Published in final edited form as:

Psychopharmacology (Berl). 2020 February ; 237(2): 479–490. doi:10.1007/s00213-019-05384-z.

Depressive Symptoms and Cannabis Use in a Placebo-Controlled Trial of N-Acetylcysteine for Adult Cannabis Use Disorder

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Abstract

Rationale.—Depression is common among individuals with cannabis use disorder (CUD), particularly individuals who present to CUD treatment. Treatments that consider this comorbidity are essential.

Objectives.—The goal of this secondary analysis was to examine whether N-Acetylcysteine (NAC) reduced depressive symptoms among adults (age 18–50) with CUD (N=302) and whether the effect of NAC on cannabis cessation varied as a result of baseline levels of depression. Bidirectional associations between cannabis use amount and depression were also examined.

Methods.—Data for this secondary analysis were from a National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) multi-site clinical trial for CUD. Adults with CUD (N=302) were randomized to receive 2400 mg of NAC daily or matched placebo for 12 weeks. All participants received abstinence-based contingency management. Cannabis quantity was measured by self-report, and weekly urinary cannabinoid levels (11-nor-9-carboxy-9-tetrahydrocannabinol) confirmed abstinence. Depressive symptoms were measured by the Hospital Anxiety and Depression Scale.

Results.—Depressive symptoms did not differ between the NAC and placebo groups during treatment. There was no significant interaction between treatment and baseline depression predicting cannabis abstinence during treatment. Higher baseline depression was associated with decreased abstinence throughout treatment and a significant gender interaction suggested that this

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Rachel L. Tomko, Nathaniel L. Baker, Caitlyn O. Hood, Amanda K. Gilmore, Erin A. McClure, Lindsay M. Squeglia, Aimee L. McRae-Clark, and Susan C. Sonne declare that they have no conflict of interest. Kevin M. Gray has provided consultation to Pfizer, Inc.

may be particularly true for females. Cross-lagged panel models suggested that depressive symptoms preceded increased cannabis use amounts (in grams) during the subsequent month. The reverse pathway was not significant (i.e., greater cannabis use preceding depressive symptoms).

Conclusions.—Results from this study suggest that depression may be a risk factor for poor CUD treatment outcome and therefore should be addressed in the context of treatment. However, results do not support the use of NAC to concurrently treat co-occurring depressive symptoms and CUD in adults.

Keywords

N-Acetylcysteine; Cannabis Use Disorder; Marijuana; Cannabis; Depression; Mood; Structural Equation Modeling

INTRODUCTION

Approximately 12% of individuals who have used cannabis in the past year are estimated to have a cannabis use disorder (CUD; Richter et al. 2017), which indicates that their use has caused functional impairment in social, occupational, or health domains. Forty percent of individuals with a lifetime diagnosis of CUD also meet criteria for a mood disorder, with major depressive disorder (MDD) being the most common among individuals with CUD (21%; Stinson et al. 2006). Adults with a CUD are 2.8 times more likely than individuals without CUD to meet criteria for MDD (Hasin et al. 2016). Several population-based, longitudinal studies and meta-analyses indicate that cannabis use, particularly heavy use, is associated with an increased risk for the subsequent development of depressive symptoms (Chen et al. 2002; de Graaf et al. 2010; Degenhardt et al. 2003; Gobbi et al. 2019; Lev-Ran et al. 2014; Pacek et al. 2013), although not all studies demonstrate significant findings (Feingold et al. 2015).

Evidence for the inverse relation has also been demonstrated, where persons with MDD are more likely to subsequently use cannabis (Feingold et al. 2015) and to develop a CUD (Pacek et al. 2013). Many individuals report using cannabis in an attempt to alleviate psychiatric symptoms (Sarvet et al. 2018; Salazar et al. 2019) and/or negative mood states (Wyckoff et al. 2018). Consistent with negative reinforcement models of drug addiction (Baker et al. 2004), individuals may use cannabis to acutely attenuate negative affective states (Metrik et al. 2011) and withdrawal symptoms (Budney et al. 2003; Cornelius et al. 2008), and the temporary relief of these symptoms can perpetuate continued use. This pattern of negative reinforcement may be especially strong for individuals prone to depressive symptoms (Wyckoff et al. 2018).

Although cannabis may acutely reduce depressive symptoms immediately following use, repeated cannabis use is associated with increases in depressive symptoms over time (Cuttler et al. 2018; Gobbi et al. 2019). Long-term, daily users of cannabis show downregulation of cannabinoid receptors (specifically CB₁) which are located in areas of the brain critical for modulation of emotion (Zhou et al. 2017) and have been shown to play an important role in the rewarding effects of cannabis and cannabis withdrawal (Cooper and Haney 2008; Hirvonen et al. 2012; Schlienz et al. 2017). Thus, further research is needed to explore the

nuanced relation between cannabis use and subsequent depressive symptoms, specifically in the context of targeted interventions for cannabis users.

Role of Depressive Symptoms in Pharmacological Treatment of Cannabis Use Disorder

Few individuals with CUD seek treatment for their cannabis use (Hasin et al. 2016; Wu et al. 2017). However, those with co-occurring mood disorders are more likely to present to treatment for CUD (Kerridge et al. 2017; Wu et al. 2017). Further, individuals who do seek treatment for CUD commonly report the negative impact of cannabis on their mental health as a primary reason for seeking treatment (van der Pol et al. 2013), and MDD may increase risk of relapse among individuals in remission from CUD (Florez-Salamanca et al. 2013). Mood symptoms are therefore critical to consider in the context of CUD treatment.

No Food and Drug Administration (FDA) approved medications currently exist for the treatment of CUD. Among candidate medications tested for potential efficacy in treating symptoms of CUD, evidence supporting efficacy is equivocal at best (Nielsen et al. 2019). Included among the candidates were several pharmacotherapies that have established efficacy for the treatment of depression, such as escitalopram (Weinstein et al. 2014), vilazadone (McRae-Clark et al. 2016), bupropion (Carpenter et al. 2009; Penetar et al. 2012), and nefazodone (Carpenter et al. 2009). None of these antidepressants were efficacious in reducing cannabis use, though one showed some promise for treating symptoms of withdrawal (Penetar et al. 2012).

Two trials to-date have examined pharmacological treatments specifically for co-occurring CUD and depressive symptoms. The first trial compared fluoxetine to placebo (in addition to cognitive-behavioral and motivational enhancement therapy) for the treatment of comorbid CUD-MDD in adolescents and young adults (Cornelius et al. 2010). While depressive and CUD symptoms were reduced in the full sample, there was no difference in depression, CUD symptoms, or number of cannabis use days between those treated with fluoxetine versus placebo, and the number of days using cannabis was not reduced in either group. A second trial compared venlafaxine to placebo for the treatment of CUD and comorbid depressive disorder (i.e., MDD or dysthymia) in adults (Levin et al. 2013). While both groups exhibited improvements in symptoms of depression, those who received venlafaxine were less likely to achieve cannabis cessation. Within the placebo group, cessation was associated with improvement in mood; however, this was not the case in the venlafaxine group. The researchers suggested that venlafaxine might have exacerbated withdrawal symptoms. Effective pharmacological treatments are lacking for individuals suffering from these co-occurring conditions.

N-Acetylcysteine as a Potential Treatment for CUD with Depressive Symptomatology

N-Acetylcysteine (NAC) is an over-the-counter antioxidant that regulates glutamate transmission and offers a potential novel mechanism of action distinct from serotonergic and dopaminergic medications previously pursued for CUD. Specifically, NAC is thought to reduce intrusive or perseverative thinking that is characteristic of both substance use disorders and depression (Kalivas and Kalivas 2016), such as perseverative craving, drug-seeking behavior, and/or ruminative, negative thinking. NAC has shown promise as a relapse

prevention or cessation aid for a number of substance use disorders (McClure et al. 2014a; Powell et al. 2019; Roberts-Wolfe and Kalivas 2015; Tomko et al. 2018c) and has mixed evidence to suggest that it may alleviate depressive symptomology (Berk et al. 2014; Berk et al. 2019; Fernandes et al. 2016; Zheng et al. 2018).

Two clinical trials have examined NAC as a treatment for CUD. As an adjunct to abstinence-based contingency management, NAC has been shown to effectively promote cannabis cessation in a double-blind placebo-controlled trial with adolescents and emerging adults with CUD (Gray et al. 2012). NAC doubled the odds of abstinence relative to placebo with roughly 40% of individuals receiving NAC achieving abstinence compared to 20% of individuals on placebo (Gray et al. 2012). Cannabis abstinence findings did not replicate in a multi-site clinical trial for adults with CUD; however, in the overlapping age group with the adolescent trial (18–21 year olds), the size of the effect was similar to the adolescent trial, albeit not significant (Gray et al. 2017).

Preliminary evidence suggests that NAC may have been most effective at promoting cannabis cessation for adolescents presenting with (mild) pre-treatment depressive symptoms (Tomko et al. 2018b), suggesting that individuals with co-occurring CUD and depressive symptoms may particularly benefit from treatment with NAC. A meta-analysis of five placebo-controlled trials showed that NAC significantly reduced depressive symptoms among adults with or without co-occurring substance use disorders (Fernandes et al. 2016); however, no studies have examined the use of NAC for co-occurring CUD and depressive symptoms among adults.

Given that NAC has shown preliminary (though mixed) evidence supporting its use for both substance use and depression, NAC may have utility in treating the two conditions concurrently. There are several possible ways in which NAC could affect symptoms of both CUD and depression. First, NAC may reduce depressive symptoms that maintain cannabis use, leading to subsequent decreases in cannabis use. Second, NAC may reverse glutamatergic dysregulation due to chronic cannabis use which maintains CUD *and* results in dysregulated mood. This is consistent with preclinical findings that suggest NAC may protect against substance-induced depression-like symptoms (Yawalkar et al. 2018). Given that results from an adolescent trial also suggest that NAC may be most effective at promoting cannabis cessation among individuals with elevated pre-treatment depressive symptoms (Tomko et al. 2018b), it is possible that elevated depressive symptoms are a marker for cannabis-induced neural adaptations. Third, NAC may specifically reduce cannabis craving/drug-seeking and reductions in cannabis use may result in secondary improvements in mood. Prior findings suggest that abstinence leads to improvement in mood (Jacobus et al. 2017) and individuals who show any reductions in cannabis use during CUD treatment, as compared to individuals who increased their use, show greater reductions in depressive symptoms over the course of treatment (Hser et al. 2017).

Current Study

The present secondary analysis utilized data from a National Drug Abuse Treatment Clinical Trials Network (NIDA CTN)-sponsored multi-site clinical trial examining the efficacy of NAC for adults with CUD (primary trial results have been previously published; Gray et al.

2017). Though secondary analyses from this trial suggested that individuals who reduced cannabis use also showed reductions in depressive symptoms (Hser et al. 2017), the effect of NAC on depressive symptoms was not examined independent of change in cannabis use, nor were more proximal temporal associations between cannabis use and symptoms of depression. It was hypothesized that: 1) NAC would reduce depressive symptoms in adults with CUD (Fernandes et al. 2016); 2) NAC would be most likely to promote cannabis cessation among individuals with higher levels of pre-treatment depressive symptoms; and 3) there would be bidirectional associations between cannabis use and depressive symptoms, such that reductions in cannabis use would lead to proximal decreases in depressive symptoms and decreases in depressive symptoms would lead to proximal decreases in cannabis use.

METHODS

Participants.

Participants (N=302) were treatment-seeking adults between the ages of 18 and 50 who met criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) cannabis dependence. Potential participants were recruited via community and media advertisements and were eligible if they were interested in CUD treatment, provided a positive urine cannabinoid test indicating cannabis use, and (if female) agreed to use birth control during the course of the trial. Exclusionary criteria included: 1) any DSM-IV-TR substance dependence diagnosis other than cannabis or tobacco, 2) a urine drug screen positive for a substance other than cannabis, 3) recent use of synthetic cannabinoids, 4) known allergy to NAC or current use of NAC, 5) current treatment for substance use, 6) asthma, 7) recent or current pregnancy or breastfeeding, 8) any uncontrolled medical or psychiatric illness as determined by the study medical clinician. Full demographic and clinical characteristics are available in Gray et al. (2017). Briefly, the randomized sample was 71.5% male, 58.3% White, 27.8% Black and had an average age of 30.3 (SD=9.0). Participants had used cannabis 26 out of the prior 30 days at baseline, on average. As noted in Gray et al. (2017), the NAC and placebo groups did not differ in gender, age, or race; however, individuals in the placebo group had slightly higher education and were more likely to be employed than those in the NAC group. Though uncontrolled medical or psychiatric illness was exclusionary, no participants were excluded for MDD. Of the 626 participants screened for eligibility, 411 completed the HAD-D at screening. There was not a significant difference in HAD-D scores at screening between those randomized and those ineligible or lost to follow-up ($t=.29$, $df=409$, $p=0.77$).

Procedures and Measures.

Prior to any data collection, this multi-site clinical trial ([Clinicaltrials.gov](https://clinicaltrials.gov):) was approved by Institutional Review Boards at each study site. As described elsewhere (Gray et al. 2017; McClure et al. 2014b), participants (N=302) recruited across six study sites were randomized to one of two treatment conditions for 12 weeks: 1) NAC (1200 mg/ twice per day) or 2) matched placebo. Both groups received abstinence-based contingency management, and medical clinician-delivered cessation counseling. Active and placebo medication were dispensed as two 600 mg tablets taken twice per day. Participants attended

weekly in-person clinic visits at which they were seen by a medical clinician, completed relevant assessments, and provided urine samples for quantitative and qualitative cannabinoid testing.

Grams Used Per Day.—Participants completed a 30-day Timeline Follow-Back (TLFB) (Sobell and Sobell 1992) to assess cannabis at the initial screening visit and past 7-day TLFB (or, the number of days between visits) at all other study visits. Participants indicated whether they used cannabis (yes/no) each day and the number of joints, blunts, pipes, bowls, vaporizers, spliffs, edibles, or other methods that they had used. For every method of cannabis endorsed at the initial visit (e.g., joints, bowls), a proxy substance (motherwort) was weighed to indicate their “typical” amount used, similar to a method used in prior studies (Hindocha et al. 2017; Mariani et al. 2011; Norberg et al. 2012). As described in a prior publication (Tomko et al. 2018a), the estimated grams of cannabis used each day were calculated by multiplying the participant’s typical grams for that method by the number used that day (i.e., 0.75 grams per blunt $\times$ 2 blunts = 1.5 daily grams). Estimated grams of cannabis are used as the outcome variable, rather than frequency of cannabis use, since our prior work has demonstrated that estimated grams may better approximate actual cannabinoid exposure than frequency of use alone (Tomko et al. 2018a). The primary abstinence analysis was determined from self-reported cannabis use at each weekly visit.

Depression.—*Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983)* is a 14-item scale used to assess past-week depression (HAD-D) and anxiety (HAD-A) at five time points: screening, week 4, week 8, end of treatment (week 12), and follow-up (week 16). Scores on the depression and anxiety subscales each range from 0–21. Scores above 7 on the HAD-D are indicative of a possible or probable depressive disorder (Zigmond & Snaith 1983; Bjelland et al. 2002). Though not a primary focus of the current analysis, scores above 7 on the HAD-A are considered indicative of a possible or probable anxiety disorder (Zigmond & Snaith 1983; Bjelland et al. 2002).

Data Analytic Procedure.

Baseline demographic, clinical, and substance use characteristics were tabulated for the entire study cohort ($N=302$), as well as stratified across treatment assignment. A Wilcoxon Rank sum test was used to evaluate continuous measures between treatment groups while the normal Pearson Chi-Square test was used to assess the relationship for categorical and ordinal variables (Fisher’s exact test was used where appropriate).

Hypothesis 1.—Depression scores were tabulated using the HAD-D and reported at study baseline as well as during treatment (weeks 4, 8, 12, week 16 Follow-up). Linear mixed effects regression models were used to assess the effect of treatment with NAC for cannabis abstinence on depressive symptoms during the study. Effects of study treatment on HAD-D scores as well as differential effects of treatment over the course of the study (Treatment $\times$ time interaction) were the primary analytic targets. Secondly, the influence of gender on efficacy of NAC on HAD-D scores were assessed. HAD-D scores were natural logarithm transformed prior to analysis to improve residual normality in linear models. Adjusted

models included randomized treatment assignment, baseline HAD-D scores, study visit, gender, and an indicator of abstinence from cannabis at relevant study visits.

Hypothesis 2.—A repeated measures logistic regression model with the methods of generalized estimating equations (GEE; Zeger and Liang 1986) was applied to assess the impact of baseline depression on weekly self-reported abstinence from cannabis during the 12 weeks of active treatment. The effect of baseline depression scores on reported cannabis abstinence during study treatment and the possible modification of treatment efficacy (NAC) by baseline depression scores were assessed. Additionally, linear mixed effects regression models were used to assess the effect of baseline depression on average weekly cannabis use amounts (grams) during the 12 weeks of active treatment. Adjusted GEE models included baseline depression scores, randomized treatment assignment, study visit, gender, age, and the interaction between baseline depression scores and gender.

Hypothesis 3.—The reciprocal prospective association between depression and cannabis use amounts (grams used since last HAD-D measure) was assessed using a cross-lagged panel design (Figure 1). Autocorrelations and cross-lagged correlations are modelled allowing variables measured at the same time point to have synchronous relationships while including random measurement error of the observed depression and cannabis use variables. Missing data are accounted for with the implementation of full-information maximum likelihood estimates (FIML) in SEM models. Fully reciprocal, single variable lagged, and autocorrelation only relationships were modeled and compared using model fit statistics. Model fit was evaluated using the comparative fit index (CFI; Bentler, 1990), the Tucker-Lewis Index (TLI; Bentler & Bonett, 1980) as well as the root means square error of approximation (RMSEA; Steiger 1980). RMSEA values less than 0.08 and CFI/TLI values greater than 0.90 indicated adequate model fit. Adjusted models included randomized treatment assignment, gender, as well as the lagged and synchronous values of HAD-D and cannabis use levels.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA). Results from categorical outcomes are presented as risk ratios with 95% confidence intervals (CI) while results from continuous outcomes are presented as group level means and associated standard errors, as well as mean group differences and standardized estimates from SEM models. Non-significant interactions were removed from the final models. Correlation structures were independently compared (1st order autoregressive, banded, and unstructured) and the final model structure was chosen using minimization of Akaike's information criterion (AIC; Bozdogan 1987) for continuous outcome models and the Quasi-likelihood under the independence model criterion (QIC; Pan 2001) for the GEE models: all models assumed a 1st order autoregressive correlation structure with the exception of the mixed effects model for Hypothesis 1 (unstructured provided a better model fit). Significance was set at a 2-sided *p*-value of .05.

RESULTS

Study Participants

Of the 302 participants randomized in the study, 278 (92%) had at least one visit with both depression scores (HAD-D) and quantified cannabis use recorded. Of the 1208 possible data points, 969 (80%) were available across the 278 participants and included in the analysis models. HAD-D scores were not different between randomized treatment groups at study baseline ($p=.27$) nor were there any differences in the proportion of participants reaching the threshold of clinically significant depression symptoms ($\text{HAD-D} > 7$; $p=.97$). Demographic, psychiatric, and cannabis use characteristics are presented in Table 1. Baseline tobacco and alcohol co-use was not associated with depressive symptoms during treatment ($p>.9$ and $p>.5$, respectively) nor did it modify the relationship between treatment with NAC and depression scores ($p>.7$ and $p>.5$, respectively). Thus, tobacco and alcohol co-use was not considered in subsequent models.

Time Naïve Relationship between NAC, HAD-D Scores, and Cannabis Abstinence (Hypotheses 1 and 2)

Hypothesis 1: There was no statistical difference in HAD-D scores during treatment between the participants randomized to NAC as compared to placebo [Treatment Average Adjusted mean=3.3 (SE=0.20) vs. 2.8 (0.19); $F_{1,250}=3.2$; $p=.076$; Figure 2]. Baseline HAD-D scores were positively associated with depression scores during treatment ($\beta=0.50$ SE=0.041; $F_{1,250}=155$; $p<.001$); however, there was no moderating effect of baseline depression across treatment assignment (baseline HAD-D $\times$ Treatment interaction; $F_{1,249}=0.01$; $p=.96$). There were no statistically significant differences in model based HAD-D scores during treatment between male and female participants [Adjusted Males=3.3 (SE=0.16) vs. Females=2.8 (0.24); $F_{1,250}=3.4$; $p=.07$] and gender did not modify the treatment effect of NAC on depression ($F_{1,249}=0.57$; $p=.45$). Sensitivity analyses were conducted in only the sub-sample of participants who endorsed elevated depressive symptoms at baseline ($\text{HAD-D} > 7$; $n=47$) and the results remained consistent with those observed in the full sample.

Hypothesis 2: The association between baseline depression and abstinence reported at subsequent study visits was assessed using all available cannabis abstinence data (self-reported abstinence). Results indicate that higher HAD-D scores at study baseline were associated with lower probability of abstinence during treatment (per 5 unit increase in HAD-D; Adjusted RR=0.76 (0.62–0.93); $p=.007$). [Of note, though abstinence was measured by self-report, the agreement between weekly negative urine cannabinoid tests and self-reported abstinence was 82% during the treatment portion of the study and the results were consistent when abstinence is defined by negative urine tests (RR=0.72 (0.54–0.94); $p=0.017$).] There was also evidence that the relationship between baseline depressive symptoms and cannabis abstinence may be less associated as the observed abstinence become more distal (baseline HAD-D $\times$ study week; $\chi^2_{11}=18.5$; $p=.07$). Treatment with NAC did not modify the relationship between baseline depression and subsequent cannabis abstinence ($\chi^2_1=0.3$; $p=.57$). The relationship between baseline depressive symptoms and subsequent cannabis abstinence during treatment was moderated by gender ($\chi^2_1=4.1$; $p=.04$).

such that the relationship between baseline HAD-D scores and cannabis abstinence for female participants [RR=0.57 (0.40–0.81); $p=.002$] was different than for males [RR=0.89 (0.70–1.14); $p=.34$]. This result indicates that increasing depressive symptoms were more strongly associated with decreasing probability of abstinence in females as compared to males. Similarly, higher baseline HAD-D scores were associated with greater cannabis use amounts during study treatment [per 5 unit increase in HAD-D on grams used in the past week; $\beta=1.4$; SE=0.6; $t_{272}=2.2$; $p=.027$]. Similar to the abstinence results above, the relationship between increasing depressive symptoms and cannabis use amounts was significant and positive for females [$\beta=2.1$; SE=0.8; $t_{73}=2.5$; $p=.015$], but not significant for males [$\beta=1.0$; SE=0.8; $t_{196}=1.3$; $p=.21$].

Cross lagged panel models (Hypothesis 3)

The magnitude of the association between HAD-D scores and cannabis use amounts (grams used in past four weeks) were evaluated using three distinct path models with separate analyses. Standardized parameter estimates for best fitting models are noted in Table 2. In all models, there were significant autoregressive effects ranging from $\beta=0.48$ (association between baseline cannabis use $\rightarrow$ Week 4 cannabis use) to $\beta=0.91$ (Week 8 depression $\rightarrow$ Week 12 depression). Also, in concordance with simple models, there were significant cross-visit and within-visit correlations between depression scores and cannabis use amounts. Specifically, higher HAD-D scores were associated with higher cannabis use grams at the current (all $ps<.006$) and future visit (all $ps<.005$). However, self-reported cannabis use amounts were *not* significantly associated with future depression scores ($p>.40$). Fit statistics indicated that the model with cross-lagged effects of depressive symptoms to cannabis use only was the superior model (Table 2) and that the effects of cannabis use on future depression scores could be removed.

DISCUSSION

The current study extends a limited literature examining the role of depressive symptoms in the pharmacological treatment of CUD. The hypotheses were largely unsupported. NAC did not directly reduce depressive symptoms in this sample of adults with CUD (Hypothesis 1) and NAC was not more efficacious in promoting cannabis cessation among participants with heightened symptoms of depression at baseline (Hypothesis 2). Heightened baseline depressive symptoms were associated with lower cannabis cessation rates, regardless of treatment condition; this effect was primarily driven by female participants. Finally, though there was no evidence of bidirectional associations between cannabis use and depressive symptoms (Hypothesis 3) in the current sample, the results suggest that elevated depressive symptoms were concurrently associated with greater cannabis use quantity and with greater subsequent cannabis use quantity during the next month.

This study does not provide evidence that NAC may effectively treat co-occurring depression symptoms in the context of CUD treatment, adding to the mixed literature of NAC's impact on depression. Relevant to NAC's mechanisms of action, accumulating evidence shows the presence of low-grade inflammation in a subset of individuals with MDD (Colpo et al. 2018). The anti-inflammatory properties of NAC are thought to reverse

this inflammation, having beneficial effects on mood (Fernandes & Gupta, 2019). Though a prior randomized controlled trial showed only limited therapeutic benefits of NAC for MDD (Berk et al. 2014), an ongoing trial is examining NAC as an adjunctive treatment for depression among individuals who specifically show elevated inflammatory markers (Yang et al. 2018). Cannabis use may increase neuroinflammation in the prefrontal cortex, consistent with preclinical findings (Zamberletti et al. 2015). It is possible that individual differences in neuroinflammatory responses have contributed to the mixed findings regarding NAC for both depression and cannabis cessation and that only a subset of individuals are likely to benefit from NAC.

Inconsistent with findings from our adolescent trial (Tomko, Gilmore, & Gray 2018), NAC did not show greater efficacy among individuals with heightened baseline depressive symptoms. This suggests pre-treatment depressive symptoms are not a marker of likely NAC response for adult CUD. It is possible that important age and/or developmental differences exist, given that there were also differences in NAC efficacy for CUD among adults and adolescents (Gray et al. 2017; Gray et al. 2012). Perhaps adolescents and adults differ in their respective rates of substance-induced depressive symptoms or independent mood symptoms due to differences in stages of neurodevelopment.

Baseline depressive symptoms were a risk factor for poor treatment response (decreased likelihood of cannabis abstinence) in the current study and this was particularly true for female participants. Though males and females did not differ on their baseline HAD-D scores, depressive symptoms were more strongly related to continued cannabis use among females, though this requires replication in an independent sample. Prior research suggests that women are more likely to show independent versus cannabis-induced depression (Dakwar et al. 2011) and have other co-occurring psychopathology (Khan et al. 2013). This may mean that co-occurring mood symptoms are particularly important to address among females attempting cannabis cessation. Though rates of CUD are generally lower among adult females (Hasin et al. 2016), some studies have shown that women with CUD have more difficulty achieving abstinence during treatment (McRae-Clark et al. 2016; McRae-Clark et al. 2015). Failure to adequately address co-occurring mood symptoms may partially explain the worse outcomes among females.

The current study did not find support for a bidirectional association between depressive symptoms and cannabis use throughout treatment. Instead, it was found that greater depressive symptoms led to subsequent increases in cannabis quantity (self-reported grams used) at the next time point, while higher quantities of cannabis use did not lead to subsequent increases in depression symptoms. Cannabis use quantity and depressive symptoms were also concurrently related. This is consistent with findings from this same dataset that suggest individuals who show any reduction in cannabis use frequency during treatment also showed an overall decrease in depression and anxiety symptoms (Hser et al. 2017). However, it is important to note that the temporal order of effects was still difficult to disentangle in this prior analysis.

The current findings also suggest that symptoms of depression (or correlated processes) may serve to maintain cannabis use and interfere with treatment for CUD. The use of substances

to relieve aversive states becomes more common as substance use disorders progress (Baker et al. 2004; Koob and Le Moal 2001) and the current sample represents a chronically using, dependent sample. Depressed mood as well as affective symptoms of withdrawal can elicit continued use to alleviate these symptoms (Baker et al. 2004). This is consistent with research linking depression to worse outcomes among individuals receiving treatment for other substance use disorders (Anand et al. 2019; Glasner-Edwards et al. 2009; Sonne et al. 2010). In contrast, at least one study examining individuals with CUD specifically did not find within-treatment associations between depressive symptoms and subsequent substance use frequency (Anand et al. 2019). However, this study measured substance use frequency across different substance types.

Additional limitations must be considered. First, overall levels of depressive symptoms were low and this may have limited the possibility of observing reductions in these symptoms. Perhaps as a function of these low levels, depressive symptoms were relatively stable over time (auto-correlations >0.82). However, despite low levels, there was enough variability in depressive symptoms to show that heightened levels were associated with poorer cannabis cessation outcomes. Second, the parent study was specifically designed to test the primary efficacy of NAC for cannabis cessation (Gray et al. 2017) and was therefore not designed to be powered to detect moderating effects of depressive symptoms. Third, the relative proportion of cannabinoid constituents [i.e., Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD)] commonly used by participants in this study were not assessed; different ratios of THC/CBD have varying impact on perceived relief of depressive symptoms (Cuttler et al. 2018). Fourth, it is possible that our results would differ had we used a different measure of depression. The HADS construct validity has been debated with some suggesting that the combined anxiety and depression scales are better characterized as a measure of general distress (Norton et al. 2013). However, the depression subscale is highly correlated with other established measures, such as the Beck Depression Inventory ($r=0.70$ – 0.73 ; Bjelland et al. 2002). The depression subscale is most consistent with symptoms of anhedonia and places less emphasis on dysphoric mood (Snaith 2003). This is critical to the interpretation of the current results because it points to a key role of anhedonia and/or reward deficits as a potential barrier to cannabis cessation. However, the literature evaluating the relation between anhedonia and cannabis use is also mixed with some studies showing that cannabis use may exacerbate and maintain anhedonia (Bovasso 2001; Feingold et al. 2017) and other research suggesting a pathway from anhedonia to cannabis use, but not the reverse (Leventhal et al. 2017). Fifth, the assessment time frames must be taken into account when interpreting these results. While we collected daily cannabis use data throughout the study with participants providing retrospective accounts of use since their last visit, our depression measure assessed past week depression symptoms only. Therefore, lagged associations between cannabis use and subsequent depressive symptoms represent a slightly longer time interval (i.e., approximately three weeks) than do lagged associations between depressive symptoms and subsequent cannabis use quantities (i.e., immediately following depression assessment). It is possible that associations between depressive symptoms and subsequent cannabis use were stronger because of the reduced lag time between assessments. Lastly, use of alcohol and tobacco was prevalent in this sample (Squeglia et al. 2018; McClure et al. 2018). More frequent use of tobacco (McClure et al. 2018), but not alcohol (Squeglia et al.

2018), was associated with greater cannabis use during treatment. Though our analysis suggests that alcohol and tobacco co-users did not differ in depressive symptoms, the concurrent co-use of other substances may be a confounding factor when examining associations between mood and cannabis use.

Summary/Future Directions

In sum, the results of this study indicate that symptoms of depression may be a barrier to cannabis cessation among adults, regardless of whether NAC is administered. Overall, these findings suggest that depressive symptoms should be considered clinically relevant within cannabis cessation programs for adults, and that more research is needed to explore treatments that could mitigate the impact of depressive symptoms on treatment outcomes. Treatments that address depressive symptoms concurrently with CUD treatment may be particularly beneficial. Ecological momentary assessment (EMA) studies that frequently assess depressive symptoms and cannabis use (i.e., multiple times per day) would provide nuanced insight on the potential association between depressive symptoms and proximal increases in cannabis use (Wycoff, Metrik, & Trull 2018). EMA studies may examine which symptoms of depression (e.g., anhedonia, sleep) are specifically associated with increased cannabis use among individuals with CUD to better inform treatment development.

Acknowledgments

This study was supported by National Institutes of Health grants UG1DA013727, UG1DA015831, UG1DA020024, UG1DA013714, U10DA013045, HHSN271201200017C, K12HD055885, K24DA038240, K23AA025399, K23DA042935, K01DA036739, and T32DA035200.

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Figure 1.

Structural equation model used to assess the cross-lagged relationship between depression scores (X_t) and cannabis use in grams (Y_t) at study baseline (0), and 4 study treatment and follow-up weeks (4, 8, 12, FU).

Note. The model illustrates the autocorrelated relationships (β) between longitudinal outcome measures (HAD-D depression scores and cannabis use quantity in grams), cross-lagged relationships (γ) between the two outcome measures and synchronous relationships (ρ) between measures taken at the same time point.

Figure 2.

Adjusted* HAD-D Scores Over Time

Note. *HAD-D scores at Weeks 4 through Follow-Up (Week 16) represent model-adjusted (adjusting for baseline HAD-D and gender) means and standard errors. Week 0 mean HAD-D score is unadjusted.

Table 1.

Demographics and Clinical Characteristics at Study Baseline

Demographic Characteristics	NAC (n=153)	Placebo (n=149)	Total (N=302)
Gender, male, no. (%)	117 (76.5)	99 (66.4)	216 (71.5)
Age (years) at Randomization, M (SD)	29.8 (8.74)	30.8 (9.32)	30.3 (9.03)
Race, no. (%)			
Black or African American	44 (28.8)	40 (26.8)	84 (27.8)
White	84 (54.9)	92 (61.7)	176 (58.3)
Other	25 (16.3)	17 (11.4)	42 (13.9)
Marital Status, no. (%)			
Married/Living with Partner	35 (22.9)	44 (30.6)	79 (26.2)
Divorced/separated	16 (10.4)	14 (9.3)	30 (9.9)
Never married	102 (66.7)	91 (61.1)	193 (63.9)
Hospital Anxiety and Depression Scale			
Depression, M (SD)	4.2 (3.4)	3.8 (3.2)	4.0 (3.3)
Anxiety, M (SD)	6.5 (4.3)	6.2 (3.6)	6.4 (3.9)
Clinically Significant Depression, no. (%) *	24 (15.7)	23 (15.5)	47 (15.6)
Substance Use Characteristics			
Self-reported smoking tobacco, no. (%)	60 (39.2)	56 (37.6)	116 (38.4)
Self-reported drinking alcohol, no. (%) **	113 (73.9)	109 (73.2)	222 (73.5)
Number of Days of Cannabis Use in 30 Days Prior to Informed Consent, M (SD)	25.7 (6.72)	26.4 (5.65)	26.0 (6.21)
Urine Cannabinoid Level, ng/mL, M (SD)	1113.4 (1477.63)	1035.2 (1382.89)	1075.1 (1430.14)
Years Since First Cannabis Use, M (SD)	14.5 (8.94)	15.7 (9.43)	15.1 (9.19)
Years since First Cannabis Dependence, M (SD)	9.1 (7.57)	9.9 (8.83)	9.5 (8.21)

Note. M=mean; SD=standard deviation; BL=baseline;

* HAD-D score >7 at BL.

** self reporting >1 drink in the past 30 days.

Table 2.

Relationship between depressive symptoms and cannabis use amounts. Standardized results are shown.

	Cross Lagged Model Structures					
	Reciprocal		Dep → Cann Use		Simple Auto Correlated	
Auto-correlated Relationships	β	<i>p</i>	β	<i>p</i>	β	<i>p</i>
BL Dep → V4 Dep (β_{X1})	.829	<.001	.814	<.001	.824	<.001
V4 Dep → V8 Dep (β_{X2})	.869	<.001	.854	<.001	.860	<.001
V8 Dep → V12 Dep (β_{X3})	.893	<.001	.878	<.001	.882	<.001
V12 Dep → FU Dep (β_{X4})	.909	<.001	.893	<.001	.896	<.001
BL Cann Use → V4 Cann Use (β_{Y1})	.477	<.001	.479	<.001	.491	<.001
V4 Cann Use → V8 Cann Use (β_{Y2})	.623	<.001	.626	<.001	.645	<.001
V8 Cann Use → V12 Cann Use (β_{Y3})	.667	<.001	.672	<.001	.693	<.001
V12 Cann Use → FU Cann Use (β_{Y4})	.686	<.001	.691	<.001	.714	<.001
Cross-Lagged Relationships						
BL Cann Use → V4 Dep (γ_{X1})	-.024	.178	--	--	--	--
V4 Cann Use → V8 Dep (γ_{X2})	-.031	.175	--	--	--	--
V8 Cann Use → V12 Dep (γ_{X3})	-.033	.173	--	--	--	--
V12 Cann Use → FU Dep (γ_{X4})	-.032	.171				
BL Dep → V4 Cann Use (γ_{Y1})	.064	.016	.062	.018	--	--
V4 Dep → V8 Cann Use (γ_{Y2})	.067	.016	.064	.018	--	--
V8 Dep → V12 Cann Use (γ_{Y3})	.071	.016	.068	.018	--	--
V12 Dep → FU Cann Use (γ_{Y3})	.076	.016	.072	.018		
Synchronous Relationships						
Visit 4 (ρ_{XY1})	.114	<.001	.106	<.001	.129	<.001
Visit 8 (ρ_{XY2})	.089	<.001	.082	<.001	.101	<.001
Visit 12 (ρ_{XY3})	.076	<.001	.071	<.001	.087	<.001
FU Visit (ρ_{XY4})	.069	<.001	.064	<.001	.078	<.001
Fit Indices						
Number of Parameters	25		21		20	
Comparative Fit Index (CFI)	.93		.93		.93	
Tucker-Lewis Index (TLI)	.91		.92		.92	
RMSEA (90% CI)	.08(.06–.10)		.08(.06–.09)		.08 (.06–.09)	
AIC	14077		14073		14077	

Note. Results are shown for the full reciprocal model (shown in Figure 1), a model where visit level HAD-D scores are associated with future HAD-D scores and cannabis grams and a simple auto correlated model where there are no cross-lagged effects. BL, V4, V8, V12, FU = Visits at study baseline, week 4, 8, 12 and week 16 follow-up. Dep=Depression as measured by HAD-D scores. Cann Use=self-reported grams of cannabis use since the prior measured visit (BL, V4, V8, V12, FU). Data shown adjusted for study treatment assignment and participant gender. **Bold** text indicates that $p < .05$.