Alcohol and Alcoholism, 2020, 1–8
doi: 10.1093/alcalc/agaa023
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Inclusion of Cannabis Users in Alcohol Research Samples: Screening In, Screening Out, and Implications

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Received 27 September 2019; Revised 10 March 2020; Accepted 0 Month 20xx

Abstract

Background: Alcohol and cannabis are frequently co-used, as 20–50% of those who drink alcohol report co-using cannabis. This study is based on the argument that alcohol researchers should enroll cannabis users in human laboratory studies of alcohol use disorder (AUD) to strengthen generalizability. This study examines how heavy drinking cannabis users differ from non-cannabis using heavy drinkers.

Methods: In a community sample of non-treatment-seeking heavy drinkers ($n = 551$, 35% female), cannabis users were identified through: (a) self-reported cannabis use in the past 6 months and (b) positive urine toxicology test for tetrahydrocannabinol (THC). Cannabis users, identified as described previously, were compared with non-cannabis users on demographic and clinical characteristics.

Results: Those who endorsed cannabis use in the past 6 months reported more binge drinking days. Participants who tested positive for THC had higher Alcohol Use Disorder Identification Test scores and more binge drinking days. Younger age and being a tobacco smoker were associated with an increased likelihood of cannabis use in the past 6 months, whereas male gender and being a tobacco use were associated with a greater likelihood of testing positive for THC. Individuals with cannabis use disorder (CUD) endorsed more depression and anxiety and had higher AUD symptom counts than cannabis users without CUD.

Conclusions: The inclusion of cannabis users in AUD samples allows for increased clinical severity. Excluding cannabis users from AUD studies may limit representativeness and expend unnecessary study resources. Lastly, tobacco use may explain a large portion of the effects of cannabis use on sample characteristics.

Short Summary: Alcohol and cannabis are frequently co-used substances. In a sample of non-treatment-seeking heavy drinkers ($n = 551$, 35% female), cannabis users reported higher alcohol use and higher likelihood of tobacco use than non-cannabis users. Including cannabis users in alcohol research studies will improve representativeness and likely increase clinical severity.

INTRODUCTION

Cannabis remains the most widely used drug among those who drink alcohol (SAMHSA, 2017), such that among those who abuse alcohol, 20–50% also report cannabis co-use (Petry, 2001). Individuals who report using both alcohol and cannabis often use them at the same time (Subbaraman and Kerr, 2015; Midanik *et al*., 2007), and such simultaneous 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 behaviors including heavy drinking and driving while intoxicated, and other adverse social sequelae (Midanik *et al*., 2007; Brière *et al*., 2011; Staiger *et al*., 2013; Metrik *et al*., 2018; Subbaraman *et al*., 2017). Further, cannabis use is predictive of both heavy drinking and the development and maintenance of alcohol use disorder (AUD) (Blanco *et al*., 2016a; Sullivan *et al*., 1989; Weinberger *et al*., 2016; Hayley *et al*., 2017; Regier *et al*., 1990; Lopez-Quintero *et al*., 2011), along with poor prognoses of treatment for AUD (Subbaraman, 2016; Sullivan *et al*., 1989; Mojarrad *et al*., 2014; Aharonovich *et al*., 2005). In fact, it has been estimated that 68% of individuals with a current cannabis use disorder (CUD) diagnosis and >86% of those with a lifetime CUD diagnosis will also meet criteria for a lifetime AUD (Agrawal *et al*., 2007; World Health Organization, 2014). Notably, however, these negative effects are not uniformly found in the literature (Mallett *et al*., 2019).

Movements to legalize and decriminalize cannabis use have changed the legal and political landscape, leading to an increased availability of cannabis, possibly influencing alcohol, tobacco and cannabis co-use patterns. In fact, the rate of co-use of cannabis and tobacco among tobacco users has increased in states where cannabis has been legalized (Wang and Cataldo, 2016). Despite recent increases in cannabis availability, there is a paucity of information regarding the profiles of regular drinkers who also use cannabis and potential implications for the inclusion of cannabis users in research studies of AUD. However, the high rates of alcohol and cannabis co-use, along with a host of clinical correlates including psychiatric severity, suggest that excluding cannabis users from clinical studies of AUD may result in non-representative samples of drinkers. For example, considering the fact that alcohol and tobacco are commonly consumed concurrently (Falk *et al*., 2006), it is well established that excluding tobacco users from AUD clinical studies would severely bias sample representativeness. Much as tobacco use has become standard inclusion criteria in alcohol studies, cannabis use may be moving in the same direction. Therefore, in order to elucidate the impact of cannabis and alcohol co-use in clinical research, *vis-a-vis* their inclusion or exclusion in AUD clinical research, we must first examine the rate of co-use in addition to their clinical correlates in AUD clinical research samples.

Concerns surrounding the extent to which tightly controlled trials generalize to individuals in community settings have persisted across many different areas of clinical research, including anxiety disorders (Goldstein-Piekarski *et al*., 2016; Hoertel *et al*., 2012), cannabis dependence (Okuda *et al*., 2010), major depression in adults (Blanco *et al*., 2008a; Halvorson and Humphreys, 2015) and children (Blanco *et al*., 2017), borderline personality disorder (Hoertel *et al*., 2015), post-traumatic stress disorder (Franco *et al*., 2016), schizophrenia (Humphreys, 2017), nicotine dependence and other substance use disorders (Blanco *et al*., 2016b; King *et al*., 2011; Le Strat *et al*., 2011; Melberg and Humphreys, 2010; Moberg and Humphreys, 2017; Robinson *et al*., 2006; Sofuoglu *et al*., 2000), neurological disorders (Trivedi and Humphreys, 2015) and randomized controlled trials of psychotherapy (Stirman *et al*., 2003; Stirman *et al*., 2005). Efforts to increase representativeness of alcohol-using samples while not compromising internal validity of findings has long been a topic of discussion in the field of alcohol research as well (Blanco *et al*., 2008b; Hoertel *et al*., 2014; Humphreys *et al*., 2007; Humphreys and Weisner, 2000; Maisto *et al*., 2001; Moberg and Humphreys, 2017; Storbjörk, 2014; Velasquez *et al*., 2000). 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 *et al*., 2005). These efforts to increase the integrity of research protocols via stringent inclusion/exclusion criteria have been questioned (Van Spall *et al*., 2007) and have been thought to increase the risk of biases in outcome estimates without gains in statistical power (Humphreys *et al*., 2008). In fact, Humphreys and Williams (2018) provide a compelling summary of the magnitude of exclusion rates across disorders. They estimate that researchers exclude between 72 and 92% of real-world individuals suffering from anxiety disorders, 75% of those with bipolar disorders and between 75 and 85% of those with depression. This number is especially striking for substance use disorder research, with investigators excluding ~64–96% of those with substance use disorders, including AUD. As such, it might be useful 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, and narrow the gap between research and clinical practice. It is also important to consider the logistical implications of such widespread exclusion of individuals within clinical research, as researchers are forced to grapple with the trade-off between tightly controlling inclusion standards so as to increase internal validity, at the cost of increased recruitment efforts, expenditure of study resources and reductions in external validity.

The present study is based on the argument that alcohol researchers should consider allowing cannabis users to enroll in AUD clinical studies to strengthen generalizability of the findings. To inform the field, this study examines how heavy drinking cannabis users differ from non-cannabis using heavy drinkers in terms of demographic and clinical characteristics—the first study to do so within the context of human laboratory research. To do so, we identify cannabis users through two distinct methods: (a) self-reported cannabis use in the past 6 months per the Cannabis Use Disorder Identification Test—Revised (CUDIT) (Adamson *et al*., 2010) and (b) positive urine toxicology test for tetrahydrocannabinol (THC), and systematically compare their alcohol use, along with their scores on other individual differences measures, to non-cannabis using heavy drinkers. A second goal of the study was to investigate the hypothesis that cannabis-using heavy drinkers report greater frequencies of alcohol use and associated problems than their non-cannabis using heavy-drinking counterparts. Given that a positive toxicology result likely indicates higher frequency of cannabis use, we hypothesized that those who tested positive for THC via toxicology testing would also show higher clinical severity of AUD.

PARTICIPANTS AND METHODS

Participants

The current sample is a combination of subsamples representing research participants from four separate human laboratory studies

with similar inclusion criteria and recruitment methods conducted at the University of California, Los Angeles. All four studies recruited community samples of non-treatment-seeking heavy drinkers from the Greater Los Angeles area. Three of these published studies examined pharmacotherapies for alcohol use: naltrexone ($n = 199$; Ray *et al*., 2018), ibudilast ($n = 138$; Ray *et al*., 2017a) and ivermectin ($n = 140$; Roche *et al*., 2016); the fourth study was an alcohol self-administration study ($n = 140$; Bujarski *et al*., 2018). The combination of these subsamples resulted in a final sample size for the present study of 551. Participation in multiple studies was not allowed.

Screening procedures

All study procedures were approved by the University of California, Los Angeles 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 for the following inclusion criteria based on previously defined criteria of hazardous alcohol drinking (US Department of Agriculture, 2015; National Institute on Alcohol Abuse and Alcoholism, 2010; Reinert and Allen, 2007): >4 drinks per occasion or 7 drinks per week for females and >6 drinks per occasion or 14 drinks per week for males, as well as an Alcohol Use Disorder Identification Test (AUDIT) (Saunders *et al*., 1993) score of 8 of higher for the naltrexone study; >48 drinks per month and a score of 2 or higher on the CAGE questionnaire (Ewing, 1984) for the ibudilast and ivermectin studies; or >7 drinks per week for females and >14 drinks per week for males for the self-administration study.

All studies had the following exclusion criteria: (a) current involvement in treatment programs for alcohol use or have received treatment in the prior 30 days to study participation; (b) use of non-prescription psychoactive drugs or use of prescription medications for recreational purposes, except for cannabis; (c) self-reported lifetime and/or current history of severe mental illness (e.g. bipolar disorder or psychotic disorders); (d) current use of antidepressants, mood stabilizers, sedatives, anti-anxiety medications, seizure medications or prescription painkillers and (e) self-reported current use of 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: (a) exclusion, for females, if pregnant (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; (b) exclusion if breath alcohol concentration (BAC) was >0.000 g/dl as measured by the Dräger Inc. Alcotest® 6510 and (c) exclusion if participant provided a positive urine toxicology screen for any drug (other than cannabis), as measured by Medimpex United Inc. 10-panel drug test. Participants in the current analysis passed both the telephone interview and the in-person assessment of BAC, toxicology test and pregnancy screening (if female).

Measures

At the in-person screening visit participants completed a comprehensive battery of individual differences, clinical and substance use measures, including: (a) the CUDIT captured cannabis-related problems; (b) the Timeline Follow-Back (TLFB) (Sobell and Sobell, 1992) interview for the past 30 days measured alcohol and cannabis use; (c) the AUDIT measured alcohol-related problems; (d) the Beck Depression Inventory (BDI-II) (Beck *et al*., 1996) and the (e) Beck Anxiety Inventory (BAI) (Beck *et al*., 1988) measured depression and anxiety symptoms, respectively; (f) the Fagerstrom Test for Nicotine Dependence (Heatherton *et al*., 1991) was used to determine smoking status; and (g) the Structured Clinical Interview for *DSM-5* (SCID-5) (adapted from First, 2014) was used to determine current (past 3-month) diagnosis of AUD and lifetime diagnoses of exclusionary psychiatric disorders. Participants who reported using cannabis at least 10 times per month over the previous 3 months also completed the CUD module of the SCID-5.

Data analysis

Comparisons consisted of univariate independent samples *t*-tests for continuous outcomes or chi-square tests for dichotomous outcomes. This study identified and compared cannabis users versus non-cannabis users based on the following two definitions: (a) self-reported cannabis use over the past 6 months per the CUDIT ($n = 286$ endorsed cannabis use) and (b) positive urine toxicology screen for THC at the time of assessment ($n = 107$ tested positive for THC). Cannabis users and non-cannabis users were compared on demographic (i.e. age, gender and education level), psychiatric (i.e. BDI-II and BAI scores) and substance use (i.e. drinking days, drinks per drinking day, binge drinking days, AUDIT score and tobacco smoking status) variables. Slight variation in sample sizes presented in the results and in Tables 1 and 2 are due to missing data generated from the full sample.

As a follow-up to the univariate models (i.e. *t*-tests), multivariate logistic regressions were performed in which the significant univariate predictors were tested concomitantly. Results from the logistic regression analyses are reported as a function of odds ratios (ORs) with 95% confidence intervals (CI). Analyses were performed using SPSS version 25. For all comparisons, statistical significance was set at $P < 0.05$, and all tests were two-tailed.

RESULTS

Of the 551 total participants who completed the in-person assessment battery, 286 (53.7%) reported using any cannabis in the past 6 months on the CUDIT and/or past 30 days on the TLFB. Of the 551 total participants, 185 reported using cannabis ≥10 times per month in the past 3 months and as such underwent the CUD module of the SCID-5, whereas 366 did not. Of the 185 individuals who underwent the CUD module of the SCID-5, 131 (23.8%) did not meet diagnostic criteria for a CUD, whereas 34 (6.2%), 11 (2.0%) and 9 (1.6%) met diagnostic criteria for mild, moderate and severe CUDs, respectively. All participants also underwent the current (past 3-month) AUD module of the SCID-5, although an AUD diagnosis was not an inclusion criterion for any study; individuals with no, mild, moderate and severe AUD enrolled in the studies. A total of 221 (40.1%) did not meet diagnostic criteria, 152 (27.6%) met criteria for mild, 95 (17.2%) met criteria for moderate and 83 (15.1%) met criteria for a severe current (past 3-month) AUD.

Comparisons across the study source (i.e. the naltrexone, ibudilast, ivermectin or alcohol self-administration study) revealed significant differences in variables of interest across study source (P's < 0.03). As such, all the multivariate logistic regression analyses described below adjust for study source.

Correlates of self-reported cannabis use per CUDIT

Table 1 presents group comparisons based on self-reported cannabis use (endorsed use in the past 6 months per CUDIT). Compared to

Table 1. Group differences between non-cannabis users and cannabis users identified by CUDIT (i.e. endorsed use in the past 6 months)

Variable	Non-cannabis users ($n = 252$)[a,c]	Cannabis users ($n = 286$)[a,c]	Test for difference
Age	32.73 (9.92)	28.10 (7.42)	$t = 6.066$, $P < 0.001$
Gender			
Female (%)	95 (50.53)	93 (49.47)	$\chi^2 = 1.52$, $P = 0.22$
Education			
Some college or higher (%)	164 (65.34)	180 (62.94)	$\chi^2 = 0.34$, $P = 0.56$
Drinking days[d]	15.96 (8.00)	16.14 (7.22)	$t = -0.28$, $P = 0.78$
Drinks per drinking day[d]	5.70 (3.89)	5.81 (3.37)	$t = -0.36$, $P = 0.72$
Binge drinking days[d]	7.70 (7.32)	10.91 (8.57)	$t = -3.55$, $P = 0.001$
AUDIT	15.61 (7.66)	15.70 (7.13)	$t = -0.14$, $P = 0.89$
Tobacco smoker			
Yes (%)	83 (32.94)	154 (53.85)	$\chi^2 = 23.76$, $P < 0.001$
BDI-II	9.28 (9.50)	9.63 (9.17)	$t = -0.43$, $P = 0.67$
BAI	5.88 (7.62)	5.92 (6.23)	$t = -0.077$, $P = 0.94$

[a]Standard deviations appear within parentheses for continuous variables.
[b]Inconsistent sample sizes due to missing data generated from the full sample ($n = 551$).
[c]Group identification determined by the CUDIT.
[d]Assessed by TLFB interview for the past 30 days.

Table 2. Group differences between non-cannabis users and cannabis users identified by positive urine toxicology screen for THC

Variable[b]	Negative toxicology ($n = 440$)[a,c]	Positive toxicology ($n = 107$)[a,c]	Test for difference
Age	30.70 (9.37)	29.42 (7.49)	$t = 1.44$, $P = 0.15$
Gender			
Female (%)	172 (39.18)	18 (17.14)	$\chi^2 = 18.10$, $P < 0.001$
Education			
Some college or higher (%)	294 (67.74)	51 (48.11)	$\chi^2 = 14.23$, $P < 0.001$
Drinking days[d]	15.46 (7.67)	17.64 (7.72)	$t = -2.64$, $P = 0.009$
Drinks per drinking day[d]	5.46 (3.60)	6.71 (3.71)	$t = -3.20$, $P = 0.001$
Binge drinking days[d]	7.70 (7.32)	10.91 (8.57)	$t = -3.55$, $P = 0.001$
AUDIT	15.00 (7.47)	17.04 (7.83)	$t = -2.50$, $P = 0.013$
Tobacco smoker			
Yes (%)	165 (38.19)	72 (67.92)	$\chi^2 = 30.53$, $P < 0.001$
BDI-II	9.12 (9.05)	11.53 (10.78)	$t = -2.12$, $P = 0.035$
BAI	5.78 (6.91)	6.40 (6.92)	$t = -0.82$, $P = 0.41$

[a]Standard deviations appear within parentheses for continuous variables.
[b]Inconsistent sample sizes due to missing data generated from the full sample ($n = 551$).
[c]Group identification determined by urine toxicology screens.
[d]Assessed by TLFB interview for the past 30 days.

non-cannabis users ($n = 252$), those who reported using cannabis in the past 6 months ($n = 286$) were younger, were more likely to be cigarette smokers and reported a higher number of binge drinking days (P's < 0.002). Self-reported use in the past 6 months (per the CUDIT) was significantly correlated with tobacco smoking status ($r = 0.21$, $P < 0.0001$). Multivariate logistic regression models following up on these univariate results predicted self-reported cannabis use in the past 6 months (per the CUDIT) as a function of age, binge drinking days and smoking status, while controlling for study source. This model was significant ($P < 0.05$) and explained 16.5% of the variance in reported cannabis use and correctly classified 64.9% of cases. Age and smoking status remained statistically significant predictors (P's < 0.05), such that younger age and being a tobacco smoker were associated with an increased likelihood of being classified as a cannabis user (ORs = 0.92 and 2.98, respectively); number of binge drinking days was not a significant predictor ($P > 0.05$).

Correlates of positive urine toxicology screens for THC

Table 2 presents group comparisons based on toxicology test results. Cannabis users, as determined by a positive urine toxicology screen for THC ($n = 107$), were more likely to be male, score higher on the AUDIT and the BDI-II, have less educational achievement, identify as cigarette smokers and report heavier drinking in the past 30 days (more drinking days, drinks per drinking days and binge drinking days) than non-cannabis users ($n = 440$, P's < 0.035). A positive urine toxicology screen for THC was significantly correlated with various substance use measures, including AUDIT score ($r = 0.11$, $P = 0.013$), drinking days in the past 30 days ($r = 0.11$, $P < 0.0001$), drinks per drinking day ($r = 0.14$, $P = 0.001$), binge drinking days ($r = 0.17$, $P < 0.0001$) and tobacco smoking status ($r = 0.24$, $P < 0.0001$). A follow-up multivariate logistic regression model predicted cannabis use (i.e. positive urine toxicology screen for THC) as a function of gender, education level, drinking days, drinks per drinking day,

binge drinking days, AUDIT score, tobacco smoking status and BDI score (which was log transformed due to the non-normality of the data across all groups), while controlling for study source. This model was also significant ($P < 0.05$) and explained 18.1% of the variance in positive urine toxicology screens for THC and correctly classified 80.3% of cases. Gender, binge drinking days and tobacco smoking status remained significant predictors of cannabis use (P's < 0.05), such that male gender, more binge drinking days and being a tobacco smoker were associated with a greater likelihood of testing positive for THC (ORs = 0.40, 1.06 and 2.98, respectively); drinking variables, AUDIT score, log-transformed BDI score and education were not significant predictors (P's > 0.05).

Exploratory analyses: CUD diagnosis

In order to examine the role of CUD diagnosis, as a comorbidity to AUD, we selected individuals who met diagnostic criteria for current AUD and who reported regular cannabis use (i.e. reported using cannabis ≥10 times per month over the previous 3 months) and therefore completed a diagnostic interview for CUD ($n = 130$). In this sample, 69.2% ($n = 90$) met criteria for AUD only and 30.8% ($n = 40$) met criteria for AUD + CUD. Regarding the CUD diagnosis, 24 individuals met criteria for mild CUD, 10 met for moderate CUD and 6 met for severe CUD. For the purpose of these analyses, and due to the small sample sizes, we collapsed CUD into present versus not, such that all severity levels were culled into a single CUD+ group. We compared the two groups on demographics (i.e. sex, age, education), alcohol use in the past 30 days (i.e. drinking days, total drinks, drinks per drinking day and binge drinking days) and on clinical variables of interest (i.e. depressive symptoms, anxiety symptoms, alcohol withdrawal and AUD symptom count). Univariate analyses (t-tests and chi-squares) revealed that CUD+ group reported significantly higher anxiety symptoms on the BAI ($M = 8.97$ (SD = 7.74)) than CUD− group ($M = 5.98$ (SD = 6.72); $t(127) = -2.22$, $P < 0.05$). A similar pattern emerged for depressive symptoms, such that the CUD+ group exhibited significantly higher BDI-II scores ($M = 15.80$ (SD = 11.86)) than the CUD− group ($M = 9.61$ (SD = 9.00); $t(128) = -2.95$, $P < 0.01$). This also held true for AUD symptom count, such that the comorbid group endorsed significantly more AUD symptoms in the diagnostic interview ($M = 4.95$ (SD = 2.64)) than those without a comorbid CUD diagnosis ($M = 3.98$ ($SD = 2.19$); $t(128) = -2.19$, $P < 0.05$). No other significant group differences were found in the remaining demographic or alcohol use variables (P's > 0.10). A multivariate logistic regression analysis, including depression, anxiety and AUD symptom count simultaneously, indicated that the overall model was significant ($\chi^2 = 9.69$, $P < 0.05$), yet no single variable was significant over and above the others.

DISCUSSION

The present study evaluated the clinical characteristics of cannabis versus non-cannabis users within a sample of heavy drinkers in order to elucidate the clinical correlates of co-use and inform clinical research practices for alcohol research studies. Of note, not all participants met diagnostic criteria for an AUD. This likely indicates that the current sample is not likely to be entirely representative of those seeking treatment for AUD; however, it is reasonable to assume that this sample is largely indicative of heavy drinkers who enroll in human laboratory studies of AUD. Additionally, >50% of the sample endorsed using cannabis. As such, the prevalence of cannabis use in heavy drinkers participating in clinical research underscores the issue of representativeness when cannabis users are included or excluded from such studies. Participants who endorsed cannabis use in the past 6 months (which includes those who tested positive for THC) reported higher levels of alcohol use compared to non-cannabis users, as indicated by higher numbers of binge drinking days. Conversely, participants who tested positive for THC at the time of assessment, exhibited higher clinical severity profiles for a host of drinking outcomes (e.g. AUDIT, drinking days, binge drinking days) compared with those who tested negative for THC. These findings are generally consistent with the emerging literature suggesting that the co-use of alcohol and cannabis is associated with greater clinical severity and poorer outcomes (Sullivan *et al*., 1989; Blanco *et al*., 2016a; Weinberger *et al*., 2016; Subbaraman, 2016; Mojarrad *et al*., 2014; Aharonovich *et al*., 2005). Follow-up multivariate models suggested that age and smoking status consistently predicted self-reported cannabis use in the past 6 months, over and above other significant predictors. A similar pattern of multivariate results was obtained for predicting positive toxicology test such that smoking status, sex and BDI scores remained significant predictors. It is noteworthy that drinking variables were significant in the univariate models but did not survive the multivariate comparison, which may be, at least in part, due to them accounting for shared variance (i.e. suppression effect). Moreover, a common factor across these analyses is the role of smoking status as consistently associated with higher frequency of cannabis use among participants in our study.

Notably, several other group differences were characteristic of the cannabis-using group but only for those identified through positive toxicology screens, including education, sex and depressive symptomatology. For example, the cannabis-using group had 20% higher proportion of males and 20% less having received any college education, demarcating potentially relevant demographic and socioeconomic factors. Cannabis users also displayed higher levels of depressive symptomatology, which is consistent with literature finding greater rates of psychiatric comorbidities among co-users of alcohol, cannabis and other substances (Midanik *et al*., 2007) as well as heightened risk for the development of depression among cannabis users specifically (Lev-Ran *et al*., 2014). Further, these patterns are seen in areas where recreational or even medicinal cannabis use is not legalized, as alleviation of psychiatric symptoms (i.e. anxiety, depression) was reported as the most common reason for medicinal cannabis use in the Southeastern USA (Salazar *et al*., 2019). This result also was found in the multivariate analyses, such that increases in depressive symptomatology per the BDI-II were associated with a greater likelihood of testing positive for THC on the urine toxicology screen. Given that a positive urine toxicology screen definitively indicates more recent cannabis use, it is also possible that it identifies those with more frequent use as well. In fact, those who tested positive for THC on the urine toxicology screen also reported more frequent cannabis use in the 30 days prior to assessment ($M = 17.26$, SD = 10.78) than those who did not ($M = 1.25$, SD = 3.63; $t = -14.81$, $P < 0.0001$). These findings indicate that more frequent cannabis and alcohol co-use patterns are associated with higher levels of clinical severity, which holds important implications for inclusion/exclusion criteria for clinical studies of AUD. Specifically, allowing for inclusion of individuals with a positive urine toxicology screen would potentially result in a more clinically severe drinking sample, albeit more likely to be representative of populations of those who seek treatment for AUD in the community (Blanco *et al*., 2008b; Grant *et al*., 2015; Humphreys, 2003).

Notably, younger age and higher likelihood of cigarette smoking was consistently different among cannabis users, identified through

either self-report or toxicology test. In keeping with the changing landscape for cannabis legalization and access, as well as the changing market of tobacco products targeting youth (e.g. electronic nicotine delivery systems, e-cigarettes) (Fadus *et al.*, 2019), these findings highlight possible cohort effects that may influence the enrollment and generalizability of AUD clinical samples for years to come, such that the inclusion of younger drinkers who are more likely to also be concurrent tobacco and cannabis users, might also increase the clinical severity of study samples. With regard to the multivariate analyses, it is important to note that group differences with regard to alcohol use outcomes are non-significant after accounting for tobacco smoking status. This suggests that tobacco use may be driving some of the observed differences between cannabis users and non-cannabis users in this sample.

While these results are informative, they must be interpreted in light of the study's strengths and limitations. Strengths include the large data set drawing from multiple human laboratory studies of AUD. Limitations include the studies being conducted in a state in which cannabis is legalized both recreationally and medicinally. Profiles of cannabis use may differ in states that regulate cannabis more restrictively. However, exploring cannabis use as a moderator of outcomes of clinical studies of AUD may prove beneficial, as findings from the present study suggest that although allowing for cannabis use results in a more representative sample of heavy drinkers in community settings, they appear to inherently differ on a host of clinical and demographic correlates from those who drink alcohol only. Another important limitation of the present study is that these data come from samples of non-treatment seekers for AUD. As such, this likely indicates that the present sample is younger and has less severe alcohol problems than those who seek treatment for AUD (Ray *et al.*, 2017b; Rohn *et al.*, 2017). However, whether those who seek treatment for AUD are more likely to be concurrent cannabis users and display similar clinical correlates to those reported herein are beyond the scope of this manuscript.

In conclusion, given that cannabis and alcohol co-users have distinct demographic characteristics, report more severe drinking profiles, have higher rates of nicotine use and report higher depressive symptomatology, it appears that the inclusion of cannabis users in AUD samples allows for higher levels of clinical severity. In fact, the results from the exploratory analyses suggest that affective symptoms, namely depression and anxiety, may be associated with the comorbidity of AUD + CUD, as compared to AUD and regular cannabis use. The comorbidity was also associated with higher symptom count for AUD, possibly indicating a worsened clinical presentation. However, excluding cannabis users from AUD clinical studies may lead to a less representative sample, whereas allowing cannabis use among AUD participants enables researchers to learn more about this sizeable subgroup. Additionally, allowing for the inclusion of cannabis users in alcohol human laboratory research poses a potential cost and efficiency advantage, such that their exclusion would significantly diminish the sampling pool from which to recruit, resulting in longer and therefore more expensive enrollment periods and study timelines.

A potential future direction for research is to compare the compositions of samples of clinical studies of AUD where cannabis concurrent use was explicitly excluded to a sample in which cannabis and alcohol-use was not exclusionary to be able to directly speak to the implications of exclusion versus inclusion of cannabis use within these studies. Additionally, additional clinical correlates that were not explored within the present analyses could also be investigated. Based on the current findings, however, cannabis use could be explored as a putative moderator of clinical outcomes in AUD studies that include co-users. Interestingly, when examining the impact of nicotine co-use on drinking outcomes, the pharmacotherapy naltrexone was found to significantly reduce drinking only among those who were nicotine co-users (Anton *et al.*, 2018). Thus, understanding characteristics of poly-substance users, which arguably represent the norm as opposed to the exception, can inform the development of targeted interventions.

FUNDING

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (R01AA021744, R21AA022214, and R21AA022752 to L.A.R.) and the UCLA Clinical and Translational Science Institute (UL1TR000124 to L.A.R.).

CONFLICT OF INTEREST STATEMENT

None declared.

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