Addictive Behaviors 63 (2016) 172–177

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

Alcohol use during a trial of *N*-acetylcysteine for adolescent marijuana cessation

Lindsay M. Squeglia Ph.D. [a], Nathaniel L. Baker M.S. [b], Erin A. McClure Ph.D. [a], Rachel L. Tomko Ph.D. [a], Vitria Adisetiyo Ph.D. [c], Kevin M. Gray M.D. [a,*]

[a] Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Addiction Sciences Division, Charleston, SC, USA
[b] Medical University of South Carolina, Department of Public Health Sciences, Charleston, SC, USA
[c] Medical University of South Carolina, Department of Radiology and Radiological Science, Charleston, SC, USA

HIGHLIGHTS

- *N*-acetylcysteine (NAC) is a promising target medication for treating addiction.
- In the NAC-treated group, less marijuana use was associated with less alcohol use.
- This relationship was not found in the placebo group.
- More research is warranted to understand the effect of NAC on adolescent alcohol use.

ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 1 July 2016
Accepted 3 August 2016
Available online 4 August 2016

Keywords:
Alcohol
Addiction
N-acetyl cysteine
Randomized controlled trial
Marijuana cessation

ABSTRACT

Aims: Current adolescent alcohol treatments have modest effects and high relapse rates. Evaluation of novel pharmacotherapy treatment is warranted. *N*-acetylcysteine (NAC), an over-the-counter antioxidant supplement with glutamatergic properties, is a promising treatment for marijuana cessation in adolescents; however, its effects on adolescent drinking have not been examined. To that end, this secondary analysis evaluated: (1) the effect of NAC vs. placebo on alcohol use over an eight-week adolescent marijuana cessation trial and (2) the role of marijuana cessation and reduction on subsequent alcohol use.
Methods: Marijuana-dependent adolescents (ages 15–21; $N = 116$) interested in treatment were randomized to NAC 1200 mg or matched placebo twice daily for eight weeks. Participants were not required to be alcohol users or interested in alcohol cessation to qualify.
Results: There were no demographic or baseline alcohol use differences between participants randomized to NAC vs. placebo ($ps > 0.05$). Of the 89 participants returning for ≥one visit following randomization, 77 reported ≥one alcoholic drink in the 30 days prior to study entry and averaged 1.3 (SD = 1.4) binge drinking days per week. During treatment, less marijuana use (measured via urine cannabinoid levels) was associated with less alcohol use in the NAC-treated group but not in the placebo-treated group ($p = 0.016$).
Conclusions: There was no evidence of compensatory alcohol use during marijuana treatment. In fact, in the NAC group, lower levels of marijuana use were associated with less alcohol use, suggesting NAC effects may generalize to other substances and could be useful in decreasing adolescent alcohol use. NAC trials specifically focused on alcohol-using adolescents are warranted.

1. Introduction

Alcohol and marijuana are the two most commonly used substances during adolescence and are often used concurrently (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2015). Several adverse outcomes are associated with adolescent alcohol and marijuana use, including poorer psychosocial (Miller, Naimi, Brewer, & Jones, 2007), cognitive (Jacobus et al., 2015; Meier et al., 2012; Nguyen-Louie et al., 2015; Squeglia & Gray, 2016; Squeglia, Spadoni, Infante, Myers, & Tapert, 2009), and educational outcomes (Latvala et al., 2014). Unfortunately, few adolescent substance use treatment options exist and current efforts have only been modestly effective (Jensen et al., 2011; Tripodi, Bender, Litschge, & Vaughn, 2010; Vandrey & Haney, 2009), with some studies suggesting

* Corresponding author at: Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, 67 President Street, MSC861, Charleston, SC 29425, USA.
E-mail address: graykm@musc.edu (K.M. Gray).

http://dx.doi.org/10.1016/j.addbeh.2016.08.001
0306-4603/

up to 86% of youth return to alcohol or drug use within 12 months following treatment (Brown, Gleghorn, Schuckit, Myers, & Mott, 1996; Winters, Stinchfield, Opland, Weller, & Latimer, 2000).

Although several medications have been efficacious in treating adult alcohol dependence, pharmacotherapy research focused on adolescent alcohol use has been sparse (Miranda et al., 2014). This limits treatment options, as safety and efficacy of medications for adolescents cannot be inferred from adult studies (Bridge et al., 2007). Evaluation of alternative and more efficacious treatments is warranted in adolescents, particularly in regards to interventions that effectively reduce both alcohol and marijuana use given their considerable co-use.

Based on preclinical findings, glutamate has emerged as a potential pharmacotherapeutic target in the treatment of addictions (Kalivas, 2009; Kalivas & Volkow, 2011). *N*-acetylcysteine (NAC) is an over-the-counter antioxidant supplement that is believed to restore glutamate homeostasis disrupted by addiction (McClure, Gipson, Malcolm, Kalivas, & Gray, 2014). Part of the appeal of NAC as a treatment for youth with substance use disorders is its long-established safety and tolerability record, with pediatric and adult FDA approval since 1963 (Gray, Watson, Carpenter, & Larowe, 2010). NAC has shown potential efficacy for promoting abstinence from a number of drugs, including marijuana (Gray et al., 2012), cocaine (LaRowe et al., 2013), methamphetamines (Grant, Odlaug, & Kim, 2010), and nicotine (Froeliger et al., 2015; Knackstedt et al., 2009; Van Schooten et al., 2002). In a double-blind placebo controlled study of marijuana-dependent adolescents, youth randomized to receive NAC had more than double the odds of negative urine cannabinoid tests during treatment compared to the placebo group (Gray et al., 2012). Secondary analyses of cigarette smokers revealed that changes in marijuana use during treatment did not affect cigarette smoking (McClure, Baker, & Gray, 2014). Despite this, there is some evidence of a "substitution effect", wherein marijuana reduction or abstinence may increase the use of other substances of abuse (Chaloupka & Laixuthai, 1997; Copersino et al., 2006; Schaub, Gmel, Annaheim, Mueller, & Schwappach, 2010). Identifying medications that can reduce both alcohol and marijuana use are ideal, given the high rates of co-use of these substances during adolescence.

While no published clinical trials to date have examined the effect of NAC on alcohol use, recent preclinical findings suggests that NAC may effectively decrease alcohol consumption. Alcohol-consuming rats who were administered NAC inhibited alcohol intake up to 70% compared to saline-treated rats ($p < 0.0001$). The effect of treatment on alcohol consumption was not transient and persisted for four days post-treatment, showing that NAC administration generates a neurochemical effect extending well past its one hour half-life in rats (Quintanilla et al., 2016). Taken together with previous promising findings in marijuana dependent youth (Gray et al., 2012), exploration of this medication in reducing adolescent alcohol use is warranted. The purpose of this secondary analysis was to explore the effect of NAC on alcohol use during a marijuana cessation trial (Gray et al., 2012), thereby determining if this could be a potentially efficacious target medication for adolescent alcohol use. Specifically, this study evaluated: (1) the effect of NAC vs. placebo on co-occurring alcohol use over an eight-week adolescent marijuana treatment trial and (2) the role of marijuana use (reductions and/or abstinence) on subsequent alcohol use. This is the first exploratory analysis from a randomized treatment trial examining the effects of NAC on adolescent alcohol use and provides a unique opportunity to explore alcohol use during NAC-assisted marijuana cessation.

2. Methods

2.1. Participants

Participants were obtained from a marijuana cessation treatment study ($N = 116$) (Gray et al., 2012). All participants were between ages 15 and 21, met criteria for marijuana dependence, used marijuana regularly (≥3 days/week), and were interested in marijuana cessation treatment. Participants were excluded if they were enrolled in substance abuse treatment, had comorbid substance dependence (other than nicotine), had any unstable psychiatric or medical issue, were pregnant, were taking carbamazepine or nitroglycerine, or had a history of adverse reaction to NAC. Recruitment occurred primarily through community media outlets and clinical referrals. As this was a marijuana cessation trial, participants were not required to be alcohol users or interested in alcohol cessation to qualify and were excluded from study participation if they met criteria for alcohol dependence but not abuse. Further description of the sample and marijuana abstinence outcomes have been previously reported (Gray et al., 2012).

2.2. Procedures

Participants were randomized to receive either active treatment (NAC, 1200 mg twice daily) or matched placebo. The study treatment lasted for eight weeks, during which participants were required to attend weekly study visits. One follow-up visit occurred at 12 weeks. In addition to study medication, contingency management procedures were used to reinforce attendance at study visits and abstinence from marijuana throughout the eight-week intervention. Brief marijuana cessation counseling was provided weekly during the in-person study visit. No psychosocial treatment targeted alcohol use.

2.3. Measures

2.3.1. Substance use

During the eight-week treatment phase, alcohol, marijuana, cigarette, and other drug use was recorded via daily diaries. Timeline Follow-back (TLFB) methods were used to measure substance use during the 30 days prior to study enrollment and through the follow-up period (Sobell & Sobell, 1992). Standard drinks were calculated based on NIAAA guidelines (http://rethinkingdrinking.niaaa.nih.gov/tools/Calculators/drink-size-calculator.aspx). Urine cannabinoid testing at baseline, during weekly study visits, and at post-treatment follow-up, was conducted as the primary biological measure of marijuana use.

2.3.2. Psychopathology

The Mini International Neuropsychiatric Interview (MINI), or MINI-KID for participants under age 18, ascertained current or lifetime history of the major DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998; Sheehan et al., 2010). None of the participants met criteria for alcohol dependence.

2.4. Outcomes

Total number of standard drinks consumed, number of drinking days, and number of binge drinking days (four or more drinks for women and five or more drinks for men) were calculated at each weekly study visit as the primary alcohol use outcomes. When missing visits occurred between attended visits, the TLFB summary alcohol use data for the next attended visit were calculated back to the last previously attended visit. This allowed use of all of the collected TLFB data even in the presence of missing visits. To account for the variable time frame of data collection between attended visits (including variable time frame of contingency management and cessation counseling), all models also adjusted for the number of days since the last attended visit. Out of the 89 participants included in this analysis, there were 22 informative visits with missing data (TLFB data available at the following visit); eight were from participants randomized to the NAC group and 14 to placebo. The mean number of days between attended visits when a visit was missing was 14.0 (SD = 2.6) for these 22 occurrences [NAC = 13.8 (1.4); placebo = 14.1 (3.2)].