Drug and Alcohol Dependence 185 (2018) 17–22

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

The effect of N-acetylcysteine on alcohol use during a cannabis cessation trial

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ARTICLE INFO

Keywords:
Alcohol
Cannabis
Marijuana
N-acetylcysteine
Medication
Treatment

ABSTRACT

Background: Individuals with alcohol use disorder (AUD) do not always respond to currently available treatments, and evaluation of new candidate pharmacotherapies is indicated. N-acetylcysteine (NAC), an over-the-counter supplement, has shown promise in treating a variety of substance use disorders, but little research has evaluated its merits as a treatment for AUD. This secondary analysis from the National Drug Abuse Treatment Clinical Trials Network examined the effects of NAC *versus* placebo on alcohol use among participants with cannabis use disorder (CUD) enrolled in a 12-week, multi-site cannabis cessation trial.

Methods: Participants (N = 302, ages 18–50) were randomized to double-blind NAC (1200 mg, twice daily) or placebo. Neither alcohol use nor desire for alcohol cessation were requirements for participation. Participants that returned for at least one treatment visit and had recorded alcohol use data (*i.e.*, total drinks per week, drinking days per week, and binge drinking days per week) were included in the analysis (n = 277).

Results: Compared to the placebo group, participants in the NAC group had increased odds of between-visit alcohol abstinence [OR = 1.37; 95% CI = 1.06–1.78; $p = 0.019$], fewer drinks per week [RR = 0.67; 95% CI = 0.48–0.99; $p = 0.045$], and fewer drinking days per week [RR = 0.69; 95% CI = 0.51–0.92; $p = 0.014$]. Changes in concurrent cannabis use amounts were not correlated to any of the alcohol use variables.

Discussion: These findings indicate that NAC may be effective at reducing consumption of alcohol by ~30% among treatment-seeking adults with CUD, suggesting a need for further trials focused on the effects of NAC on alcohol consumption among individuals seeking treatment for AUD.

1. Introduction

N-acetylcysteine (NAC) is an over-the-counter antioxidant with potential promise as a treatment option for substance use disorders. NAC targets glutamate transporters affected by substance use (McClure et al., 2014a,b,c; Roberts-Wolfe and Kalivas, 2015), which have been shown to play a role in craving and drug seeking (Kalivas, 2009; Kalivas and Volkow, 2011). Previous trials have demonstrated the potential of NAC in treating substance use disorders, including tobacco (Froeliger et al., 2015; Knackstedt et al., 2009; Van Schooten et al., 2002), cannabis (Gray et al., 2012), and cocaine (LaRowe et al., 2007). NAC may also reduce compulsive behaviors such as pathological gambling (Grant et al., 2007), trichotillomania (Grant et al., 2009), and skin-picking (Grant et al., 2016). Part of the appeal of NAC is its safety and tolerability. NAC has a long history of clinical use as a treatment for acetaminophen overdose, has been FDA approved for adult and pediatric medical use since 1963, and has an established record of being safe and well tolerated (Grandjean et al., 2000; Gray et al., 2010; Rhodes and Braakhuis, 2017).

To our knowledge, there are no published, large-scale clinical trials examining NAC as a treatment option for adults with alcohol use disorder (AUD), but animal, adolescent, and pilot adult trials have been promising. In a preclinical trial with NAC, alcohol-consuming rats showed NAC-treated rats reduced their consumption of alcohol by up to 70% compared to rats treated with saline ($p < 0.0001$)(Quintanilla et al., 2016). Reduced alcohol consumption persisted for up to four days, suggesting enduring effects of NAC on glutamate transmission. A subsequent preclinical trial studying the effects of NAC on alcohol self-administration in rats showed an 81% decrease in alcohol consumption for the NAC-treated group compared to placebo, as well as reduced rates of reacquisition in rats that had been abstinent from alcohol for 17 days (Lebourgeois et al., 2017).

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https://doi.org/10.1016/j.drugalcdep.2017.12.005
Received 19 October 2017; Received in revised form 27 November 2017; Accepted 10 December 2017
Available online 01 February 2018
0376-8716/

A pilot clinical trial examined the efficacy of NAC for reduction of alcohol and drug craving and posttraumatic stress among Veterans (N = 35) with comorbid substance use disorder and trauma (Back et al., 2016). Though an AUD diagnosis was not required for inclusion, 82% of the sample met criteria for an AUD. NAC significantly reduced amount and frequency of alcohol and drug craving relative to the placebo group. However, possibly due to low overall substance use and required initial abstinence prior to treatment start, no group differences in substance use post-treatment were observed. This study suggests that reductions in alcohol use observed in animal models may translate to humans. However, larger studies are needed to determine the effect of NAC on alcohol consumption specifically.

An earlier secondary analysis (Squeglia et al., 2016) examined alcohol use data from a NAC treatment trial for cannabis use disorder (CUD) among adolescents ages 15–21 (Gray et al., 2012). In the parent trial, 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). In the secondary analyses examining alcohol use within the parent trial, there was a significant relationship between lowering levels of cannabis use and alcohol use in the NAC-treated group, but not in the placebo group. This was encouraging, as it suggested NAC was able to reduce both alcohol and cannabis use in the treatment group. No "substitution effect" was found, wherein decreased use of one substance correlates with increased use of another (Chaloupka and Laixuthai, 1997; Copersino et al., 2006; Schaub et al., 2010).

The goal of this secondary analysis was to examine the effect of NAC on alcohol use to further gauge the potential of NAC to treat AUD based on promising preclinical (Lebourgeois et al., 2017; Quintanilla et al., 2016) and clinical (Back et al., 2016) findings. The parent study was a twelve-week trial that focused on changes in cannabis use in adults seeking treatment for CUD when treated with NAC compared to placebo (Gray et al., 2017). Unlike the adolescent trial (Gray et al., 2012), the adult study did not find NAC to be effective in reducing cannabis use (Gray et al., 2017). The current study evaluated: (1) the effect of NAC *versus* placebo on alcohol use over a twelve-week CUD treatment trial and (2) the role of cannabis 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 specifically on adult alcohol use and provides a unique opportunity to explore alcohol use during NAC-assisted CUD treatment.

2. Methods

2.1. Participants

The parent study participants were 302 adults ages 18–50 who were seeking treatment for cannabis dependence. Participants were recruited from a multisite clinical trial sponsored by the National Drug Abuse Treatment Clinical Trials Network (NIDA CTN) using community/media advertisements (Clinicaltrials.gov: NCT01675661) (Gray et al., 2017). Inclusion criteria included: a positive urine cannabinoid test at screening, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) diagnosis of cannabis dependence, interest in treatment for cannabis dependence, and, if female, agreement to use birth control. Exclusion criteria included: DSM-IV-TR substance dependence other than cannabis or tobacco, a urine drug test positive for non-cannabinoid substances, synthetic cannabinoid use in the past 30-days, current use of NAC, allergy to NAC, current treatment for substance use, asthma, pregnant or breastfeeding (if female), and any uncontrolled medical or psychiatric illness. The average age of participants was 30 (SD = 9), and the sample was 72% male, 58% White, 28% Black or African American (see Table 1). On average, participants were using cannabis almost daily. As this was a cannabis 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 DSM-IV alcohol dependence. Of the 302 participants, 277 had at least one study visit available for analysis; 207 reported alcohol use in the past 30-days. On average, participants were drinking alcohol once per week and binge drinking less than once per month.

2.2. Procedures and measures

Detailed procedures and main outcomes from the primary clinical trial have been previously published (Gray et al., 2017; McClure et al., 2014a,b,c). Participants received abstinence-based contingency management for cannabis use and were randomized to receive either NAC (1200 mg two times per day) or matched placebo for a 12-week duration. No psychosocial treatment targeted alcohol use and no specific instruction to reduce alcohol use was provided. Participants self-reported their substance use and provided urine samples for quantitative cannabinoid testing at an initial screening visit, a pre-treatment visit, weekly study visits, and at a one-month follow-up visit.

2.3. Measures

2.3.1. Substance use

Quantity and frequency of past 30-day alcohol and cannabis use were assessed at the initial screening visit *via* the Timeline Follow-Back (TLFB; (Sobell and Sobell, 1992). For alcohol use, participants reported total standard drinks (based on NIAAA guidelines (http://rethinkingdrinking.niaaa.nih.gov/tools/Calculators/drink-size-calculator.aspx) consumed each day. For cannabis, participants reported whether they had used cannabis (yes/no) and the number of joints, blunts, pipes, bowls, vaporizers, spliffs, edibles, or other administration methods used. Using dried motherwort as a proxy for cannabis, participants were asked to weigh on a scale the amount of cannabis they typically used for each administration method (*e.g.*, joints, blunts) in the previous 30-days. This is consistent with a scale-based method used by Mariani and colleagues to estimate grams of cannabis use, with the exception that oregano was used as their proxy substance (Mariani et al., 2011). At weekly and follow-up visits, participants reported daily cannabis use in between visits and the number of joints/blunts/*etc*. used on days which cannabis use was endorsed. Weekly grams of cannabis used were computed by multiplying the number of joints by the typical grams per joint, number of blunts by typical grams per blunt, and so forth for each method endorsed, and summing the total across methods.

2.3.2. Psychopathology

The Mini International Neuropsychiatric Interview 6.0 (MINI) 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.

3. Outcomes

Total standard drinks consumed, drinking days, and binge drinking days (4 or more drinks for women and 5 or more drinks for men) were calculated at each weekly study visit as the primary alcohol use outcomes. When missing visit data occurred *between* attended visits, the TLFB summary alcohol use data for the next attended visit were calculated back to the last previously attended visit (3.6% of study visits data). This allowed for the collection of continuous TLFB data even in the presence of missing visit data. To account for the possible variable time frame of data collection between attended visits, all statistical models adjusted for the number of days since the last attended visit. Out of the 302 participants included in this analysis, there were 277 with at least one study visit available for analysis. The average number of attended study visits in this cohort was 10 (SD = 3; Range 1–12) and 61% (170) attended all 12 treatment visits [Placebo 63% (n = 85/135) *vs.* NAC 60% (n = 85/142); $\chi^2_1 = 0.3$, p = 0.596].