Revista Brasileira de Psiquiatria. 2014;36:168–175

doi:10.1590/1516-4446-2013-1244

REVIEW ARTICLE

Systematic review of N-acetylcysteine in the treatment of addictions

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Objective: To conduct the first systematic literature review of clinical trials of N-acetylcysteine (NAC) for the treatment of substance abuse disorders and addictive behaviors.
Methods: A search of the MEDLINE, Embase and PsycINFO databases was conducted. The inclusion criteria for the review were clinical trials that used NAC in the treatment of a disorder related to substance use and/or addictive behaviors, limited to texts in English, Spanish, or French. The selected studies were evaluated with respect to type of trial, sample size, diagnostic input, intervention, length of follow-up, outcome variables, and results.
Results: Nine studies analyzing a total of 165 patients met the eligibility criteria and were included in qualitative analysis. These studies evaluated the role of NAC in cocaine dependence (three studies), cannabis dependence (two studies), nicotine dependence (two studies), methamphetamine addiction (one study), and pathological gambling (one study). Five of these trials were double-blind, randomized, and placebo-controlled.
Conclusions: The studies analyzed suggest a potential role for NAC in the treatment of addiction, especially of cocaine and cannabis dependence. These results are concordant with the hypothesis of the involvement of glutamatergic pathways in the pathophysiology of addiction.

Keywords: Drug dependence; addictive behaviors; N-acetylcysteine; glutamatergic receptors; smoking

Introduction

Substance use disorders and addictive behaviors are serious public health problems and major contributors to the global burden of disease.[1] Despite recent advances in technology to study the brain changes related to addiction, advances in neurobiological knowledge have not been successfully translated into clinical practice.[2,3]

Recently, changes in glutamatergic neurotransmission have been implicated in the pathophysiology of addiction.[4] Preclinical studies showed reduced basal glutamate levels in the nucleus accumbens of rodents chronically treated with cocaine, and that this reduction appears to be associated with pleasure-seeking behavior.[5-8] Reinstatement of cocaine-seeking behavior was also related to a reduction in baseline extracellular concentrations of glutamate, resulting in a lower tonic activation of group 2 metabotropic glutamate receptors (mGluR2/3), which usually inhibit presynaptic release of glutamate.[5] In the brain, basal levels of extracellular glutamate are maintained by the exchange of extracellular cystine for intracellular glutamate.[5] Thus, the restoration of basal levels of glutamate, with a consequent increase in tonic activation of the mGluR2/3 receptor, has been proposed as a promising target for pharmacological treatment of dependence.[9]

N-acetylcysteine (NAC) is a molecule derived from the amino acid cysteine and is commonly used in the treatment of respiratory diseases, in paracetamol poisoning, and in the prevention of contrast-induced nephropathy.[10,11] Its half-life is approximately 6 hours and 30% of the drug is excreted by the kidneys.[10] Side effects are mild and infrequent.[10] NAC is a precursor of cysteine and of glutathione, and works as a prodrug of these molecules.[12] Direct administration of cysteine is not possible in clinical settings because of its limited bioavailability, toxicity, and insolubility.[12]

As a prodrug of cysteine, NAC produces interesting effects in the glutamatergic system. Extracellular cysteine generated from NAC is transported into the cell, while intracellular glutamate is transported out of the cell through the cysteine/glutamate transporter. As noted above, restoration of extracellular levels of glutamate increases tonic activation of mGluR2/3 receptors.[9,13] These receptors are mostly presynaptic, and inhibit glutamatergic neurotransmission and excitotoxicity.[5] This effect of NAC and its implications for drug addiction were demonstrated in animal models, in which reestablishing normal levels of extracellular glutamate reduced

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Submitted Aug 27 2013, accepted Oct 16 2013.

relapse of drug-seeking behavior in rats chronically treated with cocaine[9] and heroin.[14]

NAC has additional actions on oxidative biology, by acting as a glutathione precursor and with OH, NO_2, CO_3 (-), and thiyl radicals.[15] It has anti-inflammatory effects, impacts apoptosis and neurogenesis, and reverses models of mitochondrial toxicity. These pathways are implicated in the pathways that underlie neuroprogression in multiple psychiatric disorders; hence, NAC has been proposed as a neuroprotective agent.[16]

Taking into consideration these mechanisms of action, several studies conducted in recent years have tested NAC for the treatment of addiction. The objective of this paper was to conduct the first systematic literature review of clinical trials of NAC for the treatment of disorders related to substance use and addictive behaviors.

Methods

A search of the electronic medical literature databases MEDLINE, Embase, and PsycINFO was conducted. The basic search strategy for MEDLINE was as follows: (addictive behavior OR addiction OR drug dependence OR drug abuse OR substance-related disorders OR substance use disorders OR substance abuse) AND (N-acetylcysteine OR NAC OR N-acetyl-l-cysteine OR acetylcysteine OR mercapturic) AND (clinical trials). The searches conducted in the other databases were analogous. Furthermore, additional studies were obtained by checking the references of selected articles. The last search date for inclusion of new references was May 5, 2013.

The eligibility criteria for the review were clinical trials that assessed NAC use as the independent variable and clinical outcomes related to an addiction. Also, the main inclusion criterion of each trial should be the diagnosis of a substance use disorder or an addictive behavior. The search was limited to texts in English, Spanish, or French.

The titles and abstracts of studies identified by the search strategy were evaluated by two investigators (EA and ACM) independently and selected items were read in full. Divergent selection of items was discussed among the investigators until a consensus was obtained. The selected studies were evaluated with respect to type of trial, sample size, diagnostic input, intervention, length of follow-up, outcome variables, and results.

Results

The MEDLINE, Embase, and PsycINFO search strategy yielded 117 citations. After removal of duplicate references and screening of titles and abstracts, 11 articles were selected for full-text reading. Using the established eligibility criteria, nine studies were selected for inclusion in the review (Figure 1). The studies analyzed included a total of 165 individuals with substance-use related disorders or addictive behaviors and 14 controls. The years of publication were 2007-2012, indicating that investigation of NAC in this clinical setting is recent. Table 1 summarizes the main characteristics of the included studies.

The next section provides a qualitative description of the analyzed studies, grouped by diagnosis at inclusion.

Cocaine dependence

Three studies evaluated the use of NAC in individuals with cocaine dependence.[17-19] Mardikian et al.[17] conducted a 4-week open trial in 23 patients, using 3 different dosages of NAC, namely, 1.2 g (n=8), 2.4 g (n=9), and 3.6 g (n=6). The sample included 22 males and one female, and the average age was 40 years. All the participants sought treatment voluntarily. Of those who took at least one dose of medication, seven (30%) did not complete treatment. The variables used to quantify the effect of intervention on cocaine use were the number of days of use and the money that was spent on use, comparing the 28 days prior to treatment with the 28-day period of treatment. The three intervention groups were pooled for this analysis, since the sample size did not allow comparisons between groups. There was a significant reduction in both the number of days of cocaine use (mean 8.1 before treatment and 1.1 during, $p = 0.001$) and in dollars spent for use ($1,292.8 before treatment and $52.2 during, $p < 0.0001$).

LaRowe et al.[18] conducted a double-blind, randomized, placebo-controlled crossover study in 15 hospitalized individuals (seven men and eight women) who had not sought treatment voluntarily. The subjects were randomized to placebo or 1.2 g/day of NAC for 3 days. After 4 days, the subjects received the other intervention. The average age of the sample was 37 years. The primary outcome was the desire to use, craving, interest in cocaine reported by the subjects, time spent on slides of a presentation showing images related to cocaine use, and electrophysiological measures during the slideshow. NAC reduced the desire to use cocaine ($F = 5.07$, degrees of freedom [df] = 1,13, $p < 0.05$), interest in cocaine ($F = 5.07$, df = 1,13, $p < 0.05$), and time spent on the slides in the presence of cues associated with cocaine use ($F = 4.79$, df = 1,13, $p < 0.05$). There were no differences with respect to craving and electrophysiological variables.

Schmaal et al.[19] conducted a magnetic resonance spectroscopy study to evaluate the effect of NAC on the levels of glutamate in the dorsal anterior cingulate cortex (dACC) in patients with cocaine dependence. They included eight patients with cocaine dependence and 14 healthy controls in an open-label crossover trial, using a single 2.4-g dose of NAC. Magnetic resonance spectroscopy was performed 1 hour after ingestion of the medication. After administration of NAC, dACC glutamate levels were reduced in the group of cocaine-dependent individuals ($t(7) = 3.08$, $p = 0.02$). There was no change in the control group (-0.64, $p = 0.53$). The Barratt Impulsiveness Scale (BIS-11) was used to estimate impulsivity. Higher scores on the BIS-11 were associated with reduction of glutamate levels in the dACC ($\beta = 0.47$, $t(22) = 2.38$, $p = 0.03$).

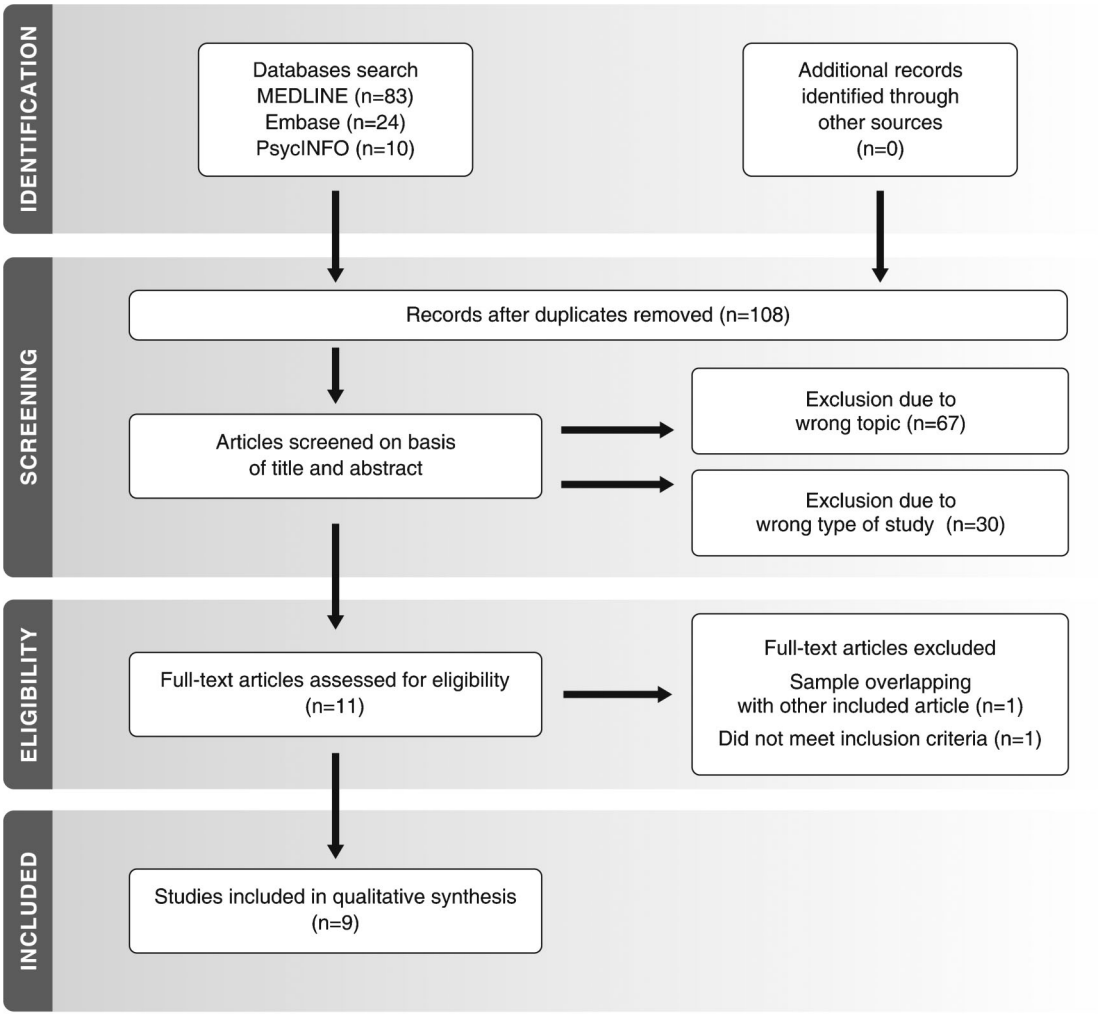

Figure 1 Systematic review flowchart

Cannabis addiction

Two studies evaluating the use of NAC in cannabis dependence were found (20, 21). Gray et al.[20] conducted a 4-week open-label study using 2.4 g/day of NAC in 24 patients with cannabis dependence voluntarily seeking treatment (18 men and six women). The mean age was 19 years. There was a small reduction in self-reported use of cannabis, from 6.1 days/week of use before treatment to 5.2 days/week in the second week ($p = 0.006$), 5.2 days/week in the third week ($p = 0.001$), and 5.3 days/week in the fourth week ($p = 0.03$). There was no significant reduction in the number of joints/day. There was a reduction in cravings for marijuana, assessed using the Marijuana Craving Questionnaire ($p < 0.01$). These findings notwithstanding, there was no reduction in urinary levels of cannabinoids during the treatment period, as measured by semiquantitative cannabinoid urinary levels corrected for creatinine.

Gray et al.[21] conducted a double-blind, randomized trial using 2.4 g/day of NAC (n=58) or placebo (n=58) for 8 weeks in adolescents with a diagnosis of marijuana dependence. In addition, individuals in both groups received a contingency management intervention and cessation counseling. The sample comprised 116 subjects (84 male and 32 female), with a mean age of 18.9 years. Outcome variables were weekly urinary dosage of cannabinoids and self-reported cannabis use. Participants in the NAC group had more than twice the odds of having a negative urine cannabinoid test compared to the placebo group (odds ratio = 2.4, 95%CI 1.1-5.2; c2 = 4.72, $p = 0.029$). There was no between-group difference in the number of reported days of marijuana use.

Nicotine addiction

Three studies evaluated the use of NAC in patients with nicotine dependence.[22,23] Knackstedt et al.[22] conducted a double-blind, randomized trial in a sample of 33 subjects (mean age 50 years; 19 male and 14 female). Of the 33 subjects randomized, four did not complete the study. Of the 29 subjects who completed the study, 14 were treated with 2.4 g of NAC and 15 received placebo for 4 weeks. The efficacy endpoints were: 1) scores of craving measured by the Questionnaire for Smoking

Table 1 Clinical trials of NAC in addictive behavior

Disorder/study	Design	n	Intervention	Results
Cocaine dependence				
Mardikian[1]	4-week open-label trial	23	NAC 1.2 g (n=8); 2.4 g (n=9); 3.6 g (n=6)	Reduction in self-reported cocaine use
LaRowe[2]	Double-blind randomized crossover trial	15	NAC 1.2 g or placebo for 3 days, followed by a 3-day crossover phase after 4 days	Less self-reported desire to use and less response to cocaine cues during the NAC phase
Schmaal[3]	Open-label randomized crossover trial	22	Single 2.4 g NAC dose phase and a placebo phase in patients (n=8) and controls (n=14)	Reduction in glutamate levels in the dACC of cocaine-dependent subjects after NAC
Cannabis dependence				
Gray[4]	4-week open-label trial	24	NAC 1.2 g	Reduction in self-reported craving
Gray[5]	8-week double-blind randomized trial	116	NAC 2.4 g (n=58) or placebo (n=58)	More negative urine tests in the NAC group (odds ratio 2.4, 95%CI 1.1-5.2)
Nicotine dependence				
Knackstedt[6]	4-week double-blind randomized trial	29	NAC 2.4 g (n=14) or placebo (n=15)	NAC group reported a non-significant reduction in the number of cigarettes smoked
Schmaal[7]	3.5-day double-blind randomized trial	22	NAC 3.6 g (n=10) or placebo (n=12)	No significant effect of NAC on craving and withdrawal symptoms
Methamphetamine dependence				
Grant[8]	8-week double-blind randomized trial	31	NAC 0.6-2.4 g + naltrexone 50-200 mg (n=14) or placebo (n=17)	No differences in primary and secondary outcomes
Pathological gambling				
Grant[9]	I) 8-week open-label and II) 6-week double-blind trial in responders	13	NAC 1.8 g (n=6) placebo (n=7)	I) Reduction in baseline symptoms (20.3 vs. 11.8, $p < 0.001$); II) More responders in NAC group (83.3 vs. 28.6)

95%CI = 95% confidence interval; dACC = dorsal anterior cingulate cortex; NAC = N-acetylcysteine.

Urges - Brief (QSU-B), 2) symptom scores of nicotine withdrawal measured by the Minnesota Withdrawal Scale (MNWS), 3) measurement of expired CO_2, and 4) self-reported cigarette use. There was no significant difference between groups in the number of cigarettes smoked daily (17.7 in NAC group vs. 19.7 in the placebo group). On exploratory analysis, there was a trend toward a time effect in cigarettes smoked weekly ($p = 0.06$) and a significant effect for day on analysis of cigarettes smoked daily ($F(26,600) = 2.4$, $p < 0.001$), although alcohol consumption was a significant covariate in this interaction. There was no significant difference in measured CO_2 levels or in QSU-B or MNWS scores.

Schmaal et al.[23] conducted a double-blind, randomized, placebo-controlled study to evaluate the effect of NAC on short-term abstinence from cigarettes. Twenty-three individuals who smoked at least 15 cigarettes/day were initially randomized. Of the 22 patients who completed the study, 10 received 3.6 g of NAC and 12 received placebo for 3.5 days. The mean age of the sample was 20.7 years (nine men and 13 women). Patients were asked to cease smoking, and abstinence was determined by measurement of expired CO_2. Severity of withdrawal symptoms and craving were assessed using the MNWS and QSU-B respectively. On the last day of treatment, participants were asked to smoke one cigarette and rate, on a visual scale of 1 to 100, the pleasure obtained from that cigarette. There was no significant between-group difference in MNWS or QSU-B scores. The group that received NAC reported significantly less pleasure in the first cigarette smoked compared to the placebo group (42.6 vs. 65.6, $p = 0.04$).

Methamphetamine addiction

Only one study has evaluated the use of NAC in individuals with methamphetamine dependence.[24] In an 8-week double-blind trial, 39 patients were randomized, and 31 returned for at least one follow-up evaluation. They received either placebo (n=17) or a combination of naltrexone and NAC (n=14). Doses ranged from 0.6 g NAC and 50 mg naltrexone in the first 2 weeks up to 2.4 g NAC and 200 mg naltrexone in the last 2 weeks. The average age of the sample was 36.8 years (22 men and nine women). The primary outcome was craving severity assessed by the Penn Craving Scale. Secondary outcomes were the number of days of methamphetamine use and urine toxicology. The authors reported a trend toward reduction in the number of days/week of use in the intervention group compared with the placebo group (6.7 vs. 4 days, $p = 0.081$). Nonetheless, there were no statistically significant between-group differences in any of the outcome variables.

Pathological gambling

Grant et al.[25] conducted a clinical trial to assess the effect of NAC in subjects with pathological gambling. The study had two phases: an initial 8-week open-label phase with increasing doses of NAC (0.6 to 1.8 g) and a double-blind discontinuation of medication in responders, lasting 6 weeks. The primary outcome variable was the severity of symptoms of pathological gambling measured by the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS). Response was defined as a reduction of 30% or more in PG-YBOCS scores. The authors also used the Gambling Symptom Assessment Scale (G-SAS), a self-report scale of symptom severity. Twenty-nine patients (15 men and 12 women) were included in the open study. Two patients did not return for any of the assessments and were excluded from the analysis. The average age was 50.8 years. There was a 41.9% reduction in PG-YBOCS scores during the open-label phase, from 20.3 to 11.8 ($t(50) = 4.7$, $p < 0.001$). There was also a 40.2% reduction in the G-SAS, from 32.3 to 19.3 ($p < 0.001$). There were 16 responders, and 13 agreed to continue in the double-blind discontinuation phase. During this phase, six patients were randomized to continue using NAC and seven to receive placebo. Of those allocated to receive NAC, 83.3% still fulfilled response criteria at the end of 6 weeks vs. 28.6% in the discontinuation group (Fisher's exact test = 0.078, φ coefficient = -0.55). There was a trend toward a difference between the groups with respect to changes in PG-YBOCS and G-SAS scores, but it was not statistically significant ($p = 0.095$ for the PG-YBOCS and $p = 0.06$ for G-SAS).

Discussion

We conducted a systematic literature review of clinical trials of NAC for the treatment of individuals with disorders related to substance use or addictive behaviors. Nine studies, representing a total of 243 patients, met the eligibility criteria and were included in the qualitative analysis. These studies evaluated the efficacy of NAC in cocaine dependence,[17-19] cannabis dependence,[20,21] nicotine dependence,[22,23] methamphetamine dependence,[24] and pathological gambling.[25] Five of these trials were double-blind, randomized, and placebo-controlled.[18,21-24] Among them, we highlight the study by Gray et al.,[21] with the largest sample size (n=116), which evaluated the use of NAC in adolescents with marijuana dependence. This study found a significant reduction in the number of negative urine tests in the NAC group. Overall, despite methodological limitations, the compiled studies indicate a potentially important role for NAC in the treatment of cocaine dependence and marijuana dependence. The findings in the treatment of pathological gambling were limited to secondary outcomes. Studies of NAC in methamphetamine addiction and smoking presented negative results.

Two relevant studies screened to be read in full did not meet the eligibility criteria and were excluded from the qualitative analysis. In a subgroup of cocaine-dependent individuals that was included in another study,[18] LaRowe et al.[26] presented preliminary results regarding safety, tolerability, self-reported craving, and withdrawal symptoms. Thirteen patients received placebo or 600 mg NAC twice daily during a 3-day hospitalization. Individuals received the other intervention during another 3-day hospitalization in the following week. No unexpected side effects were reported, and none of the serious side effects associated with intravenous NAC, such as allergic reactions or seizures, occurred. Only mild side effects were reported, without differences between conditions. There were no between-group differences in self-reported craving and withdrawal symptoms, although within-group analysis of these variables revealed a significant difference between pre- and post-treatment only in the NAC condition.

The other excluded study assessed reduction in substance use among individuals with bipolar disorder.[27] Data on substance use were collected from a 24-week, double-blind, randomized, placebo-controlled trial of NAC for depressive symptoms in bipolar disorder.[28] Individuals received 2 g/day NAC (n=38) or placebo (n=37). The frequency of substance use in the sample was as follows: 78.7% drank alcohol, 45.3% smoked tobacco, and 92% consumed caffeine. Fewer than six participants used other substances, precluding a comparison between groups. There were no between-group differences in alcohol and tobacco use. Caffeine use was significantly lower for NAC-treated participants compared with placebo at week 2 of treatment, but not at other study visits.

Despite negative findings for their main outcome variables, the studies of NAC in nicotine and methamphetamine addiction provided interesting results. In a 4-week, double-blind, randomized controlled trial, Knackstedt et al.[22] reported a non-significant reduction in self-reported daily cigarettes smoked in the NAC group as compared with placebo (17.7 vs. 19.7). However, the exploratory analysis showed a significant effect on daily cigarettes smoked in the NAC treatment group ($F(26,600) = 2.4$, $p < 0.001$). In another double-blind randomized trial of NAC in nicotine dependence, Schmaal et al.[23] assessed craving and withdrawal symptoms in short-term (3.5 days) abstinence, with negative results. Interestingly, individuals in the NAC group reported significantly less pleasure in the first cigarette smoked after the abstinence period, compared to the placebo group (42.6 vs. 65.6, $p = 0.04$). Finally, Grant et al.[24] conducted an 8-week double-blind randomized controlled trial of NAC plus naltrexone for the treatment of metamphetamine addiction. The results were negative for craving and drug use. One point to be considered in this study is the dose of NAC used. The intervention group only received 2.4 g of NAC in the last 2 weeks of the trial, ranging from 0.6 to 1.8 g in the previous 6 weeks. The effective dose of NAC in most trials was at least 2.4 g. The low dose of NAC used during most of the trial could have contributed to the negative results.

These findings provide limited support for the hypothesized neurobiological action of NAC in the treatment of

addiction: namely, restoring extracellular glutamate concentrations.[9] There is evidence from animal studies demonstrating that a reduction in the concentration of extracellular glutamate in the nucleus accumbens is associated with drug-seeking behavior and relapse.[5-8] Another important finding in animal models is the reduction in firing rates of glutamatergic projections from regions of the prefrontal cortex, such as the anterior cingulate cortex, to the nucleus accumbens.[29]

One study included in this review sought to assess whether the glutamatergic changes found in animal models of dependence occur in humans and determine whether NAC could interfere with these changes.[19] The primary outcome measure used was glutamate levels measured by nuclear magnetic resonance spectroscopy in the dACC of patients with cocaine dependence. Eight patients with cocaine dependence and 14 controls were enrolled in an open-label crossover trial, using a single dose of 2.4 g NAC. Resonance spectroscopy imaging was performed 1 hour after ingestion of the medication. In the pretreatment group, patients had lower levels of glutamate in the dACC compared to the control group ($p = 0.04$). Interestingly, after administration of a single dose of NAC, there was restoration of glutamate levels in patients, which became similar to those in the control group.

Although less highlighted in the literature, another possible mechanism of action of NAC in addiction involves its antioxidant properties. Cysteine provided by NAC increases cellular production of glutathione.[30] Glutathione is a tripeptide formed by the linkage of cysteine, glycine, and glutamate, and is the most prevalent intracellular antioxidant.[31] Intracellular availability of cysteine is the rate-limiting step in the biosynthesis of glutathione.[30] The molecule exists in the reduced form (GSH) and in the oxidized dimeric form (GSSG).[31] The reduced form serves as an electron donor, preventing cellular damage from reactive oxygen species.[30] Chemical reactions related to the biosynthesis and metabolism of glutathione form the gamma-glutamyl cycle, which is also involved in the formation of DNA precursors.[31] The redox modulation produced by NAC may have an important protective effect on the brain, possibly reducing neuroprogression[32,33] associated with psychiatric diseases and with chronic use of potentially neurotoxic drugs.[34,35] This rationale is especially relevant in individuals at early stages of disease, when less structural brain damage is expected.[33]

The safety profile of NAC and its favorable tolerability highlight its potential for clinical use.[10] Being an over-the-counter medication, it could be useful in patients hesitant to accept conventional psychotropic medications. In addition, there is an understandable concern by clinicians regarding prescription of psychotropic medications in adolescents, a target population in the treatment of addiction. Firstly, in this group of patients, there is a potential for paradoxical reactions, such as increased risk of suicidal behavior with the use of antidepressants[36] and risk of agitation using benzodiazepines.[37] Another important issue is the adverse effect profile of these medications in chronic use. Some agents may induce weight gain, hypercholesterolemia, hypertriglyceridemia, and increased peripheral insulin resistance.[38] As a consequence, there may be an increased risk of diabetes and cardiovascular disorders.[39] Finally, the effects of long-term use of these medications on the developing brain are unknown.[40] These concerns are even more justifiable in the context of addiction, in which few medications are formally approved for use and the effect size is small.[41] Two studies included in this review addressed adolescents, both in the treatment of cannabis dependence, suggesting positive results regarding self-reported craving and negative urine tests.[20,21]

The findings reported in this systematic review should be examined in light of the substantive limitations of many of the studies. The heterogeneity of the studies, with different diagnoses, designs, interventions, follow-up periods, and outcomes, precluded a pooled quantitative analysis of data. The studies were qualitatively described, thus limiting generalization of the findings of the review. More specifically, the analyzed studies included patients with cocaine dependence, marijuana dependence, nicotine dependence, methamphetamine dependence, and pathological gambling. As for design, there were open-label studies, double-blind crossover, double-blind placebo-controlled, and double-blind discontinuation designs. It goes without saying that only large-scale, randomized, double-blind, placebo-controlled studies can be used as level-one evidence; the rest are hypothesis-generating only. Regarding interventions, the studies used different doses of NAC, ranging from 0.6 to 3.6 g daily, which may have influenced the results. Low doses of NAC may have been insufficient to produce the desired increase in extracellular glutamate. On the other hand, high doses may also have been detrimental, leading to excessive levels of extracellular glutamate and indiscriminate stimulation of other glutamate receptors rather than the intended stimulation of mGluR2/3. The optimal dose of NAC for the treatment of addictions is still undetermined. Nevertheless, the finding that 2.4 g of NAC restored glutamate levels in the dACC of cocaine-dependent patients may provide a temporary reference.[19] With respect to follow-up time, a few studies have evaluated the effect of NAC in the very short term, ranging from 1 hour after administration to 3.5-day follow-up. Others assessed a longer follow-up period, of 4 to 8 weeks. Nevertheless, considering that addiction is a chronic disease, longer follow-up periods are needed to adequately determine the effect of a medication. Another important limitation of this review is the sample size of the included studies; only one study had a sample of more than 100 individuals.

To the best of our knowledge, this is the first systematic review of the literature evaluating the use of NAC in the treatment of addiction. The studies analyzed suggest a potential role for NAC in this setting, especially in cocaine and cannabis dependence. These results are concordant with the hypothesis of the involvement of glutamatergic pathways in the pathophysiology of addiction.

Acknowledgements

MB has received grants/research support from the National Institute of Health (NIH), Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, and Geelong Medical Research Foundation. EB has been supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Disclosure

MB has received grants/research support from Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, and Woolworths; has served as a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay, and Wyeth; and has served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck, and Servier. MB is also co-inventor of two provisional patents regarding the use of NAC and related compounds for psychiatric indications, which, while assigned to the Mental Health Research Institute, could lead to personal remuneration upon a commercialization event. The other authors report no conflicts of interest.

References

1 Mathers CD, Lopez AD, Murray CJL. The burden of disease and mortality by condition: data, methods, and results for 2001. New York: Oxford University Press; 2006.
2 Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005;162:1403-13.
3 Somaini L, Donnini C, Raggi MA, Amore M, Ciccocioppo R, Saracino MA, et al. Promising medications for cocaine dependence treatment. Recent Pat CNS Drug Discov. 2011;6:146-60.
4 Olive MF, Cleva RM, Kalivas PW, Malcolm RJ. Glutamatergic medications for the treatment of drug and behavioral addictions. Pharmacol Biochem Behav. 2012;100:801-10.
5 Baker DA, McFarland K, Lake RW, Shen H, Tang XC, Toda S, et al. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nat Neurosci. 2003;6:743-9.
6 Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron. 2005;45:647-50.
7 McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. J Neurosci. 2003;23:3531-7.
8 Pierce RC, Bell K, Duffy P, Kalivas PW. Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. J Neurosci. 1996; 16:1550-60.
9 Baker DA, McFarland K, Lake RW, Shen H, Toda S, Kalivas PW. N-acetyl cysteine-induced blockade of cocaine-induced reinstatement. Ann N Y Acad Sci. 2003;1003:349-51.
10 Sansone RA, Sansone LA. Getting a Knack for NAC: N-Acetyl-Cysteine. Innov Clin Neurosci. 2011;8:10-4.
11 Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci. 2013;34: 167-77.
12 Cacciatore I, Cornacchia C, Pinnen F, Mollica A, Di Stefano A. Prodrug approach for increasing cellular glutathione levels. Molecules. 2010;15:1242-64.
13 Kupchik YM, Moussawi K, Tang XC, Wang X, Kalivas BC, Kolokithas R, et al. The effect of N-acetylcysteine in the nucleus accumbens on neurotransmission and relapse to cocaine. Biol Psychiatry. 2012; 71:978-86.
14 Zhou W, Kalivas PW. N-acetylcysteine reduces extinction responding and induces enduring reductions in cue- and heroin-induced drug-seeking. Biol Psychiatry. 2008;63:338-40.
15 Samuni Y, Goldstein S, Dean OM, Berk M. The chemistry and biological activities of N-acetylcysteine. Biochim Biophys Acta. 2013;1830:4117-29.
16 Dodd S, Maes M, Anderson G, Dean OM, Moylan S, Berk M. Putative neuroprotective agents in neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2013;42:135-45.
17 Mardikian PN, LaRowe SD, Hedden S, Kalivas PW, Malcolm RJ. An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: a pilot study. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:389-94.
18 LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A, et al. Is cocaine desire reduced by N-acetylcysteine? Am J Psychiatry. 2007;164:1115-7.
19 Schmaal L, Veltman DJ, Nederveen A, van den Brink W, Goudriaan AE. N-acetylcysteine normalizes glutamate levels in cocaine-dependent patients: a randomized crossover magnetic resonance spectroscopy study. Neuropsychopharmacology. 2012;37:2143-52.
20 Gray KM, Watson NL, Carpenter MJ, Larowe SD. N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. Am J Addict. 2010;19:187-9.
21 Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry. 2012;169:805-12.
22 Knackstedt LA, LaRowe S, Mardikian P, Malcolm R, Upadhyaya H, Hedden S, et al. The role of cystine-glutamate exchange in nicotine dependence in rats and humans. Biol Psychiatry. 2009;65:841-5.
23 Schmaal L, Berk L, Hulstijn KP, Cousijn J, Wiers Rw, van den Brink W. Efficacy of N-acetylcysteine in the treatment of nicotine dependence: a double-blind placebo-controlled pilot study. Eur Addict Res. 2011;17:211-6.
24 Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. Eur Neuropsychopharmacol. 2010;20:823-8.
25 Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biol Psychiatry. 2007;62:652-7.
26 LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, et al. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. Am J Addict. 2006;15:105-10.
27 Bernardo M, Dodd S, Gama CS, Copolov DL, Dean O, Kohlmann K, et al. Effects of N-acetylcysteine on substance use in bipolar disorder: a randomised placebo-controlled clinical trial. Acta Neuropsychiatrica. 2009;21:285-91.
28 Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biol Psychiatry. 2008;64:468-75.
29 Sun W, Rebec GV. Repeated cocaine self-administration alters processing of cocaine-related information in rat prefrontal cortex. J Neurosci. 2006;26:8004-8.
30 Berk M, Ng F, Dean O, Dodd S, Bush AI. Glutathione: a novel treatment target in psychiatry. Trends Pharmacol Sci. 2008;29: 346-51.
31 Meister A, Anderson ME. Glutathione. Annu Rev Biochem. 1983;52:711-60.
32 Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Mol Psychiatry. 2013; 18:595-606.
33 Asevedo E, Cunha GR, Zugman A, Mansur RB, Brietzke E. N-acetylcysteine as a potentially useful medication to prevent conversion to schizophrenia in at-risk individuals. Rev Neurosci. 2012;23:353-62.

34 Peraile I, Granado N, Torres E, Gutiérrez-López MD, Moratalla R, Colado MI, et al. Cocaine potentiates MDMA-induced oxidative stress but not dopaminergic neurotoxicity in mice: implications for the pathogenesis of free radical-induced neurodegenerative disorders. Psychopharmacology (Berl). 2013;230:125-35.
35 Pomierny-Chamiolo L, Moniczewski A, Wydra K, Suder A, Filip M. Oxidative stress biomarkers in some rat brain structures and peripheral organs underwent cocaine. Neurotox Res. 2013;23:92-102.
36 Henry A, Kisicki MD, Varley C. Efficacy and safety of antidepressant drug treatment in children and adolescents. Mol Psychiatry. 2012;17:1186-93.
37 Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. Pharmacotherapy. 2004;24:1177-85.
38 Garcia G, Logan GE, Gonzalez-Heydrich J. Management of psychotropic medication side effects in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2012;21: 713-38.
39 De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo controlled trials and guidelines for clinical practice. Eur Psychiatry. 2011;26:144-58.
40 Singh MK, Chang KD. The neural effects of psychotropic medications in children and adolescents. Child Adolesc Psychiatr Clin N Am. 2012;21:753-71.
41 Shorter D, Kosten TR. Novel pharmacotherapeutic treatments for cocaine addiction. BMC Med. 2011;9:119.