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

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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.

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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-Δ9-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.

1. Introduction

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

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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 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 $\leq$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-Δ9-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