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The role of depressive symptoms in treatment of adolescent cannabis use disorder with N-Acetylcysteine

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Abstract

Relative to adults, adolescents are at greater risk of developing a cannabis use disorder (CUD) and risk may be exacerbated by co-occurring depressive symptoms. N-Acetylcysteine (NAC), an over-the-counter antioxidant, is thought to normalize glutamate transmission. Oxidative stress and glutamate transmission are disrupted in both depression and CUD. Thus, NAC may be particularly effective at promoting cannabis abstinence among adolescents with elevated depressive symptoms. Secondary analyses were conducted using a sub-sample of adolescents with CUD ($N = 74$) who participated in an 8-week randomized placebo-controlled clinical trial examining the efficacy of NAC for cannabis cessation. It was hypothesized that NAC would reduce severity of depressive symptoms, and that decreases depressive symptom severity would mediate decreases in positive weekly urine cannabinoid tests (11-nor-9-carboxy-9-tetrahydrocannabinol). Additionally, it was expected that adolescents with greater severity of baseline depressive symptoms would be more likely to become abstinent when assigned NAC relative to placebo. Results from linear mixed models and generalized estimating equations did not suggest that NAC reduced severity of depressive symptoms, and the hypothesis that NAC's effect on cannabis cessation would be mediated by reduced depressive symptoms was not supported. However, an interaction between treatment condition and baseline severity of depressive symptoms as a predictor of weekly urine cannabinoid tests was significant, suggesting that NAC was more effective at promoting abstinence among adolescents with heightened baseline depressive symptoms. These secondary findings, though preliminary, suggest a need for further examination of the role of depressive symptoms in treatment of adolescent CUD with NAC.

Keywords

Youth; Marijuana; Depression; Glutamate; Pharmacotherapy

1. Introduction

Approximately 11% of adolescents experience depression (Avenevoli, Swendsen, He, Burstein, & Merikangas, 2015) and chronic use of cannabis is associated with depression

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(Volkow, Baler, Compton, & Weiss, 2014). This is particularly problematic because approximately 25% of high school seniors report past 30-day cannabis use and 6% use cannabis almost daily (Miech et al., 2017). Further, adolescents are at greater risk for developing cannabis use disorder (CUD; Chen, O'Brien, & Anthony, 2005) than adults. Due to the co-occurring nature of CUD and depression, adolescent-specific treatments that target both cannabis use and depressive symptoms are essential. Reductions in cannabis use are associated with reductions in severity of depressive symptoms (Hser et al., 2017); however, it is unclear if reductions in depressive symptoms are associated with cannabis abstinence.

N-Acetylcysteine (NAC), an over-the-counter medication thought to regulate glutamate transmission and reduce oxidative stress, has some promising findings in both enhancing the efficacy of abstinence-based cannabis use treatment programs (Gray et al., 2012) as well as reducing depressive symptoms (Fernandes, Dean, Dodd, Malhi, & Berk, 2016). Therefore, an examination of the effect of NAC on severity of depressive symptoms within an abstinence-based cannabis use treatment program for adolescents is warranted.

1.1. Depressive symptoms and cannabis use

There is a strong association between depressive symptoms and cannabis use, but the directionality of the association is unknown (Volkow et al., 2014). Adolescents and young adults commonly report using cannabis to cope with negative emotions (Zvolensky et al., 2007). Further, cannabis use is associated with the development or exacerbation of depressive symptoms. In a prospective study of 1601 adolescents, daily cannabis use was associated with a fivefold risk of depressive symptoms and weekly cannabis use was associated with a twofold risk of later symptoms of depression (Patton et al., 2002). Depressive symptoms among adolescents can be particularly concerning given that suicide, often associated with depression, is the second most common cause of death in this age group (National Center for Injury Prevention and Control, 2015). Among adults, reductions in cannabis use can result in reduced severity of depressive symptoms (Hser et al., 2017). However, it is unclear if reductions in depressive symptoms are associated with abstinence within an abstinence-based treatment program. If adolescents are using cannabis to cope with negative emotions (Zvolensky et al., 2007), it would be expected that a treatment that reduces depressive symptom severity may also promote cannabis abstinence.

1.2. The effect of NAC on depressive symptoms and cannabis use

A recent meta-analysis examining the effect of NAC on depressive symptoms found that NAC, compared to placebo, was effective at reducing depressive symptom scores and global functionality across studies (Fernandes et al., 2016). This finding is particularly promising because NAC offers a medication option with only minor adverse effects compared to many psychiatric medications. NAC is thought to regulate glutamate transmission and reduce oxidative stress, and disrupted glutamate transmission and oxidative stress have both been associated with depression (Berk, Malhi, Gray, & Dean, 2013; Fernandes et al., 2016). NAC may therefore also be a promising medication to reduce depressive symptom severity among adolescents with CUD.

NAC has also had some promising findings in enhancing abstinence among adolescents receiving contingency management (CM) for CUD. In an 8-week, double-blind placebo-controlled trial, NAC doubled the odds of abstinence among adolescents with CUD (Gray et al., 2012). The very same mechanisms that NAC addresses in relation to depressive symptom reduction are also thought to be associated with abstinence or relapse prevention among individuals with substance use disorders (Kalivas & Volkow, 2011; Roberts-Wolfe & Kalivas, 2015). Therefore, addressing both depressive symptoms and increasing abstinence may be possible for adolescents with CUD using NAC.

1.3. Current study

Data from the aforementioned clinical trial testing NAC as an adjunct to CM for adolescent cannabis cessation (Gray et al., 2012; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01005810) Identifier: NCT01005810) were used for the current secondary analyses. The goals of these analyses were to a) determine if NAC reduced severity of depressive symptoms in a sample of adolescents seeking treatment for CUD and, if so, determine if reductions in depressive symptoms mediate the effect of NAC on cannabis cessation, and b) determine if baseline severity of depressive symptoms moderates NAC's effect on cannabis cessation. It was hypothesized that (1) the NAC group would report reduced depressive symptom severity over the course of treatment, (2) reductions in cannabis use would be mediated by reductions in severity of depressive symptoms, and (3) the effect of NAC in promoting cannabis abstinence would be greatest for adolescents with more severe baseline depressive symptoms.

2. Method

2.1. Participants

Adolescents (ages 13–21) seeking treatment for cannabis use and who met criteria for DSM-IV-TR cannabis dependence were recruited via community flyers, advertisements and other participant referrals. Exclusion criteria were 1) allergy or intolerance to NAC, 2) current treatment for cannabis dependence, 3) current DSM-IV-TR substance dependence other than cannabis or nicotine, 4) current or recent (past 14 day) use of carbamazepine or nitroglycerin, 5) pregnancy or lactation (if female), and 6) any other significant medical or psychiatric illness likely to interfere with safe and/or successful study participation, as evaluated by the medical clinician.

2.2. Procedures and measures

Study procedures and primary study results have been published elsewhere (Gray et al., 2012). All procedures were approved by the local Institutional Review Board prior to study onset. Potential participants provided consent (assent and guardian consent were attained if the participant was under the age of 18) prior to study participation and completed an in-person screening evaluation to determine study eligibility. If eligible, they attended an additional randomization visit, at which times participants were randomized in a 1:1, double-blind fashion to receive NAC or placebo, as described below. Randomization was stratified by age (younger than 18 vs. 18 and older) and frequency of past 30-day cannabis use (fewer than 20 days vs. 20 or more days of use). Participants were then followed for 8 weeks of active treatment.

2.2.1. Treatment—All participants received low-intensity weekly medical clinician-delivered cannabis cessation counseling (generally 10 min per session) and abstinence-based CM, in which participants were monetarily reinforced for negative urine cannabinoid tests. In addition, participants were randomized to receive either 1200 mg of NAC taken twice daily (2400 mg/day total) or matched placebo. Active treatment lasted for 8 weeks.

2.2.2. Primary outcome measure—Participants provided urine cannabinoid (11-nor-9-carboxy-9-tetrahydrocannabinol) samples at screening, randomization, and weekly during the course of treatment. Samples greater than or equal to 50 ng/mL were considered positive for cannabinoids.

2.2.3. Other measures. Baseline self-report of cannabis use—The *Timeline Follow-Back (TLFB*; Sobell & Sobell, 1992) was used to assess frequency of past 30-day cannabis use at screening. Frequency of use since last visit was assessed at all other visits. *The Marijuana Ladder* (Slavet et al., 2006), is a 1-item scale used to assess current motivation (rated on a 1–10 scale) to abstain from cannabis at each visit. *The Beck Depression Inventory (BDI-II*; Beck, Steer, & Brown, 1996) is a 21-item measure used to assess presence and severity of depressive symptoms at randomization and weeks 4 and 8 of treatment. Scores of 14 or greater on the BDI-II indicate at least mild depressive symptoms. This measure was added to the protocol after initiation of the clinical trial and is thus only available for a subsample of randomized participants.

2.3. Data management and analytic procedure

REDCap electronic data capture (Harris et al., 2009) was used to manage study data. Data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). For all analyses, $p < .05$ was considered significant. All beta estimates are unstandardized. To examine aim 1 (effect of NAC on depressive symptom severity), we conducted linear mixed effects models (LMMs) with a Gaussian distribution. A random intercept and random slope (treatment week) were included in the model and unspecified covariance structure was used. To examine aims 2 (depressive symptom severity as a mediator of NAC effect on cannabis use) and 3 (depressive symptom severity as a moderator of NAC effect on cannabis use), generalized estimating equations (GEEs; Zeger & Liang, 1986) were used to predict the probability of positive urine cannabinoid tests. An autoregressive correlation structure was assumed. Consistent with a modified intent-to-treat approach, only randomized participants who received at least one dose of medication were included in the analyses; however, all missing urine cannabinoid tests for this reduced sample were assumed to be positive. In the case of missing BDI-II assessments, the last completed assessment was carried forward.

3. Results

Demographic and clinical characteristics are tabulated for each randomized participant and shown in Table 1. Of the 84 randomized participants with BDI-II data, 74 received at least one medication dose. At randomization, the average BDI-II score was 8.4 (SD = 8.5) and 24.3% of the sample reported at least mild depressive symptoms (total score of 14 or above).

3.1. Effect of NAC on depressive symptoms

Treatment week, treatment condition (NAC versus placebo), the interaction between treatment week and treatment condition, baseline urine cannabinoid test (positive versus negative), gender, and years of cannabis use were included as predictors of severity of depressive symptoms as measured by the BDI-II. In the full model, the interaction between treatment week and treatment condition did not significantly predict severity of depressive symptoms ($p > .30$) and the interaction was not retained. As shown in Table 2, NAC did not reduce the severity of depressive symptoms, although the association was in the expected direction ($b = -2.14$, $SE = 1.86$, $p = .25$).

3.2. Depressive symptom severity as a mediator of the effect of NAC on cannabis cessation

Unlike in the full sample of 116 adolescents randomized to treatment in Gray et al. (2012), in the reduced sample of participants with BDI-II data who received at least one dose of medication ($n = 74$), there was not a main effect of NAC on the likelihood of a positive urine cannabinoid test, after accounting for treatment week, motivation to change cannabis use, age, and testing positive for cannabis at baseline ($b = -0.38$, $SE = 0.41$, $p = .35$). Consistent with the primary paper (Gray et al., 2012), the interaction between treatment condition and treatment week was not significant and not retained in the final model. Consistent with Baron and Kenny (1986), the indirect effect of NAC on likelihood of a positive urine cannabinoid test was computed to test for significant mediation ($c - c' = 0.006$) and there was no evidence to support depressive symptom severity as a mediator of treatment outcome. However, given that there was not a main effect of NAC on abstinence, these results should be interpreted with caution.

3.3. Pre-treatment depressive symptoms as a moderator of the effect of NAC on cannabis cessation

The interaction between pre-treatment depressive symptom severity and treatment condition (NAC vs. placebo) was used to predict the probability of positive weekly urine cannabinoid tests. Main effects of treatment condition, depressive symptoms, treatment week, testing positive for cannabis at baseline, age at baseline, and baseline motivation to reduce cannabis use were also included in the model. Results indicated that there was a significant interaction such that NAC was negatively associated with positive urine cannabinoid tests during treatment and that the difference between NAC and placebo was stronger for adolescents who had greater severity of baseline depressive symptoms ($b = -0.09$, $SE = 0.04$, $p = .034$), as shown in Table 3. Fig. 1 shows the percentage of positive urine cannabinoid tests across treatment by condition and depressive symptom severity with missing urine cannabinoid tests assumed to be positive. For the purpose of this figure only, depression was coded as a dichotomous variable with scores at or above 14 on the BDI-II indicative of at least mild depressive symptoms.

4. Discussion

These secondary analyses partially supported our hypotheses. NAC did not appear to significantly reduce depressive symptom severity, nor did reductions in severity of

depressive symptoms mediate NAC's effect on reduction of cannabis use. However, severity of depressive symptoms was only assessed in a sub-sample of participants randomized in the full clinical trial (Gray et al., 2012) and this study was not specifically powered to test interactive and mediation effects. The primary study was powered to detect a pre-determined difference between NAC and placebo on proportion of negative urine cannabinoid tests with a sample size of 58 per group. In fact, the main effect of NAC on cannabis abstinence was not evident with the reduced sample size in the current study. Thus, in a larger sample, it is possible that NAC reduces severity of depressive symptoms and/or mediates the effect of NAC on cannabis cessation, consistent with a recent meta-analysis showing that NAC significantly reduces secondary depressive symptoms among adults (Fernandes et al., 2016). A fully powered trial is necessary to determine whether NAC may be effective at reducing depressive symptom severity in adolescents with CUD. A comorbid depressive disorder, a comorbid depressive disorder (i.e., major depressive disorder, dysthymia) among individuals with CUD may be particularly difficult to treat and medications that are effective in treating depressive disorders among individuals without CUD comorbidity may not generalize to a CUD population (Levin et al., 2013; Cornelius et al., 2010). Given promising effects of NAC in treating depressive symptoms in other studies and some observed benefits in the current sample, it is worthy of further investigation in a fully powered trial. Despite the reduced sample size, NAC was more effective at reducing cannabis use among adolescents with greater pre-treatment depressive symptom severity, relative to adolescents with low depressive symptomology. This may indicate that NAC's specific mechanism of action is through reduction in severity of depressive symptoms, and that in a fully-powered study, the effect of NAC on depressive symptom severity would be evident. In contrast, it is possible that depressive symptoms are an indication that adolescents are experiencing disruption in glutamatergic functioning as a result of chronic cannabis use and NAC reverses this specific neuroadaptation (Kalivas & Volkow, 2011; Roberts-Wolfe & Kalivas, 2015). Consistent with this, there is more evidence to suggest that chronic cannabis use leads to depressive symptoms than there is evidence supporting the role of cannabis use to self-medicate symptoms of depression (Degenhardt, Hall, & Lynskey, 2003; Lev-Ran et al., 2014). A number of limitations should be considered. In addition to the small sample size, overall depressive symptom severity in the sample was relatively low, making it difficult to monitor changes in depression severity over the course of treatment. For example, it is unclear whether NAC would be effective for a sample of adolescents with CUD and a comorbid major depressive disorder. Baseline BDI-II scores were numerically higher in the placebo group, but not significantly different from the NAC group. Regression to the mean may have made group differences difficult to detect. Additionally, a negative urine cannabinoid test was used as a marker of abstinence, but it can sometimes take several weeks for this biomarker to become negative, perhaps underestimating abstinence and making the temporal order of abstinence versus reduction in depressive symptoms difficult to determine. Finally, participants in both conditions received low-intensity medical clinician-delivered counseling. Though this counseling was designed to address cannabis use, it is possible that the counseling had an impact on depressive symptoms, reducing symptoms in both groups and reducing power to detect a clinically significant reduction in depressive symptom severity.

Future research is necessary to replicate whether NAC's effect in reducing cannabis use is specific to adolescents exhibiting mild depressive-like symptoms in a fully powered trial. If this is a replicable effect, this moves us closer to efforts to personalize medicine for adolescent CUD. It is also necessary to determine the mechanisms underlying this effect. A future study utilizing a sample with diagnosed major depressive disorder would allow for examination of specific symptoms of depression that may be most predictive of treatment outcomes or be most amenable to change over the course of CUD treatment. As alluded to above, NAC may be effective for adolescents who have specific neuroadaptations, such as blunted positive affect/reward (i.e., anhedonia) or increased negative affect. Since glutamatergic transmission in the nucleus accumbens, an area targeted by NAC, is associated with motivation and learning, deficits in reward learning may underlie this effect. Further, NAC was not effective in promoting cannabis cessation among adults (Gray et al., 2017), but cortical regions related to reward and behavioral control are still developing in adolescence and early adulthood (Sowell et al., 2003; Squeglia & Gray, 2016) and this may be an ideal time to intervene. Future research should utilize laboratory and real-world assessments to determine specific CUD phenotypes that may respond to NAC and other treatments to increase our ability to predict who may be a potential responder.

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HIGHLIGHTS

- NAC did not reduce depressive symptoms among cannabis-dependent adolescents.
- NAC may be more effective for cannabis cessation among adolescents with depression.
- No evidence that NAC reduces adolescent cannabis use via a reduction in depression.

Fig. 1.

Percentage of positive urine cannabinoid tests over the course of treatment by condition and depressive symptom status using modified intent-to-treat.

Note. Depression = at least mild depressive symptoms on the BDI-II at baseline with a score at or above 14. NAC = N-Acetylcysteine, PBO = Placebo. Missing cannabinoid tests assumed to be positive. Model-adjusted odds ratio for mild depression group: 2.52 (95% CI: 0.75, 8.50) vs. low depression group: 1.17 (95% CI, 0.42, 3.31).

Table 1

Baseline demographic and substance use information.

	Total sample (N = 74)	NAC (N = 36)	Placebo (N = 38)	p-Value
Age	18.8 (SD = 1.5)	18.9 (SD = 1.4)	18.7 (SD = 1.5)	0.61
% female	28.4%	33.3%	23.7%	0.44
Race (%)				
White/Caucasian	83.4%	75.0%	89.5%	0.13
Black/African American	12.2%	13.9%	10.5%	
Other	4.4%	11.1%	0.0%	
Ethnicity (%)				
Hispanic or Latino	2.7%	2.8%	2.6%	N/A
Psychiatric Info				
Major depressive disorder	8.1%	5.6%	10.5%	0.67
Generalized anxiety disorder (past 6 months)	5.4%	2.8%	7.9%	N/A
BDI-II score	8.4 (SD = 8.5)	7.5 (SD = 7.4)	9.3 (SD = 9.4)	0.38
Elevated BDI-II score (> 13)	24.3%	22.2%	26.3%	0.79
Substance use (prior to study enrollment)				
% Positive urine Cannabinoid test at week 0	89.2%	91.7%	86.8%	0.71
Years of Cannabis use	4.1 (SD = 1.7)	4.2 (SD = 1.7)	4.0 (SD = 1.6)	0.62
Marijuana ladder score (1–10)	7.6 (SD = 1.5)	7.4 (SD = 1.6)	7.7 (SD = 1.4)	0.45

Note: Independent samples *t*-tests (continuous variables) and Fisher's Exact test (categorical variables) indicated that there were no significant differences between treatment conditions ($p < .05$). Due to small cell sizes, Fisher's Exact test was conducted comparing White/Caucasian participants to racial minority participants and no test was conducted for ethnicity or Generalized Anxiety Disorder (N/A = not applicable).

Table 2

Linear mixed model with treatment condition as a predictor of depressive symptoms.

	<i>b</i>	SE	<i>p</i> -Value
Intercept	18.57	13.22	0.16
NAC (ref = placebo) Covariates	-2.14	1.86	0.25
Treatment week	-0.16	0.07	0.04 *
Age	-0.64	0.71	0.37
Sex (ref = females)	0.10	2.15	0.96
Years of cannabis use	0.67	0.59	0.26
Baseline abstinence (ref = positive urine cannabinoid test)	-0.25	3.31	0.94

Note. Beta estimates are unstandardized. NAC = N-Acetylcysteine; ref. = reference group.

*
 $p < .05$.

Table 3

Generalized estimating equation with interaction between treatment condition and pre-treatment depressive symptoms as a predictor of positive urine cannabinoid tests during treatment.

	<i>b</i>	<i>SE</i>	<i>p</i> -Value
Intercept	0.60	2.23	0.79
NAC (ref = placebo)	0.35	0.63	0.57
BDI-II	< 0.01	0.02	0.87
NAC * BDI-II	-0.09	0.04	0.03 *
Covariates			
Treatment week	-0.11	0.03	< 0.01 *
Age	0.18	0.13	0.18
Marijuana ladder	-0.31	0.14	0.03
Baseline abstinence (ref = positive urine cannabinoid test)	-2.65	0.60	< 0.01 *

Note. Beta estimates are unstandardized. NAC = N-Acetylcysteine; ref. = reference group; BDI-II = Beck Depression Inventory Version II.

* $p < .05$.