, willingness to drive and performance of driving and non-driving tasks. Accid Anal Prev 42(6), 1855–1865. [PubMed: 20728636]

SAMHSA, 2012. Drug Abuse Warning Network, 2011: National Estimates of Drug-Related Emergency Department Visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39, in: Administration, S.A.a.M.H.S. (Ed.). Rockville, MD.

SAMHSA, 2013. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M, 1993. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction 88(6), 791–804. [PubMed: 8329970]

Schuckit MA, 1984. Subjective responses to alcohol in sons of alcoholics and control subjects. Arch Gen Psychiatry 41(9), 879–884. [PubMed: 6466047]

Skinner HA, Horn JL, Addiction Research Foundation of, O., 1984. Alcohol Dependence Scale (ADS) user's guide. Addiction Research Foundation, Toronto.

Sobell LC, Sobell MB, 1992. Timeline Follow-Back, in: Litten RZ, Allen JP (Eds.), Measuring Alcohol Consumption: Psychosocial and Biochemical Methods. Humana Press, Totowa, NJ, pp. 41–72.

Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T, 2005. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Depend 80(1), 105–116. [PubMed: 16157233]

Subbaraman MS, Kerr WC, 2015. Simultaneous versus concurrent use of alcohol and cannabis in the National Alcohol Survey. Alcohol Clin Exp Res 39(5), 872–879. [PubMed: 25872596]

Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM, 1989. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). British journal of addiction 84(11), 1353–1357. [PubMed: 2597811]

Venegas A, Meredith LR, Green R, Cooper ZD, Ray LA, 2020. Sex-dependent effects of alcohol administration on the urge to use cannabis. Exp Clin Psychopharmacol.

Waddell JT, 2021. Between- and within-group effects of alcohol and cannabis co-use on AUD/CUD in the NSDUH 2002-2019. Drug Alcohol Depend 225, 108768. [PubMed: 34049100]

Yurasek AM, Aston ER, Metrik J, 2017. Co-use of Alcohol and Cannabis: A Review. Current addiction reports 4(2), 184–193. [PubMed: 32670740]

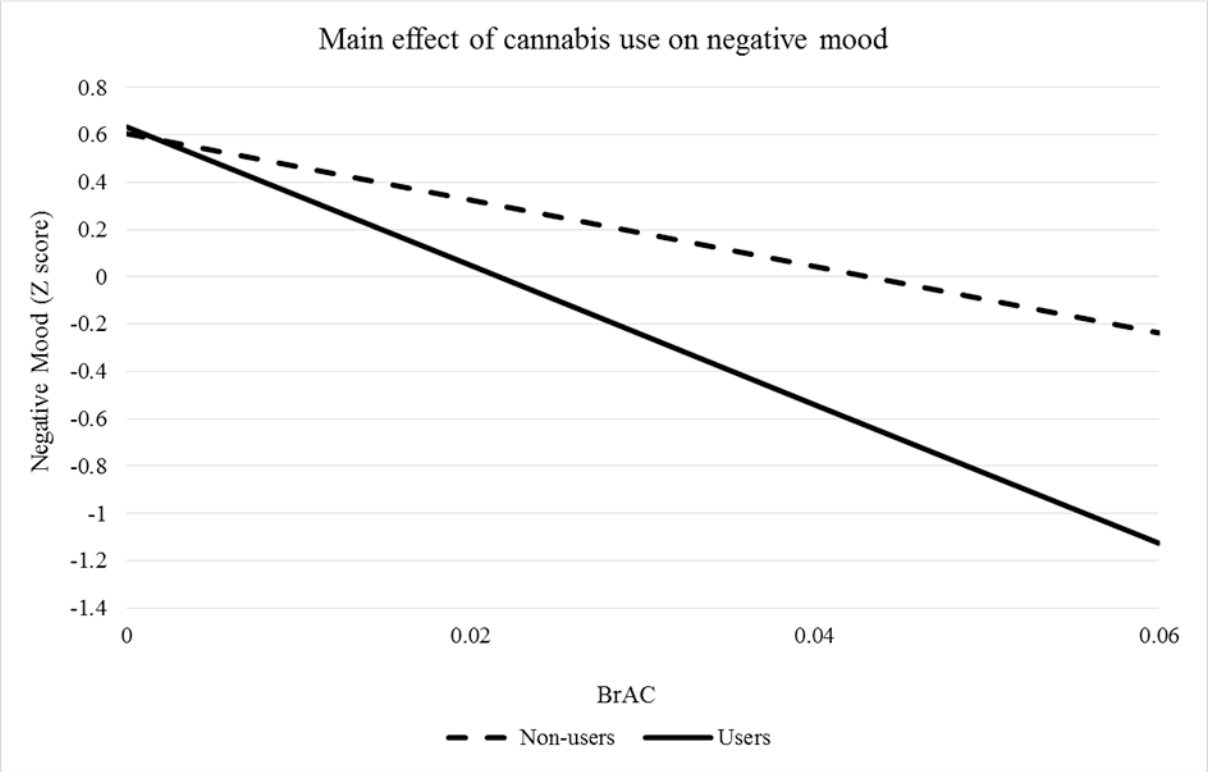


**Figure 1.**

Cannabis use and negative affect across the alcohol administration session. Mean negative affect scores are presented for cannabis users (solid line) and non-cannabis users (dashed line) as a function of breath alcohol concentration (BrAC).

**Table 1.**

Group Differences between Non-Cannabis Users and Cannabis Users.

| Variable[a] | Non-cannabis users ($n$ = 107) | Cannabis users ($n$ = 61) | Test for Difference (if applicable) |
|---|---|---|---|
| Age | 29.94 (7.74) | 26.36 (5.03) | $t(163.12) = 3.63$, $p < 0.0005$* |
| Gender | | | |
| Female (%) | 41 (38.32%) | 22 (36.07%) | $\chi^2(1) = 0.084$, $p = 0.77$ |
| Race/Ethnicity | | | |
| Non-Hispanic White | 39 (36.45%) | 30 (49.18%) | Fisher's Exact Test: $p = 0.31$ |
| African American/Black | 7 (6.54%) | 3 (4.92%) | |
| Native American | 6 (5.61%) | 1 (1.64%) | |
| Asian | 51 (47.66%) | 25 (40.98%) | |
| Latino/Hispanic | 4 (3.74%) | 2 (3.28%) | |
| Drinking days[b] | 16.79 (7.41) | 15.97 (6.72) | $t(166) = 0.71$, $p = 0.48$ |
| Drinks per drinking day[b] | 5.23 (4.72) | 5.45 (2.47) | $t(166) = -0.50$, $p = 0.61$ |
| AUDIT | 15.54 (6.50) | 14.00 (5.58) | $t(166) = 1.55$, $p = 0.12$ |
| BDI-II | 8.22 (8.19) | 8.84 (8.66) | $t(166) = -0.46$, $p = 0.65$ |
| Tobacco smoker Yes (%) | 31 (28.97%) | 29 (47.54%) | $\chi^2(1) = 5.83$, $p < 0.05$* |
| Tobacco smoking days[b] | 5.79 (11.12) | 6.57 (10.85) | $t(166) = -0.44$, $p = 0.66$ |
| Marijuana use days (past month) | 0 (0) | 4.44 (5.29) | |
| PACS | 10.75 (6.76) | 8.03 (5.06) | $t(153.94) = 2.95$, $p < 0.005$* |
| ADS | 12.50 (6.30) | 11.21 (5.49) | $t(166) = 1.34$, $p = 0.18$ |

AUDIT, Alcohol Use Disorder Identification Test; BDI-II, Beck Depression Inventory-II; PACS, Penn Alcohol Craving Scale; ADS, Alcohol Dependence Scale.

[a] Standard deviations appear within parentheses for continuous variables.

[b] Assessed by the Timeline Follow Back (TLFB) interview for the past 30 days.