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Low Pretreatment Impulsivity and High Medication Adherence Increase the Odds of Abstinence in a Trial of *N*-Acetylcysteine in Adolescents with Cannabis Use Disorder

Jessica P. Bentzley, B.A., Rachel L. Tomko, M.A., Kevin M. Gray, M.D. *

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 125 Doughty Street, Suite 190, MSC861, Charleston, SC 29425, USA

A R T I C L E   I N F O

A B S T R A C T

Background: In light of recent progress toward pharmacologic interventions to treat adolescent cannabis use disorder, it is important to consider which adolescent characteristics may be associated with a favorable response to treatment. This study presents secondary analyses from a parent randomized controlled trial of *N*-acetylcysteine (NAC) in adolescents with cannabis use disorder. We hypothesized that high pretreatment impulsivity and medication non-adherence would be associated with reduced abstinence rates.
Methods: Participants were treatment-seeking adolescents ($N = 115$) who met criteria for cannabis use disorder and were assessed for pretreatment impulsivity. They received 1200 mg NAC or placebo orally twice daily for 8 weeks. An intent-to-treat analysis using a repeated-measures logistic regression model was used to relate pretreatment impulsivity (Barratt Impulsiveness Scale) and treatment group to abstinence rates, measured by urine cannabinoid tests. To explore mechanisms by which NAC may reduce cannabis use, relationships between impulsivity, adherence, and abstinence were assessed in a second statistical model using data from participants with recorded adherence and urine cannabinoid test results ($n = 54$).
Results: In the intent-to-treat analysis, low pretreatment impulsivity, NAC treatment, and negative baseline urine cannabinoid test results independently increased the odds of having negative urine cannabinoid tests during treatment (OR = 2.1, 2.3, and 5.3 respectively). In the sample of participants with adherence data ($n = 54$), adherence tripled the odds of abstinence. Notably, the effect of adherence on abstinence was only observed in the NAC treatment group. Lastly, although the highly impulsive participants had reduced rates of abstinence, highly impulsive individuals adherent to NAC treatment had increased abstinence rates compared to non-adherent individuals.
Conclusion: Low impulsivity, NAC treatment, medication adherence, and baseline negative cannabinoid testing were associated with increased rates of abstinence in adolescents seeking treatment for cannabis use disorder. Efforts to optimize pharmacotherapy adherence may be particularly crucial for highly impulsive individuals. Understanding and addressing factors, such as impulsivity and adherence, which may affect outcomes, may aid in the successful evaluation and development of potentially promising pharmacotherapies.

1. Introduction

Cannabis is the most commonly used illicit drug by adolescents in the United States, and the percentage of 12–17 year olds who perceive great risks from its frequent use is steadily decreasing (Substance Abuse and Mental Health Services Administration, 2014a). Cannabis also accounts for the majority of adolescent substance use-related treatment admissions (Substance Abuse and Mental Health Services Administration, 2014b). Effective treatment for adolescent cannabis use disorder has become especially pressing in light of the escalating use of cannabis among this age group, recent changes in legalization, and findings linking heavy cannabis use in adolescence to behavioral problems and persistent cognitive deficits into adulthood, even after cessation of use (Meier et al., 2012; Randolph, Turull, Margolis, & Tau, 2013).

Psychosocial intervention is the current mainstay in treating adolescent substance use disorders (SUDs), including cannabis use disorder. However, this modality has only modest effect sizes and has failed to yield robust abstinence outcomes, driving the search for efficacious augmentative pharmacological agents (Budney, Vandrey, & Stanger, 2010; Waldron & Turner, 2008). In light of recent promising pharmacologic interventions to treat adolescent SUDs (Gray et al., 2012), an important question to ask is: Which group of adolescents will have a favorable response to a specific type of SUD treatment?

The pursuit to identify pretreatment factors that affect SUD treatment outcomes has persisted for decades, with genetic polymorphisms,

comorbid conditions, environmental factors, and neurobehavioral traits heavily investigated (Bauer, Soares, & Nielsen, 2014; Rounds-Bryant, Kristiansen, & Hubbard, 1999). Impulsivity is a neurobehavioral trait that has been repeatedly linked to SUD predisposition, severity, and treatment outcomes (Bickel, Koffarnus, Moody, & Wilson, 2014; MacKillop et al., 2011; Perkel, Bentzley, Andrzejewski, & Martinetti, 2015). In humans, common measures of impulsivity include behavioral tasks (i.e., delayed reward discounting paradigms) and self-report measures (i.e., Barratt Impulsiveness Scale [BIS-11]). The BIS-11 is a reliable self-report measure of impulsivity (Berg, Ahluwalia, & Cropsey, 2013) with external validity such that those known to be highly impulsive (e.g., individuals with attention-deficit/hyperactivity disorder) tend to score higher on the BIS-11 (Stanford et al., 2009).

Highly impulsive individuals may represent an important subgroup for which treatment outcomes differ. There is evidence supporting impulsivity's relationship with SUD treatment non-completion and failure (Loree, Lundahl, & Ledgerwood, 2014; Stevens et al., 2014; Winhusen et al., 2013). Impulsivity has also been associated with poor treatment outcome in short-term treatment trials for smoking and cannabis use in adolescents (Krishnan-Sarin et al., 2007; Stanger et al., 2012). Furthermore, impulsivity may also be related to non-adherence in those seeking treatment for SUDs. Non-adherence may contribute to sub-optimal therapeutic response and confounding of results in clinical trials, greatly impacting pharmacotherapy development and translation into clinical use (Vrijens & Urquhart, 2014). A recent study found that young adult heavy drinkers with co-occurring cannabis use exhibit more non-planning impulsivity and medication non-adherence than heavy drinkers without co-occurring cannabis use (Peters et al., 2012). However, adherence to medications may have multiple determinants (Kardas, Lewek, & Matyjaszczyk, 2013) and may be unassociated with impulsivity in those with psychotic or mood disorders (Liraud & Verdoux, 2001).

N-Acetylcysteine (NAC) is a promising pharmacological agent being investigated for adolescent cannabis use disorder treatment (Gray et al., 2012). It is presently unknown whether NAC has different efficacy in highly impulsive individuals seeking treatment for cannabis use disorder. In a sample of individuals with cocaine use disorder, Schmaal, Veltman, Nederveen, van den Brink, and Goudriaan (2012) found NAC to be more effective at reducing dorsal anterior cingulate cortex (dACC) glutamate levels in individuals with high levels of self-reported impulsivity assessed by BIS-11. Based on these findings, highly impulsive adolescents seeking treatment for cannabis use disorder may respond differently to NAC than adolescents with lower impulsivity scores.

This study presents secondary analyses from an intent-to-treat parent randomized controlled trial of NAC in adolescents with cannabis use disorder (Gray et al., 2012). The goals of the current report were to determine the effects of impulsivity and adherence on abstinence rates in adolescents enrolled in a placebo-controlled trial of NAC for cannabis use disorder. We hypothesized that high pretreatment impulsivity (HI) and non-adherence would be associated with reduced abstinence rates.

2. Materials and methods

2.1. Participants

Participants were 115 treatment-seeking adolescents, aged 15–21 (*mean* = 18.9 ± 1.5 years) who met criteria for cannabis use disorder (DSM-IV cannabis dependence), were enrolled in the parent trial (Gray et al., 2012), and had pretreatment impulsivity scores. Exclusion criteria included allergy to NAC, pregnancy or lactation, use of carbamazepine or nitroglycerin within 14 days of enrollment, enrollment in additional substance abuse treatment, DSM-IV substance dependence other than cannabis or tobacco, and significant medical or psychiatric illness that may increase risk in the judgment of the study physician. Participants were assessed at pretreatment for eligibility (which included a history and physical examination) and eligible individuals were

then randomized to receive 1200 mg NAC or placebo orally twice daily for 8 weeks. All participants received a contingency management intervention and weekly brief (≤10 minute) cessation counseling. Further details of the parent trial are described elsewhere (Gray et al., 2012). All participants provided informed consent and parental consent was also obtained if participants were <18 years of age. The study procedures were approved by the university institutional review board and were in accord with the Helsinki Declaration of 1975.

2.2. Measurements

2.2.1. Abstinence

Urine cannabinoid testing at baseline and during weekly clinic visits served as the primary biological measure of cannabis use. Tests were analyzed as positive or negative (cutoff 50 ng/mL, U.S. Screening Source, Inc., Louisville).

2.2.2. Impulsivity

The 30-item self-report Barratt Impulsiveness Scale, BIS-11 (Barratt, 1959; Patton & Stanford, 1995) was used to assess global impulsivity (Patton & Stanford, 1995; Stanford et al., 2009). In a review, Stanford et al. (2009) reported that the mean BIS-11 score for adults is 62.3 ± 10, and BIS-11 scores above 72 are highly impulsive. The mean BIS-11 total score in our sample at pretreatment was 67.5 ± 10.1 and the median was 66. We performed a median split of pretreatment impulsivity scores within our sample to designate pretreatment high (HI) and low impulsivity (LI) groups, an approach with ample precedence in the literature (Kiluk, Nich, & Carroll, 2010; Papachristou, Nederkoorn, Havermans, Horst, & Jansen, 2011).

2.2.3. Adherence

Medication adherence was calculated as number of capsules taken during each week of treatment (determined by blister pack pill counts reviewed by research staff) divided by number of capsules prescribed to obtain ratios (0.0–1.0). Participants with ratios of 1.0 were considered adherent and those with ratios of <1.0 were considered non-adherent for analysis purposes. Medication adherence data at one or more study visits were available for 54 participants.

2.3. Statistical analysis

Primary aims of this report included assessing how pretreatment impulsivity and adherence may be related to abstinence outcomes. For the primary analysis, an intent-to-treat (ITT) approach including all 115 randomized participants with baseline impulsivity data was used such that all participants who were lost to follow-up or were absent from visits were coded as having a positive urine cannabinoid test at every missed visit. However, when treatment adherence was included in the analysis, only individuals with adherence data and recorded urine cannabinoid test results were included.

Demographic and clinical characteristics were tabulated for all participants and compared between groups prior to statistical analyses. Standard descriptive statistics were used to summarize the demographic and clinical data. Differences in pretreatment characteristics were calculated using chi square tests, the Fisher exact text, t test or Wilcoxon rank sum test, as appropriate.

The primary outcome measure was the odds of negative weekly urine cannabinoid test results during treatment. Repeated-measures logistic regression models using the methods of generalized estimating equations were used to assess the effects of pretreatment impulsivity on urine cannabinoid test results during active treatment. All study models were adjusted for baseline urine cannabinoid test results and assessed for possible confounding of baseline demographic and clinical characteristics. Chi square, Wilcoxon rank sum, and t tests were used to detect variables that differed by pretreatment impulsivity grouping (covariates were included in the model if $p < 0.10$), and possible predictors