Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

N-acetylcysteine in the treatment of psychiatric disorders: Current status and future prospects

Alessandro Minarini, Silvia Ferrari, Martina Galletti, Nina Giambalvo, Daniela Perrone, Giulia Rioli & Gian Maria Galeazzi

To cite this article: Alessandro Minarini, Silvia Ferrari, Martina Galletti, Nina Giambalvo, Daniela Perrone, Giulia Rioli & Gian Maria Galeazzi (2016): N-acetylcysteine in the treatment of psychiatric disorders: Current status and future prospects, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2017.1251580

To link to this article: http://dx.doi.org/10.1080/17425255.2017.1251580

Accepted author version posted online: 21 Oct 2016.

Publisher: Taylor & Francis
Journal: *Expert Opinion on Drug Metabolism & Toxicology*
DOI: 10.1080/17425255.2017.1251580

N-acetylcysteine in the treatment of psychiatric disorders: Current status and future prospects

Alessandro Minarini*[1], Silvia Ferrari[1], Martina Galletti[1], Nina Giambalvo[1], Daniela Perrone[1], Giulia Rioli[1], Gian Maria Galeazzi[1]

[1]Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy

*Corresponding author:

Alessandro Minarini

Clinica Psichiatrica, Via del Pozzo 71, 41124 Modena, Italy.

Email: alessandro.minarini@hotmail.it

Abstract

Introduction: *N*-acetylcysteine (NAC) is widely known for its role as a mucolytic and as an antidote to paracetamol overdose. There is increasing interest in the use of NAC in the treatment of several psychiatric disorders. The rationale for the administration of NAC in psychiatric conditions is based on its role as a precursor to the antioxidant glutathione, and its action as a modulating agent of glutamatergic, dopaminergic, neurotropic and inflammatory pathways.

Areas covered: This study reviews the available data regarding the use of NAC in different psychiatric disorders including substance use disorders, autism, obsessive-compulsive spectrum disorders, schizophrenia, depression, bipolar disorder. Promising results were found in trials testing the use of NAC, mainly as an add-on treatment, in cannabis use disorder in young people, depression in bipolar disorder, negative symptoms in schizophrenia, and excoriation (skin-picking) disorder. Despite initial optimism, recent findings regarding NAC efficacy in autism have been disappointing.

Expert opinion: These preliminary positive results require further confirmation in larger samples and with longer follow-ups. Given its high tolerability and wide availability, NAC represents an important target to investigate in the field of new adjunctive treatments for psychiatric conditions.

Keywords: *N*-acetylcysteine; NAC; psychiatry; mechanism of action

Article highlights box

- N-acetyl cysteine (NAC) is a precursor of the aminoacid cysteine and glutathione, commonly used in various clinical settings with a growing interest in its possible use in psychiatry
- Clinical reports have documented the outcome of treatment with NAC in a variety of psychiatric disorders, mainly as an add-on agent, with generally negligible side effects
- NAC various clinical applications suggest that the drug targets downstream pathways that are common across disorders
- Data is still only preliminary for most of its psychiatric utilization. A significant fraction of the positive evidence is provided by analysis of secondary outcomes or subanalysis of samples
- Most promising areas for NAC utilization are substance use disorders, especially cannabis, depression in bipolar disorder, excoriation (skin-picking) disorder, and schizophrenia, especially to target negative symptoms
- Larger studies are needed to confirm efficacy, optimal doses, long term tolerability and side effects

1 Introduction

N-acetylcysteine NAC is a precursor of the amino acid cysteine, which is necessary for the synthesis of glutathione, and it is commonly used in various clinical settings: in particular, NAC has an indication in paracetamol/acetaminophen poisoning, as a mucolytic in chronic obstructive pulmonary disorder and other inflammatory conditions of the airways [1], and could have a role in the prevention of contrast-induced nephropathy [2]. Interest was raised on the potential application of NAC in neurological conditions such as Alzheimer's dementia, drug-induced neuropathy and progressive myoclonic epilepsy [3], due to its antioxidant action on nitric oxide systems implied in stress, infections, toxic damage, and inflammatory conditions [4]. Depletion of glutathione occurring during oxidative stress can be reversed by NAC treatment [5]. On the wave of accumulating evidence on the role of oxidative stress and inflammation in the etiology of psychiatric disorders, NAC has become a candidate as a possible new therapeutic agent in these conditions [6]. In addition to its antioxidant activity, NAC regulates intra and extra-cellular glutamate, the most important excitatory neurotransmitter [7]. Since extracellular cysteine generated from NAC is transported into the cell while intracellular glutamate is transported out of the cell through the cysteine/glutamate transporter, the restoration of extracellular levels of glutamate increases tonic activation of metabotropic autoreceptors mGluR2/3, which are mostly presynaptic, and inhibits glutamatergic neurotransmission and excitotoxicity [8].

Nevertheless, the spectrum of NAC's chemical and biochemical activities is wide and far to be fully understood, with evidence from preclinical and clinical research still contradictory. For example, tough commonly considered as an antioxidant NAC may potentially act as pro-oxidant if used in absence or in excess of oxidative stress; in fact, in these conditions, NAC may auto-oxidize and behave as an oxidant [9, 10]. The ability of NAC in crossing relevant biological barriers, most importantly the cell membrane and the blood-brain barrier in a clinically significant manner is

debated [11] and its capacity to elevate glutathione in the human brain has not been through oral supplementation has not been proven [12].

Clinical reports have suggested that treatment with NAC may improve outcome in various psychiatric disorders; the aim of the present work was to review international scientific literature about the current level of evidence available concerning the use of NAC in the treatment of psychiatric disorders. More details on the neurochemistry and pharmacological properties of NAC are also provided in the final paragraphs.

2 Methods

A search of electronic medical literature databases Pubmed, Cochrane and PsycINFO was conducted from the date of first available article up to June, 2016. The search strategy included clinical trials, systematic reviews and case-reports. We searched the following terms: (psychiatric disorders), (addictive behavior OR addiction OR dependence OR substance use disorder), (anxiety), (ADHD OR Attention-deficit/hyperactivity disorder), (autism OR autistic disorder), (bipolar disorder), (depressive disorder), (DOC OR obsessive compulsive disorder), (trichotillomania OR hair-pulling disorder), (excoriation disorder OR skin-picking disorder), (nail biting), (schizophrenia) AND (N-acetylcysteine OR NAC OR N-acetyl-l-cysteine OR acetylcysteine) AND (clinical trials OR reviews OR case-reports). Additional studies were included after checking reference lists of selected articles. The eligibility criteria for the review were clinical trials that assessed NAC use as the independent variable and clinical outcomes related to a psychiatric disorder. The search was limited to texts in English for a total of 65 reviewed studies. Studies were assessed considering research design, sample size, diagnostic definition, type of clinical intervention, length of follow-up, outcome variables, and results.

3 Results

NAC has been tested as an adjunctive treatment in a wide range of psychiatric disorders, showing potential benefits in conditions and situations offering limited therapeutic possibilities or suboptimal outcomes with main-stream treatments. The following sections outlines suggested clinical use in different psychiatric disorders. Related trials are displayed in table 1.

-insert Table 1 about here-

3.1 Substance use disorders

Several clinical trials conducted in recent years have tested NAC for the treatment of various substance use disorders, including cannabis, cocaine, methamphetamine, nicotine, and behavioural addictions such as pathological gambling.

3.1.1 Cocaine use disorder

In a small crossover study designed to determine tolerability and safety of NAC, participants were given 2400 mg of NAC or placebo during a 3-day long hospitalization. The following week, individuals were crossed over to the alternative treatment. NAC administration was associated with a significant reduction in cocaine craving compared to baseline, although there was no between-groups change in reduction of craving compared with placebo [13].

Later, in a second phase of the same study, 15 hospitalized individuals were randomized to measure their desire to use, craving, interest in cocaine, on the basis of the time spent watching slides of a presentation showing images related to cocaine use; electrophysiological measures were taken during vision of the slideshow. Results showed that, while taking NAC, participants reported less desire to use, less interest in response to cocaine slides and watched cocaine slides for less time. There were no differences in respect to craving and electrophysiological variables [14].

Amen et al., in another small controlled trial, examined the effect of repeated NAC administration (1200-2400 mg/day) on craving in cocaine-dependent patients, and reported a significant reduction in craving [15].

A larger study randomized treatment-seeking cocaine addicted patients (n=111) to receive daily doses of 1200 mg of NAC, 2400 mg of NAC, or placebo for 8 weeks. This study failed to demonstrate that NAC reduces cocaine use in cocaine-dependent individuals actively using, while there was some evidence that it prevented relapse in already abstinent cocaine-dependent individuals. As an explanation for the negative finding, it was suggested that riboflavin, added to both the NAC and the placebo groups to facilitate the measure of the level of compliance, may have been responsible for the reduced benefit of NAC over placebo [16].

Finally, a pilot study examined the safety and tolerability of NAC for the treatment of cocaine addicted. Results suggested that doses up to 3600 mg/day were well-tolerated. Furthermore it was reported that the majority of individuals who completed the trial discontinued or significantly reduced use of cocaine during the treatment [17].

Magnetic resonance studies suggest that beneficial effects of NAC in cocaine-dependent patients might in part be mediated by the ability of NAC to normalize glutamatergic abnormalities [18].

3.1.2 Cannabis use disorder

A 4-week open-label study using 2400 mg/day of NAC in 24 patients found significant improvements in self-reported use of cannabis and craving, but there was no reduction in urinary levels of cannabinoids during the treatment period [19].

Gray et al. also conducted a large double-blind, randomized trial administering 2400 mg/day of NAC or placebo for 8 weeks to (n=116) subjects aged between 15 and 21 addicted to marijuana. Both groups also received a contingency management intervention and cessation counseling. Significantly more NAC treated subjects gave a negative urine cannabinoid tests. Measure of self-reported days of cannabis use and craving favored NAC, though without reaching statistical significance [20, 21], and significant improvement of cognitive performance in the early stages of treatment-associated abstinence was found [22]. Further analyses on data from this trial found that NAC treatment was associated with increased rates of abstinence in individuals seeking treatment for cannabis use disorder, though positive correlations also related to low impulsivity, high medication adherence, and baseline negative urine cannabinoid testing [23].

These findings require replication and extension among adult cannabis users. A randomized trial recently completed to test the efficacy of NAC versus placebo, added to a behavioral intervention, for cannabis cessation in adults could provide an important contribution [24].

3.1.3 Nicotine addiction

Recent findings have suggested that NAC may positively affect dysregulated corticostriatal connectivity and help to maintain abstinence immediately following an attempt to quit smoking [25]. Schmaal et al. examined the short-term effects of NAC treatment on craving, withdrawal, and the rewarding effect of the first cigarette after 3.5 days of smoking cessation in a double-blind placebo-controlled pilot study [26]. Abstinence from smoking was confirmed using breath carbon monoxide (CO) each morning of medication administration. Subjects receiving NAC rated the first

cigarette after the abstinence period as significantly less rewarding than subjects on placebo, although there was no significant effect of NAC on craving and on withdrawal symptoms.

As far as actual number of cigarettes smoked, Knackstedt et al. conducted a 4-week double-blind randomized trial and found that there was no significant difference between the NAC group and the placebo group in the number of cigarettes smoked daily [27].

McClure et al. analyzed the effect of cigarette smoking among subjects of the adolescent cannabis cessation trial by Gray et al. [20]: no significant difference was found of compensatory cigarette smoking between NAC and placebo groups [28].

A 12-week double blind randomized controlled trial compared the efficacy of NAC 3000 mg/day versus placebo for individuals with therapy-resistant tobacco use disorder. NAC treatment significantly reduced all of the three outcome measures: self-reported daily number of cigarettes smoked, exhaled CO and severity of depression (measured by the Hamilton Depression Rating Scale) [29].

Two trials evaluated the effect of NAC on nicotine use in bipolar disorder and pathological gambling respectively [30, 31]. NAC appeared to have only little effect on participants' smoking behavior. Specifically, among pathological gamblers, a significant benefit was found in the first 6 weeks, but it was no longer evident in the subsequent 6 weeks and at follow-up. A significant additional benefit on measures of problem-gambling severity appeared only at the 24th week of follow up.

NAC shown a good profile in terms of safety and tolerability in co-administration with varenicline, a medication with indication for smoking cessation: further research on co-administration may provide evidence on effectiveness [32].

3.1.4 Methamphetamine use disorder

Grant et al. evaluated the effect of NAC plus naltrexone versus placebo in methamphetamine dependence in an 8-week double-blind trial [33]. Thirty-one patients were randomized to receive either placebo or a combination of naltrexone and NAC.

Doses ranged from 600 mg NAC and 50 mg naltrexone in the first 2 weeks up to 2400 mg NAC and 200 mg naltrexone in the final 2 weeks. The primary outcome was craving severity assessed by the Penn Craving Scale, while secondary outcomes were the number of days of methamphetamine use and urine toxicology. There were no statistically significant between-group differences for any of the outcome variables. Mousavi et al. compared NAC and placebo effectiveness in reducing metamphetamine craving in a double-blind controlled crossover study [34]. In this trial, 32 volunteers received either 1200 mg/die of NAC or placebo for 4 weeks; after 3 days of washout period, the two groups received the crossover treatment of the previous session for other 4 weeks. Craving was assessed and urine toxicology collected. NAC was found to be effective in reducing craving, but results on reduction of use as tested by urine toxicology were unclear.

3.1.5 Pathological gambling

NAC, due to its action on glutamatergic transmission, is thought to be of potential utility in the treatment of behavioral addictions such as pathological gambling (PG).

NAC was found to be effective in reducing gambling urges and behavior in the clinical trial by Grant et al. [35]. Twenty-seven PG subjects were treated for 8 weeks with NAC (mean dose was 1476.9 ± 311.3 mg/day). Response was defined as a reduction of 30% or more in the scores of the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS). Of the 16 responders, 13 were randomized in a 6-week double-blind discontinuation trial (NAC vs. placebo). Of those assigned to NAC, a higher percentage of subjects still met responder criteria at the end of the study (83.3% in NAC vs. 28.6% in placebo group). The already mentioned previous

randomized trial by Grant did not find improvement in any gambling outcome measures during the 12 weeks of treatment phase, but showed improvement after 24 of follow-up [31].

3.2 Anxiety

Despite the recent advances in understanding the pathophysiology of anxiety disorders, current available pharmacological treatments may have limited effectiveness. The role of oxidative stress in the development of anxiety-related disorders, strongly supported by animal models and human biochemical data, have encouraged the trial of antioxidant agents in these disorders [36, 37].
NAC as a potential therapeutic drug in anxiety was reported in one case study of a 17-years old adolescent patient with selective serotonin reuptake inhibitor-resistant generalized anxiety disorder and social phobia [38]. This study reported significant improvement in level of symptoms after 8 week of treatment with NAC at the dosage of 1200 mg/day for 4 weeks and 2400 mg/day for other 4 weeks. The patient did not report any adverse effect from the treatment.
No other evidence is available, particularly coming from randomized controlled clinical trials, making it impossible, at this stage, to discuss potential applications of NAC in the treatment of anxiety.

3.3 Attention-deficit/hyperactivity (ADHD) symptoms

ADHD is a common childhood-onset disorder with reported lifetime prevalence of 5.9-8.7% [39]. ADHD can negatively impact on a child's family, social, and academic life. Individuals who suffer from ADHD are also likely to experience various comorbid medical and psychiatric conditions at a higher than expected frequency.

A small, double-blind placebo-control study [40] showed that combined ADHD Self-Report Scale scores were increased in patients with Systemic Lupus Erythematosus (SLE, n= 49) compared with control healthy subjects (n = 46). These patients were randomized to receive either placebo or NAC at a dosage of 2400 mg/day or 4800 mg/day. Reduction of ADHD symptoms was greater in the NAC group, but these promising results are limited to self-reported ADHD symptoms of patients with SLE and cannot be extended the treatment of ADHD in general.

3.4 Autism

Autism spectrum disorders (ASDs) are complex developmental disorders characterized by core symptoms of significant social impairment, language and communication deficits combined with repetitive and stereotyped behaviors and restricted interests. Recent studies [41, 42] have suggested that an imbalance of oxidative stress and anti-oxidative defensive systems may be involved in the pathophysiology of autism in children. Stemming from this hypothesis, research has explored the feasibility of using oral NAC in the treatment of behavioral disturbances of children with ASDs.

A randomized double-blind placebo-controlled study on 29 participants found a statistically significant reduction of irritability (measured by ABC irritability subscale) in the NAC group [43]. Similar results on irritability were found with NAC added to risperidone [44, 45]. In any of these studies NAC was not found to be effective on other core symptoms of autism, except for hyperactivity/noncompliance.

Three case-studies reported improvements in some of the main [46, 47] and associated [48] ASDs symptoms, such as self-injurious behavior.

Wink et al. did not find any significant impact of oral NAC on social impairment measured by the Clinical Global Impression-Improvement scale [49]. No positive finding emerged even from the

most recent double-blind trial published on this subject [50], though NAC was used at a lower dose than average (500mg/day).

3.5 Bipolar disorder

Changes in oxidative metabolism have been described in patients with bipolar disorder (BD) [51], such as changes in antioxidant levels, increased markers of lipid peroxidation and protein carbonylation. These appear to be state-related, with increased oxidative stress featuring mania. This is consistent with reports of hyperdopaminergic states during manic episodes [52]. Furthermore, correlations between oxidative status and duration of illness were found [53]. This evidence supports the idea of testing potential therapeutic and prophylactic properties of NAC for BD.

A 6-month double-blind, randomized-controlled trial with 2000 mg/day NAC in addition to treatment as usual was conducted in 75 participants with BD. The NAC group showed a significant improvement at the Montgomery-Asberg Depression Scale (MADRS) and Bipolar Depression Rating Scale (BDRS), with a larger effect on depressive symptoms. After discontinuation of NAC treatment, there was a convergence with scores between the NAC and placebo groups, showing a loss of benefit following washout. However, the study failed to show any significant differences between the two groups in terms of prevention of new episodes of either depression or mania [54]. No intergroup differences were found on cognitive outcomes [55]. NAC treatment seemed to impact positively on the level of functioning and quality of life among subjects with medical comorbidities [56]. One secondary analysis including those participants meeting criteria for a major depressive episode showed large effect sizes in favour of NAC for depressive symptoms and functional outcomes at endpoint [57]. Benefits of NAC treatment also appeared to be stronger on bipolar disorder II [58]. Another small subgroup analysis examined individuals (n=15) with a manic

or hypomanic episode at baseline and reported improvement in YMRS in the NAC group and a worsening of BDRS in the placebo group. More participants in the NAC group experienced complete symptom remission, although this was not statistically significant [59].

Subsequent studies focused specifically on depressive symptoms in BD. A large 8-week open-label trial (n=149) included patients with a recent episode of moderate depression. The study showed robust improvement in BDRS, functioning and quality of life on NAC add-on to usual treatment [60]. Participants with a MADRS ≥12 at baseline were randomized to NAC or placebo add-on treatment for 24 weeks. The primary outcome measure, latency to a mood episode, was not significantly different between the treatment and placebo groups [61].

A recent analysis focused on the possible role of inflammation and glutamate neurotransmission in the pathophysiology of suicidal behavior. In this light, a post-hoc analysis was conducted on the effects of NAC on suicidal ideation in bipolar depression. Preliminary data provided a possible indication that NAC might reduce suicidal ideation in this population as an adjunctive therapy [62]. The results of a 16-week study (n=225) with bipolar disorder patients currently experiencing an episode of depression should help to clarify this encouraging evidence [63].

3.6 Depressive disorder

Being oxidative stress and abnormalities of glutamate neurotransmission implied also in the etiology of major depressive disorder (MDD), again there is interest in possible role of NAC in the treatment of this condition.

A large randomized controlled trial (n=252) in individuals with MDD and MADRS score ≥ 18 provided only limited support for the role of NAC as a novel augmentation option for the treatment of MDD, since the NAC-treated group showed improvement vs. placebo only in secondary outcome measures [64]. A case series reported successful and sustained improvement of depressive

symptoms with NAC augmentation in two patients with MDD who had responded only partially to a trial of the monoamine oxidase inhibitors (MAOI) tranylcypromine [65].

3.7 Obsessive-compulsive and related disorders

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [66] introduced a new chapter on Obsessive-compulsive and related disorders to emphasize the similarity between the disorders included and the distinction from other anxiety disorders. NAC has been tested with interesting results in several of these.

3.7.1 Obsessive-compulsive disorder

Licensed pharmacological treatments for obsessive-compulsive disorder (OCD) generally include selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA). However, a considerable proportion of patients show limited therapeutic response to these treatments, or experience disturbing side effects. The role played by the glutamatergic system on the repetitive behaviors that characterize this and other related disorders has been explored [67, 68], suggesting new possible therapeutic targets. Although other glutamate-modulating agent (i.e. riluzole, memantine and lamotrigine) have reported negative findings [69], the use of NAC in this disorder has provided encouraging results.

In a case report, a 58-year old female OCD patient treated with fluvoxamine (300 mg daily) experienced benefit with the supplement of NAC, titrated from 600 mg to 3 g/day during a 12-week open trial. In particular, the patient showed a significant decrease in the Y-BOCS (Yale Brown Obsessive Compulsive Scale) score, with improvement in the control of compulsive washing and obsessional triggers, maintained at a 2-month follow up [70]. Yazici et al. reported other cases in

children and adolescents where NAC treatment showed a beneficial role as adjunctive therapy [71, 72]. More recently, Van Ameringen et al. published a case series of patients treated with NAC supplementation for 12 weeks (mean dosage = 2800 mg/day, titrated from 500 mg for 8 weeks) [73]. All the six patients were affected by a severe and drug-resistant form of OCD. This study failed in demonstrating a therapeutic effect of NAC: no significant improvement of OCD symptoms was appreciable in 5 of the 6 patients, and the only patients who reported an improvement at the Y-BOCS suffered from a moderate form of OCD and had depressive symptoms in comorbidity.

As far as controlled studies are concerned, 39 participants with OCD and no comorbidities were enrolled and randomly double-blindly assigned on treatment, for 12 weeks, with a SSRI plus either placebo (n=19) or NAC (n=20). In the NAC group, a significant improvement in the Y-BOCS and CGI-S (Clinical Global Impression Severity Scale), but not in the CGI-I (Clinical Global Impression Improvement Scale), was measured [74]. Authors reported as a limitation of this study high dropout rates, probably also related to the reported adverse effects, i.e. nausea, vomiting and diarrhea, and the lack of a sub-stratification of patients on the basis of the severity of their OCD symptoms.

In recent times, two randomized controlled trials have been published. In the first, participants were randomized using 3000 mg/day of NAC or placebo for 16 weeks as an add-on treatment, mainly to SSRI. The primary outcome measure was score at the Y-BOCS, measured every 4 weeks. NAC was well-tolerated and associated to a significant reduction in the score at week 12, but this dissipated at week 16 [75]. In the second trial, patients were randomized into two parallel groups to receive fluvoxamine (200 mg daily) plus placebo or fluvoxamine plus NAC (2000 mg daily) for 10 weeks. NAC showed a significant effect on the Y-BOCS, suggesting it may be an augmentative agent in the treatment of moderate to severe OCD [76].

Finally, Bloch et al. did not find evidence for effectiveness of NAC in treating pediatric Tourette syndrome, which typically includes obsessive-compulsive symptoms. Indeed, of the 31 randomized subjects, no significant difference between NAC and placebo was found in reducing tic severity or

any secondary outcomes [77]. In conclusion, preliminary evidence from the reviewed literature offers some grounds to further investigate NAC possible effectiveness as an add-on agent for reducing severity of symptoms in OCD.

3.7.2 Trichotillomania

Trichotillomania is a condition characterized by repetitive hair pulling, resulting in significant hair loss. Patients affected by this condition feel a great sense of tension before the hair pulling and a sense of relief immediately after. Pharmacological treatment options include SSRIs, though with inconsistent reports on effectiveness [78]. Clomipramine also has showed moderate effectiveness, compared to placebo, but initial benefits are not always maintained over time [78]. It has been suggested that a glutamatergic dysfunction could be implied in the pathogenesis of this disorder [79], leading to research on glutamatergic modulators, NAC included, as potential add-on treatments.

Several case reports in adults reported improved hair growth after the use of NAC at the mean dosage of 1400 mg/die [80, 81, 82], including the case of a severe, treatment-resistant form of the condition [67].

In a randomized double-blind controlled trial on 50 adult patients, subjects in the NAC group were administered a 1200 to 2400 mg/day dose for 3 months: significant improvements were registered at psychometric scales [83]. Another double-blind, placebo-controlled trial on 39 children and young adults by Bloch and colleagues observed no significant differences in the reduction of hair pulling between NAC vs. placebo [84].

Results appear therefore mixed, and larger clinical controlled trials are needed to confirm the effectiveness of NAC in trichotillomania.

3.7.3 Excoriation (skin-picking) disorder

According to the DSM-5 definition, excoriation, or skin-picking, disorder is characterized by recurrent, incontrollable skin picking, resulting in skin lesions and associated to significant distress and impact on functioning. Skin picking is also a major clinical issue among patients with Prader-Willi syndrome. An open-label pilot study on 35 individuals (pediatric and adults) with Prader-Willi syndrome given 450-1200 mg/day NAC for 12 weeks demonstrated a significant improvement in skin-picking symptoms and size and numbers of skin lesions, with a large number showing complete remission of symptoms [85]. Several case series in skin-picking disorder patients also reported benefit of NAC treatment in reducing the frequency of skin picking behavior [81, 86], a case report of a 12-year old female showed clinical improvement after only 4 weeks of treatment with 1200 mg/day of NAC [87], similarly to Odlaug et al. that described the case of a 52-year old woman [67].

A recent randomized, double-blind, controlled 12-week trial on 66 adults with skin picking showed encouraging results. NAC treatment (dosing range: 1200-3000 mg/d) achieved significant reductions in skin-picking symptoms with significant improvements at the Yale-Brown Obsessive Compulsive Scale (NE-YBOCS) and Clinical Global Impression-Severity Scale compared with placebo [88].

3.7.4 Nail Biting

Only limited evidence is available for the efficacy of NAC on nail biting behavior. In their case series, Berk et al. reported improved reduced nail biting frequency in two women of 46 and 44 years and in a man of 46 years; all of them also suffered from bipolar disorder and they were

enrolled in the bipolar disorder treatment protocol previously quoted [54]. The 46-year old female patient stopped a long lasting biting after 2 weeks of treatment supplementation with 2000 mg/day NAC, the 44-year old female after 4 months of NAC treatment (same dose), and similarly the 46-year old male patient after 7 months [89].

A 2-month double-blind placebo-controlled trial study on nail-biting was conducted in 25 children and adolescents (age: 6-18 years). This study showed greater increase in nail length after 1 month of treatment with NAC 800 mg daily, compared to placebo, but this difference was not anymore significant at the end of second month [90].

3.8 Schizophrenia

Dysfunction in glutamate metabolism and decreased glutamate levels in the pre-frontal cortex have been reported in schizophrenia [91], with observed clinical phenotypes conceived as the result of interactions of multiple neurotransmitter pathways [92] that further interact with oxidative and inflammatory systems. There is an expanding body of evidence suggesting that oxidative stress occurs in individuals with schizophrenia, with possible correlations between oxidative stress, symptom severity and diagnostic subtype [93].

A large 6-month study (n=140) comparing 2000 mg/day NAC as an adjunctive therapy for schizophrenia to placebo was conducted. Improvements in the NAC group were registered, particularly on negative symptoms, measured on the Positive and Negative Symptoms Scale (PANSS). Furthermore, improvements in global function and improved abnormal movements, particularly akathisia, were also reported [94, 95]. Another small sized, randomized, 8-week trial examining the addition of NAC to risperidone found improvement in PANSS negative and total scales [96]. A case study reported improvements in symptoms in a young woman with treatment-resistant schizophrenia after 7 days of 600 mg/day of NAC [97].

A recent post-hoc analysis on the Berk et al. 2008 trial [98] to explore NAC effectiveness as add-on in a subgroup of clozapine patients showed benefits of NAC at week 8 but not at week 24 in the clozapine sub-group, in contrast to the opposite pattern seen in the primary analysis (PANSS improvement at week 24 but not at 8) [94]. Rapado-Castro et al. examined the impact of duration of illness on the response to treatment with NAC in schizophrenia in the same parent trial [94]. A significant interaction between duration of the illness and response to treatment with NAC was found for positive symptoms and functioning, but not for negative or general symptoms or for side effect related outcomes. These results suggest a potential advantage of adjunctive NAC over placebo on functioning and positive symptoms reduction in patients with chronic schizophrenia [99].

4 Pharmacology of NAC and hypothesized mechanisms of action

NAC is the acetylated form of the amino acid cysteine and is commonly used for its role as an antioxidant precursor to glutathione (γ-glutamylcysteinylglycine, GSH) in the treatment of acetaminophen/paracetamol overdose and as a mucolytic. As more is understood about the many pharmacological actions of NAC, proposals for clinical applications have also broadened. NAC use has been suggested in the past to counteract high levels of free radicals in HIV infection, without proven benefits [100], and its use has been suggested in chronic obstructive pulmonary disease and contrast-induced nephropathy [2, 101]. Specific to brain disorders, NAC has been trialed, with mixed results, on patients with Alzheimer disease, epilepsy, drug induced neuropathy and traumatic brain injury [3]. NAC utilization in such different conditions would be supported by its role in different metabolic pathways. Indeed, preclinical research studies indicate that NAC may modulate pathophysiological processes involved in multiple psychiatric conditions, including oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction, neuro-inflammation and dysregulation of

glutamate and dopamine neurotransmitter systems [11, 102]. In addition, NAC may also affect long-term neuroadaptation and neuroplasticity, processes which may play important roles in a number of psychiatric disorders [103, 104].

The efficacy of NAC in restoring glutathione levels by providing cysteine, which is the rate-limiting amino acid in glutathione production, is well-known. Glutathione, the major endogenous antioxidant, is responsible for maintaining the oxidative balance in the cell. NAC has been shown to successfully penetrate the blood-brain barrier and raise brain glutathione levels in animal models [105, 106]. Furthermore, NAC has been shown to scavenge oxidants directly, particularly the reduction of the hydroxyl radical, OH and hypochlorous acid [107].

Alterations in brain glutathione and other redox pathways have been proposed as important pathophysiologic mechanisms in depression [108], bipolar disorder [53] and schizophrenia [109]. NAC has been also shown to have direct effects on mitochondrial functioning in different animal models [110, 111] and mitochondrial functioning alterations may also occur in several psychiatric disorders [112].

NAC has anti-inflammatory properties through several cellular processes linked to oxidative pathways, which may provide another potential mechanism of action in psychiatry. In fact, alterations in pro- and anti-inflammatory cytokines have been reported in several psychiatric disorders, depression in particular [113]. The reduction in inflammatory cytokines provided by NAC treatment may be a potential mechanism by which NAC modulates some psychiatric symptoms. NAC inhibits the inflammatory cytokines TNFα, IL-1β and IL-6, at the protein and mRNA levels, in LPS-activated macrophage cell lines [114], along with exerting a direct effect on brain macrophages through increased GSH production, antioxidant properties and regulating glutamatergic excitatory neuronal damage and redox reactions [115]. Furthermore, it inhibits pro-inflammatory transcription factor NF-κB with the following down regulation expression of several pro-inflammatory genes [116].

Alterations in cysteine levels have also been shown to modulate neuro-transmitter pathways, glutamate and dopamine in particular. In fact, cysteine assists in the regulation of neuronal intra- and extracellular exchange of glutamate through the cysteine-glutamate antiporter. Concurrently with the release of non-vesicular glutamate, cysteine mainly stimulates the presynaptic metabotropic glutamate autoreceptors mGluR2/3 that negatively regulates the vesicular release of glutamate. It has also been shown that protracted treatment with NAC restores expression of GLT-1 (a high affinity astroglial glutamate transporter) suppressed by chronic cocaine abuse [117, 118, 119]. Studies have documented both increased and decreased glutamate levels in different psychiatric disorders, for example in schizophrenia [120] and substance use disorders [18]. Moreover, dysregulated glutamate homeostasis can lead to impaired synaptic potentiation and plasticity [103], mechanisms which are hypothesized to be involved in the development of various psychiatric disorders.

NAC alters dopamine release. The reciprocal interaction between dopamine and glutamate in the brain has raised interest in models of psychiatric disorders including substance use disorders. NAC influences glutamatergic neurotransmission regulation of dopamine release from presynaptic terminals [121, 122]. Following amphetamine treatment to rat striatal slices, NAC has been shown to facilitate vesicular dopamine release at low doses in striatal neurons and to inhibit release at millimolar concentrations. In monkeys, NAC has been shown to protect against reductions in dopamine transporter levels following repeated methamphetamine administration [123].

NAC as a GSH precursor acts also as an important intracellular antioxidant and may have a significant role in counteracting the toxicity of dopamine-derived free radicals.

A role of NAC on serotonergic transmission has not been explored in details as of yet, but recent findings suggest a possible action mediated by increased cysteine-glutamate antiporter modulating 5HT(2A) receptors and showing complex interaction between glutamatergic and serotonergic neurotransmission [124]. A detailed and comprehensive review of the biological properties and preclinical findings relative to NAC has been recently provided by Samuni et al [11].

5 Pharmacokinetics and side effects

NAC is considered a drug with a very good safety and tolerability profile, being widely used in many countries for the past several decades [13]. All the studies which used oral formulations found NAC to be safe, with a low incidence of adverse effects in most studies even at high doses. Side effects, should they be experienced, may involve different systems including gastrointestinal, neurological, psychological/behavioral, musculoskeletal, dermatological, and others. Most frequently reported side effects are nausea, vomiting, and diarrhea. Infrequently, primarily with intravenous administration, anaphylactic reactions occur and can consist of rash, pruritus, angioedema, bronchospasm, tachycardia, and blood pressure dysregulation [125].

Important adverse events, such as pulmonary hypertension, have been reported at very high doses in animal studies, but have not been reported in human studies [126]. NAC appears to be antiepileptic at low doses in animals, [127] while seizures are reported with overdose [128].

Drug interactions of clinical significance have been observed with paracetamol, GSH, and anticancer agents [129]. NAC strongly potentiates the effect of nitrates vasodilators and related medications, and caution should be used in patients receiving these agents, for the risk of hypotension [5].

The exact most effective dose of NAC remains to be definitively established. Dose-finding studies may reveal greater efficacy at higher doses or equal efficacy at lower doses. Further studies are needed to stress safety and tolerability of long-term use of NAC.

Reassuringly, meta-analysis of studies evaluating long-term oral treatment with NAC for the prevention of chronic bronchitis found that it was well-tolerated [130].

With oral administration NAC is rapidly adsorbed and its bioavailability has been shown to range 4-10% [131, 132]. NAC half-life is approximately 6 hours, and 30% of the drug is excreted by the

kidneys [37]. Renal clearance has been reported at 0.190-0.211 l/h per kg. After an oral dose of 200-400 mg, C_{max} is 0.35-4 mg/L and T_{max} is 1-2 hours.

Evidence on the best effective dose of NAC for use in psychiatric conditions is still uncertain or preliminary. Two cases cautioned against the risk of intoxication after intravenous administration in acetominophen overdose management [133, 134]. Toxicity, in form of delirium, seizures and severe brain injury, has been shown when NAC was administered intravenously at the dose of 150 g over 28 h in humans. The second case showed the development of hemolysis, thrombocytopenia, acute renal failure and death after the administration of 100 g loading dose of NAC 150mg/kg instead of 10 g.

Data on interaction with food is lacking. The volume of distribution ranges from 0.33 to 0.47 l/kg and protein binding is significant, being 50% at 4 h after dose administration.

Pharmacokinetic data suggest that only low plasmatic levels of oxidized NAC are detected for several hours after administration [135] and the drug itself does not accumulate in the body, but rather in its oxidized forms and in reduced and oxidized metabolites [129, 136].

It is well established that NAC may cross the blood-brain barrier, although it is still controversial that this ability could be dependent in part on its dose and mode of administration [137].

Reports in pregnant and lactating women are lacking and controversial; therefore in these patients NAC should be used only with great caution and only if clearly indicated [138].

6 Conclusions

NAC is not currently licensed for any psychiatric indication: nevertheless, it has been researched on several psychiatric disorders as an off-label medication and may offer a promising treatment approach, mainly as an adjunctive medication. Data are still only preliminary for most of NAC psychiatric use. In fact, the majority of trials showed no significant results on primary outcomes.

Much of the positive evidence is provided by analysis of secondary outcomes or analysis of subsamples. In general, available trials are small: we found only 5 double-blind controlled trials referring to samples larger than 100 subjects for all psychiatric indications combined. On the positive side, NAC treatment appears to be safe, tolerable and affordable. Further well-designed, larger controlled trials, with longer follow-up, are needed to establish reliable indications. Similarly, future research should provide clearer information on optimal dose of NAC, and its side effects, safety and tolerability in the long-term use.

7 Expert opinion

In recent times the potential efficacy of NAC in the treatment of psychiatric disorder has attracted increasing interest. Theoretically, this interest is understandable and justified by the activity that this compound exerts on multiple pathways -such as those involved oxidative stress, mitochondrial dysfunction, inflammation, glutamatergic dysregulation- which are hypothesized to underlie many psychiatric disorders.

Correspondingly, NAC has been tested, as this review shows, in a wide spectrum of conditions yielding so far mainly inconclusive results.

From the research point of view, there are a few challenging methodological problems -apart from the obvious need of larger double blind RCTs, with longer follow-up and by independent groups - which need to be addressed in further research.

First, dose ranges used in trials still varies greatly (up to circa 5x) across studies, also for the same condition, suggesting that dose finding studies are needed. Secondly, preclinical and clinical studies hint to the possibility that NAC effects may be disorder stage specific: for example, in substance abuse NAC could be (more) effective in reducing relapse in patients who have already achieved abstinence. The importance of clinical staging, both in clinical research and treatment choices, is

gaining wider recognition also for other disorders where NAC has had so far inconclusive results, such as bipolar disorder or schizophrenia. This should be taken into account in the selection of the patient population and analysis of the outcomes. Thirdly, the choice of more focused primary endpoints, addressing functional domains such as cognitive functioning, negative symptoms in schizophrenia or depressive symptoms in bipolar disorder, may be a more effective strategy than using as primary endpoint general psychopathology scales scores. This approach is also coherent with the recent emphasis in research on functional psychopathology dissection, as represented for example by the Research Domain Criteria endeavor, more than on samples recruited relying on DSM categorical diagnoses. In this perspective it may be worthwhile to test NAC efficacy for symptom dimensions, for example on compulsivity/impulsivity or irritability.

From the clinical point of view, the recent availability of negative well run double blind randomized controlled trials seem to discourage from the use of NAC in autism, which had attracted initial optimism.

The clinical usefulness of NAC for substance use disorders, apart from cannabis use disorder in young people, OCD, trichotillomania and nail biting is not currently supported by good enough evidence. Considering the extreme level of disability caused by severe, treatment resistant OCD and the generally benign side effects profile of NAC, though, according to the Author of this review its use as an add-on agent, when other licensed treatments have proved ineffective (abiding to national regulation for off license prescription of medication), could be considered on an ad hoc basis.

Of particular interest appear the potential clinical application of NAC for depressive symptoms in bipolar disorders and negative symptoms in schizophrenia. Again, given the notorious resistance to treatment of these symptoms, and the impact that they may have on patients, an off label, add-on time limited trial of NAC seems worth considering on a case by case basis when other evidence based approaches have failed.

Available data, taking into account the paucity of alternative treatments and side effects profile, favor NAC use in excoriation disorder, another condition often debilitating and not infrequently disfiguring.

Given that this field of research is very active and there are several NAC RCTs for psychiatric conditions registered in repositories, these recommendations may change and hopefully become firmer in the near future.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Dekhuijzen PN, van Beurden WJ. The role for N-acetylcysteine in the management of COPD. International journal of chronic obstructive pulmonary disease. 2006;1:99-106.

2. Quintavalle C, Donnarumma E, Fiore D, Briguori C, Condorelli G. Therapeutic strategies to prevent contrast-induced acute kidney injury. Current opinion in cardiology. 2013;28:676-82.

3. Deepmala, Slattery J, Kumar N, Delhey L, Berk M, Dean O, Spielholz C, Frye R. Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neuroscience and biobehavioral reviews. 2015;55:294-321. Epub 2015/05/11.

4. Dekhuijzen PN. Antioxidant properties of N-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease. The European respiratory journal. 2004;23:629-36.

5. Atkuri KR, Mantovani JJ, Herzenberg LA. N-Acetylcysteine--a safe antidote for cysteine/glutathione deficiency. Current opinion in pharmacology. 2007;7:355-9.

6. Berk M, Ng F, Dean O, Dodd S, Bush AI. Glutathione: a novel treatment target in psychiatry. Trends in pharmacological sciences. 2008;29:346-51.

7. Cacciatore I, Cornacchia C, Pinnen F, Mollica A, Di Stefano A. Prodrug approach for increasing cellular glutathione levels. Molecules. 2010;15:1242-64.

8. Asevedo E, Mendes AC, Berk M, Brietzke E. Systematic review of N-acetylcysteine in the treatment of addictions. Rev Bras Psiquiatr. 2014;36:168-75.

9. Chan ED, Riches DW, White CW. Redox paradox: effect of N-acetylcysteine and serum on oxidation reduction-sensitive mitogen-activated protein kinase signaling pathways. American journal of respiratory cell and molecular biology. 2001;24:627-32.

10. Domenighetti G, Quattropani C, Schaller MD. [Therapeutic use of N-acetylcysteine in acute lung diseases]. Revue des maladies respiratoires. 1999;16:29-37.

11. Samuni Y, Goldstein S, Dean OM, Berk M. The chemistry and biological activities of N-acetylcysteine. Biochimica et biophysica acta. 2013;1830:4117-29.

•• An excellent review on chemical, biological, and preclinical findings.

12. Shungu DC. N-acetylcysteine for the treatment of glutathione deficiency and oxidative stress in schizophrenia. Biological psychiatry. 2012;71:937-8.

13. LaRowe SD, Mardikian P, Malcolm R, Myrick H, Kalivas P, McFarland K, Saladin M, McRae A, Brady K. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2006;15:105-10.

14. LaRowe SD, Myrick H, Hedden S, Mardikian P, Saladin M, McRae A, Brady K, Kalivas PW, Malcolm R. Is cocaine desire reduced by N-acetylcysteine? The American journal of psychiatry. 2007;164:1115-7.

15. Amen SL, Piacentine LB, Ahmad ME, Li SJ, Mantsch JR, Risinger RC, Baker DA. Repeated N-acetyl cysteine reduces cocaine seeking in rodents and craving in cocaine-dependent humans. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2011;36:871-8.

16. LaRowe SD, Kalivas PW, Nicholas JS, Randall PK, Mardikian PN, Malcolm RJ. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2013;22:443-52.

• Double blind RCT with a good sample size. This trial did not demonstrate that NAC reduces cocaine use in cocaine-dependent individuals actively using but suggested that NAC may be more effective in already abstinent patients, coherently with preclinical research.

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. Progress in neuro-psychopharmacology & biological psychiatry. 2007;31:389-94.

18. 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 : official publication of the American College of Neuropsychopharmacology. 2012;37:2143-52.

19. Gray KM, Watson NL, Carpenter MJ, Larowe SD. N-acetylcysteine (NAC) in young marijuana users: an open-label pilot study. The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions. 2010;19:187-9.

20. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, McRae-Clark AL, Brady KT. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. The American journal of psychiatry. 2012;169:805-12.

•• The first double blind RCT of pharmacotherapy in cannabis-dependence with a positive primary outcome.

21. Roten AT, Baker NL, Gray KM. Marijuana craving trajectories in an adolescent marijuana cessation pharmacotherapy trial. Addictive behaviors. 2013;38:1788-91.

22. Roten A, Baker NL, Gray KM. Cognitive performance in a placebo-controlled pharmacotherapy trial for youth with marijuana dependence. Addictive behaviors. 2015;45:119-23.

23. Bentzley JP, Tomko RL, Gray KM. Low Pretreatment Impulsivity and High Medication Adherence Increase the Odds of Abstinence in a Trial of N-Acetylcysteine in Adolescents with Cannabis Use Disorder. Journal of substance abuse treatment. 2016;63:72-7.

24. McClure EA, Sonne SC, Winhusen T, Carroll KM, Ghitza UE, McRae-Clark AL, Matthews AG, Sharma G, Van Veldhuisen P, Vandrey RG, Levin FR, Weiss RD, Lindblad R, Allen C, Mooney LJ, Haynes L, Brigham GS, Sparenborg S, Hasson AL, Gray KM. Achieving cannabis cessation -- evaluating N-acetylcysteine treatment (ACCENT): design and implementation of a multi-site, randomized controlled study in the National Institute on Drug Abuse Clinical Trials Network. Contemporary clinical trials. 2014;39:211-23.

25. Froeliger B, McConnell PA, Stankeviciute N, McClure EA, Kalivas PW, Gray KM. The effects of N-Acetylcysteine on frontostriatal resting-state functional connectivity, withdrawal symptoms and smoking abstinence: A double-blind, placebo-controlled fMRI pilot study. Drug and alcohol dependence. 2015;156:234-42.

26. 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. European addiction research. 2011;17:211-6.

27. Knackstedt LA, LaRowe S, Mardikian P, Malcolm R, Upadhyaya H, Hedden S, Markou A, Kalivas PW. The role of cystine-glutamate exchange in nicotine dependence in rats and humans. Biological psychiatry. 2009;65:841-5.

28. McClure EA, Baker NL, Gray KM. Cigarette smoking during an N-acetylcysteine-assisted cannabis cessation trial in adolescents. The American journal of drug and alcohol abuse. 2014;40:285-91.

29. Prado E, Maes M, Piccoli LG, Baracat M, Barbosa DS, Franco O, Dodd S, Berk M, Vargas Nunes SO. N-acetylcysteine for therapy-resistant tobacco use disorder: a pilot study. Redox report : communications in free radical research. 2015;20:215-22.

30. Bernardo M, Dodd S, Gama CS, Copolov DL, Dean O, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI, Berk M. Effects of N-acetylcysteine on substance use in bipolar disorder: A randomised placebo-controlled clinical trial. Acta neuropsychiatrica. 2009;21:285-91.

31. Grant JE, Odlaug BL, Chamberlain SR, Potenza MN, Schreiber LR, Donahue CB, Kim SW. A randomized, placebo-controlled trial of N-acetylcysteine plus imaginal desensitization for nicotine-dependent pathological gamblers. The Journal of clinical psychiatry. 2014;75:39-45.

32. McClure EA, Baker NL, Gipson CD, Carpenter MJ, Roper AP, Froeliger BE, Kalivas PW, Gray KM. An open-label pilot trial of N-acetylcysteine and varenicline in adult cigarette smokers. The American journal of drug and alcohol abuse. 2015;41:52-6.

33. Grant JE, Odlaug BL, Kim SW. A double-blind, placebo-controlled study of N-acetyl cysteine plus naltrexone for methamphetamine dependence. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2010;20:823-8.

34. Mousavi SG, Sharbafchi MR, Salehi M, Peykanpour M, Karimian Sichani N, Maracy M. The efficacy of N-acetylcysteine in the treatment of methamphetamine dependence: a double-blind controlled, crossover study. Archives of Iranian medicine. 2015;18:28-33.

35. Grant JE, Kim SW, Odlaug BL. N-acetyl cysteine, a glutamate-modulating agent, in the treatment of pathological gambling: a pilot study. Biological psychiatry. 2007;62:652-7.

36. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol. 2008;11:851-76.

37. Sansone RA, Sansone LA. Getting a Knack for NAC: N-Acetyl-Cysteine. Innovations in clinical neuroscience. 2011;8:10-4.

38. Strawn JR, Saldana SN. Treatment with adjunctive N-acetylcysteine in an adolescent with selective serotonin reuptake inhibitor-resistant anxiety. Journal of child and adolescent psychopharmacology. 2012;22:472-3.

39. Rowland AS, Lesesne CA, Abramowitz AJ. The epidemiology of attention-deficit/hyperactivity disorder (ADHD): a public health view. Mental retardation and developmental disabilities research reviews. 2002;8:162-70.

40. Garcia RJ, Francis L, Dawood M, Lai ZW, Faraone SV, Perl A. Attention deficit and hyperactivity disorder scores are elevated and respond to N-acetylcysteine treatment in patients with systemic lupus erythematosus. Arthritis and rheumatism. 2013;65:1313-8.

41. Ghanizadeh A, Akhondzadeh S, Hormozi M, Makarem A, Abotorabi-Zarchi M, Firoozabadi A. Glutathione-related factors and oxidative stress in autism, a review. Current medicinal chemistry. 2012;19:4000-5.

42. Leoncini S, De Felice C, Signorini C, Pecorelli A, Durand T, Valacchi G, Ciccoli L, Hayek J. Oxidative stress in Rett syndrome: natural history, genotype, and variants. Redox report : communications in free radical research. 2011;16:145-53.

43. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, Frazier TW, Tirouvanziam R. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biological psychiatry. 2012;71:956-61.

44. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. BMC psychiatry. 2013;13:196.

45. Nikoo M, Radnia H, Farokhnia M, Mohammadi MR, Akhondzadeh S. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. Clinical neuropharmacology. 2015;38:11-7.

46. Ghanizadeh A, Derakhshan N. N-acetylcysteine for treatment of autism, a case report. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2012;17:985-7.

47. Stutzman D, Dopheide J. Acetylcysteine for treatment of autism spectrum disorder symptoms. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists. 2015;72:1956-9.

48. Marler S, Sanders KB, Veenstra-VanderWeele J. N-acetylcysteine as treatment for self-injurious behavior in a child with autism. Journal of child and adolescent psychopharmacology. 2014;24:231-4.

49. Wink LK, Adams R, Wang Z, Klaunig JE, Plawecki MH, Posey DJ, McDougle CJ, Erickson CA. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Molecular autism. 2016;7:26.

50. Dean OM, Gray KM, Villagonzalo KA, Dodd S, Mohebbi M, Vick T, Tonge BJ, Berk M. A randomised, double blind, placebo-controlled trial of a fixed dose of N-acetyl cysteine in children with autistic disorder. The Australian and New Zealand journal of psychiatry. 2016.
•• Double blind RCT with a good sample size. No benefit of adjunctive NAC in treating autistic disorder.

51. Andreazza AC, Kauer-Sant'anna M, Frey BN, Bond DJ, Kapczinski F, Young LT, Yatham LN. Oxidative stress markers in bipolar disorder: a meta-analysis. Journal of affective disorders. 2008;111:135-44.

52. Kunz M, Gama CS, Andreazza AC, Salvador M, Cereser KM, Gomes FA, Belmonte-de-Abreu PS, Berk M, Kapczinski F. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry. 2008;32:1677-81.

53. Andreazza AC, Kapczinski F, Kauer-Sant'Anna M, Walz JC, Bond DJ, Goncalves CA, Young LT, Yatham LN. 3-Nitrotyrosine and glutathione antioxidant system in patients in the early and late stages of bipolar disorder. Journal of psychiatry & neuroscience : JPN. 2009;34:263-71.

54. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biological psychiatry. 2008;64:468-75.
• Important double blind RCT of bipolar disorder patients in the maintainance phase, parent study to several publications.

55. Dean OM, Bush AI, Copolov DL, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. Effects of N-acetyl cysteine on cognitive function in bipolar disorder. Psychiatry and clinical neurosciences. 2012;66:514-7.

56. Magalhaes PV, Dean OM, Bush AI, Copolov DL, Weisinger D, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. Systemic illness moderates the impact of N-

acetyl cysteine in bipolar disorder. Progress in neuro-psychopharmacology & biological psychiatry. 2012;37:132-5.

57. Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. N-acetylcysteine for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr. 2011;33:374-8.

58. Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. Journal of affective disorders. 2011;129:317-20.

59. Magalhaes PV, Dean OM, Bush AI, Copolov DL, Malhi GS, Kohlmann K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Berk M. A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. The Australian and New Zealand journal of psychiatry. 2013;47:564-8.

60. Berk M, Dean O, Cotton SM, Gama CS, Kapczinski F, Fernandes BS, Kohlmann K, Jeavons S, Hewitt K, Allwang C, Cobb H, Bush AI, Schapkaitz I, Dodd S, Malhi GS. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. Journal of affective disorders. 2011;135:389-94.

61. Berk M, Dean OM, Cotton SM, Gama CS, Kapczinski F, Fernandes B, Kohlmann K, Jeavons S, Hewitt K, Moss K, Allwang C, Schapkaitz I, Cobb H, Bush AI, Dodd S, Malhi GS. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC medicine. 2012;10:91.

62. Waterdrinker A, Berk M, Venugopal K, Rapado-Castro M, Turner A, Dean OM. Effects of N-Acetyl cysteine on suicidal ideation in bipolar depression. The Journal of clinical psychiatry. 2015;76:665.

63. Dean OM, Turner A, Malhi GS, Ng C, Cotton SM, Dodd S, Sarris J, Samuni Y, Tanious M, Dowling N, Waterdrinker A, Smith D, Berk M. Design and rationale of a 16-week adjunctive

randomized placebo-controlled trial of mitochondrial agents for the treatment of bipolar depression. Rev Bras Psiquiatr. 2015;37:3-12.

64. Berk M, Dean OM, Cotton SM, Jeavons S, Tanious M, Kohlmann K, Hewitt K, Moss K, Allwang C, Schapkaitz I, Robbins J, Cobb H, Ng F, Dodd S, Bush AI, Malhi GS. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. The Journal of clinical psychiatry. 2014;75:628-36.

•• Large double blind RCT of NAC as add on agent with negative findings at the primary outcome.

65. Carvalho AF, Macedo DS, Goulia P, Hyphantis TN. N-acetylcysteine augmentation to tranylcypromine in treatment-resistant major depression. Journal of clinical psychopharmacology. 2013;33:719-20.

66. APA. Diagnostic and statistical manual of mental disorders (5th ed.) Washington, DC: American Psychiatric Association. 2013.

67. Odlaug BL, Grant JE. N-acetyl cysteine in the treatment of grooming disorders. Journal of clinical psychopharmacology. 2007;27:227-9.

68. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochemical pharmacology. 2008;75:218-65.

69. Grados MA, Specht MW, Sung HM, Fortune D. Glutamate drugs and pharmacogenetics of OCD: a pathway-based exploratory approach. Expert opinion on drug discovery. 2013;8:1515-27.

70. Lafleur DL, Pittenger C, Kelmendi B, Gardner T, Wasylink S, Malison RT, Sanacora G, Krystal JH, Coric V. N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Psychopharmacology. 2006;184:254-6.

71. Yazici KU, Percinel I. N-Acetylcysteine Augmentation in Children and Adolescents Diagnosed With Treatment-Resistant Obsessive-Compulsive Disorder: Case Series. Journal of clinical psychopharmacology. 2015;35:486-9.

72. Yazici KU, Percinel I. The role of glutamatergic dysfunction in treatment-resistant obsessive-compulsive disorder: treatment of an adolescent case with N-acetylcysteine augmentation. Journal of child and adolescent psychopharmacology. 2014;24:525-7.

73. Van Ameringen M, Patterson B, Simpson W, Turna J. N-acetylcysteine augmentation in treatment resistant obsessive compulsive disorder: A case series. Journal of Obsessive-Compulsive and Related Disorders 2013;2:48-52.

74. Afshar H, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, Sadeghi M, Hafezian H. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. Journal of clinical psychopharmacology. 2012;32:797-803.

75. Sarris J, Oliver G, Camfield DA, Dean OM, Dowling N, Smith DJ, Murphy J, Menon R, Berk M, Blair-West S, Ng CH. N-Acetyl Cysteine (NAC) in the Treatment of Obsessive-Compulsive Disorder: A 16-Week, Double-Blind, Randomised, Placebo-Controlled Study. CNS drugs. 2015;29:801-9.

76. Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. Journal of clinical pharmacy and therapeutics. 2016;41:214-9.

77. Bloch MH, Panza KE, Yaffa A, Alvarenga PG, Jakubovski E, Mulqueen JM, Landeros-Weisenberger A, Leckman JF. N-Acetylcysteine in the Treatment of Pediatric Tourette Syndrome: Randomized, Double-Blind, Placebo-Controlled Add-On Trial. Journal of child and adolescent psychopharmacology. 2016;26:327-34.

78. Rothbart R, Amos T, Siegfried N, Ipser JC, Fineberg N, Chamberlain SR, Stein DJ. Pharmacotherapy for trichotillomania. The Cochrane database of systematic reviews. 2013:CD007662.

79. Johnson J, El-Alfy AT. Review of available studies of the neurobiology and pharmacotherapeutic management of trichotillomania. Journal of advanced research. 2016;7:169-84.

80. Rodrigues-Barata AR, Tosti A, Rodriguez-Pichardo A, Camacho-Martinez F. N-acetylcysteine in the Treatment of Trichotillomania. International journal of trichology. 2012;4:176-8.

81. Silva-Netto R, Jesus G, Nogueira M, Tavares H. N-acetylcysteine in the treatment of skin-picking disorder. Rev Bras Psiquiatr. 2014;36:101.

82. Taylor M, Bhagwandas K. N-acetylcysteine in trichotillomania: a panacea for compulsive skin disorders? The British journal of dermatology. 2014;171:1253-5.

83. Grant JE, Odlaug BL, Kim SW. N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Archives of general psychiatry. 2009;66:756-63.

84. Bloch MH, Panza KE, Grant JE, Pittenger C, Leckman JF. N-Acetylcysteine in the treatment of pediatric trichotillomania: a randomized, double-blind, placebo-controlled add-on trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2013;52:231-40.

85. Miller JL, Angulo M. An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome. American journal of medical genetics Part A. 2014;164A:421-4.

86. Grant JE, Odlaug BL, Chamberlain SR, Keuthen NJ, Lochner C, Stein DJ. Skin picking disorder. The American journal of psychiatry. 2012;169:1143-9.

87. Percinel I, Yazici KU. Glutamatergic dysfunction in skin-picking disorder: treatment of a pediatric patient with N-acetylcysteine. Journal of clinical psychopharmacology. 2014;34:772-4.

88. Grant JE, Chamberlain SR, Redden SA, Leppink EW, Odlaug BL, Kim SW. N-Acetylcysteine in the Treatment of Excoriation Disorder: A Randomized Clinical Trial. JAMA psychiatry. 2016;73:490-6.

• Double-blind RCT of NAC for the disorder, demonstrating good efficacy.

89. Berk M, Jeavons S, Dean OM, Dodd S, Moss K, Gama CS, Malhi GS. Nail-biting stuff? The effect of N-acetyl cysteine on nail-biting. CNS spectrums. 2009;14:357-60.

90. Ghanizadeh A, Derakhshan N, Berk M. N-acetylcysteine versus placebo for treating nail biting, a double blind randomized placebo controlled clinical trial. Anti-inflammatory & anti-allergy agents in medicinal chemistry. 2013;12:223-8.

91. Marek GJ, Behl B, Bespalov AY, Gross G, Lee Y, Schoemaker H. Glutamatergic (N-methyl-D-aspartate receptor) hypofrontality in schizophrenia: too little juice or a miswired brain? Molecular pharmacology. 2010;77:317-26.

92. Carlsson A. The neurochemical circuitry of schizophrenia. Pharmacopsychiatry. 2006;39 Suppl 1:S10-4.

93. Pazvantoglu O, Selek S, Okay IT, Sengul C, Karabekiroglu K, Dilbaz N, Erel O. Oxidative mechanisms in schizophrenia and their relationship with illness subtype and symptom profile. Psychiatry and clinical neurosciences. 2009;63:693-700.

94. Berk M, Copolov D, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Judd F, Katz F, Katz P, Ording-Jespersen S, Little J, Conus P, Cuenod M, Do KQ, Bush AI. N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial. Biological psychiatry. 2008;64:361-8.

•• Double blind RCT of NAC as an add on agent with good sample size and parent study to several publications.

95. Berk M, Munib A, Dean O, Malhi GS, Kohlmann K, Schapkaitz I, Jeavons S, Katz F, Anderson-Hunt M, Conus P, Hanna B, Otmar R, Ng F, Copolov DL, Bush AI. Qualitative methods in early-phase drug trials: broadening the scope of data and methods from an RCT of N-acetylcysteine in schizophrenia. The Journal of clinical psychiatry. 2011;72:909-13.

96. Farokhnia M, Azarkolah A, Adinehfar F, Khodaie-Ardakani MR, Hosseini SM, Yekehtaz H, Tabrizi M, Rezaei F, Salehi B, Sadeghi SM, Moghadam M, Gharibi F, Mirshafiee O, Akhondzadeh S. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with

chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clinical neuropharmacology. 2013;36:185-92.

97. Bulut M, Savas HA, Altindag A, Virit O, Dalkilic A. Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2009;10:626-8.

98. Dean OM, Mancuso SG, Bush AI, Copolov D, Do KQ, Cuenod M, Conus P, Rossell SL, Castle DJ, Berk M. Benefits of adjunctive N-acetylcysteine in a sub-group of clozapine-treated individuals diagnosed with schizophrenia. Psychiatry research. 2015;230:982-3.

99. Rapado-Castro M, Berk M, Venugopal K, Bush AI, Dodd S, Dean OM. Towards stage specific treatments: effects of duration of illness on therapeutic response to adjunctive treatment with N-acetyl cysteine in schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry. 2015;57:69-75.

100. Hummelen R, Hemsworth J, Reid G. Micronutrients, N-acetyl cysteine, probiotics and prebiotics, a review of effectiveness in reducing HIV progression. Nutrients. 2010;2:626-51.

101. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. Expert opinion on biological therapy. 2008;8:1955-62.

102. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. Journal of psychiatry & neuroscience : JPN. 2011;36:78-86.

103. Moussawi K, Pacchioni A, Moran M, Olive MF, Gass JT, Lavin A, Kalivas PW. N-Acetylcysteine reverses cocaine-induced metaplasticity. Nature neuroscience. 2009;12:182-9.

104. Reichel CM, Moussawi K, Do PH, Kalivas PW, See RE. Chronic N-acetylcysteine during abstinence or extinction after cocaine self-administration produces enduring reductions in drug seeking. The Journal of pharmacology and experimental therapeutics. 2011;337:487-93.

105. Neuwelt EA, Pagel MA, Hasler BP, Deloughery TG, Muldoon LL. Therapeutic efficacy of aortic administration of N-acetylcysteine as a chemoprotectant against bone marrow toxicity after

intracarotid administration of alkylators, with or without glutathione depletion in a rat model. Cancer research. 2001;61:7868-74.

106. Farr SA, Poon HF, Dogrukol-Ak D, Drake J, Banks WA, Eyerman E, Butterfield DA, Morley JE. The antioxidants alpha-lipoic acid and N-acetylcysteine reverse memory impairment and brain oxidative stress in aged SAMP8 mice. Journal of neurochemistry. 2003;84:1173-83.

107. Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. Free radical biology & medicine. 1989;6:593-7.

108. Bilici M, Efe H, Koroglu MA, Uydu HA, Bekaroglu M, Deger O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. Journal of affective disorders. 2001;64:43-51.

109. Altuntas I, Aksoy H, Coskun I, Caykoylu A, Akcay F. Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. Clinical chemistry and laboratory medicine. 2000;38:1277-81.

110. Amrouche-Mekkioui I, Djerdjouri B. N-acetylcysteine improves redox status, mitochondrial dysfunction, mucin-depleted crypts and epithelial hyperplasia in dextran sulfate sodium-induced oxidative colitis in mice. European journal of pharmacology. 2012;691:209-17.

111. Basha RH, Priscilla DH. An in vivo and in vitro study on the protective effects of N-acetylcysteine on mitochondrial dysfunction in isoproterenol treated myocardial infarcted rats. Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie. 2013;65:7-14.

112. Shao L, Martin MV, Watson SJ, Schatzberg A, Akil H, Myers RM, Jones EG, Bunney WE, Vawter MP. Mitochondrial involvement in psychiatric disorders. Annals of medicine. 2008;40:281-95.

113. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Molecular psychiatry. 2016.

114. Palacio JR, Markert UR, Martinez P. Anti-inflammatory properties of N-acetylcysteine on lipopolysaccharide-activated macrophages. Inflammation research : official journal of the European Histamine Research Society [et al]. 2011;60:695-704.

115. Kigerl KA, Ankeny DP, Garg SK, Wei P, Guan Z, Lai W, McTigue DM, Banerjee R, Popovich PG. System x(c)(-) regulates microglia and macrophage glutamate excitotoxicity in vivo. Experimental neurology. 2012;233:333-41.

116. Yang R, Gallo DJ, Baust JJ, Watkins SK, Delude RL, Fink MP. Effect of hemorrhagic shock on gut barrier function and expression of stress-related genes in normal and gnotobiotic mice. American journal of physiology Regulatory, integrative and comparative physiology. 2002;283:R1263-74.

117. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nature reviews Neuroscience. 2009;10:561-72.

118. Reissner KJ, Gipson CD, Tran PK, Knackstedt LA, Scofield MD, Kalivas PW. Glutamate transporter GLT-1 mediates N-acetylcysteine inhibition of cocaine reinstatement. Addiction biology. 2015;20:316-23.

119. Roberts-Wolfe DJ, Kalivas PW. Glutamate Transporter GLT-1 as a Therapeutic Target for Substance Use Disorders. CNS & neurological disorders drug targets. 2015;14:745-56.

120. Baker DA, Madayag A, Kristiansen LV, Meador-Woodruff JH, Haroutunian V, Raju I. Contribution of cystine-glutamate antiporters to the psychotomimetic effects of phencyclidine. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2008;33:1760-72.

121. Baker DA, Shen H, Kalivas PW. Cystine/glutamate exchange serves as the source for extracellular glutamate: modifications by repeated cocaine administration. Amino acids. 2002;23:161-2.

122. Baker DA, Xi ZX, Shen H, Swanson CJ, Kalivas PW. The origin and neuronal function of in vivo nonsynaptic glutamate. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2002;22:9134-41.

123. Hashimoto K, Tsukada H, Nishiyama S, Fukumoto D, Kakiuchi T, Shimizu E, Iyo M. Effects of N-acetyl-L-cysteine on the reduction of brain dopamine transporters in monkey treated with methamphetamine. Annals of the New York Academy of Sciences. 2004;1025:231-5.

124. Lee MY, Chiang CC, Chiu HY, Chan MH, Chen HH. N-acetylcysteine modulates hallucinogenic 5-HT(2A) receptor agonist-mediated responses: behavioral, molecular, and electrophysiological studies. Neuropharmacology. 2014;81:215-23.

125. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. Annals of emergency medicine. 1998;31:710-5.

126. Palmer LA, Doctor A, Chhabra P, Sheram ML, Laubach VE, Karlinsey MZ, Forbes MS, Macdonald T, Gaston B. S-nitrosothiols signal hypoxia-mimetic vascular pathology. The Journal of clinical investigation. 2007;117:2592-601.

127. Devi PU, Pillai KK, Vohora D. Facilitation action of N-acetylcysteine on the anticonvulsant effect of sodium valproate in mice. Basic & clinical pharmacology & toxicology. 2006;98:521-2.

128. Bailey B, Blais R, Letarte A. Status epilepticus after a massive intravenous N-acetylcysteine overdose leading to intracranial hypertension and death. Annals of emergency medicine. 2004;44:401-6.

129. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. Clinical pharmacokinetics. 1991;20:123-34.

130. Grandjean EM, Berthet P, Ruffmann R, Leuenberger P. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. Clinical therapeutics. 2000;22:209-21.

131. Borgstrom L, Kagedal B, Paulsen O. Pharmacokinetics of N-acetylcysteine in man. European journal of clinical pharmacology. 1986;31:217-22.

132. Olsson B, Johansson M, Gabrielsson J, Bolme P. Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. European journal of clinical pharmacology. 1988;34:77-82.

133. Heard K, Schaeffer TH. Massive acetylcysteine overdose associated with cerebral edema and seizures. Clin Toxicol (Phila). 2011;49:423-5.

134. Mahmoudi GA, Astaraki P, Mohtashami AZ, Ahadi M. N-acetylcysteine overdose after acetaminophen poisoning. International medical case reports journal. 2015;8:65-9.

135. Cotgreave IA, Moldeus P. Methodologies for the analysis of reduced and oxidized N-acetylcysteine in biological systems. Biopharmaceutics & drug disposition. 1987;8:365-75.

136. Watson WA, McKinney PE. Activated charcoal and acetylcysteine absorption: issues in interpreting pharmacokinetic data. DICP : the annals of pharmacotherapy. 1991;25:1081-4.

137. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. Brain and behavior. 2014;4:108-22.

138. Ziment I. Acetylcysteine: a drug that is much more than a mucokinetic. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 1988;42:513-9.

Table 1 Overall summary of NAC treatment studies in psychiatric disorders. First authors of parent studies are indicated in bold, secondary studies in italic font.

Study	Disorder	Daily dose	Study size	Study design	Results
LaRowe et al [13]	Cocaine use disorder	2400mg	13	Open label randomized crossover trial	Significant reduction in craving
LaRowe et al [14]			15		Less desire to use and less interest in response to cocaine
Amen et al [15]	Cocaine use disorder	1200-2400mg	6	Single blind crossover	Significant reduction in craving
LaRowe et al [16]	Cocaine use disorder	1200-2400mg	111	Double blind placebo controlled	No demonstration that NAC reduces cocaine use in cocaine-dependent individuals some evidence of a possible efficacy in individuals who had already achieved abstinence from cocaine
Mardikian et al [17]	Cocaine use disorder	1200-3600mg	23	Pilot study open label trial	Reduced cocaine use
Gray et al [19]	Cannabis use disorder	2400mg	24	Pilot study open label trial	Significant decrease in use and craving. No change in urine cannabinoid levels
Gray et al [20]	Cannabis use disorder	2400mg	116	Double blind placebo controlled	Improvement in rates of abstinence
Roten et al [21]			89		Improvement for the total sample but no significant differences between NAC and placebo group
Bentzley et al [23]	Cannabis use disorder (relationship with impulsivity and adherence to therapy)		54		Effect of adherence on abstinence was observed in the NAC group. Highly impulsive individuals adherent to NAC treatment had increased abstinence rates compared to non-adherent individuals
McClure et al [24]	Nicotine addiction		68	Double blind placebo controlled trial	No significant differences
Schmaal et al [26]	Nicotine addiction	3600mg	22	Double blind placebo controlled pilot study	No significant effect on craving. A statistical trend towards fewer withdrawal symptoms in the NAC condition
Knackstedt et al [27]	Nicotine addiction	2400mg	29	Double blind placebo controlled trial	No significant differences, reduction in cigarettes smoked
Prado et al	Nicotine addiction	3000mg	34	Double blind placebo	Significant reduction of number of cigarettes smoked.

[29]				controlled trial	Improvement in the HDRS score
Bernardo et al [30]	Nicotine addiction in bipolar disorder	1200mg	75	Double blind placebo controlled trial	No improvement in nicotine use
Grant et al [31]	Nicotine addiction and pathological gambling	1200-3000mg+ imaginal desensitization	28	Double blind placebo controlled trial	Significant benefits after 6 weeks for nicotine addiction Improvement in gambling at 24 week
Grant et al [33]	Methamphetamine use disorder	600-1200-1800-2400mg + Naltrexone	31	Double blind placebo controlled	No statistically significant differences from placebo
Mousavi et al [34]	Methamphetamine use disorder	1200mg	32	Double blind crossover controlled	Significant improvement in Methamphetamine craving
Grant et al [35]	Pathological gambling	1200-1800mg	27	Pilot study open label trial	Improvement of PG-YBOCS
			13	Double blind placebo controlled trial	Improvement, but not statistically significant
Strawn et al [38]	Anxiety and social phobia	1200 to 2400mg	17	Case report	Improvement in CGI ↓ subjective anxiety
Garcia et al [40]	ADHD symptoms in SLE	2400-4800mg	46	Double blind placebo controlled trial	Improvement in ASRS score
Hardan et al [43]	Autism	900 to 1800 to 2700mg	36	Double blind placebo controlled trial	Improvement in irritability, cognition, mannerisms and stereotypies
Ghanizadeh et al [44]	Autism	1200mg + risperidone	40	Double blind placebo controlled trial	Improvement in irritability
Nikoo et al [45]	Autism	600-900mg + risperidone	40	Double blind placebo controlled trial	Improvement in irritability and hyperactivity
Ghanizadeh et al [46]	Autism (nail-biting, hyperactivity and inattentiveness)	800mg	1	Case report	Improvement on all VAS measures, improved nail-biting, hyperactivity and inattentiveness
Stutzman et al [47]	Autism	1200 mg + quetiapine	1	Case report	Reductions in the patient's aggressive behavior and irritability
Marler et al [48]	Autism	450 to 1800mg	1	Case report	Improvement in self-injurious behavior
Wink et al [49]	Autism	60mg/kg/day	31	Double blind placebo controlled trial	No significant impact on social impairment in youth with ASD
Dean et al [50]	Autism	500mg + TAU	102	Double blind placebo controlled trial	There were no differences between N-acetyl cysteine and placebo-treated groups on any of the outcome

					measures for either primary or secondary endpoints
Berk et al [54]	Bipolar disorder	2000mg	75	Double blind placebo controlled trial	Moderate to large effect on MADRS and BDRS
Dean et al [55]	Bipolar disorder		46		No significant effects
Magalhaes et al [56]	Bipolar disorder (medical comorbidities)		74		Advantage of NAC over placebo in those with a clinical comorbidity
Magalhaes et al [57]	Bipolar disorder (major depressive episode)		17		Very large effect sizes in favour of NAC were found for depressive symptoms and functional outcomes. Significantly more patients with treatment response
Magalhaes et al [58]	Bipolar disorder (II type)		14		Significant improvement in the YMRS
Magalhaes et al [59]	Bipolar disorder (manic or hypomanic episodes)		15		Significant improvement in YMRS within NAC group
Waterdrink et al [62]	Bipolar disorder (suicidal ideation)		75		↓Suicidal ideation
Berk et al [60]	Bipolar disorder (depressive symptoms)	2000mg	149	Open label trial	Significant improvement
Berk et al [61]	Bipolar disorder (depressive symptoms)			Double blind placebo controlled trial	No significant effects
Berk et al [64]	MDD	2000mg + TAU	252	Double blind placebo controlled trial	No significant effect on MADRS, response rate, remission rate at 12 wk but significant effect at 16 wk; LIFE-RIFT improved at 12 wk; no significant change in GAF and SOFAS
Carvalho et al [65]	Treatment resistant MDD	2000mg	2	Case series	Improvement in and CGI in both the cases
Lafleur et al [70]	OCD	600 to 3000mg	1	Case report	Marked improvement in Y-BOCS
Yazici et al [71]	OCD	600 to 3000mg	5	Case series	Significant improvements in four of five cases
Yazici et al [72]	OCD	600 to 2400mg + citalopram 6 mg	1	Case report	Significant improvement in obsession and compulsion
Van Ameringhen et al [73]	OCD (treatment resistant)	500 to 3000mg	6	Case series	No improvements in 5 of the 6 patients
Afshar et al [74]	OCD	600 to 2400mg add on to SSRI	48	Double blind placebo controlled trial	Significant improvement in Y-BOCS and CGI-S but not CGI-I
Sarris et al [75]	OCD	3000mg add on mainly to SSRI	44	Double blind placebo controlled trial	Significant improvement observed at 12 week

Paydary et al [76]	OCD	2000mg + fluvoxamine 200mg	44	Double blind placebo controlled trial	Significant effect of NAC as an augmentative agent
Bloch et al [77]	Tourette syndrome	1200 to 2400mg	31	Double blind placebo controlled trial	No evidence for efficacy of NAC in treating tic symptoms
Rodrigues et al [80]	Trichotillomania	1200mg	2	Case series	Complete regrowth
Taylor et al [82]	Trichotillomania	1200mg	1	Case report	Improved hair growth
Grant et al [83]	Trichotillomania	1200 to 2400mg	50	Double blind placebo controlled trial	Improved MGH-HPS, PITS and CGI
Bloch et al [84]	Trichotillomania	2400mg	39	Double blind placebo controlled trial	No significant difference compared to placebo group
Miller et al [85]	Skin picking (Prader-Willi)	450-1200mg	35	Open label pilot study	Improvement in skin-picking behaviors
Grant et al [86]	Skin picking	-	1	Case report	Improvement in skin picking frequency
Silva-Netto et al [81]	Skin picking-(+ trichotillomania)	1200mg	2-1	Case series	Improvement in skin picking (and trichotillomania)
Odlaug et al [67]	Nail biting, Skin picking, Trichotillomania	1200-2400-1800mg	3	Case series	Improvement in grooming behavior frequency
Percinel et al [87]	Skin picking	600 to 1800mg	1	Case report	Improvements in skin picking impulses and behaviors
Grant et al [88]	Skin picking	1200-3000mg	66	Double blind placebo controlled trial	Significant reductions in skin-picking symptoms
Berk et al [89]	Nail biting	2000mg	3	Case series	Improved nail biting frequency
Ghanizadeh et al [90]	Nail biting	800mg	42	Double blind placebo controlled trial	Statistically significant difference between the two groups regarding increased nail length after the first month of trial
Berk et al [94]	Schizophrenia	2000mg	140	Double blind placebo controlled trial	Improvement on CGI, PANSS but no other outcome measures
Berk et al [95]					Qualitative analysis showed improved mental state
Dean et al [98]	Schizophrenia (clozapine treated individuals)				Benefits of NAC at week 8, not week 24
Rapado-Castro et al [99]	Schizophrenia		121	Double blind placebo controlled trial	Potential advantage of adjunctive NAC over placebo on functioning and positive symptoms reduction in those patients with chronic schizophrenia
Farokhnia et al [96]	Schizophrenia	2000mg + risperidone	42	Double blind placebo controlled trial	Improvement in PANSS negative and total scales

Bulut et al [97]	Schizophrenia	600mg	1	Case report	Decrease in PANSS and CGI-S

ASRS=ADHD Self Report Scale; ASD=Autism Spectrum Disorder; BDRS=Bipolar Depression Rating Scale; CGI=Clinical Global Impression CGI-S=Clinical Global Impression Severity Scale; CGI-I=Clinical Global Impression Improvement Scale; GAF=Global Assessment of Functioning; HDRS=Hamilton Depression Rating Scale; LIFE-RIFT= Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool; MADRS=Montgomery–Asberg Depression Scale; MDD=major depressive disorder; MGH-HPS=Massachusetts General Hospital Hair Pulling Scale; NAC=N-acetylcysteine; OCD=Obsessive Compulsive Disorder; PANSS=Positive and Negative Syndrome Scale; PG-YBOCS=Pathological Gambling-Yale-Brown Obsessive Compulsive Scale; PITS=Psychiatric Institute Trichotillomania Scale; SOFAS=Social and Occupational Functioning Assessment Scale; TAU=Treatment AS Usual; VAS=Visual Analog Scale; Y-BOCS=Yale Brown Obsessive Compulsive Scale; YMRS=Young Mania Rating Scale.