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***N*-Acetylcysteine (NAC) in Young Marijuana Users: An Open-Label Pilot Study**

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Cannabis use disorders (abuse or dependence) are present in 3.6% of adolescents and 5.9% of young adults, compared with only 0.7% of adults over the age of 25 (1). While a small number of large-scale pharmacotherapy clinical trials targeting cannabis dependence have been undertaken, none have demonstrated significant medication effects on marijuana use and none have focused on young marijuana users (2,3). As such, investigation of novel pharmacotherapeutic agents targeting cannabis dependence in young people is an important focus for research.

The neurotransmitter glutamate has emerged as a potential target in the treatment of addictions, including cannabis dependence (4). Within animal studies, the anti-oxidant *N*-acetylcysteine (NAC) has been shown to reverse drug-induced down-regulation of the cystine-glutamate exchanger (5), which presumably allows for regulation of glutamate release, reducing compulsive drug-seeking behaviors. Consistent with this, preliminary studies have demonstrated significant reductions in cocaine craving (6) and cigarette use (7) during NAC treatment. Taken together, these findings implicate NAC as a potential treatment for addictive disorders, including cannabis dependence. Thus, the purpose of this open-label study was to gather tolerability and preliminary efficacy data for NAC in the treatment of cannabis dependence in young people.

Participants were 24 cannabis dependent males ($n = 18$) and females ($n = 6$), age range 18–21 (mean age $19 \pm SE 0.16$) interested in cutting down their marijuana use (i.e., without requirements to quit). Twenty-two were White, one African-American, and one Hispanic. They were required to be medically and psychiatrically stable, have no allergy or intolerance to NAC, have no history of seizures or asthma, and be free of medications known to interact with NAC.

Participants were enrolled in a four-week open-label trial of NAC 1200 mg twice daily. A baseline visit was followed by four weekly visits (Weeks 1–4) to assess tolerability and clinical effects. Medication was discontinued at the final (Week 4) visit. Participants were encouraged

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to gradually reduce marijuana use, but no formal cessation instructions or psychosocial treatments were provided.

As assessed by medication adherence logs and weekly pill counts, participants took $82.6\% \pm \text{SE } 2.6\%$ of the scheduled NAC doses during the medication trial. Weekly assessments of adverse events (coded as mild, moderate, or severe) revealed that NAC was generally well tolerated. Fifteen participants (63%) reported at least one adverse event, but all were mild to moderate, and none led to discontinuation of medication. The most common adverse events were abdominal discomfort (5/24), muscle pains/aches (5/24), insomnia (4/24), headache (3/24), nasal congestion/runny nose (3/24), nausea (3/24), weight decrease (3/24), restlessness (3/24), and dizziness (3/24).

Marijuana use during the month preceding participation was quantified at the baseline visit using timeline follow-back procedures. From the initial assessment visit forward, daily marijuana use diaries were completed by participants and turned in at weekly visits. During the month preceding the trial, participants reported using marijuana $6.1 \pm \text{SE } 0.24$ days per week. A generalized estimating equation (GEE) analysis revealed a reduction in reported days per week of marijuana use over the course of NAC treatment (overall time effect: $p = 0.003$). Post-hoc pair-wise comparisons (comparator: baseline visit) revealed significant decrease from baseline in days per week of use during the second ($5.2 \pm \text{SE } 0.33$; $p = 0.006$), third (5.2 ± 0.39 $p = 0.001$), and fourth (5.3 ± 0.32 ; $p = 0.03$) week of NAC treatment.

During the month preceding the trial, participants reported using an average of $15.9 \pm \text{SE } 2.4$ potency-adjusted “hits” (8) of marijuana per day, and GEE analysis revealed an overall trend-level reduction in “hits” per day over time ($p = 0.07$). Average “hits” per day decreased to $14.8 \pm \text{SE } 1.6$ at Week 1, 11.6 ± 1.7 at Week 2, 12.4 ± 2.0 at Week 3, and 11.9 ± 2.1 at Week 4. Pair-wise comparison (comparator: baseline visit) revealed significant reduction at the second week of NAC treatment ($p = 0.02$).

In addition to self-report data, semi-quantitative urine cannabinoid levels (quantitative range 0 to 135 ng/dL) and urine creatinine levels, to determine creatinine-normalized urine cannabinoid levels, were collected at each visit to serve as a biomarker of marijuana use (9). In contrast to self reports, semi-quantitative, creatinine-normalized urine cannabinoid levels did not significantly change over the course of the trial. Of note, though, 13 participants remained above the semi-quantitative urine cannabinoid range (0 – 135 ng/mL) throughout the trial, thus limiting the utility of this measure.

Craving for marijuana was measured using the 12-item version of Marijuana Craving Questionnaire (MCQ) (10). The four domains of the MCQ represent four constructs characterizing marijuana craving: *Compulsivity* (inability to control marijuana use), *Emotionality* (anticipation of using marijuana to relieve withdrawal or negative mood), *Expectancy* (anticipation of positive outcomes from smoking marijuana), and *Purposefulness* (intention and planning to use marijuana for positive outcomes). GEE analyses revealed that participants reported significantly reduced ratings on three of the four MCQ domains over the course of NAC treatment (MCQ Emotionality $p < 0.001$, Purposefulness $p = 0.003$, and Compulsivity $p = 0.008$) (Figure 1).

To our knowledge, this is the first study to date investigating the effects of NAC in young people with cannabis dependence. Results from this preliminary open-label study indicate that treatment with NAC was well tolerated and associated with significant decreases in self-report measures of marijuana use and craving. These reductions parallel those noted in prior NAC treatment studies in cocaine and nicotine dependent individuals (6,7). Although the present findings should be interpreted in light of the limitations of this preliminary study (i.e. open-label study without a control group, limited semi-quantitative urine drug testing), data strongly

suggest the need for a more rigorous examination of NAC for treatment of cannabis dependence.

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Figure 1.
 Marijuana Craving Questionnaire (MCQ) domain scores (mean $\pm$ SE) over the course of treatment.
 Range for each domain score is 1–7
 Some error bars were omitted for visual clarity