Addictive Behaviors 38 (2013) 1788–1791

Contents lists available at SciVerse ScienceDirect

Addictive Behaviors

Short Communication

Marijuana craving trajectories in an adolescent marijuana cessation pharmacotherapy trial

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HIGHLIGHTS

- Craving was measured using the short form of the Marijuana Craving Questionnaire.
- Total MCQ scores decreased significantly during the trial among the total sample.
- Total MCQ scores not decrease differentially between the NAC and placebo groups.
- NAC's cessation effects may be mediated by effects other than marijuana craving.

ARTICLE INFO

Keywords:
Marijuana
Craving
N-acetylcysteine
Adolescents

ABSTRACT

Marijuana is the most widely used illicit substance among youths and recent epidemiological data indicate that rates of marijuana use are on the rise. The purpose of this study was to examine marijuana craving trajectories among adolescents in an eight-week, placebo-controlled pharmacotherapy trial targeting marijuana cessation. All participants received contingency management and cessation counseling, and were randomized to either *N*-acetylcysteine (1200 mg NAC twice daily; $n = 45$) or placebo ($n = 44$). Craving for marijuana was measured using the short-form of the Marijuana Craving Questionnaire (MCQ). Results demonstrated a significant decrease in MCQ scores over time for the total sample, but no significant differential change in scores between the NAC and placebo groups. This lack of significant difference is in the setting of NAC participants submitting significantly more negative urine cannabinoid tests as compared to placebo participants. This suggests that cessation effects associated with NAC may be mediated by effects other than marijuana craving.

1. Introduction

Marijuana is the most widely used illicit substance among youths, and its use has steadily risen in recent years. The Monitoring the Future survey indicates that 6.6% of high school seniors use marijuana daily, the highest rate in the last 30 years (Johnston, O'Malley, Bachman, & Schulenberg, 2012). Marijuana use in adolescents is associated with fewer completed years of education as well as an increased risk of affective, anxiety, and psychotic disorders in vulnerable individuals (Casadio, Fernandes, Murray, & Di Forti, 2011). Given the increase in use as well as the detrimental effects of marijuana use during adolescence, a greater understanding of ideal treatments and factors that affect treatment is needed.

Craving is one of the key elements of addiction and is, therefore, one of the primary targets of treatment (Coffey et al., 2002; Gray, LaRowe, & Upadhyaya, 2008; McRae, Hedden, Malcolm, Carter, & Brady, 2007). A study by McRae and colleagues of treatment-seeking individuals found that individuals with marijuana dependence ($n = 50$) reported higher craving than individuals with cocaine dependence ($n = 153$) (McRae et al., 2007). Little is known about the trajectory of marijuana craving among adolescents receiving cessation treatment, and whether psychosocial or pharmacological therapies might specifically influence craving.

Preclinical evidence suggests that NAC reduces drug seeking and relapse via glutamate modulation in the nucleus accumbens (Baker et al., 2003; Kalivas, LaLumiere, Knackstedt, & Shen, 2009; Madayag et al., 2007). Similarly, preliminary clinical evidence suggests that NAC may play a therapeutic role in the treatment of substance use disorders (Gray et al., 2012; Knackstedt et al., 2009; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007). Given the salience of craving in addiction, it is possible that the effects of NAC are due, at least in part, to a reduction in craving. In two studies by LaRowe and colleagues, NAC reduced self-reported craving in individuals seeking treatment for cocaine dependence (LaRowe et al., 2006, 2007).

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0306-4603/$ – see front matter
http://dx.doi.org/10.1016/j.addbeh.2012.11.003

The purpose of the current study was to evaluate the trajectory of marijuana craving among adolescents participating in a marijuana cessation trial. A recently completed randomized controlled trial of *N*-acetylcysteine (NAC), added to brief weekly cessation counseling and a contingency management intervention, provided the opportunity to monitor self-reported marijuana craving over the course of treatment (Gray et al., 2012).

2. Materials and methods

2.1. Participants

Participants were 89 treatment-seeking adolescents, aged 15–21, who met DSM-IV criteria for cannabis dependence, enrolled in the parent trial, and completed sufficient questionnaires for the present study's objective (see Section 2.2). 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, substance dependence other than cannabis or nicotine, and significant medical or psychiatric illness that may increase risk in the judgment of the study physician. All participants received a contingency management intervention and weekly brief ($\leq$10 minute) cessation counseling. Participants were assessed at baseline for eligibility (which included a history and physical examination) and eligible individuals were then randomized to receive 1200 mg NAC orally twice daily or placebo for 8 weeks. Further details of the parent trial are described elsewhere (Gray et al., 2012).

2.2. Measurements

Craving was assessed with the 12-item, short form of the Marijuana Craving Questionnaire (MCQ). The MCQ has been shown to be a reliable and valid form for measuring craving (Heishman, Singleton, & Liguori, 2001; Heishman et al., 2009). The short form of the MCQ includes 12 items that are divided into four factors: (1) compulsivity, (2) emotionality, (3) expectancy, and (4) purposefulness. The four factors are defined as follows: (1) an inability to control marijuana use; (2) use of marijuana in anticipation of relief from withdrawal or negative mood; (3) anticipation of positive outcomes from smoking marijuana; and (4) intention and planning to use marijuana for positive outcomes (Heishman et al., 2009). Participants rate the items using a 7-item Likert scale ranging from strongly disagree to strongly agree, and the total score ranges from 12 to 84. Participants completed the MCQ at baseline and at each weekly visit. Out of those enrolled and randomized in the parent trial (n = 116), 89 participants (77%) completed the MCQ at baseline and at least once during the 8-week treatment phase. These participants were included in the current study.

2.3. Statistical analysis

The primary aim of interest was to test for differential treatment effects on marijuana craving as measured by the MCQ between participants receiving *N*-acetylcysteine versus placebo. Prior to analyses, demographic and clinical characteristics were tabulated for all participants and compared between groups. Standard descriptive statistics were used to summarize the demographic and clinical data. Treatment group differences for baseline continuous variables were assessed using a Wilcoxon rank sum test, and for categorical characteristics, a Pearson's chi square test was used. Demographic, clinical, and marijuana use characteristics were also examined for univariate predictive relationships with MCQ total score response, as well as possible confounding effects within the primary treatment analysis models.

Initial models were fit using the treatment assignment, baseline MCQ score, time, and the interaction of treatment and time. As the primary aim of the parent study was to test the effects of NAC on abstinence from marijuana use, all models were also adjusted for the time varying effect of the weekly urine cannabis testing results. Additional models were developed using an expanded range of possible covariates based on baseline imbalances between treatment groups ($p<0.10$) and covariates showing evidence as prognostic factors of the MCQ total score ($p<0.20$). To test the primary hypothesis of differential treatment effects on the MCQ total score during the study, a repeated measures analysis of variance (ANOVA) framework was used and model estimation was constructed in SAS Proc Mixed. Restricted maximum likelihood (REML; Patterson & Thompson, 1971) methods were used to estimate the fixed effects and variance components in the presence of unbalanced data. Additional analyses examined the percent change in MCQ scores from baseline to the last available visit during treatment. In addition to the MCQ total score, the four factor components of the MCQ were also tested. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, 2011). Significance for all planned comparisons was set at a 2-sided *p*-value of 0.05 and no correction for multiple testing was applied to reported *p*-values.

3. Results

Of the 116 participants who were randomized in the parent trial, 89 (77%) completed the MCQ at baseline and at least once during subsequent visits and were included in the analysis. There were no significant differences in age, gender, or race between the treatment groups (all $p>0.20$). Similarly, cannabis use characteristics and the number of weekly treatment visits attended during treatment did not significantly differ by group (all $p>0.20$). Significantly more participants in the placebo group were diagnosed with current or past psychiatric disorders (NAC = 4.4% vs. placebo = 18.2%; $p=0.05$); this was thus adjusted for in the analyses. Univariate predictive analyses showed that age, gender, race, and the number of days using marijuana in the previous 30 days were also possibly predictive of MCQ total score over time.

Mean total MCQ scores at baseline were not significantly different between the placebo and NAC groups (mean $\pm$ SEM: 48.4 ± 1.9 vs. 47.9 ± 1.8; $p=0.84$). Although there was a significant decrease in MCQ scores over the course of the treatment, there was no significant differential change between the NAC and placebo groups ($F_{8,524}=0.61$, $p=0.77$; Fig. 1). Individual analysis of the MCQ subscales revealed similar findings; the emotionality, expectancy, and purposefulness subscales all showed a significant decrease during the treatment phase (all $p<0.02$) while the compulsion subscale showed no significant change during the treatment phase ($p=0.61$). Similar to the MCQ total score, no differences were seen in the four subscale scores between groups over the course of the treatment portion of the study. Following adjustment for additional prognostic covariates (age, gender, race, marijuana use history) and the baseline imbalance in psychiatric diagnosis, the MCQ total score as well as the subscale scores continued to show no difference between the NAC and placebo groups over time ($F_{8,524}=0.59$, $p=0.78$; Fig. 1).

In addition to the *baseline* MCQ score ($p<0.001$), both time (visit) and weekly urine cannabinoid test results were significantly associated with the MCQ scores over time. Participants with negative urine cannabinoid tests were more likely to have lower MCQ scores measured at the same visit than those with positive tests ($\Delta = 3.2 \pm 1.0$, $p=0.003$). None of the other covariates attained statistical significance in the fully adjusted model.

To account for possible ceiling and floor effects of marijuana craving, the percent change from the baseline visit to the last treatment visit as well as the follow-up visit was assessed between the NAC and placebo groups. Fig. 2 shows the percent change from baseline to the end of treatment for the 89 participants with at least one