Published in final edited form as:

Addiction. 2017 April ; 112(4): 685–694. doi:10.1111/add.13693.

Cannabis use during treatment for alcohol use disorders predicts alcohol treatment outcomes

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Abstract

Aims—(1) Compare post-treatment alcohol use between those who use cannabis and those who abstain during treatment for alcohol use disorders (AUD). (2) Examine potential cannabis use thresholds by comparing post-treatment alcohol use between four frequency groups of cannabis users relative to abstainers.

Design—Secondary analyses of the COMBINE Study, a randomized control trial of AUD treatments. The current study compares longitudinal drinking data between those who used cannabis vs. those who abstained during COMBINE treatment.

Setting—The COMBINE Study treatments were delivered on an outpatient basis over 16 weeks. The current analyses include 206 cannabis users and 999 cannabis abstainers.

Participants—All participants met diagnosis of primary alcohol dependence (N = 1,383).

Measurements—Primary exposures were any cannabis use and quartiles of cannabis use (Q1: 1–4 use days during treatment, Q2: 5–9 days, Q3: 10–44 days, Q4: 45–112 days). Outcomes were percent days abstinent from alcohol (PDA), drinks per drinking day (DPDD), and percent heavy drinking days (PHD), all measured at treatment end and one year post-treatment.

Findings—Compared with no cannabis use, any cannabis use during treatment was associated with 4.35% (95% CI: –8.68, –0.02), or approximately four fewer alcohol abstinent days at the end of treatment. This association weakened by one-year post-treatment (95% CI: –9.78, 0.54). Compared with no cannabis use, only those in the second quartile of cannabis use (those who used once or twice per month during treatment) had 8.81% (95% CI: –17.00, –0.63), or approximately ten fewer days alcohol abstinent at end of treatment, and 11.82% (95% CI: –21.56, –2.07), or approximately 13 fewer alcohol abstinent days one-year post-treatment. Neither any cannabis use nor quartiles were associated with DPDD or PHD at either time-point.

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The authors have no conflicts of interest to declare.

Conclusions—Among individuals in alcohol treatment, any cannabis use (compared with none) is related to significantly lower percent days abstinent from alcohol post-treatment, though only among those who used cannabis once or twice per month.

INTRODUCTION

Cannabis is the most commonly used drug among individuals with alcohol use disorders (AUD), with almost a quarter of individuals with past-year AUD reporting concurrent cannabis use (1). Adolescent and young adult cannabis use has been linked to increased risk of AUD later in life (2), and international studies have shown significant associations between cannabis use and AUD (3–5). Concurrent use of marijuana and alcohol is associated with heavy episodic drinking, and the combined use of cannabis and alcohol may lead to more substance use and related problems compared to the use of alcohol alone (6–8). Cannabis use has been examined as a predictor of substance use outcomes in a few treatment studies (9, 10), and was found to have deleterious impact.

Still, evidence regarding the impact of cannabis use on alcohol consumption specifically among those in treatment for AUD remains sparse. Co-occurring drug use (including drugs other than cannabis) and alcohol use more broadly can negatively impact the treatment of substance use disorders (11). Recent results from the National Epidemiological Study of Alcohol Use and Related Disorders (NESARC; Wave 1, 2001–2001; Wave 2, 2004–2005) show that among adults with a history of AUD, any cannabis use at Wave 1 was related to 1.74 times the odds of AUD persistence at Wave 2 when compared to no cannabis use (12). Cannabis users who are also heavy drinkers report higher alcohol use, as well as more negative alcohol-related consequences (13). In a sample of psychiatric treatment-seekers with AUD, cannabis use was related to increased likelihood of alcohol relapse and decreased likelihood of stable abstinence (9). Furthermore, the odds of alcohol dependence are substantially higher among those with cannabis dependence (12, 14, 15), suggesting that hazardous alcohol use may increase as cannabis use increases. Results from a clinical trial which tested the effectiveness of chronic disease management and examined the relationship between cannabis use and the odds of abstinence 3, 6, and 12 months later showed that any cannabis use in the past 30 days at study entry was related to a 27% reduction in the odds of abstinence from drug and heavy alcohol use at later time-points (10).

Few experimental studies have directly examined the interactions between alcohol and cannabis. One experimental study of 16 male concurrent alcohol/cannabis users showed that when subjected to conditions in which alcohol only, cannabis only, or both alcohol and cannabis were available, participants tended to reduce alcohol intake when cannabis was also available (compared to not) (26). A more recent laboratory study examined whether combinations of ethanol and Δ^9 -tetrahydrocannabinol (THC, one of the primary psychoactive compounds in cannabis) act synergistically on physiological and subjective measures; results showed that while THC alone did not affect ratings of “wanting more” THC, THC did weaken the effects of ethanol-only administration on increased desire for alcohol (27). Furthermore, and contrary to what was originally hypothesized, cannabis and alcohol did not act additively or multiplicatively on any measures, which included heart rate, blood pressure, blood alcohol concentration, and subjective drug effects like hunger and

sedation (27). On the other hand, a review regarding the combined effects of cannabis and alcohol concluded that compared to either substance alone, the combination may have the strongest effects in terms of impaired driving tasks, subjective sensations, and physiological measures, such as heart rate (28). Physiologically, while smoking cannabis may slow absorption of alcohol, which then reduces alcohol's psychoactive effects (Lukas et al., 1992), plasma THC levels can be enhanced if alcohol is consumed immediately after smoking cannabis (29, 30). Thus cannabis combined with alcohol can lead to greater impairment than ingestion of either substance alone.

Despite some evidence that cannabis use adversely impacts alcohol use severity, there are a number of contradictory findings from case report and correlational studies suggesting that cannabis can substitute for alcohol and reduce drinking (31). High rates of cannabis substitution for alcohol have been reported by medical cannabis patients and their doctors (32–35), although results are limited by retrospective self-report and selection bias. A 30-year prospective study of alcohol abusers showed that almost half maintained a year of alcohol abstinence, with some claiming to substitute cannabis for alcohol (36). Some even propose that medical cannabis could help individuals with AUD reduce drinking (32–34); however, these recommendations are based on retrospective data, highlighting the need for more rigorous research in this area.

Rationale for current study

Collectively, the literature indicates that marijuana use is strongly linked with alcohol use; however, the evidence on whether cannabis users reduce or increase alcohol use when using or abstaining from cannabis is mixed. The mixed evidence may be partially explained by the heterogeneous samples (e.g., general population vs. clinical samples), and/or variation in assessments of frequency of use (e.g., dichotomous vs. continuous measures). Furthermore, no prior study has examined cannabis use during AUD treatment, and findings from general population or non-clinical studies are not necessarily generalizable to individuals who are currently in treatment for AUD. The current study builds on previous findings by (1) restricting the sample to individuals currently in treatment for AUD and (2) examining use frequency categories, which is a more nuanced and potentially more powerful measure than dichotomized cannabis use and prevalence variables. Specifically, the aims of this study are: (1) to compare post-treatment alcohol use outcomes between those who use cannabis and those who abstain from cannabis during treatment for AUD; and (2) to examine potential cannabis use thresholds by comparing post-treatment alcohol use outcomes between four frequency groups of cannabis users and cannabis abstainers.

METHODS AND STATISTICS

Sample

For a detailed description of the COMBINE study, please see (37, 38). Briefly, the COMBINE study was a large (n=1,383), multi-site randomized control trial in which newly alcohol-abstinent alcohol-dependent participants received one of four medication regimens (placebo, naltrexone, acamprosate or naltrexone + acamprosate) either with or without a behavioral intervention, for a total of eight possible treatments including medication. The

ninth and final group received the behavioral intervention only, without any placebo or active medication. The COMBINE data span 68 weeks with measures at baseline, and 4, 8, 16 (end of treatment), 26, 52 and 68 weeks (37, 38). Current dependence on other psychoactive substances, except for cannabis and nicotine, resulted in exclusion for participation in the COMBINE Study.

Design

We performed secondary analyses of the COMBINE Study, comparing longitudinal drinking data between those who used cannabis vs. those who abstained during the COMBINE treatment period. In order to derive a potential threshold for cannabis use, we also compared post-treatment alcohol use outcomes between groups based on quartiles of cannabis use frequency and cannabis abstainers.

Measures

Exposures/Key Predictors—The exposures, any cannabis use during treatment (0 = none, 1 = at least one day) and quartiles of days of cannabis use during treatment, were calculated from Form-90 (37, 38); if the individual had used cannabis on any 1 day between baseline and the last day of treatment (16 weeks, or 112 days post-baseline), then s/he was considered a “1.” Quartiles of days cannabis use were based on the distribution of the percent days cannabis use among users only. Specifically, those in the lowest quartile, Q1, used approximately 1–4% of days, or 1–4 days during treatment; the second quartile, Q2, used approximately 5–8% of days, or 5–9 days during treatment; the third quartile used approximately 8–39% of days, or 10–44 days during treatment; and the highest quartile, Q4, used approximately 40–100% of days, or 45–112 days of treatment.

Outcomes—The first outcome, percentage of days abstinent (PDA) was the proportion of days abstinent between baseline and 16 weeks (end of treatment) as well as between 16 weeks and 68 weeks (one-year post-treatment). The second outcome, drinks per drinking day (DPDD), was the average number of drinks consumed on days drinking occurred. The final outcome of interest, percent days heavy drinking (PHD) was the proportion of days when 4+/5+ drinks were consumed by women/men respectively. Drinks per drinking day and PHD were also measured at 16 and 68 weeks. All outcomes were calculated using Form-90 (37, 38).

Covariates—All analyses controlled for age (years), gender, education (years), employment, income, marital status, race/ethnicity, baseline Alcohol Dependence Severity (maximum possible score = 47) (37), baseline PDA, baseline DPDD, baseline PHD, any nicotine use, any other drug use, COMBINE treatment assignment and COMBINE treatment site; these covariates have been shown to relate to cannabis and/or alcohol use in prior studies. Race/ethnicity was self-reported by participants in accordance with National Institutes of Health guidelines. Responses were categorized as non-Hispanic Black, non-Hispanic White, Hispanic, or other in order to be consistent with the original COMBINE study. Other drug use was based on whether participants answered yes to using any of the following during treatment: sedatives/tranquilizers, hypnotics, steroids, amphetamines, cocaine, hallucinogens, inhalants, opiates, or unspecified other drugs.

Statistical Methods

We assessed whether cannabis use was related to PDA, DPDD, and PHD at the end of treatment (16 weeks) and one year post-treatment (68 weeks) using multilevel linear regression models with random slopes and intercepts for COMBINE treatment site; random effects were included to adjust for clustering as well as potential heterogeneity of cannabis effects across locations. Model fit statistics indicated that the mixed model with both random slopes and intercepts fit best compared to random-intercept only and single-level linear models. The covariates described in the Covariates section (above) were included in all models, and all analyses were performed in Stata V.13.

RESULTS

Sample Characteristics

Overall, the sample was mostly male, non-Hispanic White, and employed, with an average age of 44.4 years (Table 1). Table 1 also displays demographics and substance use characteristics of the cannabis user (those who used cannabis during treatment) and abstainer (those who did not use cannabis during treatment) subgroups. Users and abstainers significantly differed ($P < 0.05$) in terms of gender, age, education, income, marital status, and alcohol dependence severity; specifically, users tended to be younger, less educated, lower income, less likely married/cohabitating, and less likely female. In terms of substance use, cannabis users had higher alcohol dependence severity, were more likely to use nicotine during treatment, and more likely to use other drugs during treatment. Users and abstainers did not significantly differ in terms of baseline past 90-day percent days abstinent from alcohol, drinks per drinking day, or percent days heavy drinking.

Any cannabis use during treatment

Table 2 displays results from the first set of regressions, which examined the relationship between any cannabis use during treatment and 16-week (end of treatment) and 68-week (one-year post-treatment) PDA. The first two columns show that cannabis use was significantly ($P < 0.01$) related to lower PDA at end of treatment, in both the unadjusted and adjusted models. In the unadjusted model, the association appeared to persist until 68 weeks ($P < 0.05$), but weakened when controlling for covariates. Any cannabis use during treatment was not related to DPDD or PHD at either 16 weeks or 68 weeks (results not shown).

Regarding other correlates of PDA, non-Hispanic African Americans had higher PDA than non-Hispanic Whites at both 16 weeks and 68 weeks, while those who were not married had higher PDA at 68 weeks than those who were married. More severe alcohol dependence was not associated with PDA, though baseline PDA and PHD were ($P < 0.01$). Participants assigned to COMBINE treatment groups who received naltrexone, CBI, and/or both naltrexone and CBI generally had higher PDA compared to the placebo-only group at both 16 and 68 weeks, though these associations were not always significant at the $P < 0.05$ level. Most notably, any other drug use consistently was a stronger predictor of PDA than any cannabis use; post-hoc Wald and delta-method based tests of equality showed that the coefficient for other drug use was significantly larger than the coefficient for cannabis use at both time-points (one-sided $p < 0.10$).

Quartiles of cannabis use during treatment

The second set of analyses compared quartiles of days of cannabis use during treatment to the referent group of cannabis abstainers (Table 3). Only the second quartile of cannabis users, those who used approximately 5–8% or 5–9 days during treatment (about 1–2x/month) had significantly lower PDA than cannabis abstainers; although effects were stronger in unadjusted models, they retained significance in models adjusted for covariates and persisted through one-year post-treatment. Compared to no cannabis use, none of the cannabis use quartiles were associated with DPDD or PHD at either 16 or 68 weeks (results not shown). The pattern of associations between other covariates and drinking outcomes was almost identical to those described above, both in terms of significance and magnitude.

DISCUSSION

Results show that compared to no cannabis use, any cannabis use during treatment for AUD was related to reduced alcohol abstinence at end of treatment; specifically, each additional day of cannabis use was associated with approximately 4–5 fewer days of abstinence from alcohol. However, when attempting to derive a threshold of cannabis use, the examination of cannabis quartiles demonstrated that the relationship between cannabis and alcohol use is more nuanced, and may depend more on frequency than the simple presence of use; only the second quartile of cannabis use appeared to have significantly lower PDA than cannabis abstainers, with the first, third, and fourth quartiles showing no significant differences. Cannabis use was not related to drinks per drinking day or heavy drinking days at either time-point. Unexpectedly, we found that being unmarried (vs. married) was associated with approximately five more abstinent days one year post-treatment, while being African American or Hispanic (vs. White) was associated with approximately eight more abstinent days at end of treatment and eleven more abstinent days one year post-treatment. *Post hoc* analyses comparing alcohol use severity, prevalence of other drug use, prevalence of cannabis use, and frequency of cannabis use across races and marital did not explain the unanticipated findings. However, a recent review and summary of NESARC findings concluded that African Americans and Hispanics had lower risk of SUD than Whites, signifying that this “paradox” has been observed in the general population (39).

Although we did not have any *a priori* hypotheses regarding other drug use, other drug use appears to be a stronger predictor of alcohol outcomes than cannabis use in this sample. Higher rates of other drug use (opiates, sedatives, and stimulants) have been found among individuals with AUD compared to those without (40), and other drug use can exacerbate treatment outcomes (11). Still, cannabis use remained a significant predictor of alcohol use even when controlling for other drug use; this suggests that all drugs, including cannabis, might best be avoided if the ultimate goal is alcohol abstinence.

The current findings support those from the clinical trial of chronic disease management, which found that cannabis use in individuals with AUD was linked with reduced odds of successfully achieving abstinence from alcohol (10). Similarly, post-discharge cannabis use among participants with AUD in inpatient psychiatric/substance abuse treatment has been shown to be related to reduced likelihood of stable remission from any substance use (9). In a randomized trial of treatments for cigarette smoking cessation in heavy drinkers, weekly

marijuana users actually decreased their drinking at a faster rate than non-users at the 8-week follow-up (41); however, weekly cannabis users also cut down their cannabis use steadily (at 8-, 16-, and 26-week follow-ups) by more than 24%, which suggests that reduced cannabis use can lead to better alcohol outcomes.

On the other hand, when examining more detailed levels of cannabis use relative to non-use through the analyses of quartiles, the findings in relation to alcohol outcomes do not appear to be linear. Unexpectedly, only the second quartile of cannabis use (using approximately 1–2x/month) was related to lower PDA, while the highest levels of cannabis use (using 3x/month or more) did not significantly differ in PDA as compared to cannabis abstainers. Although the COMBINE data are not detailed enough to discern whether participants were using alcohol and cannabis concurrently vs. separately, there may be a non-linear relationship between cannabis and alcohol use driven by individuals who were substituting cannabis for alcohol by using cannabis more frequently and alcohol less frequently.

A number of observational studies of individuals with AUD suggest that cannabis substitution for alcohol does occur. A within-subjects study of daily cannabis users not trying to change cannabis consumption examined whether cannabis abstinence would be related to changes in alcohol and other drug use (42). Controlled abstinence from cannabis was indeed significantly linked with increased alcohol consumption (by 52%) and alcohol craving among individuals with past history of AUD but not those without past AUD (3% increase), suggesting substitution among those with past alcohol-related problems (42). Cannabis substitution for alcohol has been observed among medical cannabis patients with alcohol problems as well (31, 34, 35, 43), though these studies are retrospective and likely affected by recall bias, which may account for at least part of the relationships observed between cannabis use and reduced drinking. Furthermore, medical marijuana patients might reduce drinking for other reasons, and are likely not representative of individuals with AUD who are attempting to reduce/quit drinking.

However, any speculation regarding substitution/complementarity is limited by the nature of the data in that it is unknown whether participants were using cannabis on the actual days that they were drinking. To date, the bulk of published literature regarding event-level alcohol and cannabis use appears to focus on the relationship between substance use and sexual risk behaviors (44–48). To our knowledge, no prior study has collected daily cannabis and alcohol use data from individuals in AUD treatment. Finer-grained, event-level data are needed in order to assess whether cannabis and alcohol act as substitutes or complements among individuals in treatment for AUD. Ongoing research will also examine moderators (effect modifiers) and mediators (mechanisms) of the relationship between cannabis use and alcohol outcomes, and focus on understanding which subgroups, if any, are more prone to substitution vs. complementarity. Future analyses will also include studying the costs and benefits of attending to cannabis use during AUD treatment, as this information is absolutely crucial for making informed treatment recommendations.

While the current findings are novel, the results are preliminary and require further confirmation and replication. Therefore, clinical implications must be limited to recommendations of avoiding using cannabis during alcohol treatment, as any cannabis use

vs. non-use appears to be linked with worse clinical outcomes. For cannabis users who are not motivated for abstinence from cannabis but may be contemplating reducing frequency of use, more research is needed to recommend a specific threshold at which alcohol treatment outcomes are not compromised by cannabis use. Still, the set of results highlights two critical issues. First, cannabis use is not an “all or nothing” phenomenon for individuals in treatment for AUD, and broadly saying that all levels of cannabis use exacerbate alcohol use may be misleading. Second, and related to the first point, the relationship between cannabis and alcohol is most certainly nuanced (43), and likely non-linear; this underscores the importance of identifying how individuals use cannabis and alcohol simultaneously vs. separately, especially since concurrent users are at highest risk of alcohol-related problems compared to both those who use the two substances separately and those who use alcohol only (8). An event-level analysis of cannabis and alcohol use data can potentially address this limitation by examining situational factors in a natural setting.

Conclusion

Understanding the impact of concurrent cannabis use on AUD treatment outcomes is crucial for guiding clinical decisions in AUD treatment programs. In many AUD treatment settings, which expect patients to maintain abstinence from all substances while in treatment, a positive urine drug test (e.g., cannabis) may delay treatment initiation or lead to treatment termination. Such policy decisions have wide-ranging implications with respect to service utilization and barriers to treatment.

The current results show that among participants in a large, randomized control trial of treatment for AUD, any cannabis use during treatment was associated with fewer abstinent days at treatment end when compared to no cannabis use; each additional day of cannabis use was related to approximately four fewer days of alcohol abstinence. When examining levels of cannabis use as defined by quartiles, only those in the second quartile of cannabis use had significantly fewer alcohol abstinent days when compared cannabis abstainers; on average, those who used cannabis once or twice per month during AUD treatment had approximately 10 fewer alcohol abstinent days at treatment end and 56 fewer abstinent days one year post-treatment. Cannabis use was not associated with post-treatment frequency of heavy drinking. However, this was a study of associations, rather than an event-level analysis of cannabis and alcohol use. We cannot discern from these data whether participants use cannabis on the same days they used alcohol. Future studies should consider a more comprehensive analysis of alcohol and marijuana use patterns to establish the impact of cannabis use alone and in conjunction with alcohol use on alcohol treatment outcomes. These findings signal a need for clinicians to better understand how patients are using alcohol and cannabis together vs. separately, which is especially timely given the recent movements towards cannabis legalization in many US states and the expected increases in cannabis and conjoint use.

Acknowledgments

This work was supported by NIAAA R21 AA023039.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs. MSS and DP had full access to all of the data in the study and take

responsibility for the integrity of the data and the accuracy of the data analysis. This study was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) Grant R21 AA023039. The NIAAA had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

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Table 1

Demographics and alcohol use among COMBINE participants stratified by cannabis use during treatment for Alcohol Use Disorders^a

	Sample Overall N = 1381	Cannabis Users n=206	Cannabis Abstainers n=999
Female (%) ***	30.92	19.9	33.03
Age (mean (SE)) ***	44.43 (0.27)	39.77 (0.61)	45.81 (0.32)
Years of Education (mean (SE)) *	14.55 (0.74)	14.19 (0.18)	14.64 (0.09)
Employment (%)			
Full or part-time	71.35	73.79	70.35
Unemployed/ Retired/Homemaker/Other	28.65	26.21	29.64
Income (%) ***			
< \$15K	10.15	13.3	9.85
\$15K – \$29, 999	16.1	27.09	13.71
\$30K – \$59, 999	29.93	25.62	31.57
\$60K – \$89, 999	19.56	15.76	20
> \$90K	24.26	18.23	24.87
Marital status (%) ***			
Married/cohabitating	46.23	35.44	48.55
Single/ Divorced/Widowed/Separated	53.77	64.57	51.46
Race (%)			
Non-Hispanic White	76.90	77.48	75.24
Non-Hispanic Black or African American	7.89	8.11	9.22
Hispanic	11.08	10.41	10.68
Other	4.13	4	4.85
Alcohol Dependence Severity (mean (SE)) ***	16.66 (7.32)	18.10 (7.21)	16.19 (7.40)
Baseline percent days abstinent, past 90 days (mean (SE))	25.08 (0.67)	24.86 (1.73)	24.87 (0.78)
Baseline # drinks/drinking days, past 90 days (mean (SE))	12.44 (0.21)	12.83 (0.48)	12.19 (0.25)
Baseline percent heavy drinking days, past 90 days (mean (SE))	65.49 (28.57)	65.23 (29.18)	65.53 (28.17)
Any nicotine use during COMBINE treatment	51.04	69.90	47.15
Any other drug use during COMBINE treatment	6.06	16.10	4.00
COMBINE treatment (%)			
Placebo only	10.93	11.17	10.51
Acamprosate only	11.01	12.62	10.21
Naltrexone only	11.15	9.71	11.11
Acamprosate + Naltrexone	10.72	14.56	10.21
Placebo + CBI	11.3	12.14	11.71
Acamprosate + CBI	10.93	10.19	11.81
Naltrexone + CBI	11.22	7.28	12.41
Acamp + Naltrex + CBI	11.37	9.22	11.51
CBI only	11.37	13.11	10.51

^a Comparison of means between cannabis users and abstainers. Boldface indicates statistical significance.

^b Computed as the ratio of pills taken from returned blister pack counts to those prescribed throughout the 16 weeks of treatment

 $P < 0.001$;

**
 $P < 0.01$;

*
 $P < 0.05$;

[†]
 $P < 0.10$

Table 2

Unadjusted and adjusted beta coefficients with 95% confidence intervals from regressions End-of-Treatment Percent Days Abstinent from alcohol comparing Cannabis Users to Abstainers^a

<i>Predictors</i>	<i>Outcomes</i>			
	16-week PDA	16-week PDA	68-week PDA	68-week PDA
	Unadjusted	Adjusted	Unadjusted	Adjusted
Any cannabis use during treatment (vs. none)	-6.05 (-10.32, -1.79) ^{**}	-4.35 (-8.68, -0.02) ^{**}	-5.68 (-10.76, -0.61) [*]	-4.62 (-9.78, 0.54) [†]
Age (years)		-0.05 (-0.22, 0.128)		-0.04 (-0.24, 0.17)
Gender (vs. Female)		3.33 (-0.19, 6.86) [†]		3.30 (-0.91, 7.52)
Education (years)		-0.27 (-0.92, 0.39)		-0.88 (-1.66, -0.10) [*]
Employment (vs. Full- or part-time)				
Unemployed/Retired/Homemaker/Other		-1.33 (-4.96, 2.30)		0.76 (-3.57, 5.09)
Income (vs. < \$15K)				
\$15K – \$29, 999		1.07 (-5.16, 7.31)		-1.47 (-8.93, 6.00)
\$30K – \$59, 999		1.58 (-4.30, 7.46)		-1.17 (-8.20, 5.87)
\$60K – \$89, 999		3.47 (-3.14, 10.07)		0.07 (-7.80, 7.94)
> \$90K		1.97 (-4.89, 8.84)		0.80 (-7.35, 8.95)
Marital status (vs. Married/cohabitating)				
Single/Divorced/Widowed/Separated		-0.15 (-3.70, 3.40)		4.56 (0.33, 8.79) [*]
Race (vs. Non-Hispanic White)				
Non-Hispanic Black or African American		7.51 (1.49, 13.53) [*]		11.08 (4.01, 18.15) ^{**}
Hispanic		-2.52 (-8.35, 3.31)		-0.08 (-6.89, 6.72)
Other		-6.40 (-14.33, 1.52)		-8.00 (-17.45, 1.44) [†]
SCID Alcohol Dependence Severity		0.17 (-0.07, 0.42)		0.19 (-0.10, 0.48)
Baseline percent days abstinent		0.36 (0.24, 0.47) ^{***}		0.49 (0.35, 0.62) ^{***}
Baseline # drinks/drinking day		0.12 (-0.12, 0.37)		0.10 (-0.20, 0.39)
Baseline percent heavy drinking days		0.13 (0.04, 0.23) ^{**}		0.14 (0.02, 0.26) [*]
Any nicotine use (vs. none)		-2.48 (-5.81, 0.86)		-4.21 (-8.18, -0.24) [*]

Predictors	Outcomes			
	16-week PDA	16-week PDA	68-week PDA	68-week PDA
	Unadjusted	Adjusted	Unadjusted	Adjusted
Any other drug use (vs. none)				
COMBINE treatment (vs. Placebo only)		-13.27 (-19.92, -6.62) ***		-13.37 (-21.30, -5.44) **
Acamprosate only		3.63 (-3.04, 10.30)		3.87 (-4.10, 11.83)
Naltrexone only		7.85 (1.26, 14.44) *		8.23 (0.34, 16.12) *
Acamprosate + Naltrexone		9.30 (2.73, 15.86) **		7.31 (-0.53, 15.15) [†]
Placebo + CBI		8.81 (2.36 (15.26) **		9.16 (1.44, 16.88) *
Acamprosate + CBI		6.48 (-0.03, 12.99) [†]		6.50 (-1.28, 14.28)
Naltrexone + CBI		6.20 (-0.27, 12.67) [†]		9.18 (1.45, 16.91) *
Acamp + Naltrex + CBI		8.56 (1.97, 15.15)		11.02 (3.13, 18.91) **
CBI only		-2.11 (-8.74, 4.51)		5.42 (-2.53, 13.38)

^aBoldface indicates statistical significance, $P < 0.05$.

*** $P < 0.001$;

** $P < 0.01$;

* $P < 0.05$;

[†] $P < 0.10$

All models include random slopes and intercepts for treatment site

Table 3

Unadjusted and adjusted beta coefficients with 95% confidence intervals from regressions of Percent Days Cannabis Use during treatment on End-of-Treatment Percent Days Abstinent from alcohol

Predictors	Outcomes			
	16-week PDA	16-week PDA	68-week PDA	68-week PDA
	Unadjusted	Adjusted	Unadjusted	Adjusted
Quartiles of cannabis use days (vs. no use)				
Q1: ~1–4% days use during AUD treatment	–0.42 (–7.93, 7.10)	–0.17 (–7.22, 6.88)	–0.73 (–9.67, 8.20)	–1.10 (–9.49, 7.30)
Q2: ~5–8% days use during treatment	–12.77 (–21.25, –4.30)**	–8.81 (–17.00, –0.63)*	–15.59 (–25.67, –5.51)*	–11.82 (–21.56, –2.07)*
Q3: ~9–39% days use during treatment	–6.14 (–14.05, 1.78)	–7.92 (–15.66, –0.19)*	–5.07 (–14.48, 4.33)	–6.60 (–15.82, 2.61)
Q4: ~40–100% days use during treatment	–6.45 (–14.44, 1.54)	–1.68 (–9.95, 6.59)	–3.19 (–12.68, 6.31)	0.08 (–9.75, 9.92)
Age (years)		–0.05 (–0.22, 0.12)		–0.03 (–0.24, 0.17)
Gender (vs. Female)		3.52 (–0.007, 7.05) [†]		3.51 (–0.70, 7.73)
Education (years)		–0.25 (–0.91, 0.40)		–0.87 (–1.65, –0.09)*
Employment (vs. Full- or part-time)		–1.46 (–5.09, 2.16)		0.68 (–3.65, 5.01)
Unemployed/Retired/Homemaker/Other				
Income (vs. < \$15K)				
\$15K – \$29, 999		1.25 (–4.99, 7.49)		–1.46 (–8.93, 6.01)
\$30K – \$59, 999		1.85 (–4.02, 7.73)		–0.88 (–7.91, 6.16)
\$60K – \$89, 999		3.57 (–3.03, 10.16)		0.18 (–7.68, 8.04)
> \$90K		2.26 (–4.61, 9.12)		1.15 (–7.00, 9.30)
Marital status (vs. Married/cohabitating)		–0.10 (–3.65, 3.44)		4.61 (0.39, 8.84)*
Single/Divorced/Widowed/Separated				
Race (vs. Non-Hispanic White)				
Non-Hispanic Black or African American		7.19 (1.16, 13.21)*		10.71 (3.64, 17.78)**
Hispanic		–2.60 (–8.43, 3.22)		–0.18 (–7.00, 6.61)
Other		–6.75 (–14.68, 1.18)		–8.27 (–17.71, 1.17)
SCID Alcohol Dependence Severity		0.18 (–0.07, 0.42)		0.19 (–0.10, 0.49)
Baseline percent days abstinent		0.35 (0.24, 0.47)***		0.48 (0.34, 0.62)***

Predictors	Outcomes			
	16-week PDA	16-week PDA	68-week PDA	68-week PDA
	Unadjusted	Adjusted	Unadjusted	Adjusted
Baseline # drinks/drinking day		0.13 (−0.12, 0.37)		0.10 (−0.19, 0.39)
Baseline percent heavy drinking days		0.13 (0.03, 0.23) **		0.13 (0.02, 0.25) *
Any nicotine use (vs. none)		−2.32 (−5.65, 1.02)		−4.00 (−7.97, −0.03) *
Any other drug use (vs. none)		−13.20 (−19.91, −6.47) ***		−13.63 (−21.64, −5.62) **
COMBINE treatment (vs. Placebo only)				
Acamprosate only		3.54 (−3.13, 10.20)		3.66 (−4.29, 11.62)
Naltrexone only		7.81 (1.22, 14.40) *		8.08 (0.19, 15.96) *
Acamprosate + Naltrexone		9.07 (2.51, 15.63) **		6.96 (−0.87, 14.80) †
Placebo + CBI		8.67 (2.22, 15.11) **		8.94 (1.23, 16.65) *
Acamprosate + CBI		6.43 (−0.07, 12.94) †		6.31 (−1.46, 14.09)
Naltrexone + CBI		6.27 (−0.20, 12.74) †		9.11 (1.38, 16.84) *
Acamp + Naltrex + CBI		8.62 (2.04, 15.20) *		11.00 (3.12, 18.88) **
CBI only		−2.19 (−8.81, 4.43)		5.23 (−2.72, 13.18)

^aBoldface indicates statistical significance, $P < 0.05$.

*** $P < 0.001$;

** $P < 0.01$;

* $P < 0.05$;

† $P < 0.10$

All models include random slopes and intercepts for treatment site