

Anti-Craving Properties of N-Acetylcysteine (NAC) in Adolescent Cannabis Dependent Inpatients with co-Occurring Psychiatric Disorders: a Case Series

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Abstract

Cannabis is the most commonly used illicit drug, particularly among adolescents. Currently, there are no formally approved pharmacotherapeutic options for the treatment of cannabis dependence and behavioral interventions have been found to be only moderately effective. One strategy to enhance outcomes is the addition of pharmacotherapy to complement behavioral treatment. Various studies suggest that N-acetyl cysteine (NAC) may assist in treating cannabis misuse. However, these studies excluded patients with co-occurring psychiatric disorders. In this article we present a case series of four adolescent patients with co-occurring psychiatric disorders in which NAC reduced craving for cannabis.

Keywords: Pharmacological treatment; N-acetylcysteine; NAC, Relapse; Cannabis use disorder; Adolescent, Co-occurring psychiatric disorders.

Introduction

Cannabis is among the most commonly used psychoactive substances, with 3.8% of the global population estimated to have used cannabis in the past year [1]. Despite the development of evidence-based psychosocial treatments for cannabis use disorders (including dependence), relapse rates of cannabis use remain as high as low rates of initial abstinence [2]. Several pharmacological treatment options have been tested in animal studies (mainly in rats), including the cannabinoid receptor agonist naboline and the adrenergic agonist lofexidine, as well as antidepressants, anxiolytics and antipsychotic drugs, but all generally failing to show consistent efficacy [2].

Recent studies have demonstrated that N-acetylcysteine (NAC) may be effective in treating cannabis use disorders [3]. NAC has clinical efficacy as a mucolytic agent for bronchopulmonary disorders and in the treatment of chronic obstructive pulmonary disease [4, 5]. It is also used as an oral or intravenous antidote to treat acetaminophen poisoning. NAC has a long-established safety record in adults and children, and has been approved by the United States Food and Drug Administration since 1963 [2].

It is thought that NAC exerts its anti-craving effects through normalization of extra-cellular glutamate levels that play an important role in subjective experience of craving for a drug [6].

Extracellular cysteine generated from NAC is transported into the cell, in exchange for intracellular glutamate, which is transported out of the cell through the cysteine/glutamate transporter. Restoration of extracellular levels of glutamate increases tonic activation of mostly presynaptic mGluR2/3 receptors, inhibiting glutamatergic neurotransmission and excito-toxicity [7, 8]. Indeed, reestablishing normal levels of extracellular glutamate.

Several studies have shown potential efficacy of NAC in youth with cannabis use disorders, without co-occurring mental health conditions [10, 11]. For instance, one randomized controlled trial (RCT) with adolescent cannabis dependent patients (n=116) showed that at 12 weeks' follow-up the group given NAC (1200mg) two times a day had double the proportion of urine tests negative for cannabis compared to the placebo group (19% vs. 10%) (9). It has also shown promise with other psychoactive substances, with a study on animals previously exposed to cocaine showing reduced reinstatement of cocaine use after treatment with NAC (7). However, a study did not show any difference in craving between the NAC and placebo group [10].

Clinical studies have also found potential for NAC in the treatment of other psychiatric conditions, including obsessive-compulsive disorder, schizophrenia, mood disorders (unipolar and bipolar), autism, and neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [11]. Therefore, it seems reasonable to assume that NAC might assist in the treatment of cannabis dependence, particularly in those with psychiatric comorbidity.

However, current studies excluded patients with psychiatric comorbidity. Here we present a case series on the effects of off-label treatment with NAC on cannabis craving among a group of inpatient adolescents with cannabis dependence and diverse psychiatric co-morbidity. The diagnostic classification during the admittance was done according to DSM-IV as required by the Health insurance companies.

Case description

Case-1

A 24-year-old female had been cannabis dependent for approximately seven years. She smoked two joints (marijuana) a day and drank around 10 energy drinks a day, containing 30 mg caffeine each. She was nicotine dependent for approximately five years, smoking 15 cigarettes a day. She was admitted for inpatient detoxification, after having failed several outpatient detoxification attempts, because of severe withdrawal symptoms, including tremors and sweating. She had no history of physical symptoms. Psychological problems included mood-swings, self-mutilating behaviour, an unstable self-image and a history of trauma, consisting of being bullied and neglected by her parents. Cannabis was her way to cope with stress, providing temporary relief of negative feelings. During inpatient treatment whilst abstinent for at least six weeks, she was diagnosed with reactive attachment disorder and personality disorder not otherwise specified (NOS) with borderline and schizoid features.

Treatment with NAC (400 mg) three times a day alleviated subjective craving levels (see Figure 1) and helped her to abstain from cannabis use. No adverse effects were reported. After four weeks she stopped using NAC because of the costs. After seven months of inpatient treatment, she used NAC for four more weeks. She stopped using NAC because of the costs of NAC. After the inpatient treatment she successfully completed outpatient day treatment, without any relapse in cannabis use for at least 14 months.

Case 2

A 20-year-old male had been cannabis dependent for approximately six years and had also had an alcohol abuse disorder for approximately six years. At the start of inpatient detoxification he was smoking five grams of cannabis (marijuana) a day and was drinking 10 units of mixed alcoholic drinks once a week. He had been nicotine dependent for approximately seven years, smoking 15 cigarettes a day. He was admitted for inpatient detoxification and treatment because of co-existing psychological problems, including attention deficit and hyperactivity disorder (ADHD) and reactive attachment disorder. Cannabis and alcohol were his way to cope with restlessness, anger and insomnia. He reported no physical problems or illness. During inpatient treatment he reported sleeping problems for which he received mirtazapine (15mg) once daily. Treatment with NAC (400mg) three times daily alleviated subjective craving levels (see Figure 1). He abstained from cannabis use. No adverse effects were reported. After four months inpatient treatment, he declined outpatient treatment and stopped using NAC because of the costs. Three days later he relapsed.

Case 3

An 18-year-old male had been dependent on cannabis (marijuana) for approximately two years and was smoking seven joints a day at the start of inpatient treatment. He was admitted for inpatient detoxification because of a combination of cannabis use disorder and ADHD, dysthymia, identity disorder and personality disorder

NOS with avoidant features. Cannabis was his way to cope with restlessness and negative emotions. He reported no physical problems or physical illness. During inpatient treatment, before the treatment with NAC, he reported sleeping problems for which he received mirtazapine (15mg) once daily. Treatment with NAC (400mg) three times daily started two weeks after admission. NAC alleviated subjective craving levels (see Figure 1). He abstained from cannabis use. No adverse effects were reported. After 2, 5 months of inpatient treatment he stopped using NAC because he wanted to try to stay abstinent without medication. He started outpatient day treatment, but stopped after two weeks. He reported being abstinent from cannabis for three months and reported no craving for cannabis.

Case 4

A 19-year-old man who had been cannabis dependent for approximately two years, smoking two joints (hashish) a day. He was admitted for inpatient detoxification because of several unsuccessful outpatient treatment attempts, which had failed because of family problems and having peers who also used cannabis. He reported no physical problems or physical illness. Cannabis was his way to cope with restlessness and chaos.

During the inpatient treatment, for which he was abstinent for at least six weeks, he was diagnosed with pervasive development disorder NOS and a moderate intellectual disability.

Treatment with NAC (400mg) three times daily started four weeks after admission. NAC alleviated subjective craving levels (see Figure 1) and helped the patient abstain from cannabis use. No adverse effects were reported. Having completed inpatient treatment, he began outpatient treatment and was abstinent for at least four weeks and reported no craving for cannabis.

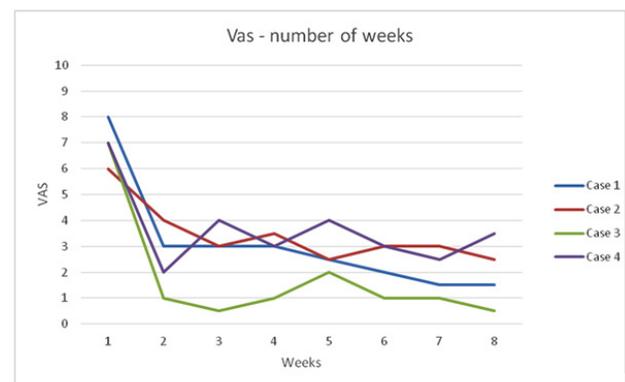


Figure 1: Subjective cannabis craving in four patients (VAS) over eight weeks of treatment.

Discussion

All four patients were admitted for treatment of cannabis dependence. They met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for cannabis dependence [12]. After inpatient detoxification with tapering benzodiazepine treatment, which was conducted according to the Dutch detoxification guidelines, the patients were offered the option of off-label treatment with NAC [13]. After being provided information on the potential risks and benefits of NAC, patients provided written informed consent for off-label treatment to comply with Dutch regulations and consented to the publication of their NAC

treatment and case history as a case series [14]. All four patients started with NAC 200 mg three times a day. If no side-effects were reported, NAC was increased to 400 mg three times a day after one week for a minimum of eight weeks and a maximum of 10 weeks. Below we summarize the effects of NAC on subjective craving (see Figure 1), cannabis use and report on adverse events. None of the patients reported any side effects of NAC and their urine tests were negative for cannabis for the entirety of their treatment with NAC. Blood tests showed no abnormalities.

These four patients used NAC during their inpatient treatment, completed the visual analogue scale (VAS) and provided urine for laboratory analysis. The VAS results show clinically relevant reductions to the patients' subjective cannabis craving. The laboratory results suggest the patients were indeed abstinent from cannabis. Furthermore, they reported no side effects.

NAC is a safe and well-tolerated agent and shows promising potential for the treatment of substance abuse disorders (SUDs) involving multiple substances of abuse [3]. Gray *et al.* studied the effect of NAC on cannabis dependence without co-morbid addiction or psychiatric disorders [9].

In our cases had various series all four patients have co-occurring psychiatric co-morbidity and were taking other medications in addition to NAC, such as mirtazepine. The study was carried out under controlled conditions (at the clinic) and therefore since all were inpatients, it is not particularly surprising that they remained abstinent during treatment. Given the treatment conditions, we do not regard abstinence as the best primary outcome measure; rather we regard the reduction of craving as a more important step, which may eventually result in abstinence.

A limitation of our results is that we do not have any long-term data on craving or abstinence during outpatient treatment. Furthermore the study was of an open design without a control group and only used inpatient treatment, meaning the findings may not apply to real world circumstances where the patients are not confined to a clinic.

The next step would be to perform a large scale RCT. Due to small research budgets available we recommend a consecutive series of case studies that will follow a double-blind cross-over design with ABAB or BABA conditions (An experimental NAC, B placebo).

Conclusion

We report the treatment of four patients with cannabis dependence and psychiatric co-morbidity using NAC resulting in a significant and clinically relevant reduction of craving for cannabis.

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