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Tobacco use during cannabis cessation: Use patterns and impact on abstinence in a National Drug Abuse Treatment Clinical Trials Network study

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Abstract

Background: It is common for cannabis users to also use tobacco. While data suggest that tobacco users have more difficulty achieving cannabis cessation, secondary analyses of clinical trial data sets may provide insight into the moderating variables contributing to this relationship, as well as changes in tobacco use during cannabis treatment. Those were the aims of this secondary analysis.

Methods: The parent study was a multi-site trial of *N*-acetylcysteine for cannabis dependence conducted within the National Drug Abuse Treatment Clinical Trials Network. Participants were treatment-seeking adults (ages 18–50) who met criteria for cannabis dependence (N=302). For cigarette smokers (n=117), tobacco use was assessed via timeline follow-back and nicotine dependence was assessed via the Fagerström Test for Nicotine Dependence (FTND). Outcome measures included: 1) changes in tobacco use based on treatment assignment, nicotine dependence, and concurrent cannabis reduction/abstinence, and 2) independent associations between nicotine dependence and cannabis abstinence.

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Results: Cigarette smokers accounted for 39% of the sample (117/302), with a median FTND score of 3.0 (10-point scale). Among those with lower baseline nicotine dependence scores, cigarette smoking was reduced in the active treatment group compared to placebo. Those with moderate/high levels of nicotine dependence showed slight increases in smoking following active treatment. Nicotine dependence did not affect cannabis cessation.

Conclusions: Cigarette smoking during cannabis treatment was affected, but depended on baseline nicotine dependence severity, though dependence levels did not impact cannabis abstinence. Interventions that address both tobacco and cannabis are needed, especially due to an increasing prevalence of cannabis use.

Keywords

cannabis; marijuana; tobacco; pharmacotherapy; co-use; *N*-Acetylcysteine

1. Introduction

The co-use of tobacco and cannabis is a common practice (Agrawal et al., 2012; Agrawal and Lynskey, 2009; Agrawal et al., 2008; Leatherdale et al., 2006; Richter et al., 2004; Tullis et al., 2003) and rates of co-use were shown to have increased from 2003 through 2012 in the United States (US) (Schauer et al., 2015). Of additional concern, tobacco use rates (mostly in the form of cigarette smoking) tend to be elevated among cannabis users. Among a national sample in the US of past-month cannabis users, tobacco use was highly prevalent (60.1% for cigarette smoking co-use; 68.6% overall tobacco co-use prevalence excluding blunts [cigars hollowed out and filled with cannabis] and 78.3% including blunts) (Schauer et al., 2016). Unlike rates of tobacco use, which have been steadily declining (Jamal et al., 2016), cannabis use rates have been increasing amid reduced perception of harm (Hasin et al., 2016; Johnston et al., 2015) partially due to state-level legalization of medical and recreational cannabis (Cerda et al., 2012; Martins et al., 2016).

Tobacco and cannabis co-use carries public health burden in the form of greater prevalence of psychiatric and psychosocial problems (Peters et al., 2014; Ramo et al., 2012) and additive health risk (Meier and Hatsukami, 2016). There are also cessation-related concerns relevant to the co-use of these substances. First, during reduction or abstinence from one substance, substitution/compensatory use of the other substance may occur. Data supporting substitution are mixed, with some studies supporting a substitution effect, demonstrated by an increase in tobacco use during cannabis abstinence/reduction (Allsop et al., 2014; Copersino et al., 2006; Levin et al., 2010; Schaub et al., 2010), while others have found no evidence of increases in tobacco use during cannabis cessation (McClure et al., 2014a; Peters and Hughes, 2010). Yet, others have found reductions in tobacco use among those who reduced their cannabis use by more than 50% (Gray et al., 2011). Second, use of one substance may alter trajectories and severities of use on the other. Cannabis use has been associated with an increased risk of nicotine dependence and greater nicotine dependence severity among co-users (Agrawal et al., 2008; Okoli et al., 2008). Tobacco use has been associated with increased risk of cannabis use and progression to the development of cannabis dependence (Agrawal et al., 2009) and has been shown to mediate the relationship between cannabis use and dependence (Hindocha et al., 2015). Third, co-users of tobacco

and cannabis may have worse cessation outcomes. Worse cannabis cessation outcomes have been demonstrated among co-users compared to former and never cigarette smokers (Moore and Budney, 2001; Peters et al., 2012). Co-users have also been shown to have lower rates of sustained tobacco abstinence (Schauer et al., 2017), though another study found no impact of cannabis use on tobacco cessation (Rabin et al., 2016). Taken together, the impact of tobacco cannabis co-use may adversely affect cessation success among co-users.

As cannabis use rates continue to increase, current data are needed to better characterize and treat a co-using population. While studies suggest that tobacco users have more difficulty achieving cannabis cessation, data from large multi-site clinical trials may provide insight into potentially moderating variables contributing to this relationship. Additionally, some treatment strategies used to promote cannabis cessation may also have secondary efficacy for tobacco use and assessing changes in tobacco use patterns during cannabis cessation is important to capture. Finally, regional differences in tobacco and cannabis co-use are relevant within the US given substantial variation in cannabis legislation and tobacco control efforts. For example, tobacco use rates among adults in the US were 15.5% in 2016 (Jamal et al., 2018), but vary widely by state, ranging from 8.8% to 24.8% across the US (Centers for Disease Control and Prevention, 2016). Therefore, the current secondary analysis explored tobacco use within the context of a multi-site pharmacotherapy trial for cannabis dependence (parent trial) conducted within the National Drug Abuse Treatment (Jamal et al., 2018) Clinical Trials Network (NIDA CTN) (Gray et al., 2017; McClure et al., 2014b). The aims of this secondary analysis were to: 1) assess tobacco use changes during treatment for cannabis dependence based on treatment assignment (active medication or placebo; Aim 1a) and concurrent cannabis reduction/abstinence (Aim 1b); and 2) determine if tobacco users had more difficulty achieving cannabis cessation based on their nicotine dependence severity at baseline (Aim 2). Since cigarette smoking status was found to be a moderator of cannabis treatment outcomes in the parent trial (Gray et al., 2017), it was of interest in this secondary analysis to determine if nicotine dependence was independently associated with cannabis abstinence during treatment.

2. Methods

2.1 Participants and Study Sites

The parent trial from which these data were analyzed was a multi-site pharmacotherapy trial conducted in the US within the NIDA CTN evaluating cannabis dependence treatment (Achieving Cannabis Cessation: Evaluating *N*-Acetylcysteine Treatment [ACCENT]). This trial was registered with Clinicaltrials.gov (NCT01675661). Participants were adult men and women (N=302) between the ages of 18–50 years who met criteria for cannabis dependence (based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV) criteria (First, 1994), were interested in quitting (cannabis), and had a positive urine cannabinoid test during the screening assessment. Participants did not have to be interested in quitting their tobacco use (i.e., cigarette smoking) to be included in this study and tobacco cessation was not a standardized part of treatment in this study. Methodological details for this study can be found elsewhere (McClure et al., 2014b). Briefly, study participants were randomized to receive *N*-Acetylcysteine (NAC; 1200 mg twice daily) or matched placebo (PBO) for 12

weeks, while contingency management procedures were used in both conditions to reinforce abstinence from cannabis and attendance at study visits. Participant randomization to treatment condition was stratified by study site and self-reported tobacco use status (cigarette smoker vs. non-smoker). Tobacco use status emerged as an important randomization stratum as results from both laboratory and outpatient studies have shown that tobacco users have greater odds of relapse to cannabis compared to non-tobacco users (de Dios et al., 2009; Haney et al., 2013). Participants meeting criteria for substance dependence (based on DSM-IV, not including tobacco and cannabis) were not eligible for study procedures and participants had to submit a negative urine drug screen at the randomization visit (for all drugs other than cannabis) to continue in the study. Primary cannabis abstinence outcomes can also be found elsewhere (Gray et al., 2017). Six geographically diverse study sites across the US participated in the ACCENT trial (Behavioral Health Services of Pickens County [Pickens, SC], The APT Foundation [New Haven, CT], University of Kentucky Medical Center [Lexington, KY], University of California, Los Angeles Integrated Substance Abuse Programs [Los Angeles, CA], The University of Texas Health Science Center at San Antonio [San Antonio, TX], and CODA, Inc. [Portland, OR]). All study procedures were completed in August 2015.

2.2 Baseline Measures

Demographic information was collected and measures are described elsewhere (Gray et al., 2017; McClure et al., 2014b). Cannabis use measures included; gram quantification at screening (Mariani et al., 2011), frequency of cannabis use (through time-line follow-back methods), quantitative urine cannabinoid tests (UCT; abstinence cut-point was set at <50 ng/ml), cannabis use history (age of first use, years to abuse and dependence), the Marijuana Craving Questionnaire (Heishman et al., 2001), the Cannabis Withdrawal Scale (Allsop et al., 2011), and the Marijuana Problems Scale (Stephens et al., 2000).

Tobacco use (i.e., combustible cigarette use) was self-reported and cigarettes per day were collected for the 30 days preceding the screening visit, at all study visits throughout the 12-week trial, and during the post-treatment follow-up visit through timeline follow-back (TLFB) methods (Sobell et al., 1988). Tobacco use history was collected via Tier 1 tobacco measures from the PhenX toolkit (http://www.phenxtoolkit.org). Participants were categorized as cigarette smokers or non-cigarette smokers based on their self-reported status on tobacco use measures at baseline. Nicotine dependence was assessed via the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). The FTND items are summed to yield a score between 0–10, with higher scores indicating greater levels of nicotine dependence. Baseline nicotine dependence scores were categorized as low dependence (0–2), moderate dependence (3–5) and high dependence (6 or higher). FTND scores of 6 or higher have been proposed as an appropriate cut-point indicating high nicotine dependence (Fagerstrom et al., 1996). There is little consensus in the literature regarding categorizing lower levels of nicotine dependence, though many clinical programs have adopted their own cut-points for patients, and it has been suggested that the FTND may not be the most relevant measure among light cigarette smokers (Etter et al., 1999). Since many of the cigarette smokers in this sample were clustered at the lower end of the FTND scale, moderate and high dependence levels were aggregated for analyses (Low: FTND<3,

Moderate/High: FTND≥3) which also corresponds to the median FTND scores reported at study entry.

2.3 Outcome Measures

The number of cigarettes per day (CPD; intensity of use) and the number of smoking days (frequency of use) measured between visits were used as tobacco-related outcome measures. Given that 22% of current self-reported cigarette smokers in the trial did not smoke daily, frequency of use (smoking days) as an outcome provided a potentially sensitive method to detect reductions in smoking, as opposed to analysis of only CPD.

2.4 Statistical Analyses

Standard descriptive statistics were used to summarize baseline demographic, tobacco and cannabis use characteristics for both cigarette smokers (n=117) and non-cigarette smokers (n=185). A Wilcoxon rank sum test statistic was used to assess group differences among continuous variables while differences in categorical variables were assessed using a Pearson chi-square test statistic. Baseline smoking rates were analyzed across treatment sites for homogeneity. Baseline characteristics were assessed for associations with planned study outcomes as well as any modification of treatment effects and when significant, these variables were included in the model building process.

Aims 1a and 1b.—Secondary efficacy analysis of treatment assignment (NAC versus PBO) on changes in tobacco outcome measures was analyzed over the 12-week treatment period and at the follow-up visit in the cohort of self-identified cigarette smokers (n=117). A generalized linear mixed effect regression model (GLMM) for count data using the methods of maximum likelihood was applied to assess the overall treatment effect on self-reported smoking (CPD and number of smoking days) during the active treatment period. Initial models contained randomized treatment group assignment (NAC vs. PBO) and study visit (Time). Adjusted models controlled for baseline cigarette smoking rates, the number of days since the last study visit, and race. Additionally, the frequency of co-occurring cannabis use (cannabis use days since the last visit) was added to adjusted models. Although not specifically powered to do so, the differential effects of baseline nicotine dependence (FTND; low, moderate/high), gender and race on tobacco outcomes were investigated through the addition of interaction terms into the adjusted model. Due to the imbalance in cigarette smoking rates across study sites and to test for differential effects of treatment across the study sites, a treatment by site interaction term was included in the model development process. When insignificant, site was included as a covariate and assessed. When there was no evidence of these fixed site effects, the terms were removed from the model and a random site effect was included. In the final cigarette smoking days models, site and site x treatment covariate effects were insignificant, thus site was included in the model as a random effect. In the final CPD models, site was a significant predictor of CPD and was retained in the model as a covariate.

Aim 2.—The moderating effects of nicotine dependence levels and cigarette smoking amount (CPD) on the primary study outcome of efficacy of NAC on cannabis abstinence were also assessed with the tobacco-using cohort. Statistical models were developed with

appropriate interactions (nicotine dependence/CPD by treatment assignment) as well as stratified by treatment assignment. Additionally, cannabis use outcome models were developed in concert with the models previously developed for the primary efficacy analysis (Gray et al., 2017). To remain consistent with the primary study analysis, an intent-to-treat approach that included all randomized participants was used in the modeling process and all missing UCTs were considered positive. In the current analysis, the influence of cigarette smoking and nicotine dependence on cannabis abstinence was assessed using a generalized linear mixed effect regression model (GLMM) for binary outcomes similar to the model specified to assess cigarette smoking outcomes. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Significance was set at a 2-sided *p*-value of 0.05.

2.5 Missing Data

Of the cigarette smokers enrolled in the study (n=117), 11% (n=13 out of 117) were lost to follow-up immediately after randomization and therefore, did not have data on cigarette use following randomization. Of the remaining 104 cigarette smokers with data available, the median (interquartile range) number of weekly treatment visits with available cigarette data was 8 (7–9) of 12 total treatment visits. Additionally, TLFB CPD data at weekly visits, among the cigarette smoking cohort, was available for 69% (974/1404) of the possible weekly TLFB reports [NAC= 70% (510/732) and PBO= 69% (464/672)]. Methods of Maximum Likelihood (ML) were used as the primary parameter estimation method for the examination of all smoking measures as they consistent and asymptotically normal estimates in the presence of missing repeated measures data (Molenberghs and Kenward, 2007).

3. Results

3.1 Demographic and Clinical Characteristics

Demographics and clinical characteristics for the entire study cohort as well as stratified by self-reported smoking status are presented in Table 1. Enrolled participants (N=302) were an average of 30 ± 9.0 years of age, with the majority of participants being male (72%) and white (58%). Twenty-two percent of the sample was of Hispanic or Latino ethnicity. At screening, 39% (n=117) of the sample self-reported being a current cigarette smoker. Approximately 16% reported being former smokers, and 42% were never smokers (had never smoked 100 cigarettes or more in their lifetime). Current cigarette smokers were similar to non-cigarette smokers on distribution of age and gender ($p>0.140$). However, non-cigarette smokers were more likely to have attained greater education ($p<0.001$) and be employed ($p<0.002$) than cigarette smokers. Race also statistically differed between cigarette smokers and non-cigarette smokers ($p<0.034$). Although there were no statistical differences in reported cannabis use frequency at baseline (days of cannabis use, $p=0.094$), cigarette smokers reported greater quantity of use per day (in grams) ($p=0.027$) and were more likely to have initiated cannabis use at an earlier age ($p=0.018$) but had longer durations from initiation of cannabis use to cannabis dependence ($p=0.027$).

Within the sample of cigarette smokers (n=117), 52% were randomized to the NAC treatment group (n=61), 72% were male (n=84) and 61% were white (n=71). There were no

statistically significant differences in age, race, gender, or attained education between treatment groups among the cigarette smoking sub-sample. Cigarette smokers randomized to receive PBO were more likely to be employed as compared to cigarette smokers randomized to receive NAC (57% vs. 33%; p=0.040). There were no statistically significant differences in cannabis or tobacco use measures prior to study entry between the two treatment groups. Nicotine dependence scores (FTND) at baseline averaged 3.1 ± 2.3 on a 10-point scale (median = 3), and participants who identified as daily cigarette smokers reported smoking an average of 10.5 ± 7.8 cigarettes per day, while non-daily cigarette smokers reported an average of 3.1 ± 2.2 cigarettes on smoking days. Cigarette smokers with greater levels of nicotine dependence (FTND≥3, n=66) were more likely to have greater baseline cannabis use intensity (3.6 ± 4.9 vs. 2.1 ± 2.0 grams per day of use; p=0.044) and higher Marijuana Problems Scale scores (7.6 ± 4.1 vs. 5.7 ± 3.3; p=0.023) prior to study entry than cigarette smokers with lower nicotine dependence. No other statistically significant differences were found.

The percentage of self-reported cigarette smokers at each study site is shown in Table 2. The site with the largest proportion of cigarette smokers was Connecticut (60%), while the lowest proportion of cigarette smokers was California (19%). Among all study sites, both age and baseline number of smoking days (past 30 days) were similar among cigarette smokers. Most sites were similar in reported cigarettes smoked per day and FTND scores. However, one study site (South Carolina) had markedly increased levels of smoking intensity and nicotine dependence severity among cigarette smokers as compared to the other five sites (CPD: SC=15.6 ± 10.2 vs. Others=6.3 ± 5.3; p<0.001; FTND: 4.2 ± 2.4 vs. 2.7 ± 2.2; p=0.006).

3.2 Tobacco Use during Study Treatment (Aim 1a)

During study treatment, cigarette smokers reported smoking an average (± SD) of 6.0 ± 3.5 days per week and 7.2 ± 7.7 cigarettes smoked per day (range 0–50). Models were adjusted for study design variables (treatment and visit), those that were significantly associated with outcomes in simple models (race, days between study visits, baseline smoking behavior) and concurrent cannabis use frequency (days of cannabis use since last visit). Model-based means and adjusted rate ratios are shown in Table 3. In the cigarette smoking cohort, NAC showed no effect on the number of reported cigarette smoking days (RR=1.13; 95% CI=0.92–1.38; p=0.259) or cigarettes smoked per day (RR=1.21; 95% CI=0.86–1.70; p=0.268) during study treatment. Treatment efficacy of NAC on cigarette smoking days had a moderate differential effect between those with low and moderate/high baseline nicotine dependence during study treatment (FTND × treatment interaction: p=0.037). Specifically, participants with moderate/high baseline nicotine dependence showed no significant effect of treatment with NAC as compared to PBO on cigarette smoking days (RR=0.90; 95% CI=0.70–1.17; p=0.449). However, NAC showed moderate evidence of attenuation of cigarette smoking days per week in those with low baseline nicotine dependence as compared to PBO (RR=1.40; 95% CI=1.02–1.92; p=0.037). Conversely, treatment with NAC had an insignificant, differential effect on CPDs between those with low and moderate/high baseline nicotine dependence during treatment (FTND × treatment interaction: p=0.117). Participants with moderate/high baseline dependence showed no effect of NAC

treatment on CPD (RR=0.96; 95% CI=0.62–1.47; p=0.846). However, NAC showed moderate numerical, though insignificant evidence of attenuation of CPD in those with low baseline dependence (RR=1.54; 95% CI=0.92–2.57; p=0.112).

3.3 Tobacco Use at Study Follow-Up (Aim 1a)

Seventy-four of the 117 randomized cigarette smokers (63.2%) attended the 1-month follow up visit; 30 (40.5%) in the PBO treatment group and 44 (59.5%) in the NAC treatment group. Results from adjusted models for follow-up data are shown in Table 3. Treatment with NAC did not reduce overall cigarette smoking days (RR=1.08; 95% CI=0.97–1.22; p=0.136) nor was there a significant effect on overall CPD (RR=0.94; 95% CI=0.74–1.20; p=0.613). Similar to the differential seen during the treatment phase of the study, the efficacy of NAC compared to PBO to reduce the number of cigarette smoking days was moderated in those with low baseline dependence as compared to PBO at the follow-up visit (FTND × treatment interaction: p<0.001; Low Dependence: RR=1.39; 95% CI=1.16–1.66; p<0.001) but there was a significant increase in cigarette smoking days at follow-up among the NAC group with moderate to high dependence (RR=0.85; 95% CI=0.75–0.97; p=0.019). Similarly, the efficacy of NAC to reduce CPD was moderated by nicotine dependence level (FTND × treatment interaction: p<0.001) at study follow up. In the group with moderate to high dependence, the effect of NAC was associated with greater CPD (RR=0.63; 95% CI=0.49–0.82; p<0.001) but not in those with low dependence (RR=1.41; 95% CI=0.94–2.10; p=0.094)

3.4 Concurrent Cannabis and Tobacco Co-Use during Study Treatment (Aim 1b)

Cannabis use amount (average daily use in grams) was collected concurrently with cigarette smoking outcomes and included as a covariate in the efficacy models described in study Aim 1a. During study treatment, cannabis use amounts were significantly and positively associated with the number of cigarette smoking days [RR=1.10; 95% CI=1.06–1.14; p<0.001] and mean reported CPD [RR=1.05; 95% CI=1.01–1.09; p<0.001], indicating that both the number of smoking days and average daily cigarette use increased when concurrent cannabis use increased (Table 4). Baseline nicotine dependence levels appeared to moderate this relationship in cigarette smoking days (Cigarette Smoking Days: Cannabis use x Nicotine Dependence interaction p<0.001) but not CPD (Cannabis use x Nicotine Dependence interaction p=0.360). In cigarette smokers with low nicotine dependence, weekly cigarette smoking days were significantly and positively associated with concurrent cannabis use [RR=1.18 (1.10–1.26); p<0.001]. This relationship was weaker in cigarette smokers with moderate/high nicotine dependence [Cigarette Smoking Days: RR=1.03 (0.99–1.06); p=0.054].

3.5 Nicotine Dependence and Cigarette Smoking on Cannabis Cessation Outcomes (Aim 2)

Results from the parent trial demonstrated that baseline tobacco use status was a strong indicator of cannabis use outcomes, with tobacco users being half as likely as non-tobacco users to achieve cannabis abstinence, but there was no significant tobacco use-by-treatment interaction (Gray et al., 2017). When considering nicotine dependence severity among the cigarette smoking cohort, nicotine dependence levels were not associated with cannabis

cessation [RR=1.02; 95% CI=0.38–2.73; p=0.966] nor did nicotine dependence moderate the efficacy of NAC to treat cannabis dependence [FTND × Treatment interaction: p=0.298]. Similarly, in the cigarette smoking cohort, CPD measured concurrently with cannabis use was not associated with negative UCTs during the same week [5 CPD increase: RR=0.92; 95% CI=0.60–1.41; p=0.692] nor did it moderate the efficacy of NAC [NAC × CPD interaction: p=0.765].

4. Discussion

The aims of this secondary analysis were to assess tobacco use changes during cannabis dependence treatment and determine if nicotine dependence severity at baseline had impact on cannabis cessation. Tobacco use (i.e., combustible cigarette smoking) did change during the trial and at follow-up, but only under certain conditions. Results showed that those with lower baseline nicotine dependence (FTND<3) had fewer reported smoking days (during treatment and at follow-up) and fewer cigarettes smoked per day (follow-up) for the NAC group compared to PBO. Those with moderate to high levels of nicotine dependence (FTND≥3) appeared to have been smoking more at follow-up if randomized to the NAC condition (Aim 1a). This study also found that cannabis and tobacco use were related, as cannabis use amounts were positively associated with concurrent tobacco use (Aim 1b). Finally, while tobacco use status did impact cannabis treatment outcomes in the parent trial (Gray et al., 2017), the severity of nicotine dependence was not found to affect cannabis cessation outcomes in this analysis (Aim 2). Of note, this study was not powered to detect effects on tobacco measures, so results should be interpreted cautiously.

The finding that cigarette smoking rates decreased among those with lower nicotine dependence scores randomized to NAC, but that cigarette smoking rates increased among those with higher dependence scores randomized to NAC (but only at follow-up) is worthy of further investigation. It is possible that NAC may demonstrate efficacy for reducing tobacco use, and there is preliminary evidence in the literature to suggest that NAC may be effective for tobacco use disorder (Froeliger et al., 2015; Prado et al., 2015; Schmaal et al., 2011). NAC for tobacco use has not been tested among a tobacco cannabis co-using population, and it may only be efficacious as a pharmacotherapy in cigarette smokers with low nicotine dependence and only when cannabis use is also reduced. These results also suggest that cannabis and tobacco use patterns may be interrelated at certain dependence levels. Indeed, results showed an association between weekly tobacco and cannabis use, with a stronger association among the low nicotine dependence group. Among lighter cigarette smokers, tobacco use may be more closely tied to their cannabis use, and cannabis use may potentially elicit cue-induced cigarette craving. If one substance serves as a cue for the other, cannabis and tobacco use may decrease simultaneously. Among more dependent cigarette smokers, tobacco and cannabis use may occur more independently given the wide range of situations/environments in which smoking occurs. Substitution/compensatory use of tobacco during cannabis reduction/abstinence may be more likely among heavier cigarette smokers, who may use tobacco to reduce cannabis withdrawal symptoms more so than less dependent tobacco users. Results from this study showed that co-users with greater nicotine dependence levels also reported greater amounts of cannabis use and higher scores on the Marijuana Problems Scale, which may suggest a more severe cannabis use profile among

heavier tobacco users and may lead to compensatory tobacco use during cannabis reduction/abstinence. These suggestions are speculative and require further investigation, but the current findings suggest that future studies with cannabis tobacco co-users should consider the severity of use of each substance and should attempt to more precisely characterize these relationships and the degree of relatedness between the two substances.

Among this geographically diverse sample of treatment-seeking, cannabis-dependent adults, cigarette smoking was less prevalent (39%) compared to national estimates of tobacco use among those who also use cannabis (Schauer et al., 2016). These rates of concurrent tobacco use are also much lower when compared to other psychiatric and substance use disorder populations (~70–90% smoking prevalence) (Guydish et al., 2016; Smith et al., 2014). The current study excluded individuals with a history of severe psychiatric disorders (psychosis or bipolar disorder) or current substance dependence (other than cannabis or nicotine), which may partially explain the lower rate of tobacco use found in this sample. The inclusion of geographically diverse study sites may have also contributed to the overall lower average of tobacco co-use. Study sites in California and Oregon had low rates of tobacco co-use, not surprisingly given general tobacco prevalence rates in those states (11% and 16% respectively) (Centers for Disease Control and Prevention, 2016). Additionally, this study recruited those who were interested in quitting cannabis, which may not represent the general population of cannabis users, potentially contributing to a unique sample.

There were meaningful baseline differences found between cigarette smokers and non-cigarette smokers in the study, which may help to explain why those who were cannabis-tobacco co-users had worse cannabis cessation outcomes in the parent trial (Gray et al., 2017). Cigarette smokers in this trial completed fewer years of education, were more likely to be unemployed, used more cannabis per day, and had an earlier age of first use, but interestingly, reported a longer latency to developing cannabis dependence compared to non-cigarette smokers. Cannabis-tobacco co-users may present as more severe in their cannabis use, with a more extensive history of use, thus making abstinence more challenging.

The public health issue of tobacco and cannabis co-use still has a number of unanswered questions to be addressed. Mechanisms to explain the prevalent co-use of these substances have been proposed in the literature (Rabin and George, 2015), but human laboratory and prospective studies are required to confirm potential mechanisms contributing to co-use and eventual dual cessation treatment strategies. While tobacco users demonstrate evidence of poorer cannabis treatment outcomes, it remains unclear if cannabis use impacts tobacco cessation success rates (Rabin et al., 2016; Schauer et al., 2017). Also, as the legal status of cannabis and the prevalence of use changes, considerations should be given to how these policies impact tobacco-cannabis co-use. A recent study found that in states with legalized medical marijuana, co-use was associated with greater odds of nicotine dependence compared to tobacco-only users (Wang et al., 2016). Even with many unanswered questions regarding co-use, the literature to date raises treatment-related concerns for interventions that are developed for cannabis alone, but are recruiting a co-using sample, and in the development of interventions for both substances.

This study has several limitations. First, tobacco use status was self-reported and not biochemically verified. Participants were asked about their tobacco use via different questionnaires, which led to discrepant self-reports of current tobacco use in a small number of participants (n=12). It is also possible that participants with low rates of smoking may not identify themselves as cigarette smokers. Second, the aims of the parent trial were not focused on tobacco use and therefore, the study was not powered to detect changes in tobacco use or evaluate the efficacy of NAC for tobacco use disorder. As such, the results of this study are exploratory, and fully-powered studies focused on tobacco use among cannabis co-users should be conducted. Third, the prevalence of non-combustible and other forms of tobacco/nicotine product use was not assessed. It is possible that combustible tobacco use was low in the current sample, but use of electronic cigarettes or smokeless products could have been higher. Given the ubiquity of non-combustible products, future studies should assess their use in addition to combustible cigarette use. Fourth, nicotine dependence severity was explored as a moderating variable of the relationship between tobacco use status and poorer cannabis treatment outcomes. Categorizing FTND scores may not be the most appropriate method for analyses and this measure may not be ideal for lighter cigarette smokers (Etter et al., 1999), which was a large portion of the current study sample. However, detailed tobacco assessments are challenging to collect in a trial that is not focused on tobacco use, and the FTND remains one of the most common nicotine dependence assessments across the world (Fagerstrom et al., 1996). Finally, given that co-occurring psychiatric disorders were exclusionary in this trial, this study sample may not have been truly representative of the general population of those meeting for a cannabis use disorder. Indeed, in a comparison of the current study sample with national datasets, there was greater representation of non-tobacco users within the current study sample (McClure et al., 2017). Those with cannabis use disorder and other co-occurring disorders may have complex presentations and future studies should work to improve sample representativeness.

Overall, cigarette smoking appeared to be less prevalent in the current study sample compared to other substance use disorder and psychiatric populations. Those with lower nicotine dependence scores appeared to have benefited from NAC treatment and smoked fewer cigarettes per day and had fewer smoking days. Those with moderate or high nicotine dependence appeared to show no benefit from NAC treatment and showed increases in tobacco measures at follow-up. These results suggest that future studies may benefit from a more nuanced approach to treatment based on variables such as nicotine dependence severity. It will also be important to consider the complex interactions of cannabis and tobacco on cessation outcomes. In future trials, adding tobacco cessation to cannabis cessation interventions should be considered and tailoring interventions based on nicotine dependence may be warranted. Though tobacco users were in the minority of this treatment-seeking cannabis use sample, interventions that address both tobacco and cannabis are needed for this population, especially in light of increasing cannabis use.

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Table 1.

Demographics and clinical characteristics for the entire treatment cohort and compared across self-reported cigarette smokers and non-cigarette smokers.

	Total sample (N=302)	Non-cigarette smokers (n=185)	Cigarette smokers (n=117)	P-value
Demographics				
Age – Mean (SD)	30.3 (9.0)	29.7 (8.9)	31.3 (9.2)	0.140
Male - % (N)	71.5 (216)	71.4 (132)	71.8 (84)	0.934
Race				
White - % (N)	58.3 (176)	58.9 (109)	57.3 (67)	***0.034***
African American/Black - % (N)	27.8 (84)	23.8 (44)	34.2 (40)	
Other - % (N)	13.9 (42)	17.3 (32)	8.5 (10)	
Education				
< HS - % (N)	9.3 (28)	3.2 (6)	18.8 (22)	***<0.001***
HS/GED - % (N)	29.5 (89)	25.4 (47)	35.9 (42)	
Some College- % (N)	35.4 (107)	41.1 (76)	26.5 (31)	
College Graduate - % (N)	25.8 (78)	30.3 (56)	18.8 (22)	
Employment				
Employed - % (N)	51.3 (155)	55.7 (103)	44.4 (52)	***0.002***
Unemployed - % (N)	30.1 (91)	23.8 (44)	40.2 (47)	
Student - % (N)	11.6 (35)	15.1 (28)	6.0 (7)	
Other - % (N)	7.0 (21)	5.4 (10)	9.4 (11)	
Treatment Arm (NAC) - % (N)	50.7 (153)	49.7 (92)	52.1 (61)	0.684
Cannabis Use				
Days Using Cannabis (past 30 days) – Mean (SD)	26.0 (6.2)	25.8 (6.3)	26.5 (6.1)	0.094
Total Cannabis Use (past 30 days; grams) – Mean (SD)	75.0 (103.0)	67.8 (89.0)	86.5 (122.1)	***0.027***
Cannabis Use per Day (past 30 days; grams) – Mean (SD)	2.5 (3.4)	2.9 (4.1)	2.3 (3.0)	***0.027***
Urine Cannabinoid Level (ng/ml) – Mean (SD)	1075 (1430)	1079 (1451)	1069 (1401)	0.847
Age at First Use – Mean (SD)	15.2 (3.4)	15.5 (3.3)	14.8 (3.5)	***0.018***
Years to Dependence – Mean (SD)	5.6 (6.0)	4.6 (4.4)	7.2 (7.6)	***0.027***
Tobacco Use				
Cigarette Smoking Frequency				
Every Day - % (N)	-	-	77.8 (91)	-
Some Days - % (N)	-	-	22.2 (26)	-

	Total sample (N=302)	Non-cigarette smokers (n=185)	Cigarette smokers (n=117)	P-value
Cigarettes per Day (past 30 days) – Mean (SD)	-	-	8.2 (7.6)	-
Smoking Days (past 30 days) – Mean (SD)	-	-	26.1 (7.7)	-
FTND Score – Mean (SD)	-	-	3.1 (2.3)	-

Table 2.

Percentage of self-reported cigarette smokers and non-cigarette smokers by study site.

	% (n) Cigarette Smokers	% (n) Non-cigarette Smokers	% Cigarette Smokers for all sites
Study Site (State)			
CA (n=48)	19 (9)	81 (39)	8
OR (n=66)	27 (18)	73 (48)	15
TX (n=53)	34 (18)	66 (35)	16
SC (n=53)	47 (25)	53 (28)	21
KY (n=37)	54 (20)	46 (17)	17
CT (n=45)	60 (27)	40 (18)	23
Total	**39 (117)**	**61 (185)**	-

Table 3.

Model-based tobacco outcome measures and adjusted rate ratios separated by low and moderate/high baseline nicotine dependence levels for each treatment group (NAC and PBO) and the entire cigarette smoking sub-sample (n=117).

Outcome	Cohort	Mean (SEM)		Rate Ratio (95% CI) ≠
		NAC	PBO	(PBO vs. NAC)
Weekly Outcomes Measured During Treatment				
Cigarette Smoking Days	Overall	5.4 (0.2)	5.8 (0.2)	1.13 (0.92–1.38)
	Low FTND	***4.5 (0.4)***	***5.6 (0.4)***	***1.40 (1.02–1.92)***
	High FTND	6.3 (0.3)	6.1 (0.3)	0.90 (0.70–1.17)
Cigarettes Per Day	Overall	6.5 (0.9)	7.4 (0.9)	1.21 (0.86–1.70)
	Low FTND	3.0 (1.3)	4.5 (1.4)	1.54 (0.92–2.57)
	High FTND	10.0 (1.1)	10.4 (1.2)	0.96 (0.62–1.47)
Outcomes Measured During Follow-up				
Cigarette Smoking Days	Overall	5.5 (0.4)	5.3 (0.5)	1.08 (0.97–1.22)
	Low FTND	***4.3 (0.6)***	***5.7 (0.7)***	***1.39 (1.16–1.66)***
	High FTND	***6.6 (0.5)***	***4.9 (0.6)***	***0.85 (0.75–0.97)***
Cigarettes Per Day	Overall	6.5 (0.9)	5.7 (1.0)	0.94 (0.74–1.20)
	Low FTND	***2.8 (1.4)***	***5.7 (1.6)***	1.41 (0.94–2.10)
	High FTND	***10.2 (1.1)***	***5.8 (1.4)***	***0.63 (0.49–0.82)***

≠The rate ratio (RR) represents the increased risk of smoking outcome rates per week in the Placebo (PBO) group as compared to NAC and is derived from the Poisson regression model. RR results are shown adjusted for study treatment, visit number, baseline smoking dependence level, race, and concurrent cannabis use. In the final cigarette smoking days models, site and site x treatment covariate effects were insignificant, thus site was included in the model as a random effect. In the final CPD models, site was a significant predictor of CPD and was retained in the model as a covariate.

$p<0.05$

Table 4.

Model-based tobacco outcome measures and adjusted rate ratios (***1 gram increase in average daily cannabis***) separated by low and moderate/high baseline nicotine dependence levels for the entire cigarette smoking sub-sample (n=117).

Outcome	Cohort	Rate Ratio (95% CI) ǂ (1 Gram Increase in Avg. Cannabis Use)
Weekly Outcomes Measured During Treatment		
Cigarette Smoking Days	Overall	***1.10 (1.06–1.14)***
	Low FTND	***1.18 (1.10–1.26)***
	High FTND	1.03 (0.99–1.06)
Cigarettes Per Day	Overall	***1.05 (1.01–1.09)***
	Low FTND	***1.16 (1.07–1.25)***
	High FTND	1.04 (1.00–1.08)

ǂThe rate ratio (RR) represents the increased risk of greater tobacco use rates per week for a 1 gram increase in self-reported cannabis use amounts and is derived from the Poisson regression model. RR results are shown adjusted for study treatment (NAC or PBO), study visit, baseline nicotine dependence level, race, and concurrent cannabis use. In the final models for cigarette smoking days, site and site x treatment covariate effects were insignificant, thus site was included in the model as a random effect. In the final models for cigarettes per day, site was a significant predictor of CPD and was retained in the model as a covariate.

$p<0.05$