



## EDITORIAL

# N-acetylcysteine in the treatment of substance use disorders

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### ABSTRACT

N-acetylcysteine (NAC) is an agent best known for its clinical efficacy in bronchopulmonary disorders due to its mucolytic properties, and in the treatment of acetaminophen overdose. Given the strong clinical evidence from animal studies of its critical role in regulating glutamatergic receptors, NAC has also been the subject of research related to several psychiatric disorders as a promising treatment approach. This editorial is a brief discussion of the characteristics of NAC and its place in substance use disorders and other psychiatric disorders.

N-acetylcysteine (NAC) is an N-acetylated derivative of the naturally occurring amino acid cysteine (1). NAC is a white, crystalline compound; the molecular formula is  $C_5H_9NO_3S$  (2). As a drug, it has been available for several years in intravenous, oral, and nebulizer forms (2,3). Inside several organs (including the brain), free cysteine is formed by deacetylation of NAC. Two cysteine molecules are then homodimerized via a disulfide bond, forming cystine. NAC is therefore a cystine prodrug that binds to the cystine-glutamate exchanger (or system xc-) and supports the synthesis of glutathione (4-6), the most important non-enzymatic substance scavenging free radicals in the intracellular spaces of the brain with the most generic action of all endogenous antioxidants. The level of glutathione in the brain is replenished by NAC as a precursor molecule (7,8). As a result, it is relevant as an antioxidant (9,10). Not only does system xc- promote glutathione synthesis; it also functions as antiporter protein carrying extracellular cystine into glial cells and moving intracellular glutamate from inside the glial cells

into the extracellular environment, thus raising extracellular glutamate levels in many tissues including the brain (1,4,6).

The clinical efficacy of NAC as a mucolytic agent for bronchopulmonary disorders and in the treatment of acetaminophen overdose has been proven worldwide (6). On the other hand, an increasing number of clinical studies indicate the efficacy of NAC in various psychiatric conditions through mechanisms including glutamate modulation and other processes (11), such as substance use disorders (SUDs) (12), pathological gambling (13), obsessive-compulsive disorder (14) and other compulsive disorders (15-17), mood disorders (8,18), schizophrenia (19), and autism (20) as well as neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (21).

It is a safe and well-tolerated agent, even at relatively high doses (22), with mild side effects like headache, lethargy, fever, and skin rash occurring approximately 1-5% of the time (23). The most commonly reported

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adverse events include pruritus, headache, gastrointestinal issues including flatulence, diarrhea, and abdominal cramps, dizziness, and elevated blood pressure (24).

### **Substance Use Disorders and N-acetylcysteine**

Traditionally, dopamine and associated reward-based behavior have been in the focus of research into substance abuse; however, it has been suggested that glutamate dysregulation could be another path toward the development and maintenance of addiction (25,26). Preclinical studies in animal models suggest that NAC could restore the imbalanced cysteine-glutamate exchange in the brain and thus decrease drug-seeking behaviors (27-29).

For more than two decades, animal studies have created increasing preclinical evidence indicating that glutamate transmission and glutamate receptors play a major role in drug reward, reinforcement, and relapse (6,30-39). Accordingly, treatment of SUDs with NAC in clinical populations has been an active area of research (26). The role of glutamate dysregulation, the target of NAC treatment, has been proposed as a ubiquitous finding and underlying feature across SUDs (32,33,40). Thus, SUDs involving the abuse of a number of different substances are treated using glutamatergic agents (3). Considering that NAC influences craving, withdrawal, and the rewarding properties of substances of abuse, a number of studies have tried to establish how the administration of NAC affects these processes (3).

While not providing clear results, randomized clinical trials have pointed towards certain mechanistic and methodological factors through which NAC could promote abstinence and help prevent relapses with different substances of abuse (3). In recent findings, NAC is suggested to be most effective in maintaining abstinence rather than in promoting initial cessation (12,41,42). Despite inconsistent results in human clinical trials (41,43,44), the latest systematic review and meta-analysis found NAC to be significantly superior to placebo for reducing craving symptoms in SUDs. As a potential anti-craving agent, NAC could be important for relapse prevention (45).

### **Cocaine and N-acetylcysteine**

Cocaine has so far been in the focus of clinical research regarding the therapeutic effects of NAC on addictive behaviors (24). While findings have been mixed, they seem to suggest efficacy over placebo to prolong abstinence and reduce cue-related cocaine cravings for individuals past acute withdrawal (46). The review by

Echevarria et al. (42) found studies demonstrating the potential of NAC to “reduce cravings, the desire to use cocaine, cocaine-cue viewing-time and cocaine-related spending” (2,22,43,44). As these studies either had small samples or had been carried out as open-label trials, their results are to be considered as preliminary, warranting further research (42).

In a large randomized control trial to assess efficacy of NAC in the treatment of cocaine dependence, while no significant correlation was found between NAC and relapse-related measures, a small subset of patients who had already been abstinent for at least one week before participating in the study showed a dose-dependent prolongation of days to relapse, suggesting that NAC might protect abstinent SUDs patients from resumption of substance use. In the majority of cases, however, the outcome was negative, indicating the need for further research (41).

One open-label, randomized, crossover clinical study with 22 human subjects (8 cocaine-dependent, 14 healthy) used proton magnetic resonance spectroscopy to image glutamate concentration in the dorsal anterior cingulate cortex (dACC) after a single dose of NAC, finding significantly higher baseline levels of glutamate in the dACC of the cocaine-dependent subjects. While glutamate levels of these individuals were reduced after administration of NAC, no effect was observed in healthy controls (25). These results indicate the capabilities of NAC to address imbalance in glutamate homeostasis (24,25).

### **Methamphetamine and N-acetylcysteine**

Preclinical research studying the effect of NAC on the administration or reinstatement of methamphetamine has not been found in the literature (24) with the exception of one study conducted on female rats, where NAC was not found to have any effect on methamphetamine self-administration or reinstatement (47). However, in the absence of FDA-approved pharmacotherapies for methamphetamine use, clinical research with NAC has been undertaken (24).

In a study conducted in 2010, a combination of NAC and naltrexone was used for methamphetamine cravings and self-reported methamphetamine use. Participants in treatment showed no significant difference in cravings or drug use frequency (48).

A second study on methamphetamine use disorder used a double-blind, crossover design to examine craving (49). In contrast with the study discussed above, NAC treatment significantly reduced methamphetamine craving.

NAC's effect on methamphetamine use and other clinically related endpoints is uncertain. A study protocol to "evaluate the safety and efficacy of NAC as a take-home pharmacotherapy for methamphetamine dependence" was published in 2019; however, the results have not yet been released. The authors suggested that, "given the lack of approved medications currently available for managing methamphetamine dependence and the challenges involved in translating effective psychological interventions into practice settings, the discovery of a safe and effective pharmacotherapy would fill an important gap in treatment options for methamphetamine use" (50).

### **Cannabis and N-acetylcysteine**

The strongest clinical findings to date for NAC in relation to SUDs are adolescent- and cannabis-specific (12). One open-label study treated 24 cannabis-dependent individuals aged 18-21 over a period of 4 weeks with 1200 mg NAC twice daily. In week 4 of the NAC treatment, subjects reported a significantly decreased number of days per week when they used cannabis and a tendency to reduce the daily quantity of marijuana. Objective evaluation did not find any change in the cannabinoid content of urine samples but a significant reduction of the scores on the Marijuana Craving Questionnaire, suggesting a relevant role for NAC in the treatment of cannabis abuse and dependence (51).

In a double-blind, randomized, placebo-controlled trial in cannabis-dependent adolescents using NAC in addition to a behavioral platform to promote abstinence, participants receiving NAC were twice as likely to have a negative urine cannabinoid test as those who received placebo (52).

A subsequent 12-week multisite, double-blind randomized, placebo-controlled trial with 302 treatment-seeking adults with cannabis use disorder (age range 18-50 years) obtained overall negative findings for the effect of NAC on cannabis abstinence. Subgroup analyses for participants aged 18-21 years (the range of the sample in the previous adolescent NAC cannabis trial) found this group to be twice as likely to have negative drug screens after receiving NAC vs. placebo, suggesting that NAC might be used specifically for treating adolescent cannabis use disorder (53). However, the efficacy of NAC in the treatment of cannabis use disorder has so far not been studied without adjunctive contingency management. Therefore, further research should single out the clinical effect of NAC among adolescents (12).

A recent study examined the effect of NAC on depressive symptoms in adults with cannabis use disorder and a possible correlation between NAC's effect on cannabis cessation and baseline levels of depression. The outcome, however, did not support the use of NAC for treating co-occurring depressive symptoms and cannabis use disorder in adults concurrently (54).

### **Synthetic Cannabinoids and N-acetylcysteine**

There is only one case report that demonstrates a full recovery of a patient suffering from hepatotoxicity caused by synthetic cannabinoids. The patient was treated with NAC, and the effects were attributed to its hepatoprotective properties, as NAC restores hepatic glutathione that scavenges oxygen-derived free radicals and improves endothelium-dependent vasodilation, offering protection from ongoing injury (55).

### **Alcohol and N-acetylcysteine**

Beneficial effects of NAC treatment in ethanol withdrawal have been demonstrated in preclinical studies. NAC treatment prevented locomotor deficits and anxiety-like behavior as well as the lipid peroxidation and ethanol withdrawal-induced depletion of antioxidant defenses observed during ethanol withdrawal (56).

A recent preclinical study in an animal model of comorbid post-traumatic stress disorder and SUDs showed that NAC could be used prophylactically to prevent or reverse the vulnerability to undergo stress-induced escalation of alcohol use and conditioned stress-induced alcohol (57).

In one cannabis cessation trial, NAC was associated with decreased cannabis use as well as concurrent reduction in alcohol use among adolescents (58). In another cannabis cessation trial conducted with adults, subjects assigned randomly to the NAC group showed reduced alcohol use when compared to the placebo group, regardless of cannabis use, indicating that NAC might be used for treating AUD and possibly co-occurring alcohol and cannabis use (59).

There is a growing preclinical literature suggesting that NAC could help reducing alcohol use (60); however, there have been no clinical trials to date directly investigating the potential role of NAC on alcohol use disorder (61).

### **Nicotine and N-acetylcysteine**

Chronic NAC administration has been shown to lead to an inhibition of nicotine-seeking and transient increases

in synaptic plasticity within the nucleus accumbens in preclinical research with rodent models of nicotine self-administration (24,62). Similarly, acute administration of NAC was effective at reducing nicotine self-administration (63), indicating a high potential for NAC to be used in an effective treatment of nicotine addiction in a clinical setting. There are clinical studies that have shown that NAC leads to a reduction in withdrawal scores and measures of the rewarding properties of the first cigarette posttreatment (64), along with effects on reduction in cigarettes smoked per day and craving (65).

One clinical imaging study used functional magnetic resonance imaging (fMRI) to investigate the effects of NAC on the frontostriatal resting-state functional connectivity (rsFC) in nicotine withdrawal symptoms (66). The results of this study demonstrated that NAC led to an increase in the rates of abstinence, reduction in reported craving, and an increase in rsFC compared to placebo, helping to restore regular glutamate homeostasis and signaling (24).

So far, only small pilot studies have been carried out to establish the efficacy of NAC for treating tobacco-use disorder, providing promising initial evidence; however, without a comprehensive randomized clinical trial, it would be premature to suggest the use of NAC for smoking cessation (12).

### **Opioids and N-acetylcysteine**

NAC has been shown to produce positive outcomes in rodents for opioids (29), and a recent study in opioid-dependent neonatal rats demonstrated that NAC mitigated behavioral withdrawal symptoms and oxidative stress (67). However, the efficacy of NAC in opioid dependence has not yet been tested in clinical populations (24), neither as a stand-alone treatment nor in addition to opioid-replacement therapies or behavioral treatment (3).

### **N-acetylcysteine and Other Psychiatric Disorders**

NAC as a precursor of glutathione and an important antioxidant with the ability to modulate glutamatergic, dopaminergic neurotropic, and inflammatory pathways has created interest in its use for treating a number of psychiatric disorders (68). Oxidative stress may be a factor in psychiatric disorders such as bipolar and anxiety disorders, depression, and SUDs, but also in diagnoses such as autism and attention-deficit hyperactivity disorder (3,69).

The depletion of glutathione during oxidative stress can be reversed with NAC treatment (3,70) and there is evidence supporting the study of glutathione as a novel

therapeutic target in psychiatric disorders (3,71).

While NAC is not currently licensed for any psychiatric indication, its off-label use in a number of several psychiatric disorders has been researched as a promising treatment approach, mainly as an adjunctive medication, so far producing only preliminary data for areas of psychiatric use. Results on primary outcomes in most trials were not significant, while secondary outcomes or the analysis of subsamples has given some positive evidence. As most studies have used small samples, additional well-designed, larger controlled trials with longer follow-up periods would be desirable to establish reliable indications and clearer information on optimal dosage and side effects, safety and tolerability in the long-term use of NAC (68).

### **Conclusion**

Current evidence supports NAC as a novel and effective treatment for some psychiatric conditions, with the best evidence being available for addictions and SUDs, reducing craving and preventing relapse in patients who are already abstinent. Yet the results of available studies and reviews are not uniform, indicating that more robust evidence should be generated in future clinical trials (26).

The role of NAC in reducing damage caused by oxidative stress is another area of research to be pursued. As oxidative stress has been shown to affect psychiatric disorders (69), avoiding this effect will be of particular relevance for the treatment of SUDs. Thus, the role of the oxidative stress mechanism in psychiatric disorders and its treatment with NAC appear to offer relevant guidance for future research addressing poly-substance use and psychiatric comorbidities (3).

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