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N-acetylcysteine: A potential treatment for substance use disorders

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Pharmacologic treatment options for many substance use disorders (SUDs) are limited. This is especially true for cocaine use disorder and cannabis use disorder, for which there are no FDA- approved medications. FDA-approved medications for other SUDs often take the form of replacement or agonist therapies (eg, nicotine replacement therapy) that substitute the effects of the substance to aid in cessation. Other pharmacotherapies treat symptoms of withdrawal, reduce craving, or provide aversive counter-conditioning if the patient consumes the substance while on the medication (eg, disulfiram).

The over-the-counter (OTC) antioxidant *N*-acetylcysteine (NAC) may be a potential treatment for SUDs. Although NAC is not approved by the FDA for treating SUDs, its proposed mechanism of action differs from that of current FDA-approved medications for SUDs. NAC's potential for broad applicability, favorable adverse-effect profile, accessibility, and low cost make it an intriguing option for patients with multiple comorbidities, and

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potentially for individuals with polysubstance use. This article reviews the current evidence supporting NAC for treating SUDs, to provide insight about which patients may benefit from NAC and under which circumstances they are most likely to benefit.

NAC may correct glutamate dysregulation

Approximately 85% of individuals with an SUD do not seek treatment for it, and those who do are older, have a longer history of use, have more severe dependence, and have sought treatment numerous times before.[1] By the time most people seek treatment, years of chronic substance use have likely led to significant brain-related adaptations. Individuals with SUDs often indicate that their substance use began as a pleasurable activity—the effects of the drug were enjoyable and they were motivated to use it again. With repeated substance use, they may begin to develop a stronger urge to use the drug, driven not necessarily by a desire for pleasure, but by compulsion.[2]

Numerous neural adaptations underlie the transition from “liking” a substance to engaging in the compulsive use that is characteristic of an SUD.[2] For example, repeated use of an addictive substance may result in excess glutamate in the nucleus accumbens,[3,4] an area of the brain that plays a critical role in motivation and learning. As a result, it is has been proposed that pharmacotherapies that help correct glutamate dysregulation may be effective in promoting abstinence or preventing relapse to a substance.[5,6]

NAC may reverse the neural dysfunction seen in SUDs. As an OTC antioxidant that impacts glutamatergic functioning in the brain, NAC has long been used to treat acetaminophen overdose; however, in recent years, researchers have begun to tap its potential for treating substance use and psychiatric disorders. NAC is thought to upregulate the glutamate transporter (GLT-1) that removes excess glutamate from the nucleus accumbens.[6] Several published reviews provide more in-depth information about the neurobiology of NAC.[6–10]

The adverse-effect profile of NAC is relatively benign. Nausea, vomiting, diarrhea, and sleepiness are relatively infrequent and mild.[11,12] The bioavailability of NAC is about 4% to 9%, with an approximate half-life of 6.25 hours when orally administered.[13] Because NAC is classified as an OTC supplement, the potency and preparation may vary by supplier. To maximize consistency, NAC should be obtained from a supplier that meets United States Pharmacopeia (USP) standards.

NAC for SUDs: Emerging evidence

Several recent reviews have described the efficacy of NAC for SUDs and other psychiatric disorders. Here we summarize the current research examining the efficacy of NAC for stimulant (ie, cocaine and methamphetamine), alcohol, cannabis, and tobacco use disorders.

Stimulant use disorders

The United Nations Office for Drugs and Crime estimates that worldwide, more than 18 million people use cocaine and more than 35 million use amphetamines.[14] There are currently no FDA-approved treatments for stimulant use disorders, and clinicians treating

patients with cocaine or amphetamine dependence often are at a loss for how best to promote abstinence. Recent studies suggest that NAC may decrease drug-seeking behavior and cravings in adults who seek treatment. The results of studies examining NAC for treating cocaine use and methamphetamine use are summarized in Table 1[15–17] and Table 2,[18,19] respectively.

Cocaine cessation and relapse prevention

Several small pilot projects[15,16] found that compared with placebo, various doses of NAC reduced craving (as measured with a visual analog scale). However, in a double-blind, placebo controlled study, NAC did not decrease cravings or use after 8 weeks of treatment in individuals with cocaine use disorder who were still using cocaine (ie, they had not yet become abstinent). Interestingly, those who were abstinent when treatment began reported lower craving and remained abstinent longer if they received NAC (vs placebo), which suggests that NAC may be useful for preventing relapse.[17]

Methamphetamine cessation and relapse prevention

A single study (N = 32) that evaluated the use of NAC, 1,200 mg/d for 4 weeks, vs placebo found reduced cravings among methamphetamine users who were seeking treatment.[18] In contrast, a study of 31 methamphetamine users who were not seeking treatment evaluated the use of NAC, 2,400 mg/d, plus naltrexone, 200 mg/d, vs placebo for 8 weeks.[19] It found no significant differences in craving or use patterns. Further research is needed to optimize the use of NAC for stimulant use disorders, and to better understand the role that abstinence plays.

Appropriate populations

There is the most support for use of NAC in treatment-seeking adults as an anti-relapse agent.

Safety and dosing

Suggested dosages for the treatment of cocaine use disorder range from 1,200 to 3,600 mg/d (typically 600 to 1,800 mg twice daily, due to NAC's short half-life), with higher retention rates noted in individuals who received 2,400 mg/d and 3,600 mg/d.[16]

Clinical implications

NAC is thought to act as an anti-relapse agent, rather than an agent that can help someone who is actively using stimulants to stop. Consequently, NAC will likely be most helpful for patients who are motivated to quit and are abstinent when they start taking NAC; however, this hypothesis needs further testing.

Cannabis use disorder

There are no FDA-approved treatments for cannabis use disorder. Individuals who use marijuana or other forms of cannabis may be less likely to report negative consequences or seek treatment compared with those who use other substances. Approximately 9% of individuals who use marijuana develop cannabis use disorder[20]; those who begin using

marijuana earlier in adolescence are at increased risk.[21] Commonly reported reasons for wanting to stop using marijuana include being concerned about health consequences, regaining or demonstrating self-control, saving money, avoiding legal consequences, obtaining or keeping employment, and reducing interpersonal conflict.[22,23] Table 3[24–27] summarizes initial evidence that suggests NAC may be particularly useful in reducing marijuana use among adolescents (age 15 to 21 years).[24,25]

Cessation

An open-label, pilot clinical trial found significant reductions in self-reported marijuana use and craving—but not in biomarkers of use—among 24 adolescents after 4 weeks of NAC, 1,200 mg twice daily.[24] In an 8-week, double-blind randomized controlled trial of 116 adolescents, NAC, 1,200 mg twice daily, plus contingency management doubled the odds of abstinence, but had no effect on self-reported craving or use.[25,26] In a sample of 302 adults, a 12-week trial of NAC, 1,200 mg twice daily, plus contingency management was no more effective than contingency management alone in promoting abstinence.[27]

Appropriate populations

Evidence is stronger for use of NAC among adolescents (age 15 to 21 years) than for individuals older than age 21.[25,27] Further research is needed to explore potential reasons for age-specific effects.

Safety and dosing

A safe and potentially efficacious dosage for the treatment of cannabis use disorder is 2,400 mg/d (1,200 mg twice daily).[24,25,27]

Clinical implications

Combined with contingency management, NAC might be efficacious for adolescents with cannabis use disorder, with treatment gains evident by the fourth week of treatment.[24–25] To date, no clinical trials have examined the efficacy of NAC for treating cannabis use disorder without adjunctive contingency management, and research is needed to isolate the clinical effect of NAC among adolescents.

Tobacco use disorder

Cigarette smoking remains a leading cause of preventable death in the United States,[28] and almost 70% of people who start using tobacco become dependent.[20] Existing FDA-approved treatments include nicotine replacement products, varenicline, and buproprion. Even though efficacious treatments exist, successful and sustained quit attempts are infrequent.[29] NAC may exert a complementary effect to existing tobacco cessation interventions, such as varenicline.[30] While these medications promote abstinence, NAC may be particularly beneficial in preventing relapse after abstinence has been achieved (Table 4[30–36]).

Cessation and relapse prevention

Several pilot studies found that adult smokers who received NAC (alone or in combination with another treatment) had lower carbon monoxide levels,[31,32] smoked fewer cigarettes,

[32,33] and had fewer self-reported symptoms of nicotine dependence[34] and/or less craving for cigarettes.[31] However, one study of 33 smokers did not find a reduction in craving or carbon monoxide for NAC compared with placebo.[33] Another pilot study of 22 young adult smokers found that those who received NAC rated their first cigarette after treatment (smoked in the laboratory) as less rewarding, relative to smokers who received a placebo.[35]

Secondary analyses of adults with bipolar disorder[36] and adolescents with cannabis use disorder[37] found no decreases in tobacco use among those who received NAC compared with placebo. However, the studies in these analyses did not specifically recruit tobacco users, and participants who were tobacco users were not necessarily interested in quitting. This may partially explain discrepant findings.

Appropriate populations

NAC has been studied mostly in adult cigarette smokers.

Safety and dosing

Suggested dosages for treating tobacco use disorder range from 1,200 to 3,600 mg/d (600 to 1,800 mg twice daily).

Clinical implications

Data on NAC's efficacy for tobacco use disorder come from small, pilot trials. Though initial evidence is promising, it is premature to suggest NAC for smoking cessation until a fully powered, randomized clinical trial provides evidence of efficacy.

Alcohol use disorder

Alcohol use disorders are widely prevalent; 13.9% of US adults met criteria in the past year, and 29.1% of US adults meet criteria in their lifetime.[38] Alcohol use disorders can result in significant negative consequences, including relationship problems, violent behavior, medical problems, and death. Existing FDA-approved medications for alcohol use disorder include naltrexone, acamprosate, and disulfiram.

Due to the severe potential health consequences of alcohol, NAC has been examined as a possible aid in preventing relapse. However, most studies have been conducted using animals. Three studies have examined alcohol use in humans (Table 5[36,39,40]). One was a pilot study,[39] and the other 2 were secondary data analyses.[36,40] None of them specifically focused on alcohol use disorders. A pilot study of 35 veterans with co-occurring posttraumautic stress disorder (PTSD) and SUDs (82% of whom had an alcohol use disorder) found that compared with placebo, NAC significantly decreased in PTSD symptoms, craving, and depression.[39] In a study of 75 adults with bipolar disorder, secondary alcohol use was not significantly reduced.[36] However, one study suggested that NAC may decrease adolescent alcohol and marijuana co-use.[40] Future work is needed to examine the potential clinical utility of NAC in individuals with alcohol use disorders.

Findings from animal studies indicate that NAC may:

- reduce alcohol-seeking[41]
- reduce withdrawal symptoms[42]
- reduce the teratogenic effects of alcohol[43]
- prevent alcohol toxicity[44]
- reduce health-related consequences of alcohol (eg, myocardial oxidative stress[45] and alcohol-related steatohepatitis[46]).

Appropriate populations

Pilot studies have suggested that appropriate populations may include veterans with SUD and PTSD[39] and adolescents with marijuana dependence who use alcohol.[40]

Safety and dosing

Suggested dosages for the treatment of alcohol use disorder based on these studies range from 1,000 to 2,400 mg/d (500 to 1,200 mg twice daily).

Clinical implications

Future work is needed to determine if NAC is effective for treating alcohol use disorders. Ongoing randomized clinical trials are examining the efficacy of NAC in reducing alcohol use among individuals with alcohol use disorder. It is premature to recommend NAC for treatment of alcohol use disorders.

Other psychiatric uses

Although we have highlighted NAC's effect on glutamatergic transmission, evidence suggests that NAC may have multiple mechanisms of action that could impact psychiatric functioning. For example, NAC may also reverse oxidative stress, which is frequently observed in psychiatric disorders such as schizophrenia and bipolar disorder.[10,12] NAC also has antinflammatory properties. When inflammatory pathways of the CNS are dysregulated, production of neurotransmitters may be impaired, resulting in depression-like symptoms.[10,12,47] Preliminary evidence suggests that NAC may be effective in treating mood-related symptoms (eg, irritability, depression) in individuals with psychiatric disorders (eg, bipolar and depressive disorders, PTSD, and SUDs) and general symptoms of schizophrenia, obsessive-compulsive disorder, and trichotillomania, although mixed findings in controlled studies suggest a need for further research.[12,39]

NAC: A promising candidate

Initial evidence suggests NAC may be helpful for treating patients with SUDs. A patient seeking SUD treatment who is treated with NAC may experience a decreased drive, craving, or compulsion to use. Notably, NAC may be particularly useful in preventing relapse after an individual has achieved abstinence. Evidence suggests that NAC may be useful in the treatment of adults with cocaine use disorders who have achieved some abstinence, and adolescents with cannabis use disorders. Preliminary results for adult tobacco use disorder are also promising. Human data examining the efficacy of NAC for alcohol use disorder is

limited. Researchers' ongoing challenge is to identify which patients with which SUDs are most likely to benefit from NAC, and to create clear clinical guidelines for the provider.

Bottom Line

N-acetylcysteine is likely to have modest effects for some patients who have a substance use disorder, particularly for adults who use cocaine and adolescents who use marijuana. It may be particularly useful in preventing relapse after an individual has achieved abstinence.

Related Resources

- Deepmala, Slattery J, Kumar N, et al. Clinical trials of *N*-acetylcysteine in psychiatry and neurology: a systematic review. Neurosci Biobehav Rev. 2015;55:294-321.
- Roberts-Wolfe D, Kalivas P. Glutamate transporter GLT-1 as a therapeutic target for substance use disorders. CNS Neurol Disord Drug Targets. 2015;14(6): 745-756.
- National Institute on Drug Abuse. Treatment approaches for drug addiction. https://www.drugabuse.gov/publications/drugfacts/treatment-approaches-drug-addiction.

Drug Brand Names

Acetaminopen • Tylenol

Acamprosate • Campral

Disulfiram • Antabuse

Buproprion • Zyban

Naltrexone • Revia,Vivitrol

Varenicline • Chantix

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Table 1

NAC for the treatment of cocaine use disorder

Study	Sample	Dosing	Outcomes
Amen et al[15] (2011)	N = 6 inpatients, treatment seeking adults with cocaine dependence	400 to 800 mg 3 times a day (1,200 to 2,400 mg/d) vs baclofen 20 mg 3 times a day (60 mg/d) for 4 days (single- blind)	• Reduction in self-reported cocaine cravings (using visual analog scale) during a cue-induction, visual stimuli task • No reduction in subjective level of high or rush during cocaine challenges
Mardikian et al[16] (2007)	N = 23 treatment-seeking adults with cocaine dependence (96% male, 52% white)	1,200 mg/d vs 2,400 mg/d vs 3,600 mg/d for 4 weeks (open- label)	• Reduction in self-reported cocaine amount of cravings (using visual analog scale), frequency of cravings, amount spent on cocaine, and self-reported use • Increased study retention rates with higher doses (88% at 2,400 mg/d, 83% at 3,600 mg/d, and 37.5% at 1,200 mg/d)
LaRowe et al[17] (2013)	N = 111 non- abstinent adults with cocaine dependence (43% white, 55% African American, and 2% Hispanic)	1,200 mg/d vs 2,400 mg/d vs placebo for 8 weeks (double- blind)	• No reduction in self-reported cocaine amount of cravings or cocaine use when participants were not previously abstinent • Those in the NAC group who were abstinent at the beginning of treatment were more likely to remain abstinent longer and report lower craving levels (relative to those abstinent in the placebo group at treatment onset)

NAC: *N*-acetylcysteine

Table 2

NAC for the treatment of methamphetamine use disorder

Study	Sample	Dosing	Outcomes
Mousavi et al[18] (2015)	N = 32 treatment- seeking adults with methamphetamine dependence (83% male, 100% recruited from Iran)	1,200 mg/d vs placebo (crossover design) for 4 weeks each	Reduction in methamphetamine cravings during treatment (but not after crossover) using the Cocaine Craving Questionnaire brief (CCQ- brief)
Grant et al[19] (2010)	N = 31 non- treatment seeking adults with methamphetamine dependence (71% male)	2,400 mg/d NAC plus 200 mg/d naltrexone vs placebo for 8 weeks	No reduction in craving as measured by the Penn Craving Scale or frequency of use (urine drug screen)

NAC: *N*-acetylcysteine

Table 3

NAC for the treatment of cannabis use disorder

Study	Sample	Dosing	Outcomes
Gray et al[24] (2010)	N = 24 adolescents/ emerging adults (age 18 to 21) with cannabis dependence (75% male, 92% white)	1,200 mg twice daily (2,400 mg/d) for 4 weeks (open-label)	• Reduction in self-reported number of cannabis use days and number of “hits” per day • Reduction in self-reported craving • Non-significant reduction in semi-quantitative creatinine- normalized cannabinoid levels
Gray et al[25] (2012); Roten et al[26] (2013)	N = 116 adolescents (ages 15 to 21) with cannabis dependence (72% male, 84% white)	1,200 mg twice daily (2,400 mg/d) vs placebo for 8 weeks (double- blind) added to contingency management	• Double the odds of abstinence in NAC group relative to placebo (as confirmed via urine cannabinoid test) at end of treatment • No group differences in self- reported number of cannabis use days or craving
Gray et al[27] (2017)	N = 302 adults with cannabis use disorder (77% male, 55% white, 29% black/African American)	1,200 mg twice daily (2,400 mg/d) vs placebo for 12 weeks (double- blind) added to contingency management	• No group differences in odds of abstinence • No group differences in self- reported number of cannabis use days • Numerical, non-significant trend for double odds of abstinence among younger age group receiving NAC vs placebo (age 18 to 21)

NAC: *N*-acetylcysteine

Table 4

NAC for the treatment of tobacco use disorder

Study	Sample	Dosing	Outcomes
McClure et al[30] (2014)	N = 116 adolescents (age 15 to 21) with cannabis dependence (72% male, 84% white; 59% smokers)	1,200 mg twice daily (2,400 mg/d) vs placebo for 8 weeks (double-blind) added to contingency management	No group differences in reported cigarettes smoked
Froeliger et al[31] (2015)	N = 16 adult smokers (69% male; 56% black/African American, 44% white)	1,200 mg twice daily (2,400 mg/d) vs placebo for 3.5 days (double- blind)	• NAC group more likely to maintain abstinence during 3.5-day monetarily-incentivized abstinence period, as evidenced by lower carbon monoxide values • NAC group reported decreased craving and higher positive affect relative to placebo group
Prado et al[32] (2015)	N = 34 outpatients with therapy-resistant tobacco use disorder (26.5% male)	1,500 mg twice daily (3,000 mg/d) vs placebo for 12 weeks (double-blind)	NAC group reported fewer cigarettes and had lower carbon monoxide levels at end of treatment, compared with placebo group
Knackstedt et al[33] (2009)	N = 33 adults with nicotine dependence (58% male; 70% white, 21% black/African American)	1,200 mg twice daily (2,400 mg/d) vs placebo for 4 weeks (double-blind)	• When excluding 2 heavy drinkers from analysis, the NAC group reported fewer cigarettes smoked per day than the control group • No group differences in carbon monoxide levels • No group differences in self- reported craving or withdrawal
Grant et al[34] (2014)	N = 28 adults with nicotine dependence and pathological gambling (82% male; 82% white)	1,200 to 3,000 mg/d (titrated based on clinician's judgment) vs placebo for 12 weeks (double-blind)	NAC group reported fewer symptoms of nicotine dependence in first half of treatment
Schmaal et al[35] (2011)	N = 22 undergraduate smokers (41% male)	1,800 mg twice daily for 3 days (3,600 mg/d) and once on Day 4 (1,800 mg) vs placebo (double-blind)	• No group differences in self- reported craving • A trend for the NAC group to report reduced withdrawal symptoms • Post-treatment cigarette smoked in the laboratory was rated as less rewarding by the NAC group, compared with the placebo group
Bernardo et al[36] (2009)	N = 75 adults with bipolar disorder (30% male; 45% smokers)	1,000 mg twice daily (2,000 mg/d) vs placebo for 6 months (double-blind)	No group differences in self-reported frequency of tobacco use

NAC: *N*-acetylcysteine

Table 5

NAC for the treatment of alcohol use disorder

Study	Sample	Dosing	Outcomes
Bernardo et al[36] (2009)	N = 75 adults with bipolar disorder (30% male; 78.7% drank alcohol)	1,000 mg twice daily (2,000 mg/d) vs placebo for 24 weeks (double-blind)	• No group differences in alcohol use, tobacco use, or caffeine use (except as described below) • NAC reduced caffeine use compared with placebo at week 2 of treatment
Back et al[39] (2016)	N = 35 veterans with SUD (82% with AUD) and PTSD	1,200 mg twice daily (2,400 mg/d) vs placebo for 8 weeks (double- blind)	• NAC combined with CBT reduced PTSD symptoms and craving compared with placebo • NAC combined with CBT reduced depression symptoms compared with placebo • No group differences in substance use
Squeglia et al[40] (2016)	N =116 adolescents (age 15 to 21) with cannabis dependence (72% male; 84% white)	1,200 mg twice daily (2,400 mg/d) vs placebo for 8 weeks (86.5% used alcohol in past 30 days)	• Adolescents in NAC group with reductions in cannabis use also had reductions in number of drinks per week • No differences in alcohol use among adolescents in the placebo group

AUD: alcohol use disorder; CBT: cognitive-behavioral therapy; NAC: *N*-acetylcysteine; PTSD: posttraumatic stress disorder; SUD: substance use disorder