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REVIEW ARTICLE

The Potential of *N*-Acetyl-L-Cysteine (NAC) in the Treatment of Psychiatric Disorders

Richard C. J. Bradlow[1] · Michael Berk[2,3,4,8] · Peter W. Kalivas[5,6] · Sudie E. Back[6,7] · Richard A. Kanaan[4,8]

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Abstract

N-acetyl-L-cysteine (NAC) is a compound of increasing interest in the treatment of psychiatric disorders. Primarily through its antioxidant, anti-inflammatory, and glutamate modulation activity, NAC has been investigated in the treatment of neurodevelopmental disorders, schizophrenia spectrum disorders, bipolar-related disorders, depressive disorders, anxiety disorders, obsessive compulsive-related disorders, substance-use disorders, neurocognitive disorders, and chronic pain. Whilst there is ample preclinical evidence and theoretical justification for the use of NAC in the treatment of multiple psychiatric disorders, clinical trials in most disorders have yielded mixed results. However, most studies have been underpowered and perhaps too brief, with some evidence of benefit only after months of treatment with NAC. Currently NAC has the most evidence of having a beneficial effect as an adjuvant agent in the negative symptoms of schizophrenia, severe autism, depression, and obsessive compulsive and related disorders. Future research with well-powered studies that are of sufficient length will be critical to better understand the utility of NAC in the treatment of psychiatric disorders.

Key Points

Through its antioxidant, anti-inflammatory, and glutamate modulation activity *N*-acetyl-L-cysteine may have a role in the treatment of multiple psychiatric disorders.

Whilst there have been some promising results, especially in schizophrenia, autism, depression, and obsessive compulsive and related disorders, findings have been mixed, and better powered and longer studies are needed.

✉ Richard A. Kanaan
richard.kanaan@unimelb.edu.au

1 Turning Point, Eastern Health, Richmond, VIC, Australia

2 IMPACT-The Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Deakin University, Geelong, VIC, Australia

3 Orygen, The National Centre of Excellence in Youth Mental Health, Centre for Youth Mental Health, Melbourne, VIC, Australia

4 Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia

5 Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA

6 Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, USA

7 Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

8 Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia

1 Introduction

N-acetyl-L-cysteine (NAC), the acetylated precursor of L-cysteine, is used in medicine as a mucolytic agent to treat drug toxicity or overdose, given orally, intravenously, or by inhalation [1]. Though these uses are well established, there has been much recent interest in the use of NAC in treating neuropsychiatric conditions, including schizophrenia, mood and anxiety disorders, and substance-use disorders (SUDs). In the following, we review the growing body of research

evidence for therapeutic benefits of NAC in psychiatric disorders and the potential mechanisms by which it may exert these beneficial effects.

We conducted literature searches in PubMed/MEDLINE and Google Scholar using the key terms "NAC", "*N*-acetyl-L-cysteine", "psychiatric disorders", "mental illness", and terms specific to each disorder. Manual searches were done of the bibliographies of included studies. Studies included are those that were published before December 2021. We discuss the potential therapeutic mechanisms of NAC in psychiatric disorders as well as the published literature pertaining to each individual psychiatric disorder. Within each psychiatric disorder, the underlying neurobiological deviations will be explained, followed by preclinical literature, and lastly (clinical) human literature, when available. The disorders are grouped and ordered as per their appearance in DSM-5, with the exception of Williams Syndrome, which does not appear in DSM-5 but was placed under neurodevelopmental disorders in this paper; onychophagia, which is not listed in DSM-5 but is generally considered an obsessive-compulsive-related disorder (OCRD); and Chronic Pain, which likewise is not in DSM-5 and was placed at the end of the paper.

2 Potential Therapeutic Mechanisms of *N*-Acetyl-L-Cysteine (NAC)

NAC has multiple relevant actions including antioxidant effects, reduction of cytokine activity, modulation of dopamine release, reversal of mitochondrial dysfunction, reductions in apoptosis and ferroptosis, anti-inflammatory activity, increased neurogenesis, and increased glutamate release [1–10]. Perhaps the most important of these for the treatment of psychiatric disorders is its antioxidant activity, which it achieves through multiple mechanisms. NAC functions as an antioxidant through stimulating the synthesis of glutathione, enhancing glutathione-S-transferase activity, scavenging free radicals, and stimulating group II metabotropic glutamate receptors to decrease glutamate transmission [2]. Glutathione is the primary endogenous antioxidant in the brain. Its production rate is limited by L-cysteine availability, so increasing the supply of L-cysteine via NAC supplementation leads to an increase in brain glutathione [3].

Antioxidants reduce oxidative stress, which is implicated in the pathogenesis of many psychiatric disorders [11]. Oxidative stress represents a state in which there is an imbalance between reactive oxygen species, such as hydrogen peroxide, superoxide, and peroxynitrite, and tissue redox defenses. It can be the result of having increased reactive oxygen species, decreased antioxidant defenses, or unrepaired oxidative damage [12]. Reactive oxygen species cause cellular lipid peroxidation, inactivation of important enzymes, malfunction of the respiratory chain, and DNA modification [11, 12]. Antioxidant enzymes, such as superoxide dismutase, glutathione reductase and peroxidase, metabolize reactive oxygen species into less toxic molecules, protecting the brain from harms caused by oxidative stress [12]. Severe prolonged oxidative stress can lead to glutathione depletion via the increase in glutathione disulfide formation and accumulation, leading to export and extracellular hydrolysis, protein S-glutathionylation, and formation of glutathione adducts [13]. Oxidative stress is linked to mitochondrial dysfunction, which NAC has been shown to prevent [4, 5].

NAC is most frequently used in paracetamol toxicity, where mitochondrial protein adducts are formed causing oxidative stress that eventually leads to liver failure [14]. NAC prevents this through its action as a glutathione precursor, thus supporting mitochondrial metabolism [14]. Mitochondrial dysfunction is a common element linked to bipolar disorder, depression, schizophrenia, and autism spectrum disorder (ASD) [4, 7, 15]. In bipolar disorder, mitochondrial overactivity is associated with mania and under functioning is associated with the depressed and euthymic phase of the disorder [15]. NAC has also been shown to increase mitochondrial complex I- and IV-specific activities in synaptic mitochondrial preparations in aged mice [16].

The anti-inflammatory activity of NAC is protective against chronic inflammation, which is implicated in the pathogenesis of many psychiatric disorders [17]. Chronic inflammation is characterized by elevated pro-inflammatory cytokines and acute phase proteins. Patients acutely unwell with depression or schizophrenia are more likely to have raised inflammatory markers, and patients who have chronic inflammatory conditions, such as lupus or rheumatoid arthritis, are at a higher risk of developing depression or schizophrenia [18]. Moreover, inflammation and psychiatric disorders are genetically linked, for example, the risk of developing schizophrenia is associated with polymorphisms in the major histocompatibility complex on chromosome 6 [18]. Anti-inflammatory treatment may improve the therapeutic efficacy of antidepressants, especially in patients with high baseline levels of inflammation [6]. Increased oxidative stress and increased inflammation are intimately linked, and NAC has both antioxidant and anti-inflammatory properties [6]. NAC has immuno-modulation activity, having been demonstrated to reduce the levels of inflammatory cytokines tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), nuclear factor kappa B (NF-κB), IL-6, and IL-10 in rodents [1, 5].

NAC also modulates the glutamatergic system, dysfunction of which is linked to multiple psychiatric disorders [5, 19]. By forming cystine outside the cells, NAC drives the astrocytic cystine–glutamate antiporter, which increases intracellular cysteine for glutathione synthesis and simultaneously extrudes glutamate into the extracellular space

[7]. Rising concentrations of extracellular glutamate stimulates presynaptic metabotropic glutamate receptors, which decreases the synaptic release of glutamate [7]. Glutathione may also have a role in regulating glutamate levels in the brain as it has been shown to potentiate brain N-methyl-d-aspartate (NMDA) receptor response to glutamate in rats [7].

NAC has also been demonstrated to alter dopamine release in animal models [7]. At sufficiently high doses, it has been demonstrated to reduce striatal dopamine in rats given amphetamines; however, that same study found that at lower doses NAC increased striatal dopamine release [20]. NAC has also been shown to reduce methamphetamine-induced reduction of dopamine transporters in the striatum of rhesus monkeys [16]. NAC may reduce dopamine through facilitating increased glutathione production, which has a significant role in reducing oxidative stress. Amphetamine use is associated with excessive release of dopamine and suppressed action of dopamine metabolites [20]. Glutathione increases glutamate agonist-evoked striatal dopamine release likely via glutathione's activity at NMDA and non-NMDA glutamate receptors [21].

3 Neurodevelopmental Disorders

3.1 Williams Syndrome

Patients with Williams syndrome, a genetic disorder caused by a microdeletion in chromosome 7q11.23, commonly present with neuropsychiatric disorders [22]. A case report is published on the successful treatment with NAC (1800 mg/day) of a 19-year-old female with Williams syndrome who developed anger, aggression, and hair-pulling following a psychotic episode precipitated by a gastroscopy in which she was sedated with fentanyl, midazolam, and propofol [22]. The patient's behavior improved within 2 days of NAC treatment and she had continued NAC for 14 months by the time of publication [22]. The authors believed NAC was having its effect by normalizing the glutaminergic system, which is abnormal in Williams syndrome and was further altered by propofol [22].

3.2 Autism Spectrum Disorder (ASD)

ASD is associated with increased oxidative stress, mitochondrial dysfunction, abnormal glutamate transmission, and serotonin transporter dysfunction, all of which imply a potential therapeutic benefit for NAC [23, 24]. NAC supports mitochondrial metabolism in animal models of ASD and reduces oxidative stress by promoting glutathione production [23, 24].

Animal studies of NAC in ASD have yielded mixed results. Male rats exposed prenatally to valproate in order to phenotypically mimic ASD were treated with NAC (150 mg/kg/day). On dissection, the glutaminergic system in the amygdala of the NAC-treated rats normalized, and their social interactions improved [25]. Mice with deletions of chromosome 16p11.2, which is associated with ASD in humans, exhibited ASD phenotype (slowed hyperlocomotion, reduced sociability, and displayed a strong anxiolytic phenotype) when under stress [26]. A single dose of NAC (150 mg/kg) did not normalize the anxiety-like behaviors but did increase sociability [26]. Conversely, mice treated with a single dose of NAC (150 mg/kg) had a decrease in striatal glutamate, mimicking striatal changes in ASD, and were less active and more anxious [27].

In humans, case studies of NAC (800–2400 mg) suggest increased social behavior, decreased aggression, and decreased self-harm, facilitating lowering of doses of antipsychotics in males with ASD aged 4–17 years [28–31]. Five [23, 32–35] randomized controlled trials (RCTs) have investigated NAC as a treatment for ASD in children and adolescents, all of which were included in a meta-analysis published in 2021 [36]. The trials' interventions lasted from 8 to 24 weeks, had 31–102 participants (combined $N = 256$), and 500–4200 mg/day [36]. The meta-analysis found that NAC significantly improved Aberrant Behaviour Checklist (ABC) total scores, and irritability and hyperactivity subscales compared to placebo; however, it found no significant improvement in the social responsiveness scale or the repetitive behavior scale compared to placebo [36]. However, the largest study could not be included in this analysis as it did not use the ABC as an outcome [35]. That study was the largest (102 participants) and longest (24 weeks) randomized controlled trial (RCT) conducted so far on NAC treating ASD and did not demonstrate any benefit for NAC over placebo, although it used a much smaller dose of NAC (500 mg/day) and had a more heterogeneous population [35].

Currently the limited evidence available indicates that NAC may be a useful treatment for irritability and hyperactivity in severe autism but this is yet to be demonstrated in well-powered, longer trials (see Table 1).

3.3 Tourette's Disorder

NAC may have a role in treating Tourette's Disorder by regulating the glutaminergic system, which has been implicated in its pathogenesis [37]. There is some evidence for glutaminergic drugs treating trichotillomania and OCD, which share genotypes, phenotypes, and neurological abnormalities with Tourette's [37]. There is one double-blinded RCT of 31 children aged 8–17 years investigating the effects of NAC (1200 mg/day for the first 1–2 weeks, then 2400 mg a day), which found no significant difference between NAC and placebo [37] (see Table 1).

Table 1 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) in neurodevelopmental disorders

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other medications	Outcome measures	Results
Hardan et al. [23]	ASD (as per DSM-IV-TR, ADOS, or expert clinical evaluation)	12 weeks	33 (15/18)	900 mg/day for 4 weeks, 1,800 mg/day for 4 weeks, 2,700 mg/day for 4 weeks	Treatment as usual	ABC, CGI-I, CGI-S, TESS, SRS, RBS-R	Significant reduction in ABC irritability subscale compared to placebo
Ghanizadeh & Moghimi-Sarani [32]	ASD (as per DSM-IV-TR)	8 weeks	40 (20/20)	1,200 mg/day	Risperidone and treatment as usual	ABC	Significant reduction in ABC irritability subscale compared to placebo
Nikoo et al. [33]	ASD (as per DSM-IV-TR)	10 weeks	50 (25/25)	600–900 mg/day	Risperidone only	ABC-C, CGI, RBS-R, SRS	No significant difference between groups, NAC had significant reduction in ABC irritability and hyperactivity from baseline
Wink et al. [34]	ASD, Asperger's disorder, PDD NOS (as per DSM-IV)	12 weeks	31 (16/15)	60 mg/kg/day (titrated up from 300 mg/day over the first 3 weeks, max dose 4,200 mg/day)	Treatment as usual	CGI-I, CGI-S, ABC, SRS, VABS-II	No significant difference between groups
Bloch et al. [37]	Tourette's Disorder	12 weeks	31 (17/14)	1,200 mg/day for 2 weeks, then 2,400 mg/day	Treatment as usual	YGTSS, PUTS, CYBOCS, ADHD-RS, MASC, PAERS	No significant difference between groups
Dean et al. [35]	ASD (as per DSM-IV-TR)	24 weeks	102 (51/51)	500 mg/day	Treatment as usual	SRS, CCC-2, RBS-R, VABS-II, DBC-P, PGI-I, CGI-I, CGI-S	No significant difference between groups

ASD Autism Spectrum Disorder, *DSM-IV-TR* Diagnostic and Statistical Manual of Mental Disorders: Text Revision, *ADOS* Autism Diagnostic Observation Schedule, *ABC* Aberrant Behaviour Checklist, *ABC-C*: Aberrant Behaviour Checklist-Community, *CGI-I* Clinical Global Impressions-Improvement, *CGI-S* Clinical Global Impression-Severity, *TESS* Treatment-Emergent Symptom Scale, *SRS* Social Responsiveness Scale, *RBS-R* Repetitive Behaviour Scale-Revised, *PDD NOS* Pervasive Developmental Disorder Not Otherwise Specified, *VABS-II* Vineland Adaptive Behaviour Scales 2nd edition, *YGTSS* Yale Global Tic Severity Scale, *PUTS* Premonitory Urge for Tics Scale, *YBOCS* Yale-Brown Obsessive Compulsive Scale,Children's, *ADHD-SR* Attention Deficit Hyperactivity Disorder-Self Report Rating, *MASC* Multidimensional Anxiety Scale for Children, Paediatric Adverse Events Rating Scale, *CCC-2* Children's Communication Checklist 2nd edition, *DBC-P* Developmental Behaviour Checklist-Primary Carer Version, *PGI-I* Parent Global Impression-Improvement

4 Schizophrenia Spectrum and Other Psychotic Disorders

Schizophrenia may be characterized by neuroprogression, potentially mediated by free radical-mediated neurotoxicity, inflammation, apoptotic pathways, mitochondrial dysfunction, or neurogenesis, against all of which NAC shows preventative action [8]. NAC increases glutathione levels, which are decreased in the cerebrospinal fluid, medial prefrontal cortex, and caudate region of patients with schizophrenia [38]. Magnetic resonance (MR) spectroscopy studies have demonstrated that patients with schizophrenia have altered glutamate and compromised glutathione levels in the prefrontal cortex [9]. A single dose of NAC (at 2400 mg) decreases glutamate in the anterior cingulate cortex in people with schizophrenia [39]. Polymorphisms in the genes involved in glutathione synthesis (glutamate cysteine ligase modifier subunit and the catalytic subunit for glutamate cysteine ligase) are associated with an increased risk for schizophrenia [38]. Abnormalities in the levels of *N*-acetyl metabolites in the serum are associated with first episode schizophrenia [40]. Glutathione may also have a treatment effect in schizophrenia by modulating NMDA receptor activity. Glutathione deficiency is associated with NMDA receptor hypofunction in rats [41].

In animal models of schizophrenia, NAC has been shown to improve mitochondrial dysfunction and apoptosis, reduce oxidative stress and inflammation, reverse mitochondrial toxicity, reduce apoptosis, and enhance neurogenesis [8, 9].

Deficits in mismatch negativity (MMN), a measurement of NMDA receptor dysfunction by auditory-evoked potentials, are associated with symptoms and poor functioning in patients with schizophrenia [42]. Secondary analysis of 11 participants in Berk et al. [43] found that NAC significantly improved auditory evoked potential by increasing the NMDA-dependent MMN compared to placebo in patients with schizophrenia. However, this finding was not reproduced by an 8-week placebo-controlled RCT ($N = 19$) that found no difference in MMN between NAC (at 2400 mg a day) compared to placebo [42]. NAC supplementation in patients with schizophrenia may increase neural synchronization on electroencephalography (EEG) [42, 44]. Neural synchronization on EEG is believed to be dependent on NMDA receptor function, which implies NAC's effect on it occurs via glutamate and the glutathione [42].

There have been eight RCTs examining NAC's effectiveness as augmentation to antipsychotic therapy, five [38, 41, 45–47] of which were included in a meta-analysis published in 2020 [48]. It found that at 8 weeks NAC (at 1000–3600 mg/day) had no significant effect on Positive and Negative Syndrome Scale (PANSS) scores; however, at 24 weeks, NAC showed a significant advantage over placebo in total and negative PANSS scores [48]. This finding reflects the results of individual longer trials that found the effects of NAC were slow to emerge and not statistically significant at 8 weeks of intervention [38, 46]. Of the RCTs not included in that analysis, one was excluded due to missing data and two had not yet been published [48]. The two papers published since the publication of the meta-analysis have had mixed findings; Yang et al. [42] found no effect of NAC on PANSS, whilst Pyatoykina et al. [49] found a significant reduction in negative PANSS and total PANSS compared to placebo. NAC significantly improves working memory [48].

The limited existing literature indicates that NAC may have a role in treating the negative symptoms of schizophrenia, although this is yet to be demonstrated in well-powered trials (see Table 2). There is currently a large RCT being conducted on NAC's effect on patients with clozapine-resistant schizophrenia [50]. There is also a case series suggesting NAC may reduce sialorrhea from clozapine, possibly by reducing oxidative stress in the salivary glands [51].

4.1 Early Psychosis

Clinical practice places a strong emphasis on early intervention to prevent or improve the prognosis of psychotic illness. People in the early stages of illness might derive greater benefit from treatment with NAC than those with more entrenched illness where neuroprogression has already occurred. Early stages of schizophrenia are strongly associated with increased frontal hyperconnectivity [52]. A single dose of NAC (2,400 mg) reduces resting functional connectivity in the default mode network and salience network in patients with schizophrenia [53]. Fornix white matter integrity deteriorates in patients with schizophrenia, and NAC supplementation in patients with early psychosis protects fornix white matter integrity, suggesting NAC may protect white matter integrity in early psychosis patients [54]. NAC supplementation also increased functional connectivity along the cingulum bundle in patients with early psychosis compared to placebo ($N = 20$) [55]. Treatment with NAC has also been shown to improve auditory processing in patients ($N = 15$) with early psychosis [56].

Clinical trials investigating adjuvant NAC therapy in early psychosis have had mixed results; two studies found that NAC (at 600 mg/day and 3600 mg/day, respectively) significantly decreased PANSS scores [45, 46]. However, the largest study found that NAC (at 2700 mg/day) had no effect on PANSS scores but did increase cognitive speed [47], although subgroup analysis found that low serum glutathione at baseline was significantly associated with improvement in positive PANSS score with NAC treatment.

Subgroup analysis of Berk et al. [8] demonstrated that duration of illness was positively associated with treatment effect of NAC on positive symptoms and functioning. There is currently a large RCT being conducted into NAC's effect on patients with first-episode psychosis [9].

Based on the limited current available evidence, it's uncertain if NAC has clinical utility in early psychosis. Future, better-powered studies are needed to clarify this (see Table 2).

4.2 The At-Risk Stage of Psychosis

A role for NAC in preventing the onset of psychosis in models of at-risk individuals has been explored. In rats with the neonatal ventral hippocampal model of schizophrenia, oxidative stress caused prefrontal cortex dysfunction [57]. Treatment of these rats with NAC during adolescence and prior to the onset of symptoms prevented the reduction of prefrontal parvalbumin immunoreactive interneuron activity [57].

MMN is reduced in individuals at risk for psychosis compared to healthy controls [58, 59]. Smaller MMN has been found to be associated with a higher likelihood of at-risk individuals to develop psychosis [59]. It is not known if improving MMN in at-risk individuals reduces the likelihood of them developing psychosis, and there is mixed evidence that treatment with NAC improves MMN in patients with schizophrenia [42, 43]. This is a possible area for future investigation.

A small case series ($N = 5$) of NAC at 2,000 mg/day in at-risk individuals found four participants no longer met the criteria for an at-risk mental state at the end of 12 weeks. NAC treatment also significantly improved scores on Brief Assessment of Cognition in Schizophrenia and the Schizophrenia Cognition Rating Scale [60]. However, it failed to show a statistically significant improvement in scores on the Scale of Prodromal Symptoms across all participants [60]. A large RCT is currently underway investigating the effect of NAC (2,000 mg/day) and an integrated preventive psychological intervention (IPPI) on preventing conversion to psychosis in at-risk individuals [61]. The study has four arms: IPPI with placebo, IPPI with NAC, psychological stress management alone with NAC, and psychological stress management placebo [61].

5 Bipolar and Related Disorders

The use of antidepressants in bipolar depression is controversial as there is no conclusive evidence for their efficacy and they may precipitate rapid cycling or a manic episode [3]. Psychotherapy also has limited evidence in treating the depressive symptoms of bipolar affective disorder (BPAD) [3]. Thus, there is a strong desire for novel therapies for bipolar depression.

BPAD is associated with dysregulated oxidative defenses, and mood stabilizers appear to buffer oxidative defenses and protect neuronal cells from damage related to oxidative stress [3, 63]. A rat model of mania increases brain oxidative stress by administering d-amphetamine [64]. NAC combined with deferoxamine in rat models, protects against protein damage in the hippocampus and the prefrontal cortex [64]. There is evidence from animal studies that NAC may prevent lithium-induced renal dysfunction [65]. Unfortunately, power and duration requirements suggest that massive and lengthy trials will be needed to definitively confirm this signal in humans, and as such, this lead is likely to remain unexplored.

Multiple clinical trials have investigated NAC in BPAD. The first significant trial was an RCT by Berk et al. published in 2008 that found positive results. It investigated the effects of adjunctive NAC (2000 mg/day) over 28 weeks (24 weeks of intervention and an additional 4 weeks of follow-up) in 74 patients with bipolar disorder (I and II) and found that the NAC group showed significant improvement in the Montgomery Åsberg Depression Rating Scale (MADRS) and Bipolar Depression Rating Scale (BDRS) at 24 weeks compared to placebo [66]. Secondary analysis of this paper found that NAC significantly reduced suicidal ideation as measured on the MADRS and BDRS; however, it had no significant effect on cognitive functioning compared to placebo [67, 68]. Secondary analysis also suggested that NAC may reduce manic symptoms [69]. Subgroup analysis of patients with bipolar disorder II in the sample did not demonstrate that NAC was superior to placebo on MADRS or BDRS scores; however, six out of seven participants in the NAC group achieved full remission of both depressive and manic symptoms, whilst two out of the seven participants in the placebo group did the same [70]. A future better powered study is needed to explore this further.

These findings have been replicated in a smaller RCT that ran over 24 weeks [71]. However, the findings were not replicated in a Danish RCT investigating the effects of adjunctive NAC (3,000 mg/day) over 24 weeks (20 weeks of intervention and an additional 4 weeks of follow-up) in 80 patients with bipolar disorder (I and II), which found no significant improvement MADRS and a clinically insignificant but statistically significant Young Mania Rating Scale (YMRS) improvement in NAC compared to placebo at 20 weeks [72]. A change greater than four is generally considered clinically significant on the YMRS, whereas the change was 1.6 (confidence interval 3.1–0.2) in the study [72]. Another large study of three adjunctive treatment groups—NAC (2,000 mg/day), combination nutraceutical treatment (including NAC at 200 mg/day), and placebo—with an

Table 2 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating schizophrenia

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other medications	Outcome measures	Results
Berk et al. [38]	Schizophrenia (as per DSM-IV)	24 weeks (with 4 weeks follow up)	140 (71/69)	2,000 mg/day	Treatment as usual	PANSS, CGI-S,CGI-I, GAF, SOFAS, AIMS, SAS, BAS	Significant reduction in PANSS negative, general, and total, CIG-S, and BAS compared to placebo
Farokhnia et al. [41]	Schizophrenia (as per DSM IV-TR)	8 weeks	46 (23/23)	1,000 mg/day for 1 week then 2,000 mg/day	Risperidone	PANSS, HDRS	No significant difference between groups, NAC had significant reduction in PANSS negative and total, from baseline
Zhang et al. [45]	First episode psychosis (as per ICD-10)	8 weeks	121 (61/60)	600 mg/day	Risperidone	PANSS	Significant reduction in PANSS negative, positive, general and total, compared to placebo
Breier et al. [46]	Schizophrenia, schizophreniform, schizoaffective or psychosis not otherwise specified (as per DSM-IV)	52 weeks	60 (30/30)	3,600 mg/day	Treatment as usual	PANSS, CGI-S, BACS, PSP	Significant reduction in PANSS, cognition/disorganized factor, and total, and BACS compared to placebo
Sepehrmanesh et al. [62]	Schizophrenia (as per DSM IV-TR)	12 weeks	84 (42/42)	1,200 mg/day	Treatment as usual	PANSS, MMSE, DSST, Stroop color-word test	Significant reduction in PANSS negative, positive, and total, MMSE, DSST, and Stroop test compared to placebo
Conus et al. [47]	Psychotic disorder (reaching "psychosis threshold" on the CAARMS)	6 months	63 (32/31)	2,700 mg/day	Treatment as usual	PANSS GAF, SOFAS, MCCB	Significant improvement in cognitive speed, verbal fluency, and trail making, compared to placebo
Yang et al. [42]	Schizophrenia (as per DSM-5)	8 weeks	19 (9/10)	2,400 mg/day	Treatment as usual	EEG (MMN & ASSR), MCCB, CAINS	Significant increase in ASSR at 40 hertz, compared to placebo
Pyatoykina et al. [49]	Schizophrenia (as per ICD-10)	60 days	18 (10/8)	2,000 mg/day	Treatment as usual	PANSS, CDS, BACS	Significant reduction in negative and overall PANSS compared to placebo

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, *PANSS* Positive and Negative Syndrome Scale, *CGI-I* Clinical Global Impressions-Improvement, *CGI-S* Clinical Global Impression-Severity, *GAF* Global Assessment Functioning, *SOFAS* Social and Occupational Functioning Assessment Scale, *AIMS* Abnormal Involuntary Movements Scale, *SAS* Simpson-Angus Scale, *BAS* Barnes Akathisia Scale, *HDRS* Hamilton Depression Rating Scale, *ICD-10* International Classification of Diseases 10th edition, *BACS* Brief Assessment of Cognition in Schizophrenia, *PSP* Personal and Social Performance Scale, *MMSE* Mini-Mental State Examination, *DSST* Digit Symbol Substitution Test, *CAARMS* Comprehensive Assessment of At Risk Mental States, *MCCB* MATRICS Consensus Cognitive Battery, *EEG* Electroencephalogram, *MMN* Mismatch Negativity, *ASSR* Auditory Steady State Response, *CAINS* Clinical Assessment Interview for Negative Symptoms, *CDS* Calgary Depression Scale

intervention period of 16 weeks and follow-up at 20 weeks found no significant difference at 16 weeks [15]. However, the nutraceutical group showed significant improvement in MADRS, BDRS, and quality-of-life scores at 20 weeks, implying a delayed treatment effect [15].

Another large (149 participants) 24-week maintenance RCT demonstrated that NAC (at 2,000 mg/day) significantly delayed the onset of a depressive episode in patients with bipolar disorder [65], although it too failed to recreate the positive findings of the 2008 study, as there was no significant difference in symptom rating scales at the end of the intervention [65]. This trial was preceded by an 8-week single-arm open-label run-in phase with all participants of the double-blind RCT, which demonstrated NAC (2,000 mg/day) to have significant improvement in MADRS and BDRS compared to baseline [3]. Secondary analyses of NAC's effects on biological markers of inflammation found it had no significant effect on serum levels of C-reactive protein (BDNF), IL-6, IL-8, IL-10, TNF-α, or C-reactive protein (CRP) [73].

The anti-inflammatory effects of NAC in treating bipolar depression have been studied further. A Brazilian RCT of 67 patients with both bipolar and unipolar depression found that NAC significantly reduced CRP over 12 weeks compared to placebo [6]. It also found that NAC significantly reduced depression and anxiety ratings from baseline, but not compared to placebo, in patients with CRP > 3 mg/L [6]. The anti-inflammatory effects of NAC in treating bipolar depression were also investigated in a very small four-arm study of 24 patients treated with NAC (at 1,000 mg/day), aspirin, both, or placebo for 16 weeks, which found that the NAC and aspirin treatment arm had a higher probability of treatment response [74]. Subgroup analyses of Berk et al. found that in participants who self-reported cardiovascular or endocrine conditions, NAC showed significant improvement compared to placebo in functioning (as measured on the Global Assessment of Functioning, SOFAS, and LIFE-RIFT scales) but not depressive symptoms [75].

An open-label study investigated the effects of NAD (2,400 mg/day) for 8 weeks in nine adolescents (aged 15–24 years) with depressive symptoms and a first-degree relative with BPAD I, finding a significant reduction in depression and anxiety symptoms (measured on HDRS and Hamilton anxiety rating scale (HARS)) from baseline [76]. Symptom improvement was significantly correlated with a change in glutamate levels in the left ventrolateral prefrontal cortex from baseline as seen on MR spectroscopy [76].

In summary, although initial results demonstrated NAC as superior to placebo in the treatment of bipolar depression, especially in Berk et al. [66], these results have not been consistently reproduced. A meta-analysis of five RCTs [15, 65, 71, 72, 74] examining NAC for BPAD depression published in 2021 found that NAC did not demonstrate any significant improvement in all outcomes measured [77]. However, a contemporaneous meta-analysis of six RCTs [6, 15, 66, 72, 74] did suggest significant benefit on symptoms of depression (as measured on HDRS and MADRS) [78]. NAC could currently not be recommended for clinical use in BPAD and further better powered studies are needed to provide more clarity (see Table 3).

6 Depressive Disorders

Unipolar depression is associated with several oxidative disturbances, including oxidative damage in erythrocytes, elevated antioxidant enzymes (particularly superoxide dismutase) in peripheral tissues that reduce with antidepressant therapy, and significant oxidative stress seen in the frontal lobe on brain biopsy in patients with depression [12]. It is thought that NAC's antidepressant effects are in part the result of easing oxidative stress by increasing glutathione levels [2]. NAC may also have antidepressant effects through its anti-inflammatory properties and by increasing extracellular glutamate levels [2, 6]. The anti-inflammatory effects of NAC may be particularly important in treatment-resistant depression [63].

In animal studies, NAC reduces immobility time during forced swim tests on rats [2]. In male Wistar rats that underwent bulbectomy (removal of the olfactory bulbs), which is a model for depression, chronic administration of NAC had a similar effect to that of imipramine [11].

Clinical studies have shown mixed results. A large RCT with 269 participants found that NAC (at 2000 mg/day) showed a modest but significant improvement in MADRS scores at 16 weeks' follow-up (intervention having ceased at 12 weeks) compared to placebo [79]. As with other antidepressants, there was an indication of greater effects in those with more severe depression (MADRS score > 24) [79]. They also found significant improvement in the functioning measures of Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) and Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE-LIFE) [79]. MR spectroscopy of a subgroup in that study found higher glutamate-glutamine and N-acetyl-aspartate and lower myo-inositol levels were predictive of the patient being in the NAC treatment arm [80]. Higher glutamate-glutamine and N-acetyl-aspartate was predictive of lowered oxidative stress [80]. A large RCT is currently investigating the effect of NAC augmenting antidepressant therapy in treatment-resistant depression [63].

Secondary analysis of the effect of NAC on depressive symptoms of a trial investigating NAC (2,400 mg/day) treating cannabis use disorder in 74 adolescents for 8 weeks, found that NAC had no effect on depressive symptoms as

Table 3 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating bipolar disorder

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other medications	Outcome measures	Results
Berk et al. [66]	BPAD I or BPAD II (as per DSM-IV)	24 weeks (with 4 weeks follow up)	75 (38/37)	2,000 mg/day	Treatment as usual	CGI-I-BP, CGI-I-M, CGI-I-D, CGI-S-BP, CGI-S-M, CGI-S-D, MADRS, YMRS, BDRS, GAF, SLICE-LIFE, LIFE-RIFT, Q-LES-Q	Significant improvement in MADRS, BDRS, CGI-S-BP, Q-LES-Q, LIFE-RIFT, GAF, SLICE-LIFE, compared to placebo at 24 weeks
Magalhães et al. [71]	BPAD I or BPAD II (as per DSM-IV)	24 weeks	17 (10/7)	1,000 mg/day	Treatment as usual	BDRS, MADRS, YMRS, CGI, LIFE-RIFT, Q-LES-Q	Significant improvement in BDRS, MADRS, LIFE-RIFT, Q-LES-Q at 24 weeks compared to placebo
Berk et al. [65]	BPAD I, BPAD II, or BPAD NOS (as per DSM-IV-TR)	24 weeks (preceded by 8 weeks of all participants receiving NAC)	156 (79/77)	2,000 mg/day	Treatment as usual	MADRS, BRDS, YMRS, CGI-BP, PGI, GAF, SOFAS, SLICE-LIFE, LIFE-RIFT, Q-LES-Q	Significant improvement from baseline in open label study. No significant difference between groups
Bauer et al. [74]	BPAD I or BPAD II (as per DSM-IV-TR)	16 weeks	24 (8 placebo/8 NAC/4 NAC & aspirin/4 aspirin)	1,000 mg/day	Treatment as usual	MADRS, YMRS, GAF	No significant difference between groups
Porcu et al. [6]	MDD and BPAD depression (as per ICD-10 and DSM-IV)	12 weeks	67 (25/42)	1,800 mg/day	Treatment as usual	HDRS, HARS, CGI, YMRS, WHOQOL, SDS, MARS, CRP, Cholesterol, BMI	In CRP <4 significant improvement in CGI compared to placebo. In CRP >3 no significant difference between groups
Ellegaard et al. [72]	BPAD I or BPAD II (as per DSM-IV)	20 weeks (with 4 weeks follow up)	80 (40/40)	3,000 mg/day	Treatment as usual	MADRS, YMRS, WHO-5, GAF-F, GAF-S, CGI-S	Statistically significant but clinically insignificant improvement in YMRS compared to placebo
Berk et al. [15]	BPAD I, BPAD II, or BPAD NOS (as per DSM-IV-TR)	16 weeks (with 4 weeks follow up)	181 (61 nutraceutical therapy/ 59 NAC/ 61 placebo)	2,000 mg/day	Treatment as usual	MADRS, HARS, BDRS, YMRS, CGI-I, CGI-S, SOFAS, LIFE-RIFT, Q-LES-Q-SF, PGI-I	No significant difference between NAC and placebo groups. Nutraceutical group showed significant improvement in MADRS, BDRS, SOFAS, and LIFE-RIFT scores at 20 weeks compared to placebo but not at 16

BPAD bipolar affective disorder, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, *CGI-I-BP,-M,-D* Clinical Global Impressions-Improvement for bipolar disorder, mania, and depression, *CGI-S-BP,-M,-D* Clinical Global Impression-Severity for bipolar disorder, mania, and depression, *MADRS* Montgomery Åsberg Depression Rating Scale, *YMRS* Young Mania Rating Scale, *BDRS* Bipolar Depression Rating Scale, *GAF* Global Assessment Functioning, *SOFAS* Social and Occupational Functioning Assessment Scale, *SLICE-LIFE* Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation, *LIFE-RIFT* Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, *Q-LES-Q* and Quality of Life Enjoyment and Satisfaction Questionnaire, *PGI* Patient Global Impression, *MDD* Major Depressive Disorder, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *WHOQOL* World Health Organization Quality of Life, *SDS* Sheehan Disability Scale, *MARS* Medication Adherence Rating Scale, *BMI* body mass index, *CRP* C-reactive protein, *WHO-5* Who-Five Well-being Index

measured on the Beck Depression Inventory second edition (BDI-II) [81]. However, in the NAC treatment arm, higher baseline depressive symptoms were predictive of cannabis cessation [81]. Secondary analysis of the effect of NAC on depressive symptoms in a trial investigating NAC (2,400 mg/day) treating cannabis use disorder in 302 adults (18–50 years of age) for 12 weeks with an additional 4 weeks follow-up found that NAC had no effect on depressive symptoms as measured on the Hamilton Depression Rating Scale (HDRS) nor was it more effective in promoting cannabis cessation in participants with higher baseline depressive symptoms [82].

A meta-analysis of seven RCTs investigating adjunctive NAC therapy in treating unipolar or bipolar depression found that NAC significantly improved functioning as measured on Clinical Global Impression Scales-Severity (CGI-S) compared to placebo, but on no other measures of functioning (including SLICE-LIFE, Social and Occupational Functioning Assessment Scale (SOFAS), and LIFE-RIFT), nor was it found to significantly improve depression and anxiety symptom rating scales compared to placebo [83].

In summary, there has been one RCT investigating NAC in unipolar depression alone that showed a modest but significant result (see Table 4). Further, longer, and better-powered studies are needed before it can be advised to be used clinically.

7 Anxiety Disorders

Anxiety disorders are associated with oxidative stress, neuroinflammation, and glutamatergic hyperactivity [84]. It is unclear if NAC's anti-anxiolytic effects are mediated through glutamate modulation, its antioxidant properties, anti-inflammatory properties, or all three. In mice, increased microglial activation (inflammation, phagocytosis, blood–brain barrier breakdown, and elevated 2-OH-estradiol production) was correlated with increased oxidative stress and increased anxiety behaviors [85]. In that model, NAC reduced both oxidative stress and anxiety behaviors [85]. NAC also reduced hippocampal oxidative stress and anxiety behaviors in rats [86]. NAC reduced anxiety behaviors as measured by the open field, light/dark, hole-board, social interaction, and stress-induced hyperthermia models in mice and the light/dark test in zebrafish [87, 88]. In zebrafish, 7

Table 4 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating depressive disorders

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other medications	Outcome measures	Results
Berk et al. [79]	MDD (as per DSM IV), BPAD I and II excluded	12 weeks (with 4 weeks follow up)	269 (135/134)	2,000 mg/day	Treatment as usual	MADRS, HARS, GAF, SOFAS, SLICE-LIFE, Q-LIS-Q, CGI-S, LIFE-RIFT	Significant improvement in MADRS, CGI-S, SLICE-LIFE, and LIFE-RIFT at 16 weeks compared to placebo
Porcu et al. [6]	MDD and BPAD depression (as per ICD-10 and DSM-IV)	12 weeks	67 (25/42)	1,800 mg/day	Treatment as usual	HDRS, HARS, CGI, YMRS, WHOQOL, SDS, MARS, CRP, Cholesterol, BMI	In CRP <4 significant improvement in CGI compared to placebo. In CRP >3 no significant difference between groups

BPAD bipolar affective disorder, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, *CGI-S* Clinical Global Impressions-Severity, *MADRS* Montgomery Åsberg Depression Rating Scale, *YMRS* Young Mania Rating Scale, *GAF* Global Assessment Functioning, *SOFAS* Social and Occupational Functioning Assessment Scale, *SLICE-LIFE* Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation, *LIFE-RIFT* Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool, *Q-LES-Q* Quality of Life Enjoyment and Satisfaction Questionnaire, *MDD* major depressive disorder, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *WHOQOL* World Health Organization Quality of Life, *SDS* Sheehan Disability Scale, *MARS* Medication Adherence Rating Scale, *BMI* body mass index

days of NAC treatment reversed the behavioral and physiological effects of 14 days of chronic stress [89].

Cisplatin, which is commonly used in oncology, has neurotoxic anxiogenic effects mediated by increased oxidative stress [90]. In rats, augmenting cisplatin with NAC reduced hippocampal oxidative stress and cisplatin-induced apoptosis [90]. However, an RCT investigation using cisplatin augmentation with NAC (600 mg/day for 7 days) in 57 patients (28 NAC arm, 29 placebo) treated with cisplatin for head and neck cancer found that NAC did not reduce oxidative stress as measured in peripheral blood mononuclear cells [91]. It should be noted, however, that the dose of NAC in this paper was low and the length of treatment was short compared to other studies with positive results, and they did not measure anxiety as an outcome [91]. The study did demonstrate that NAC did not alter the antitumor efficacy of cisplatin, suggesting that future investigations in cancer would be safe [91].

There has been one published case report of NAC (at 2,400 mg/day) as an augmentation to sertraline in treating a 17-year-old male with generalized anxiety disorder and social phobia resulting in a reduction in his CGI-S from 5 to 2 over an 8-week period [92].

In summary, whilst there is some preclinical evidence and theoretical explanation for NAC's potential treatment in anxiety disorders, there have been no controlled trials investigating NAC treating any anxiety disorders to date.

8 Obsessive-Compulsive and Related Disorders (OCRD)

8.1 Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is associated with hyperactivity in the cortico-striato-thalamic-cortical region, abnormal glutamate metabolism, and glutamatergic system abnormalities [93]. High levels of glutamate can result in excitotoxicity and oxidative stress, which have been found in patients with OCD [93]. NAC is thought to have a possible therapeutic effect on OCD by modulating glutamate and easing oxidative stress [93].

In animal studies, NAC has been shown to reduce OCD-like behaviors [94, 95]. There have been five case reports/series published studying NAC in treating OCD. Target doses ranged from 1800–3000 mg/day and results varied from no effect to substantial improvement [96–101].

There have been six RCTs investigating NAC treating OCD, four with NAC as adjuvant therapy to selective serotonin reuptake inhibitors (SSRIs) and two as single therapy, with doses ranging from 2000 to 3000 mg/day [102–107]. Five of those RCTs were included in a meta-analysis published in 2020 that found that NAC significantly reduced Yale-Brown Obsessive Compulsive Scale (YBOCS) scores compared to placebo [108]. However, the effect of NAC was not substantial, and only two papers demonstrated a greater than 35% reduction in the YBOCS score, which is indicative of clinical improvement of OCD patients [108]. The RCT not included in the meta-analysis investigated adjuvant NAC (2,700 mg/day) treatment of 11 patients with OCD aged 8–17 years and found a significant reduction in YBOCS compared to placebo [107].

In summary, NAC may be effective in treating OCD; however, the extent of its effect may be too small to warrant use. Given the signs from mood and psychotic disorders of delayed effects, longer studies need to be conducted (see Table 5).

8.2 Trichotillomania

Given trichotillomania's phenomenological links to OCD, it was suspected that glutamatergic dysfunction is implicated in its pathogenesis, as it is with OCD [109]. Trichotillomania's classification as an OCRD reflects this [110]. This theory was supported by a small study of 14 participants with trichotillomania, in which five participants had lower than the standard range serum glutathione level, which was correlated with higher motor impulsiveness on the Barratt Impulsiveness Scale [111].

There have been multiple case reports of successful treatment of trichotillomania with NAC, with target doses ranging from 1200 to 2400 mg/day and treatments lasting for as long 6 months [112–119]. However, only two RCTs have been published on NAC treating trichotillomania, and both were 12-week placebo-controlled trials with target doses of 2400 mg/day [109, 120]. Grant, Odlaug, and Kim studied 50 adult participants (45 female) and found that NAC significantly reduced Massachusetts General Hospital Hair Pulling Scale (MGH-HPS) scores compared to placebo [109]. Bloch et al. studied 39 adolescents aged 8–17 years (34 female) and found no significant difference in MGH-HPS scores compared to placebo [120]. A meta-analysis of these two RCTs published in 2020 concluded that NAC was significantly superior to placebo in treating trichotillomania seen on MGH-HPS [121].

In summary, there have been only two controlled studies investigating NAC treating trichotillomania and results have been mixed. From the evidence available it appears NAC may be useful in treating trichotillomania; however, better powered studies are required before it can be recommended clinically (see Table 5).

8.3 Excoriation Disorder

Excoriation disorder is also classified as an OCRD [110]. NAC might again treat skin-picking disorders by decreasing levels

Table 5 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating obsessive-compulsive and related disorders

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other interventions	Outcome measures	Results
Grant et al. [109]	Trichotillomania (as per DSM-IV)	12 weeks	50 (25/25)	1,200 mg/day for 6 weeks, then 2,400 mg/day	Treatment as usual	MGH-HPS, PITS, CGI-S, SDS, HARS, HDRS, QoLI	Significant improvement in MGH-HPS, PITS and CGI-S compared to placebo
Afshar et al. [102]	OCD (as per DSM-IV)	12 weeks	48 (24/24)	600 mg/day for 1 week, 1,200 mg/day for 1 week, then 2,400 mg/day	SSRI	YBOCS, CGI-I, CGI-S, CGI-E	Significant reduction in YBOCS and CGI-S compared to placebo
Bloch et al. [120]	Trichotillomania (as per DSM-IV)	12 weeks	39 (20/19)	600 mg/day for 1 week, 1,200 mg/day for 1 week, then 2,400 mg/day	Treatment as usual	MGH-HPS, TSC-C,P, NIMH-TSS, MIST-C, MASC, CDI, CGI, PAERS,	No significant difference between groups. Significant reduction in MGH-HPS, TSC-C,P, and CDI from baseline in NAC group
Ghanizadeh et al. [128]	Onychophagia	2 months	42 (21/21)	200 mg/day titrated up to 800 mg/day in first week	No concurrent psychotherapy for nail biting	Nail length in millimeters	No significant difference between groups at 2 months
Sarris et al. [103]	OCD (as per DSM-IV-TR)	16 weeks	44 (22/22)	1,000 mg/day for 1 week, 2,000 mg/day for 1 week, then 3,000 mg/day	No concurrent psychotherapy	YBOCS, CGI-S, CGI-I, HARS, MADRS, GHQ-28	No significant difference between groups
Paydary et al. [104]	OCD (as per DSM-IV-TR)	10 weeks	46 (23/23)	1,000 mg/day for 1 week, then 2,000 mg/day	Fluvoxamine 200mg/day	YBOCS	No significant difference between groups. Significant reduction in YBOCS from baseline in both groups
Grant et al. [125]	Excoriation disorder (as per DSM-5)	12 weeks	66 (35/31)	1,200 mg/day for 3 weeks, 2,400 mg/day for 3 weeks, then 3,000 mg/day	Treatment as usual	NE-YBOCS, SPSAS, SDS, CGI-I, CGI-S, HDRS, HARS, QoLI, Cognitive assessments	Significant improvement in NE-YBOCS and CGI-S compared to placebo
Ghanizadeh et al. [105]	OCD (as per DSM-IV-TR)	10 weeks	34 (19/15)	600 mg/day for 1 week, 1,200 mg/day for 1 week, 1,800 mg/day for 2 weeks, then 2,400 mg/day	SSRI	YBOCS, PedsQL	Significant reduction in YBOCS compared to placebo
Costa et al. [106]	OCD (as per DSM-IV)	16 weeks	40 (20/20)	1,200 mg/day for 1 week, 2,400 mg/day for 1 week, then 3,000 mg/day	Treatment as usual	YBOCS, CGI-S, BDI, BAI, SAFTEE, BABS	Significant reduction in BAI compared to placebo

Table 5 (continued)

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other interventions	Outcome measures	Results
Li et al. [107]	OCD	12 weeks	11 (5/6)	900 mg/day for 1 week, 1,800 mg/day for 1 week, then 2,700 mg/day	Treatment as usual	CYBOCS, CGI, PAERS	Significant reduction in CYBOCS compared to placebo

MGH-HPS Massachusetts General Hospital Hair Pulling Scale, *PITS* Psychiatric Institute Trichotillomania Scale, *SDS* Sheehan Disability Scale, *QoLI* Quality of Life inventory, *YBOCS* Yale-Brown Obsessive Compulsive Scale, *TSC-C,P* Trichotillomania Scale for Children-Child and Parent, *NIMH-TSS* National Institute of Mental Health-Trichotillomania Severity Scale, *MIST-C* Milwaukee Inventory for Styles of Trichotillomania, *MASC* Multidimensional Anxiety Scale for Children, *CDI* Children's Depression Inventory, *SSRI* Serotonin Reuptake Inhibitor, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, *OCD* Obsessive Compulsive Disorders, *CGI-I* Clinical Global Impressions-Improvement, *CGI-S* Clinical Global Impression-Severity, *CGI-S* Clinical Global Impression-Efficacy, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *MADRS* Montgomery Åsberg Depression Rating Scale, *GHQ-26* General Health Questionnaire, *PedsQL* Pediatric Quality of Life Inventory, *CYBOCS* Children's Yale-Brown Obsessive Compulsive Scale, *PARES* Pediatric Adverse Events Ratings Scale, *NE-YBOCS* Yale-Brown Obsessive Compulsive Scale for Excoriation Disorder, *SPSAS* Skin Picking Symptoms Assessment Scale, *BAI* Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *SAFTEE* Systematic Assessment for Treatment Emergent Effects, *BABS* Brown Assessment of Belief Scales

of glutamate in the NA, assisting the control of compulsive behavior [122]. There are several case reports ($N = 10$) published of NAC successfully treating skin-picking disorders, with doses ranging from 1200 to 1800 mg/day [29, 112, 115, 119, 122–124].

There have been two interventional studies investigating NAC treating excoriation disorders; an open-label trial in 35 participants with Prader-Willi syndrome and a blinded RCT of 66 participants [125, 126]. Miller and Angulo treated 35 participants with Prader-Willi syndrome and skin-picking behavior with NAC, with doses ranging from 450 to 1,200 mg/day (the paper did not explain how doses were arrived at) for 12 weeks [126]. All participants had a reduction in skin picking (measured by the number of lesions on their skin) and 25 had a complete cessation of skin-picking behavior [126]. Grant et al. is the only RCT investigating NAC in treating skin-picking behavior; 66 participants were treated with NAC (target dose 3000 mg/day) or placebo for 12 weeks [125]. Participants treated with NAC had significant and substantial improvements in the skin-picking behavior as measured on the Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation (NE-YBOCS) and clinical global impressions-improvement (CGI-I) and CGI-S scales compared to those treated with placebo [125].

In summary, there has been one controlled study investigating NAC treating excoriation disorder that found a significant effect. From the evidence available it appears NAC may be useful in treating excoriation disorder; however, better powered studies are required before it can be recommended clinically (see Table 5).

8.4 Onychophagia

Onychophagia is also classified as an OCRD [110]. It is thought that NAC may reduce nail biting by modulating the glutamatergic system within the nucleus accumbens (NA), altering the subjective feeling of cravings and by reducing oxidative stress [112, 127]. There are four case reports ($N = 6$) published on NAC treating nail biting, with treatment doses ranging from 800 to 2000 mg/day [28, 112, 119, 127]. The one RCT investigating NAC (800 mg/day) treating onychophagia in 42 children (aged 6–18 years) found that those treated with NAC had significantly longer nails compared to placebo at 1 month; however, this difference was no longer significant at 2 months [128].

In summary, as with the other OCRDs, there have been very few controlled studies (one) investigating NAC treating onychophagia disorder (see Table 5). The one RCT published found no evidence of NAC's potential in treating onychophagia; however, better powered studies are required (see Table 5).

9 Post-Traumatic Stress Disorder

In post-traumatic stress disorder (PTSD), people exhibit hypoactive executive functioning and hyperactive fear circuitry activity secondary to increased oxidative stress, inflammatory processes, and stress-related adaptations at glutamatergic synapses [129, 130]. Glutathione is dysregulated in patients with PTSD [131]. By facilitating glutathione production, NAC may ease oxidative stress in PTSD, normalizing corticostriatal glutamate transmission and reducing levels of inflammatory cytokines [129, 131].

A small (35 participants) double-blinded RCT investigated NAC (2,400 mg/day) combined with cognitive behavioral therapy (CBT) for substance-use disorders (SUDs) in the treatment of PTSD and co-occurring SUD (81.5% alcohol-use disorder) in US veterans. There was a significant difference between NAC and placebo on self-rated PTSD symptoms (PTSD Checklist-Military (PCL-M)) and the BDI-II during the intervention but not at 1 month after the cessation of intervention [129]. There are two larger RCTs currently underway investigating NAC in PTSD: one in Australia, aiming for 126 participants, using 2,700 mg/day [131], and another in the USA, treating PTSD and co-morbid alcohol-use disorder aiming for 200 participants using 2,400 mg/day [132].

In summary, current limited evidence does not indicate NAC is effective in treating PTSD, but two large RCTs currently underway will hopefully shed further light on this (see Table 6).

10 Substance-Use Disorders

Chronic substance use results in changes to frontostriatal glutamatergic circuitry, resulting in compulsive alcohol/drug seeking and loss of adaptive behavior in the presence of substance-associated environmental or interoceptive stimuli [133]. NAC may assist in the treatment of SUD through glutamatergic reorganization [134]. Through direct effects on cysteine/glutamate exchange and by promoting astroglial glutamate uptake, which are reduced in animal models of SUD, NAC restores the homeostatic relationship in glutamate transport and release between neurons and astroglia. The action of NAC in the nucleus accumbens reduces substance-associated intrusive thoughts (e.g., cravings or urges to use), thereby allowing more adaptive behaviors to emerge to help maintain abstinence from use [135]. In a rat model, NAC reduced stress-induced alcohol use and cue-related reinstatement of alcohol, heroin, nicotine, cannabis, and cocaine use [136]. In functional magnetic resonance imaging (fMRI)

Table 6 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating post-traumatic stress disorder

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Other interventions	Outcome measures	Results
Back et al. [129]	PTSD and SUD (as per DSM-IV)	8 weeks (with 4 weeks follow up)	35 (18/17)	2,400 mg/day	CBT for SUD	MINI, CAPS, PCL-M, TLFB, VAS, UDS, BDI, C-SSRS	Significant reduction in VAS compared to placebo

PTSD post-traumatic stress disorder, *SUD* substance-use disorder, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, *CBT* Cognitive Behavioral therapy, *MINI* Mini International Neuropsychiatric Interview, *CAPS* Clinician Administered PTSD Scale, *PCL-M* PTSD Checklist-Military, *TLFB* Timeline Follow Back, *VAS* Visual Analog Scale, *UDS* Urine Drug Screen, *BDI* Beck Depression Inventory, *C-SSRS* Columbian Suicide Severity Rating Scale

studies, NAC normalizes frontostriatal glutamate and prevents tobacco cravings [137].

Secondary analysis of Berk et al. [66], which investigated NAC (2000 mg/day) over 28 weeks (24 weeks of intervention and an additional 4 weeks of follow-up) in 74 patients with bipolar disorder found that NAC had no significant effect on substance use in that patient cohort [138]. A recent meta-analysis of RCTs investigating NAC's effect on substance use found that NAC had a small but statistically significant effect on reducing craving scores, although significant heterogeneity between trials was noted [139].

10.1 Alcohol

There is preclinical evidence that NAC may reduce the severity of withdrawal symptoms. In rat models of alcohol withdrawal, NAC administration ameliorates the reduced motivation and increased anxiety, and prevents serum corticosteroid and leptin rise seen post alcohol cessation [140]. In a mouse study, NAC prevented delta FosB accumulation in the medial prefrontal cortex, thereby reducing nucleus accumbens neuroadaptations, craving and relapse seen in chronic alcohol use [141]. NAC also reduces ethanol intake in abstinent but ethanol-dependent rats [142].

To date there have been no clinical trials published that directly investigate NAC in treating alcohol-use disorder. A study of US veterans with PTSD and SUD (of whom 82% had alcohol-use disorder) found that NAC (at 2400 mg/day) significantly reduced craving compared to placebo [129]. Secondary analysis on alcohol consumption in participants of a trial investigating NAC (at 2400 mg/day) in treating cannabis dependence in adolescents found that NAC had no effect on alcohol consumption [143]. However, in the NAC treatment group a reduction in cannabis use was associated with a reduction in alcohol use where no such association was found in the placebo group [143]. Secondary analysis on alcohol consumption in participants in a trial investigating NAC in treating cannabis dependence in adults found that NAC was significantly associated with a reduction in alcohol use but was not related to changes in cannabis use [144]. In a trial of 49 volunteers, there was no benefit of NAC (at 600–1,800 mg) in prevention of alcohol-induced hangover, although post hoc analysis suggested a benefit in females [145]. There is an RCT currently underway in Australia investigating NAC (at 2,400 mg/day) for the treatment of alcohol-use disorder [146].

10.2 Cannabis

NAC prevents cue-induced tetrahydrocannabinol- and cannabidiol-seeking behavior in rat models [147]. An open-label study of 24 cannabis-dependent youths investigating NAC (2,400 mg/day) for 4 weeks found a significant decrease in self-reported cannabis use from baseline; however, urine studies in the same group did not confirm this [148]. There was also a significant reduction in three out of four domains on the marijuana craving questionnaire (MCQ) [148]. An Indian retrospective cohort study (72 participants) that compared standard treatment, NAC (at a mean dose of 1,800 mg/day), and baclofen combined with standard treatment, found that NAC and standard treatment was significantly associated with a longer period of abstinence compared to placebo and baclofen [149]. However, that trial was open label and relied on patient self-report of cannabis use [149].

A large (116 participants) follow-up 8-week RCT found that NAC (2,400 mg) combined with contingency management and cessation counseling, significantly reduced cannabis use (as measured in urine) compared to placebo with the same interventions [150]. This difference wasn't present at the 4-week post-intervention follow-up; however, this was likely to have been influenced by significant dropout [150]. Adherence to NAC was assessed by calculating the number of pills left in the blister packs. This was associated with negative urine tests, while adherence to placebo had no effect on abstinence [151]. These findings were not replicated in a large (302 participants) 12-week RCT that failed to show that NAC (2,400 mg/day) combined with contingency management was superior to placebo and contingency management in achieving abstinence from cannabis in adults [152]. In the adolescent study, higher baseline depressive symptoms were predictive of cannabis cessation, which was also not replicated in the follow-up study of adults [81, 82].

10.3 Opioids

Glutamatergic neurotransmission drives opioid-seeking behaviors [153]. Thus, medications that alter the functioning of glutamatergic synapses may reduce the reinforcing effects of opioids. In a rat study, NAC reduced cue- and heroin-induced drug-seeking behavior [154]. These effects continued for up to 40 days post cessation of NAC [154]. The finding that NAC reduces cue-related heroin seeking has been reproduced in another rat study [155]. However, to date there have been no clinical trials investigating NAC in treating opioid-use disorders.

10.4 Amphetamines

NAC has not been found to reduce methamphetamine self-administration and produced no effect on [156] or decreased [157] reinstatement in rats. However, it may reduce the neurotoxic effects of chronic amphetamine use. Chronic methamphetamine use results in loss of dopamine transporter expression in the striatum [16]. Rhesus monkeys that were given intravenous NAC prior to methamphetamine administration preserved significantly more dopamine transporter

in their striatum, as seen on positron emission tomography [16].

A small RCT (31 participants) found that NAC combined with naltrexone had no significant effect on cravings or methamphetamine use compared to placebo [158]. Participants were commenced on a very low dose (NAC 600 mg/day and naltrexone 50 mg/day), which was increased every 2 weeks if they had continued drug use and cravings [158]. This methodology shortened the amount of time that participants were on a potentially effective NAC dose in an already short study. A small (23 participants) and brief (8-week) Iranian crossover trial in which participants were given 4 weeks of NAC (600 mg/day for the first week then 1,200 mg/day) or placebo, then switched, found that NAC was associated with a significant reduction in cravings scores. Switching from NAC to placebo was, however, associated with a significant increase in cravings [159]. A large (153 participants) 12-week RCT in Australia investigating NAC (2,400 mg/day) treating methamphetamine dependence found no significant difference between NAC and placebo in all measures including craving and amphetamine use [160].

10.5 Cocaine

A study of rats demonstrated that repeated cocaine use is associated with reduced firing rates of glutamatergic projections from the medial prefrontal cortex to the nucleus accumbens [161]. In rats, repeated cocaine use decreases extracellular glutamate levels in the nucleus accumbens, and reinstatement post cessation of use increases levels [162]. NAC normalized these changes and inhibited cocaine reinstatement [162]. These findings have been replicated in humans. A spectroscopy study demonstrated that cocaine dependence was associated with an elevated glutamate to phosphocreatine ratio in the left dorsal anterior cingulate cortex, which was normalized by a single 2,400 mg dose of NAC [163]. This was replicated in a crossover trial (1 week of intervention with 12 participants) that found that NAC (3,600 mg/day) significantly reduced glutamate and glutamine levels in the rostral anterior cingulate [164]. However, this finding was not replicated in an RCT (38 participants) that found that NAC (2,400 mg/day for 25 days) did not significantly reduce glutamate and glutamine levels in the dorsal rostral anterior cingulate compared to placebo [165].

In rat models, NAC prevents cue-induced relapse and reduces cocaine-induced increases in drug seeking [136, 166, 167]. However, again in human trials NAC has had mixed results. A 1-week crossover trial with 12 participants found that NAC (3,600 mg/day) reduced cocaine-induced cocaine-seeking behaviors [164], whilst a small RCT (38 participants) found that NAC had no effect on cue-induced craving or reactivity [168].

NAC has been investigated as a treatment for cocaine-use disorder. The first human trial of NAC as a treatment for cocaine use disorder was in 2006, a small (13 participants) and brief (3 days of intervention) crossover trial that demonstrated the safety and tolerability of NAC [169]. NAC (2,400 mg over 36 h) found no significant reduction in craving for cocaine as measured by the Cocaine Selective Severity Assessment [169]. NAC significantly reduced cocaine cue-related cravings as measured on reactions to slides shown to participants [170]. A small (four participants) brief (4 days) single-arm study found that NAC (1,200–2,400 mg/day) significantly reduced craving post cocaine administration from baseline; however, NAC did not affect the subjective euphoric effects of cocaine [166].

NAC has not significantly reduced cravings for cocaine compared to placebo in RCTs [171, 172]. However, subanalysis of participants who had already achieved abstinence (17 participants) found that NAC significantly increased the time to relapse of use and reduced cravings in a dose-respondent manner, suggesting a potential effect of NAC in preventing relapse of cocaine use in people with cocaine dependence who have already achieved abstinence [171].

10.6 Tobacco

Nicotine dependence results in glutamatergic adaptations in brain areas associated with reinforcement [173]. It is thought that NAC's antioxidant properties, both increasing glutathione and modulating the glutamatergic system, could reverse the neuroplastic alterations associated with nicotine dependence and assist with smoking cessation [174]. NAC reduces nicotine-conditioned place preference and withdrawal signs in nicotine-dependent mice [175]. NAC seems more effective in reducing nicotine-seeking behavior in male than female rats [176]. It is thought that this may be secondary to the effects of estrogen and progesterone on nicotine seeking [176].

A small RCT (29 participants) investigating NAC (2,400 mg/day) in treating nicotine dependence failed to show a significant reduction in cigarette use in the NAC group compared to placebo at 4 weeks [173]. There was also no significant reduction in craving rating scales [173]. These findings were replicated by a small RCT (28 participants) that found that 12 weeks of NAC (1200–3000 mg/day) did not significantly reduce smoking (as measured on the Fagerström-Test for Nicotine Dependence) compared to placebo [177]. Although there was a difference at 6 weeks of intervention, this had disappeared by 12 weeks [177]. A single-arm open-label study demonstrated that NAC (2,400 mg/day) and varenicline are well tolerated when taken together and demonstrated a significant reduction in cigarettes smoked from baseline [178]. A 12-week similarly sized RCT (34 participants) found no significant difference between NAC

(3,000 mg/day) and placebo on smoking levels [179]. A similar 2-week RCT (48 participants) also found no significant difference between NAC (2,400 mg/day) and placebo on smoking levels, cravings scores, carbon monoxide levels, and anterior cingulate cortex glutamate, glutamine and glutathione on spectroscopy [180]. A large RCT is currently underway investigating the effects of NAC (1,800 mg/day) compared to placebo in ceasing tobacco use [174].

Studies looking at NAC's effect on reducing craving and relapse in tobacco users who are already abstinent have likewise not shown promising results. A very brief (4 days at 3,600 mg/day), small (22 participants) RCT found no significant reduction in ratings scales [181]. In this study, participants were instructed not to smoke during the 4-day trial period and there was a significant difference between the NAC and placebo group in the rating of the reward felt from the first cigarette post abstinence, with the NAC group rating it as considerably less rewarding than the placebo group [181]. In a similarly brief (4 days at 2,400 mg/day) and small (16 participants) placebo-controlled RCT, NAC was associated with significantly lower craving scores, lower carbon monoxide values, and using fMRI, stronger resting-state functional connectivity in four striatal pathways between right nucleus accumbens and left medial prefrontal cortex and bilateral precuneus, and between the left nucleus accumbens and ventromedial prefrontal cortex and bilateral cerebellum [137]. Resting-state functional connectivity in all four striatal pathways were negatively correlated with carbon monoxide levels, and three of them were negatively correlated with cravings [137].

10.7 Pregabalin

Pregabalin, a medication primarily prescribed for nerve pain, has the potential for being abused [182]. Pretreatment with NAC reduced pregabalin-seeking behaviors in mice, suggesting it could possibly have a role in treating pregabalin abuse [182].

10.8 Gambling

A small open-label study (27 participants) demonstrated that NAC (600–1,800 mg/day) significantly reduced the severity of gambling symptoms from baseline, as measured on the Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBOCS) [183]. Then, 13 of the 16 responders participated in a 6-week placebo-controlled RCT that failed to show a significant improvement in NAC compared to placebo [183]. However, another small RCT (28 participants) found that 12 weeks of NAC (1,200–3,000 mg/day) and psychotherapy significantly reduced gambling severity (as measured on the PG-YBOCS) at 24 weeks' follow-up (12 weeks post cessation of intervention) compared to placebo and therapy [177]. This difference was not present at the end of the intervention at week 12, suggesting a delayed effect of NAC [177]. This pattern has also been seen in studies investigating NAC's effect on bipolar disorder and schizophrenia [38, 46].

10.9 Non-Suicidal Self Injury

Self-harm may be conceptualized as an addictive behavior in that it relieves a negative affective state and provides negative reinforcement (in the form of endogenous opioids release) where people experience strong urges to engage in self-harm behaviors. It is a habitual behavior that is difficult to cease [184, 185]. If self-harming has elements of addiction, then people who engage in self-harm may have impaired functioning of the mesocortical dopamine reward system, endogenous opioid systems, and an overactive stress system [184]. Thus, normalizing the glutamatergic system and easing oxidative stress may reduce the urge to self-harm. A case study was published in which a 17-year-old female was treated with NAC (1,800 mg/day) resulting in a reduction in the frequency of self-harming by cutting and reduction in the symptoms of her attention-deficit hyperactivity disorder (ADHD) and depression [186].

A non-blinded, single-arm study of 35 female adolescents treated with NAC (initially 1,200 mg/day increased to 4,600 mg/day over the study) demonstrated a significant decrease in the frequency of self-harm [185]. A follow-up RCT is currently being conducted that will first determine the dose of NAC that meaningfully changes levels of glutathione and glutamate in the brain (as measured on MR spectroscopy) and then will investigate the effect of NAC on self-harm in adolescent females [187].

In summary, there have been multiple small RCTs investigating NAC in treating SUDs, with the majority demonstrating no significant improvement with NAC compared to placebo (see Table 7). Due to NAC's theoretical treatment effect being through the reduction of craving, future studies may have to focus on patient populations that have already achieved abstinence. Future studies may also have to be longer given the evidence that NAC's treatment effects are slow to emerge.

11 Neurocognitive Disorders

Oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis are associated with the process of neuroprogression in several disorders leading to cognitive decline [188]. Memory impairments secondary to neuroinflammation may be due to the hippocampus being particularly vulnerable to the effects of neuroinflammation and pro-inflammatory cytokines [188]. In cell studies, NAC suppresses

Table 7 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating substance-use disorders and addictive behaviors

Study	Substance	Duration	Number of participants (NAC/placebo)	NAC dosage	Outcome measures	Results
Grant et al. [183]	Gambling	6 weeks (preceded by 8 week open label study)	13 (6/7)	Mean dose 1,476.9 mg/day	PG-YBOCS, G-SAS, CGI-I, CGI-S, SDS, HARS, HDRS, QoLi	No significant difference between groups
Knackstedt et al. [173]	Tobacco	4 weeks	29 (14/15)	2,400 mg/day	QSU-B, MNWS, CO, self-reported cigarette and alcohol use	No significant difference between groups
Grant et al. [158]	Methamphetamine	8 weeks	31 (14/17)	600–2,400 mg/day and 50–200 mg/day naltrexone	PCS, UDS, CGI-S, HARS, HDRS, QoLi, self-reported days per week of methamphetamine use,	No significant difference between groups
Schmaal et al. [181]	Tobacco	4 days	22 (10/12)	3,600 mg/day (1,800 mg on the last day)	FTND, QSU-B, MNWS, VAS	Significant reduction in VAS compared to placebo
Gray et al. [150]	Cannabis	8 weeks (with 4 weeks follow up)	116 (58/58)	2,400 mg/day with contingency management	Self-reported cannabis use, UDS	Significantly more cannabis abstinence in urine at 8 weeks, compared to placebo. No significant difference between groups at 12 weeks
Grant et al. [177]	Tobacco and gambling	12 weeks (with 12 weeks follow up)	28 (13/15)	1,200–3,000 mg/day with psychotherapy	PG-YBOCS, FTND, HDRS, HARS	No significant difference between groups
LaRowe et al. [171]	Cocaine	8 weeks	111 (40 at 1,200 mg/day/33 at 2,400 mg/day/38)	1,200 mg/day or 2,400 mg/day	BSCS, CSSA, UDS, self-reported cocaine use	No significant difference between groups
Froeliger et al. [137]	Tobacco	4 days	16 (8/8)	2,400 mg/day	FTND, CES-D, CFQ, SJWQ, PANAS, CO, fMRI	Significant reduction in craving, CO, and stronger resting-state functional connectivity in four striatal pathways compared to placebo
Prado et al. [179]	Tobacco	12 weeks	34 (17/17)	3,000 mg/day	FTND, CO, HDRS, SDS, self-reported cigarettes per day	No significant difference between groups
Mousavi et al. [159]	Methamphetamine	8 weeks (crossover at 4 weeks)	32 (16/16)	600 mg/day for 1 week, then 1,200 mg/day	CCQ-B, UDS, self-reported days per week of methamphetamine use	Significant reduction in cravings compared to placebo
Back et al. [129]	PTSD and SUD (as per DSM-IV)	8 weeks (with 4 weeks follow up)	35 (18/17)	2,400 mg/day	MINI, CAPS, PCL-M, TLFB, VAS, UDS, BDI, C-SSRS	Significant reduction in craving (VAS) compared to placebo

Table 7 (continued)

Study	Substance	Duration	Number of participants (NAC/placebo)	NAC dosage	Outcome measures	Results
Schulte et al. [180]	Tobacco	14 days	48 (24/24)	2,400 mg/day	CO, VAS, QSU, MNWS cigarettes per week, fMRI	No significant difference between groups
Gray et al. [152]	Cannabis	12 weeks (with 4 weeks additional follow up)	302 (153/149)	2,400 mg/day with contingency management	UDS	No significant difference between groups
Schulte et al. [172]	Cocaine	25 days	38 (17/21)	2,400 mg/day	DUDIT, QCU, OCDUS, DDQ, VAS, Working memory tests	No significant difference between groups
McKetin et al. [160]	Methamphetamine	12 weeks	153 (76/77)	2,400 mg/day	SoDS, CEQ, AWQ, BPRS, Self-reported methamphetamine use, Oral fluid samples	No significant difference between groups

PG-YBOCS Yale-Brown Obsessive Compulsive Scale Modified for Pathological Gambling, *G-SAS* Gambling Symptom Assessment Scale, *CGI-I* Clinical Global Impressions-Improvement, *CGI-S* Clinical Global Impression-Severity, *SDS* Sheehan Disability Scale, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale, *QoLI* Quality of Life Inventory, *QSU-B* Questionnaire for Smoking Urges-Brief, *MNWS* Minnesota Nicotine Withdrawal Scale, *BDI* Beck Depression Inventory, *CO* carbon monoxide, *PCS* Penn Craving Scale, *UDS* Urine Drugs Screen, *FTND* Fagerström-Test for Nicotine Dependence, *VAS* visual analog scale, *BSCS* Brief Substance Craving Scale, *CSSA* Cocaine Selective Severity Assessment, *CES-D* Centre for Epidemiological Studies-Depression Scale, *CFQ* Cognitive Failures Questionnaire, *SJWQ* Shiffman-Jarvik Withdrawal Questionnaire, *PANAS* positive and negative affect schedule, *fMRI* functional magnetic resonance imaging, *CCQ-B* Cocaine Craving Questionnaire-Brief, *DUDIT* Drug Use Disorder Identification Test, *QCU* Questionnaire for Cocaine Urges, *OCDUS* Obsessive Compulsive Drug Use Scale, *DDQ* Desire for Drug Questionnaire, *QSU* Questionnaire for Smoking Urges, *SoDS* Severity of Dependence Scales, *CEQ* Craving Experience Questionnaire, *AWQ* Amphetamine Withdrawal Questionnaire, *BPRS* Brief Psychiatric Rating Scale

the TNF-induced activation of nuclear factor κB, which is thought to be a risk factor for Alzheimer's disease [189, 190].

Oxidative stress is associated with the pathology of traumatic neurological damage from surgery, sports, and explosions [188]. Thus, NAC may have a role in reducing the severity of traumatic brain injuries. Several preclinical models confirm the potential veracity of this notion. An RCT of 81 actively serving US military members in Iraq explored this topic [191]. All participants had mild traumatic brain injuries (TBIs) and were treated with 7 days of NAC (3,000 mg/day); it was found that NAC was associated with significant improvement in trail-making tests and reduced symptoms of TBI compared to placebo [191].

NAC has been studied for its potential pro-cognitive effects in multiple patient populations from the well to patients with severe dementia. A 6-month RCT of 47 participants investigating NAC (50 mg/kg/day) in treating symptoms in people with probable Alzheimer's disease found that NAC was associated with significantly better letter fluency at 6 months compared to placebo [192]. A 6-week RCT of 40 participants investigating NAC (1,800 mg/day) and physical exercise in treating muscle strength in people above the age of 65 years with no diagnosis of cognitive impairment had serum inflammatory markers and cognitive tests (trail-making test and digit symbol substitution test) as secondary outcomes [193]. Whilst there were no significant differences between the placebo and NAC groups in cognitive tests, NAC showed improvement in cognitive tests from baseline, where placebo did not [193]. The NAC group also showed lower serum TNF-α levels compared to placebo [193].

The effects of NAC on cognition have been investigated in multiple trials that pair NAC with other nutraceuticals. A small (21 participants) open-label study of nutraceutical therapy (including NAC at 1,200 mg/day) for 12 months found that nutraceutical therapy significantly improved cognition compared to baseline [194]. A small (12 participants) RCT that compared 9 months of nutraceutical therapy (which included NAC at 1,200 mg/day) for moderate- to late-stage Alzheimer's disease found no significant effect of nutraceutical therapy compared to placebo [195]. However, this study had a small sample size and high attrition, reducing the reliability of its results [195]. A larger follow-up double-blind RCT demonstrated that nutraceuticals (including NAC at 1,200 mg/day) significantly improved cognitive performance (measured on Clox-1) compared to baseline but not compared to placebo [196]. Another small (30 participants) double-blind crossover trial that investigated nutraceutical therapy (including NAC at 400 mg/day) found that NAC significantly improved subscales of neurocognitive assessments and the brief symptom inventory [197]. Nutraceutical therapy was also associated with improved regional cerebral blood flow in the prefrontal cortex, anterior and posterior cingulate gyrus, hippocampus, and cerebellum [197].

NAC's effect on cognition has also been investigated in secondary analyses of other papers. NAC was found to have no significant effect on performance in working memory tasks by cocaine users [180]. Likewise, NAC was found to have no significant effect on cognition in patients with bipolar disorder compared to placebo [67]. However, NAC was shown to significantly improve working memory in patients with schizophrenia [43].

In summary, NAC may have potential in treating cognitive deficits in those with TBI and neurodegenerative disorders; however, the heterogeneity of the neurocognitive disorders makes it difficult to discuss them as a whole (see Table 8). More research needs to be conducted, especially given the increased demand for treatment of traumatic-induced cognitive difficulties from sport and neurodegenerative disorders, and due to the increased aging population, this represents an area where NAC may have high clinical relevance.

12 Chronic Pain

Chronic pain is heterogeneous; however, some chronic pain states are associated with increased oxidative stress [198]. All types of chronic pain involve the development of nociceptive sensitization [14]. Pain transmission is amplified across the entire "pain matrix" increasing the perceptive, cognitive, and emotional aspects of pain [14]. Chronic pain and depression often coexist and the "pain matrix" is associated with mood regulation and stress resilience [14]. Metabotropic glutamate receptor 2 (mGlu2) receptors are involved in the "pain matrix" and downregulate pain transmission [14].

Animal studies have shown that NAC can reduce pain in inflammatory and neuropathic pain models by increasing mGlu2 receptor activation [199]. NAC may also assist neuropathic pain by the activation of type-9 matrix metalloprotease and the decreased phosphorylation of p38 mitogen-activated protein kinase in the spinal cord [14]. In animal models, NAC reduces diabetic neuropathic pain by modulating calcium influx in the dorsal root ganglion transient receptor potential cation channel subfamily M member 2 (TRPM2) channel and reducing oxidative stress [200].

There have been multiple RCTs examining NAC's effects on chronic pain, from multiple origins, with mixed results [198]. A meta-analysis of nine studies (five of which were RCTs) published in 2021 found no significant effect of NAC in treating chronic pain [198]. The meta-analysis was hampered by the small scale of the studies, interstudy heterogeneity, and different assessment tools being used across studies [198].

Table 8 Blinded placebo-controlled trials of N-acetyl-L-cysteine (NAC) treating neurocognitive disorders

Study	Diagnosis	Duration	Number of participants (NAC/placebo)	NAC dosage	Outcome measures	Results
Adair et al. [192]	Probable Alzheimer's Disease (as per NINCDS ADRDA criteria)	24 weeks	47(25/22)	50 mg/kg/day	MMSE, ADLS, BNT, GC, WMS FR, HVLT R-I, HVLT R, LF, CF, JLO	Significantly better performance in LF compared to placebo
Hauer et al. [193]	People with no diagnosis over 65 years old	6 weeks	40 (21/19)	1,800 mg/day and resistance training	Trail-making test, digit symbol substitution test	No significant difference between groups
Remington et al. [195]	Late-stage Alzheimer's Disease (as per NINCDS criteria)	9 months	12 (6/6)	1,200 mg/day as part of a nutraceutical cocktail	DRS-2, CLOX-1, NPI, ADCS-ADL,	No significant difference between groups
Amen et al. [197]	Healthy adults	4 months (with crossover at 2 months)	30 (15/15)	400 mg/day as part of a nutraceutical cocktail	BDI-II, BSI, QoLI, neurocognitive assessments, SPECT scan	Nutraceutical associated with significant improvement on some subscales of neurocognitive assessment and BSI compared to placebo
Hoffer et al. [191]	Mild TBI	Seven days	81 (41/40)	400 mg/day for 4 days, then 3,000 mg/day	Trail making tests, COWA, animal naming	Significant improvement in trail making tests compared to placebo
Remington et al. [196]	Probable Alzheimer's Disease or Alzheimer's Disease	3 months followed by open label extension	143 (86/57)	1,200 mg/day as part of a nutraceutical cocktail	DRS, CLOX-1, NPI, ADCS-ADL,	Significant improvement in DRS and CLOX-1 compared to placebo

NINCDS ADRDA National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association, *MMSE* Mini-Mental State Examination, *NINCDS* National Institute of Neurological and Communicative Disorders and Stroke, *ADLS* Activities of Daily Living Scales, *BNT* Boston Naming Test, *GC* Gesture to Command, *WMS FR* Wechsler Memory Scale Figure Reproduction, *HVLT R-I* Hopkins Verbal Learning Task Recall (immediate), *HVLT R* Hopkins Verbal Learning Task Recognition, *LF* Letter Fluency, *CF* Category Fluency, *JLO* Judgement of Line Orientation, *NINCDS* National Institute of Neurological and Communicative Disorders, *DRS-2* Dementia Rating Scale 2, *CLOX-1* Drawing Test, NPI Neuropsychiatric Inventory, ADCS-ADL Alzheimer's Disease Cooperative Study-Activities of Daily Living, *BDI-II* Beck Depression Inventory Second Edition, *SPECT* Single-Photon Emission Computerized Tomography, *TBI* Traumatic Brain Injury, *COWA* Controlled Oral Word Association

Due to the heterogeneity of chronic pain it is difficult to discuss it as a single entity. The evidence currently indicates that NAC has a limited role in its treatment; however, further better powered studies are needed.

13 Discussion

There is ample preclinical evidence and theoretical justification for NAC's treatment of multiple psychiatric disorders. However, there is a paucity of clinical trials in most disorders, and those trials that have been undertaken usually have small numbers of participants and are often brief (see Table 9). This is an important point as there is a suggestion across the examined trials that the benefits of NAC are delayed or late to emerge, requiring upwards of 6 months in some studies. Initial early studies of NAC in many psychiatric disorders have shown promising results that have not been consistently replicated by larger studies. This pattern is seen across autism, bipolar disorder, and SUDs. The paucity of studies, many of which are poorly powered, likely drives these mixed results. However, there are multiple unknowns remaining in studying NAC.

The effective treating dose of NAC remains unknown and the majority of papers have attempted to estimate the required dose based on previous studies. It is possible that some studies investigated NAC at subtherapeutic doses. Many published papers have slowly up-titrated NAC resulting in many interventions being at a low dose. Given that there is evidence that NAC needs to be administered for several months to have a treatment effect in mood disorders and schizophrenia, short trials with slow dose titration may be particularly unreliable [43]. Given that in animal studies NAC has been found to have divergent effect at lower doses and at higher doses (increasing striatal dopamine at lower doses and decreasing at higher doses), a trial with too low a treatment dose could have misleading results [20]. NAC's delayed effect may be due to its mechanism of action being through neuro-regenerative pathways, which would be a slow process [43]. The next generation of trials may need to have a considerably longer duration.

Several studies noted that blinding NAC can be difficult due to its strong and distinctive sulfur odor [37]. Many attempted to obscure this by masking the scent or placing a small amount of NAC in the placebo. However, very few of the studies documented the success of blinding, with three notable exceptions [37, 120, 137]. It is possible that the breaking of blind is a source of bias in some papers.

Heterogeneity in measurements of efficacy and diagnosis is also a factor preventing replication of results. The lack of consensus about which efficacy measurements are the best to use has resulted in high variance in measurement tools across trials. For instance, the two placebo-controlled blinded trials investigating NAC's effects on cocaine-use disorder used seven different rating scales as outcomes with none in common between the two studies [171, 172]. This adds unnecessary barriers to reproducing results and conducting meta-analyses. The heterogeneity of diagnosis and inclusion criteria may have played a factor in negative findings in ASD trials in which two studies that included patients from severe to mild disease were negative [34, 35]. In trials of SUDs, some trials require abstinence prior to study start and others do not, which is another source of heterogeneity.

Another difficulty in studying the potential use of NAC clinically is that its effects may be subtle and may fail to reach clinical significance. If NAC has a small overall effect on the user, this may be more difficult to recognize in clinical trials. However, NAC has consistently been found to be highly tolerable, and its adverse effects, such as nausea, are minimal. This gives it potential as an add-on therapy for psychiatric disorders, rendering its small clinical effects more acceptable.

A few studies were conducted in a controlled setting in which adherence could be monitored by investigators; however, the majority occurred as outpatients with intermittent reviews. In the majority of trials, adherence was assessed by pill counting, which introduces bias as the pill being removed from the pack doesn't necessarily equal the participant taking it. Some studies added riboflavin to both NAC and placebo capsules and tested for this in urine to assess adherence to reduce this bias. Adherence is very important in NAC due to its poor bioavailability, which requires dosing multiple times a day. This is especially challenging in patients suffering from psychiatric disorders. Thus, underdosing and poor adherence may help explain some of the mixed results.

This review discussed psychiatric disorders as distinct disorders without consistently accounting for comorbidity and the majority of the studies included did the same. Comorbidity is common in psychiatry and many psychiatric conditions share common etiological factors and operative pathways. Both studies that looked at NAC's effect on comorbidities showed a significant effect on treatment outcomes compared to placebo [81, 129]. Further investigation of NAC's effects on comorbid disorders could have value in guiding future clinical practice.

There is no condition in which there is currently enough evidence for NAC to be unequivocally recommended clinically; however, due to NAC's high tolerability the barrier for its clinical use may be lower than a less tolerable medication. NAC currently has the most evidence for its use in the treatment of negative symptoms of schizophrenia (if treatment continues for at least 24 weeks), severe autism spectrum disorder, OCD, and obsessive-compulsive-related disorders. There has been much less published on NAC's treatment of bipolar and unipolar depression, although what little has

Table 9 Summary of N-acetyl-L-cysteine (NAC)'s treatment of psychiatric disorders

Diagnosis	Theoretical biological therapeutic pathway	Summary of evidence
Williams syndrome	Williams syndrome is associated with abnormalities in the glutamate system which NAC could have a regulatory effect on [22]	No published RCTs, one positive case report [22]
Autism Spectrum Disorder (ASD)	Some theories of ASD's pathogenesis have proposed glutamatergic dysfunction and excessive oxidative stress. NAC may exert potential therapeutic effects through amelioration of both of those processes [23]	Meta-analysis of five small trials (combined N=256) demonstrated significant improvement in ABC total score, and irritability and hyperactivity subscales compared to placebo [36]
Tourette's disorder	Tourette's disorder is associated with glutamatergic abnormalities seen in neuroimaging, brain tissue, and genetic studies [37]. NAC's modulation is hypothesized to reduce the frequency and intensity of the premonitory urges [37]	One RCT (N=31) found no significant difference between groups [37]
Schizophrenia	Schizophrenia is associated with a chronic deterioration of key brain circuits mediated by oxidative stress, inflammation, decreased neurotropic growth factors, apoptosis, mitochondrial dysfunction, and impaired neuroplasticity [8]. NAC's effect is hypothesized through its role in reduction of oxidative stress (through being a glutathione precursor), modulation of the glutamatergic system, neurotropic and inflammatory action [8] Reduction of abnormalities in resting state functional connectivity in the default mode network and salience network seen in patients with schizophrenia [53]	Meta-analysis of five of eight RCTs published found no significant improvement in PANSS compared to placebo at 8 weeks (combined N=430), and significant improvement in total and negative PANSS at 24 weeks (combined N=263) [48]
Early psychosis	NAC's reduction of oxidative stress could lead to prevention of key brain circuits, the deterioration of which is associated with early psychosis and schizophrenia [54]	Mixed results in three small RCTs [45, 46, 62]
At risk of psychosis	NAC's reduction of oxidative stress may prevent the development of psychosis, which is associated with increased oxidative stress [57]	No published RCTs, case series (N=5) failed to show a statistically significant improvement in SOPS from baseline [60]
Bipolar disorder	Bipolar is associated with increased oxidative stress which NAC reduces [3] NAC's anti-inflammatory processes may treat depressive symptoms of bipolar in patients with increased general inflammation associated with depressive symptoms [6]	Meta-analysis of five small RCTs (combined N=335) found no significant improvement in all outcomes (including MADRS, YMRS, and BDRS) compared to placebo in bipolar depression [77] However, another meta-analysis of six small RCTs (combined N=302) demonstrated significant improvement in HDRS and MADRS compared to placebo in bipolar depression [78]
Unipolar depression	NAC reduces oxidative stress (through being a glutathione precursor) which is associated with unipolar depression [12] NAC's anti-inflammatory processes may treat depressive symptoms in patients with increased general inflammation associated with depressive symptoms [6]	One RCT (N=269) demonstrated significant improvement in MADRS, CGI-S, SLICE-LIFE, and LIFE-RIFT at 16 weeks compared to placebo [79]
Anxiety disorders	Anxiety disorders have been associated with increased oxidative stress, neuroinflammation, and glutamatergic system hyperactivity, NAC may exert potential therapeutic effects through the amelioration of all of those processes [84]	One case report of NAC successfully augmenting sertraline in the treatment of generalized anxiety disorder and social phobia [92]
OCD	OCD is associated with neuroinflammation, oxidative stress, and abnormal glutamate metabolism, NAC may exert potential therapeutic effects through the amelioration of all of those processes [93]	Meta-analysis of five small RCTs (combined N=212) demonstrated statistically significant, but possibly clinically insignificant reduction in YBOCS [108]
Trichotillomania	Reduction of compulsive behaviors through manipulation of the glutamatergic system in the nucleus accumbens [109]	Meta-analysis of two RCTs (combined N=89) found statistical improvement in MGH-HPS compared to placebo [121]

Table 9 (continued)

Diagnosis	Theoretical biological therapeutic pathway	Summary of evidence
Excoriation disorder	Reduction of compulsive behaviors through manipulation of the glutamatergic system in the nucleus accumbens [122]	One RCT (N=66) demonstrated significant improvement in NE-YBOCS and CGI-S compared to placebo [125]
Onychophagia	Reduction of reward seeking behaviors through manipulation of the glutamatergic system in the nucleus accumbens [112]	One RCT (N=42) found no significant difference between groups at 2 months [128]
PTSD	PTSD is associated with increased oxidative stress, neuroinflammation, and stress-related adaptations to the glutamatergic system. NAC may exert potential therapeutic effects through the amelioration of all of those processes [130]	No controlled studies published examining NAC treating PTSD alone. One small RCT (N=35) investigating NAC and CBT treating PTSD and SUD found no significant improvement in PCL-M and BDI [129]
Substance-use disorders	Reduction of intrusive thoughts (cravings) through manipulation of the glutamatergic system in the nucleus accumbens [135]	Multiple small RCTs investigating NAC in treating multiple substance use disorders, majority demonstrating no significant improvement over placebo
Neurocognitive disorders	Neurocognitive disorders are associated with increased neuroinflammation, mitochondrial dysfunction, and increased oxidative stress, NAC may exert potential therapeutic effects through the amelioration of all of those processes [188]	Multiple small studies with mixed results
Chronic pain	Reduction of increased oxidative stress associated with chronic pain [198] Modulation of abnormal glutamatergic activity in the pain matrix [14]	Meta-analysis of controlled and non-controlled trials (combined N=863) found no significant effect of NAC in treating chronic pain [198]

ASD Autism Spectrum Disorder, *ABC* Aberrant Behaviour Checklist, *RCT* randomized controlled trial, *PANSS* Positive and Negative Syndrome Scale, *SOPS* Scale of Prodromal Symptoms, *MADRS* Montgomery Åsberg Depression Rating Scale, *YMRS* Young Mania Rating Scale, *BDRS* Bipolar Depression Rating Scale, *HDRS* Hamilton Depression Rating Scale, *CGI-S* Clinical Global Impressions-Severity, *SLICE-LIFE* Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation, *LIFE-RIFT* Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning, *GAD* generalised anxiety disorder, *SP* social phobia, *OCD* obsessive compulsive disorder, *MGH-HPS* Massachusetts General Hospital Hair Pulling Scale, *NE-YBOcCS* Yale-Brown Obsessive Compulsive Scale for Excoriation Disorder, *PTSD* post-traumatic stress disorder, *CBT* cognitive behavioral therapy, *SUD* substance-use disorder, *PCL-M* PTSD Checklist-Military, *BDI* Beck Depression Inventory

been published indicates that NAC may have a role in treatment. There have been no controlled trials published investigating NAC's treatment of anxiety disorders and PTSD. Whilst there have been comparatively more investigations into NAC's treatment of SUDs, the findings have been less promising than in other psychiatric disorders.

Future research into NAC treating schizophrenia, autism spectrum disorder, obsessive compulsive disorder, and obsessive-compulsive-related disorders may be the most useful in terms of bringing NAC into the clinical sphere. However, given the large and growing demand for treatment of neurocognitive disorders from sports-related chronic traumatic encephalopathy and aging populations, future research of NAC's treatment of neurocognitive disorders may be highly clinically relevant. Future research into NAC's use in SUDs may be more fruitful if it focuses on prolonging abstinence in populations who have already achieved abstinence, given NAC's theorized mechanism of reducing cravings.

14 Conclusions

There are multiple treatment-resistant illnesses in psychiatry and fewer new psychotropic medications being developed now than in previous decades. This increases demand for novel uses of existing medications such as NAC. NAC has shown mixed results in treating many psychiatric disorders, as initial significant findings have often not been replicated or are limited to subgroup analysis. It is unclear at this stage whether this is due to underpowered studies or NAC's ineffectiveness as a treatment, thus there is a need for longer and better powered studies before NAC can be recommended clinically.

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