Clinical Treatment of Addictive Disorders with N-Acetylcysteine

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13.1 Introduction

Substance use disorders (SUDs) and addictive behaviors constitute a global health concern, with significant societal costs in health care, crime, and productivity. Recent estimates totaled by the United States (US) National Institute on Drug Abuse (NIDA) for the total costs of SUDs in the USA alone surpassed $700 billion (Centers for Disease Control and Prevention 2016; National Institute on Drug Abuse 2017; National Drug Intelligence Center 2011; US Department of Health and Human Services 2014). It is therefore overwhelmingly beneficial to examine the ability of pharmacotherapies to reduce the use of drugs of abuse and addictive behaviors.

13.2 N-Acetylcysteine as a Potential Treatment for Addiction

There are several advantages for the potential use of NAC to treat SUDs and addictive behaviors. NAC is cost-effective and readily available and has a favorable safety profile. NAC received approval from the Food and Drug Administration (FDA) in 1963 as a mucolytic and still is used clinically as a mucolytic agent for bronchopulmonary disorders (Grandjean et al. 2000) and in the treatment of chronic obstructive pulmonary disease (COPD) (Repine et al. 1997). It is also used as an oral or

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intravenous antidote to treat acetaminophen poisoning (Smilkstein et al. 1988). NAC has a long history of safe use in both adults and children and is commonly available at retail nutritional supplement stores. However, while supplies are readily available, bioavailability is low, ranging from 4% to 10% with oral dosing (Borgström et al. 1986; Olsson et al. 1988; McClure et al. 2014), and thus large doses must be taken when delivered orally.

13.3 Modulation of Glutamate Neurotransmission by N-Acetylcysteine

Preclinical and clinical works have become increasingly focused in recent years on a glutamatergic cystine prodrug, NAC, and its potential therapeutic use against addiction has been extensively reviewed (Gass and Olive 2008; Olive et al. 2012; Asevedo et al. 2014; McClure et al. 2014; Deepmala et al. 2015; Roberts-Wolfe and Kalivas 2015; Minarini et al. 2016; Sherman and McRae-Clark 2016). This chapter will provide a brief background on NAC's potential as a pharmacotherapeutic treatment and examine the clinical literature on NAC in the treatment of addiction.

NAC's hypothesized mechanism of action as an addiction pharmacotherapy is tied to the glutamate homeostasis hypothesis of addiction (Kalivas 2009), where glutamate signaling within the mesocorticolimbic reward system has been disrupted. For a detailed discussion of the glutamate neurotransmitter system and the effect of NAC on glutamate neurotransmission, see Chap. 2 "Neurotransmitter Systems: Glutamate". However, the involvement of the glutamate system in addiction will be reviewed here.

In a drug naïve state, glutamate is released by corticostriatal fibers onto medium spiny neurons of the nucleus accumbens where it binds to postsynaptic receptors (reviewed by Scofield and Kalivas (2014)). Nearby glia are responsible for absorption of glutamate surrounding the synapse, clearing excess excitatory neurotransmitter, primarily through the glutamate transporter GLT-1 (Williams et al. 2005). Glutamate is also released from glia via the cystine-glutamate exchanger system Xc- (containing the catalytic subunit xCT, a potential pharmacotherapeutic target), which transports cystine into glial cells in exchange for outward transport of glutamate (Malarkey and Parpura 2008). After outward transport, glutamate can bind to presynaptic metabotropic glutamate receptors (mGluRs) (Moussawi and Kalivas 2010). These 2/3 subunit mGluRs provide inhibitory feedback on the presynaptic terminal, limiting synaptic glutamate release.

In the dysregulated synaptic environment of the nucleus accumbens in the addicted brain, there are multitudes of drug-induced alterations that potentially influence glutamate transmission. Most notable among them are reductions in levels of GLT-1 (Knackstedt et al. 2009, 2010; Rao and Sari 2012; Gipson et al. 2013) and the catalytic subunit of Xc- (Pierce et al. 1996; Baker et al. 2003a; Berglind et al. 2009). These reductions in glial-mediated glutamate uptake lead to an increase of extrasynaptic glutamate, which activates *N*-methyl-D-aspartate (NMDA) receptors on postsynaptic dendritic spines resulting in an increase in relapse vulnerability

(Gipson et al. 2013, 2014; Shen et al. 2014) and decreases presynaptic inhibitory mGluR2/3 tone. Without normal inhibitory feedback, excess glutamate is released from the presynaptic terminal, further derailing normal glutamate homeostasis (Knackstedt et al. 2010).

NAC has seen significant preclinical investigation as a potential addiction pharmacotherapy based on its interaction with the Xc- system. NAC is de-acetylated to form the amino acid cysteine and then oxidized to cystine, whereupon it is transported into glia in exchange for glutamate. It is this glia-released glutamate that provides inhibitory feedback on mGluR2/3 presynaptic receptors (Kalivas et al. 2005), thereby limiting the synaptic release of glutamate into the synapse. In slice electrophysiology studies, it has been shown that introducing NAC at low concentrations reduces postsynaptic glutamatergic currents through the presynaptic mGluR2/3 mechanism. However, at higher concentrations of NAC, these same currents are potentiated through the mGluR5 pathway (Kupchik et al. 2012). In addition to increased activation of xCT and GLT-1, NAC has been shown to increase expression of both transporters (Baker et al. 2003b), helping to restore glutamatergic homeostasis.

13.4 Methods

Exhaustive online literature searches of broad search terms include "clinical," "addiction," or specific substance use disorder—"cocaine," "cannabis," "marijuana," "methamphetamine," "nicotine," "tobacco," and "gambling." Where possible, filters were set on the search to limit to studies in humans and only clinical trials. We also searched the references cited in the identified publications for additional studies. One reviewer screened titles and abstracts of all potentially relevant publications.

13.5 Treatment Studies of Addiction with N-Acetylcysteine

This section will review the clinical treatment studies of addiction to cannabis, cocaine, methamphetamine, nicotine, and gambling disorder using NAC (Table 13.1) (See Online Tables 13.1, 13.2, 13.3, 13.4, and 13.5 for summary of studies).

13.5.1 NAC and Cocaine Use Disorder

Preclinical research using rodent self-administration of cocaine has yielded promising results for the ability of NAC to reduce cocaine-seeking behavior, cocaine intake, and cocaine-induced behavioral sensitization (Baker et al. 2003b; Madayag et al. 2007; Moussawi et al. 2009; Amen et al. 2011; Moussawi et al. 2011; Reichel et al. 2011; Murray et al. 2012; Reissner et al. 2015). Importantly, these preclinical works have supported the underlying hypothesis of imbalances in glutamatergic signaling within the nucleus accumbens as a driver of addictive behaviors.

The majority of clinical research thus far examining NAC's therapeutic effects on addictive behaviors has been conducted with cocaine (Online Table 13.1). Initial clinical work on the treatment of cocaine use disorder with NAC was published in 2006 and utilized a double-blind, placebo-controlled, within-subject, inpatient study design to assess the safety and tolerability of NAC in adults with cocaine dependence confirmed by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV; First et al. 1994). Thirteen subjects reported significant decreases in cocaine-related withdrawal symptoms, reduced cravings, and less cocaine use for 1 week following the inpatient phase and NAC dosing (LaRowe et al. 2006). A follow-up study containing a portion of LaRowe et al. (2006) subjects investigated NAC's effectiveness on cue-induced craving and demonstrated a reduced desire in adults to use cocaine when in the presence of cocaine-related cues, a reduced interest evoked by viewing cues, and a decrease in time the cues were viewed (LaRowe et al. 2007). NAC also significantly decreased reported craving following cocaine injection in a single-blind study but had no effects on the euphoric components (sensations of the "rush" and "high") of cocaine use (Amen et al. 2011). An open-label trial of NAC among cocaine users showed a reduction in biochemically confirmed cocaine use (Mardikian et al. 2007). Lastly, a large double-blind, placebo-controlled, randomized clinical trial study of NAC intervention failed to show a reduction in active cocaine use (LaRowe et al. 2013). Interestingly in this study, when examining only subjects abstinent from cocaine at the start of the trial, NAC seemed to increase the time to relapse and reduced craving, consistent with previous studies, though this study was not powered to find that effect. This finding suggests that NAC may be more effective at preventing psychostimulant relapse than promoting initial cessation, but that has yet to be directly tested.

There has been one clinical study to image glutamate concentration in the dorsal anterior cingulate cortex (dACC) of 22 human subjects (8 cocaine-dependent, 14 healthy) using proton magnetic resonance spectroscopy after a single dose of NAC (Schmaal et al. 2012). This open-label, randomized, crossover study demonstrated significantly higher baseline levels of glutamate in the dACC of the cocaine-dependent subjects. Administration of NAC reduced glutamate levels of the cocaine-dependent subjects, while no effect was seen in healthy controls. Impulsivity was recorded using the Barratt Impulsiveness Scale and compared to glutamate levels: higher baseline levels of glutamate were associated with exhibited higher impulsivity. Furthermore, both higher impulsivity and higher glutamate levels were predictive of a reduction in glutamate levels in response to NAC treatment. This study is therefore illustrative of NAC's capabilities to address imbalance in glutamate homeostasis and clinical potential.

13.5.2 NAC and Cannabis Use Disorder

Similar to cocaine, there are no FDA-approved pharmacotherapies for cannabis use disorder, though clinical work has also explored NAC as a candidate pharmacotherapeutic agent (Online Table 13.2). There is a notable dearth of preclinical work specifically investigating the effects of NAC on cannabis administration. However,

due to NAC's hypothesized mechanism of action and considerable preclinical success for other drugs of abuse, NAC has been investigated clinically for cannabis use disorders.

An open-label study by Gray and colleagues tested NAC's efficacy among adolescents and young adults, reporting a decrease in self-reported cannabis use throughout the duration of the study and a significant reduction in certain constructs of cannabis craving, but no difference was seen in urine cannabinoid tests (Gray et al. 2010). Gray and colleagues (Gray et al. 2012) conducted a double-blind, randomized, placebo-controlled trial of NAC, in addition to a behavioral platform to promote abstinence, in cannabis-dependent adolescents, and found that participants receiving NAC had more than twice the odds of a negative urine cannabinoid test compared to those who received placebo. In a secondary analysis from that clinical trial, Roten and colleagues (Roten et al. 2013) examined cannabis craving changes among participants treated with NAC and found no treatment effect compared to placebo using the Marijuana Craving Questionnaire (MCQ; Heishman et al. 2001), though a decrease in craving was seen over time for both groups. This is potentially indicative of NAC's cessation effects being due to another mechanism and not through craving as initially hypothesized.

13.5.3 NAC and Methamphetamine Use Disorder

As with cannabis, there has been no published preclinical research on the effectiveness of NAC in reducing methamphetamine administration or reinstatement. Regardless, NAC has been explored in clinical research for methamphetamine use (Online Table 13.3), which also currently lacks any FDA-approved pharmacotherapies. Grant and colleagues (Grant et al. 2010) examined a combination of NAC and naltrexone on methamphetamine cravings. Adult men and women were tested in a double-blind, placebo-controlled study where NAC treatment also included a minimum of 50 mg/day of naltrexone. Cravings were measured using a modified Penn Craving Scale (PCS) (Flannery et al. 1999), with additional measurement of self-reported methamphetamine use, urine tests, and tests for illness severity, depression, anxiety, disability, and quality of life at various study time points. Participants on treatment showed no significant difference in cravings or drug use frequency nor any differences in other measured clinical characteristics as compared to placebo. A second study on methamphetamine use disorder utilized a double-blind, crossover design to examine craving (through a cocaine craving scale) (Mousavi et al. 2015). NAC treatment significantly reduced methamphetamine craving, counter to the study discussed previously.

13.5.4 NAC and Tobacco Use Disorder

NAC as a treatment for tobacco use disorder has seen considerable increase over the last decade for both preclinical and clinical research (Online Table 13.4). Preclinical

research using rodent models of nicotine self-administration has shown that chronic NAC administration inhibits nicotine-seeking and transient increases in synaptic plasticity within the nucleus accumbens (Gipson et al. 2015). Additionally, acute NAC administration has proven effective at reducing nicotine self-administration without altering motivation for food responding (Ramirez-Niño et al. 2013). NAC therefore has a high potential of effectiveness at treating nicotine addiction in a clinical setting.

A study of 33 healthy individuals attempting to quit smoking measured cigarette craving, withdrawal, and biochemical verification of smoking (through breath carbon monoxide [CO]). Daily oral treatment with 2400 mg NAC yielded no differences in any measurements, though a trend toward fewer cigarettes smoked per day did occur (Knackstedt et al. 2009). In a study of 23 young adults asked to refrain from smoking during a 4-day double-blind, placebo-controlled study, 3600 mg/day NAC produced no difference in nicotine craving but did reduce withdrawal scores and measures of the rewarding properties of the first cigarette posttreatment (Schmaal et al. 2011). Another study tested open-label NAC in combination with the α4β2 nicotinic receptor antagonist varenicline (Chantix®) in daily cigarette smokers and found a reduction in cigarettes smoked per day and decreases in craving and smoking reward, as well as safety and tolerability of this combination pharmacotherapy (McClure et al. 2015). A study from Prado and colleagues (Prado et al. 2015) investigated smoking cessation in 34 tobacco-dependent patients, analyzing the number of cigarettes smoked, exhaled CO, depression severity, and occupational, social, and familial disability according to the Sheehan Disability Scale (Leon et al. 1997). All ratings were made at baseline and 4, 8, and 12 weeks post-baseline. All treatment administration was double-blinded and placebo-controlled and simultaneous with monthly group behavioral therapy. NAC patients received 3000 mg/day in two daily doses. NAC treatment resulted in a significant reduction in cigarette consumption at 12 weeks. Furthermore, at 12 weeks NAC significantly decreased exhaled CO, depression severity, and all disability scores on the Sheehan Disability Scale. Finally, a study investigating the effects of NAC on cannabis smoking also examined NAC's effects on the subset of the study population who smoked cigarettes (McClure et al. 2014). NAC did not alter the number of cigarettes smoked per day in this subpopulation, and co-consumption of nicotine had no apparent effects on cannabis abstinence, though there was a reported trend toward poorer cannabis outcomes for cigarette smokers vs. non-smokers.

There has been one clinical imaging study using functional magnetic resonance imaging (fMRI) to investigate NAC's effects on the frontostriatal resting-state functional connectivity (rsFC) on nicotine withdrawal symptoms (Froeliger et al. 2015). As chronic drug use is thought to produce alterations in synaptic plasticity, the investigation of systems-level functional connectivity between the prefrontal cortex and the striatum could provide significant evidence for NAC's ability to treat disruptions in glutamate homeostasis. In a double-blind, randomized, placebo-controlled study of 16 adult nicotine-dependent subjects, 2400 mg/day NAC increased rates of abstinence, reduced reported craving, and demonstrated increased rsFC compared to placebo. These results are similar to the previous imaging study reported for

NAC's treatment effects on cocaine dependence (Schmaal et al. 2012), suggesting NAC does indeed help to restore regular glutamate homeostasis and signaling.

Studies of NAC for tobacco use disorder have also been conducted with patient populations with co-occurring psychiatric disorders. In one study assessing tobacco use and gambling, NAC augmented behavioral therapy after 6 weeks of treatment in a double-blind, placebo-controlled study of 28 adults. Nicotine dependence scores reduced during the treatment period but returned to baseline at the 3-month follow-up (Grant et al. 2014). Another study on the efficacy of NAC on tobacco, alcohol, and caffeine use in patients with bipolar disorder demonstrated significant decreases in caffeine consumption at one time point, but no effect on tobacco use (Bernardo et al. 2009).

13.5.5 NAC and Gambling Disorder

In addition to SUDs, the DSM-5 lists gambling disorder as similar to drugs of abuse in regard to the activation of the brain reward system and symptom overlap (American Psychiatric Association 2013). NAC, which has been shown to influence intake of other drugs of abuse, therefore has potential as a treatment option for gambling disorder (Online Table 13.5). Grant and colleagues (Grant et al. 2007) utilized NAC in an 8–12-week open-label trial, after which subjects transitioned to a 6-week double-blind, placebo-controlled study. The Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS; Grant et al. 2004), Gambling Symptom Assessment Scale (G-SAS; Kim et al. 2001), Clinical Global Impression—Improvement and Severity scales (Guy 1976), Sheehan Disability Scores (Sheehan 1983), and Hamilton Depression and Anxiety Rating Scales (Hamilton 1959, 1960) were utilized as reporters. At the end of the open-label phase of the trials, NAC treatment reduced PG-YBOCS scores, greater than half of subjects listed CGI-improvement scores of "much" to "very much improved," and level of functioning, quality of life, depressive symptoms, and anxiety symptoms all improved, though not to significant levels. The double-blinded portion of the trials showed a statistical trend toward a prolonged response to NAC, indicative of NAC's effectiveness compared to placebo. In a study reported previously for nicotine treatment, double-blind, placebo-controlled administration of 1200–3000 mg/day NAC concurrent with psychosocial intervention showed significant benefits on measures of problem gambling severity after 3 months post-treatment (Grant et al. 2014).

13.6 Tolerability and Safety of NAC

Across multiple studies for several different addictive pathologies, little to no serious adverse events have been reported for NAC. A total of 8 of the 20 studies discussed here report no adverse events. Of the remaining 12, the most commonly reported adverse events include pruritus, headache, gastrointestinal issues including

flatulence, diarrhea, and abdominal cramps, dizziness, and elevated blood pressure. One study reported vivid dreams, while another reported insomnia. Dosing for the studies discussed here ranged from 1000 to 3600 mg NAC per day, with consistent use for up to 24 weeks for one study (Bernardo et al. 2009). Most studies were 4 and 12 weeks in duration. This prolonged duration of use also speaks to tolerability profile of NAC. Additionally, NAC does not require a dose induction period to reach the goal dose of medication, which can be started immediately with little issue. In sum, NAC profiles as safe and tolerable for the treatment of addiction and general use, consistent with its availability at many health-focused retail stores.

13.7 Limitations and Future Directions of NAC in the Clinic

In summary, NAC has seen considerable use as a clinical treatment for substance use disorders across several different substances and addiction behaviors with some important successes. NAC has had mixed efficacy in terms of cessation outcomes. Based on preclinical work, NAC may be successful as a relapse prevention pharmacotherapeutic, as it is able to restore balance to the glutamatergic system that is targeted by drugs of abuse. Limited success as a cessation treatment may indicate that its effectiveness is potentially limited to those who have already achieved some initial measure of success to stop drug use.

In addition to NAC's use to treat addiction and addictive-like behaviors, NAC has also seen use for a variety of other psychiatric disorders, as reviewed by Deepmala and colleagues and Berk and colleagues (Berk et al. 2013; Deepmala et al. 2015). These include Alzheimer's disease, amyotrophic lateral sclerosis (ALS), autism spectrum disorders, epilepsy, neuropathy, and schizophrenia, among others. Results from these psychiatric and neurological disorder studies have been mixed, though it is speculated that NAC's effects on multiple metabolic pathways could explain why some clinical results are positive and some negative (Deepmala et al. 2015). Additional investigation is necessary to acquire a better understanding of NAC's viability as a treatment option for a broad spectrum of disease and disorder. Further preclinical investigation of NAC is necessary and ongoing as well, with emphasis on translating NAC's preclinical effectiveness for both alcohol and opioid addiction to the clinic. Efforts should be made to better understand the mixed results from the clinical literature to determine the populations for which NAC will serve as an efficacious pharmacotherapy. NAC has been shown to produce positive outcomes in rodents for both alcohol (Ozaras et al. 2003; Seiva et al. 2009, 2009) and opioids (Zhou and Kalivas 2008), but neither has been tested in clinical populations. The promise of NAC seen with other drugs of abuse highlights the need to expand testing in these instances and has been promoted as such in a review by Holmes et al. (Holmes et al. 2013). Recently, a study investigating NAC's effects on short- and long-term access to cocaine in rodents indicated no effect on either escalation of cocaine self-administration or the overall motivation for cocaine (Ducret et al. 2015). However, treatment with NAC promoted cessation of intake in long-access animals when self-administration was paired with contingent foot shocks, indicative

of a reduction in compulsivity, and NAC also reduced consumption and increased latency upon returning to a non-punished schedule. Furthermore, Ducret and colleagues utilized a lower, more human-relevant dose of NAC [60 mg/kg] than most preclinical studies employ. This study therefore underscores the importance of treatment regimen with NAC as seen with previous clinical studies, as animals receiving chronic NAC did not fail to elevate cocaine intake upon starting longer access regimens, but did still alter the neurobiology thought to underlie one potential addiction mechanism. Therefore, NAC treatment during non-abstinent periods may be ineffective at promoting long-term abstinence (Gipson 2016).

Further research into other glial modulators has demonstrated promising results similar to NAC (see reviews by Cooper et al. (2012) and Scofield and Kalivas (2014)). For example, propentofylline (PPF), an atypical methylxanthine derivative, is known as a neuroprotective compound (Sweitzer and De Leo 2011) shown to increase expression of GLT-1 following spinal cord injury in mice (Tawfik et al. 2008). In preclinical tests of PPF in cocaine-administering rats, daily treatment reduced reinstatement through a GLT-1-dependent mechanism (Reissner et al. 2014). Furthermore, acute intraperitoneal injection of PPF suppressed conditioned place preference for methamphetamine and morphine in mice, indicative of a potential role for glial cells in the rewarding properties of both drugs (Narita et al. 2006). Another glial modulator, ibudilast [AV411], has been investigated as it shares similar phosphodiesterase inhibitor properties to PPF (see review by Rolan et al. (2009). Ibudilast has also demonstrated significant effects on methamphetamine consumption, locomotion, sensitization, and reinstatement (Beardsley et al. 2010; Snider et al. 2012), ethanol consumption (Bell et al. 2015), and morphine-induced neurobiological alterations and conditioned place preference (Rolan et al. 2009; Schwarz and Bilbo 2013). In sum, glial modulation represents an exciting research avenue to explore for the reduction of substance use disorders in both the preclinical and clinical fields.

In sum, clinical investigation of NAC's potential as a pharmacotherapeutic treatment of SUDs has shown variable success across drugs, and clinical studies are ongoing (Table 13.2). Controlled studies of NAC in cocaine use disorder and cannabis use disorder have had 50% or greater positive outcomes (Table 13.3).

Table 13.1 Summary of NAC mechanisms of action across different substance use and addictive disorders

Substance use or addictive disorder	Mechanism of N-Acetylcysteine (NAC)
Cocaine use disorder	NAC is thought to restore the balance of glutamate within the mesocorticolimbic reward system typically disrupted by drugs of abuse. Notably, expression levels of the astroglial glutamate transporter GLT-1 are reduced (Knackstedt et al. 2009, 2010; Rao and Sari 2012; Gipson et al. 2013) along with reductions in the catalytic subunit of Xc- (Pierce et al. 1996; Baker et al. 2003a; Berglind et al. 2009). It is thought that NAC, de-acetylated and oxidized into cystine, will activate Xc- and cause glial glutamate release onto inhibitory mGluRs located on presynaptic terminals (Kalivas et al. 2005), reducing further glutamate release onto postsynaptic receptors
Cannabis use disorder	
Methamphetamine use disorder	
Tobacco use disorder	
Gambling disorder	

Table 13.2 Ongoing clinical trials on N-Acetylcysteine for addiction

Trial title	NCT #	Trial status
Effects of N-Acetylcysteine on brain chemistry and behavior in cocaine abusers (NAC)	NCT01392092	Recruiting
Glutamate-glutamine cycling (VCYC) during cocaine abstinence using 13C-MRS	NCT02124941	Recruiting
Neurobiological adaptations and pharmacological interventions in cocaine addiction	NCT02626494	Recruiting
N-Acetylcysteine for tobacco use disorder	NCT02737358	Recruiting
Clinical trial for alcohol use disorder and post-traumatic stress disorder (PTSD)	NCT02966873	Recruiting
Efficacy of N-Acetylcysteine in bipolar disorder and tobacco use disorder (NACBD)	NCT02252341	Recruiting
Achieving cannabis cessation-evaluating N-Acetylcysteine treatment (ACCENT)	NCT01675661	Completed. No results posted

Table 13.3 Overall ratings of NAC based on clinical studies presented by condition

Substance use or addictive disorder	Uncontrolled studies positive% (positive/total)	Controlled studies positive% (positive/total)	Grade of recommendation	Recommendation for treatment
Cocaine use disorder	100% (1/1)	62.5% (2.5/4)	B	Mixed
Cannabis use disorder	50% (0.5/1)	50% (0.5/1)	B	None
Methamphetamine use disorder	–	25% (0.5/2)	B	None
Tobacco use disorder	50% (0.5/1)	50% (3/6)	B	Mixed
Gambling disorder	100% (1/1)	25% (0.5/2)	B	None

Controlled studies of methamphetamine use disorder, tobacco use disorder, and gambling disorder have had less than 50% positive outcomes (but no less than 25%), though the literature remains sparse for some drugs. All uncontrolled studies yielded greater than or equal to 50% positive outcomes. It is therefore necessary to continue investigation of NAC's efficacy as a SUD treatment option. Of particular interest is examination of NAC's apparent differential effects in cessation vs. relapse and how administration timing alters NAC's impact.

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