Review

The promise of *N*-acetylcysteine in neuropsychiatry

Michael Berk[1,2,3,4], Gin S. Malhi[5,6], Laura J. Gray[1], and Olivia M. Dean[1,2,4]

[1] School of Medicine, Deakin University, Geelong, Victoria, Australia
[2] Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia
[3] Orygen Research Centre, Parkville, Victoria, Australia
[4] The Florey Institute of Neuroscience and Mental Health, Victoria, Australia
[5] Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney, Australia
[6] CADE Clinic, Department of Psychiatry, Level 5 Building 36, Royal North Shore Hospital, St Leonards, 2065, Australia

***N*-Acetylcysteine (NAC) targets a diverse array of factors germane to the pathophysiology of multiple neuropsychiatric disorders including glutamatergic transmission, the antioxidant glutathione, neurotrophins, apoptosis, mitochondrial function, and inflammatory pathways. This review summarises the areas where the mechanisms of action of NAC overlap with known pathophysiological elements, and offers a précis of current literature regarding the use of NAC in disorders including cocaine, cannabis, and smoking addictions, Alzheimer's and Parkinson's diseases, autism, compulsive and grooming disorders, schizophrenia, depression, and bipolar disorder. There are positive trials of NAC in all these disorders, and although many of these require replication and are methodologically preliminary, this makes it one of the most promising drug candidates in neuropsychiatric disorders. The efficacy pattern of NAC interestingly shows little respect for the current diagnostic systems. Its benign tolerability profile, its action on multiple operative pathways, and the emergence of positive trial data make it an important target to investigate.**

Overview

NAC has been in use for over 30 years as an antidote in the treatment of paracetamol overdose, as a mucolytic for chronic obstructive pulmonary disease (COPD), as a renal protectant in contrast-induced nephropathy, and as therapeutic agent in the management of HIV [1]. A groundswell of recent evidence suggests that NAC may also have therapeutic benefits in multiple neuropsychiatric disorders.

The principal victories in biological psychiatry have arisen from the quest to reverse engineer serendipitous clinical findings. Exploring the biological effects of tricyclics, antipsychotics, and lithium have, respectively, led to elucidating the role of monoamines in depression, dopamine in schizophrenia, and second messenger systems in bipolar disorder [2]. In a similar vein, NAC provides a dual opportunity, first as a novel therapy, and second as a key to unlocking the pathophysiology of targeted disorders. It is noteworthy that the mechanisms of action of NAC overlap with the pathophysiology of a diverse range of neuropsychiatric disorders, including autism, addiction, depression, schizophrenia, bipolar disorder, and Alzheimer's and Parkinson's diseases [3]. Determining precisely how NAC works is crucial both to understanding the core biology of these illnesses, and to opening the door to other adjunctive therapies operating on these pathways. The current article will initially review the possible mechanisms of action of NAC, and then critically appraise the evidence that suggests it has efficacy in the treatment of neuropsychiatric disorders.

NAC biochemistry

NAC is the *N*-acetyl derivative of the amino acid L-cysteine and is rapidly absorbed following an oral dose [4]. L-Cysteine is rapidly oxidised to cystine in the prooxidant milieu of the brain. Cystine is the substrate of the cystine–glutamate antiporter, which shuttles glutamate out of the cell in exchange for cystine, thereby regulating extracellular glutamate levels and facilitating cysteine entry to the cell [5]. Inside the cell, cystine can be reduced to cysteine, which is the rate-limiting component of the key endogenous antioxidant molecule glutathione (GSH) [6]. The capacity for NAC to regulate both cystine–glutamate antiporter activity and biosynthesis of GSH is key to its therapeutic efficacy (Figure 1).

Effects on neurotransmission

Glutamate

NAC modulates several key neurotransmitter systems that are known to be involved in a range of psychopathology, including glutamate and dopamine [7]. Regulation of glutamate synthesis, release, synaptic levels, and recycling is tightly controlled, and dysfunction of this system is implicated in many neuropsychiatric disorders including schizophrenia [8] and addiction [9]. Excessive activation of the *N*-methyl-D-aspartate (NMDA) glutamate receptor is central to the excitotoxic damage associated with many forms of neuronal damage and degeneration [10]. The cystine/glutamate antiporter, or x(c)-system, is a key element in the control of extracellular glutamate and feedback regulation of glutamate release [11]. Predominantly expressed in astrocytes in the brain, activity of this transporter is the primary determinant of non-vesicular release

Corresponding author: Berk, M. (mikebe@barwonhealth.org.au).
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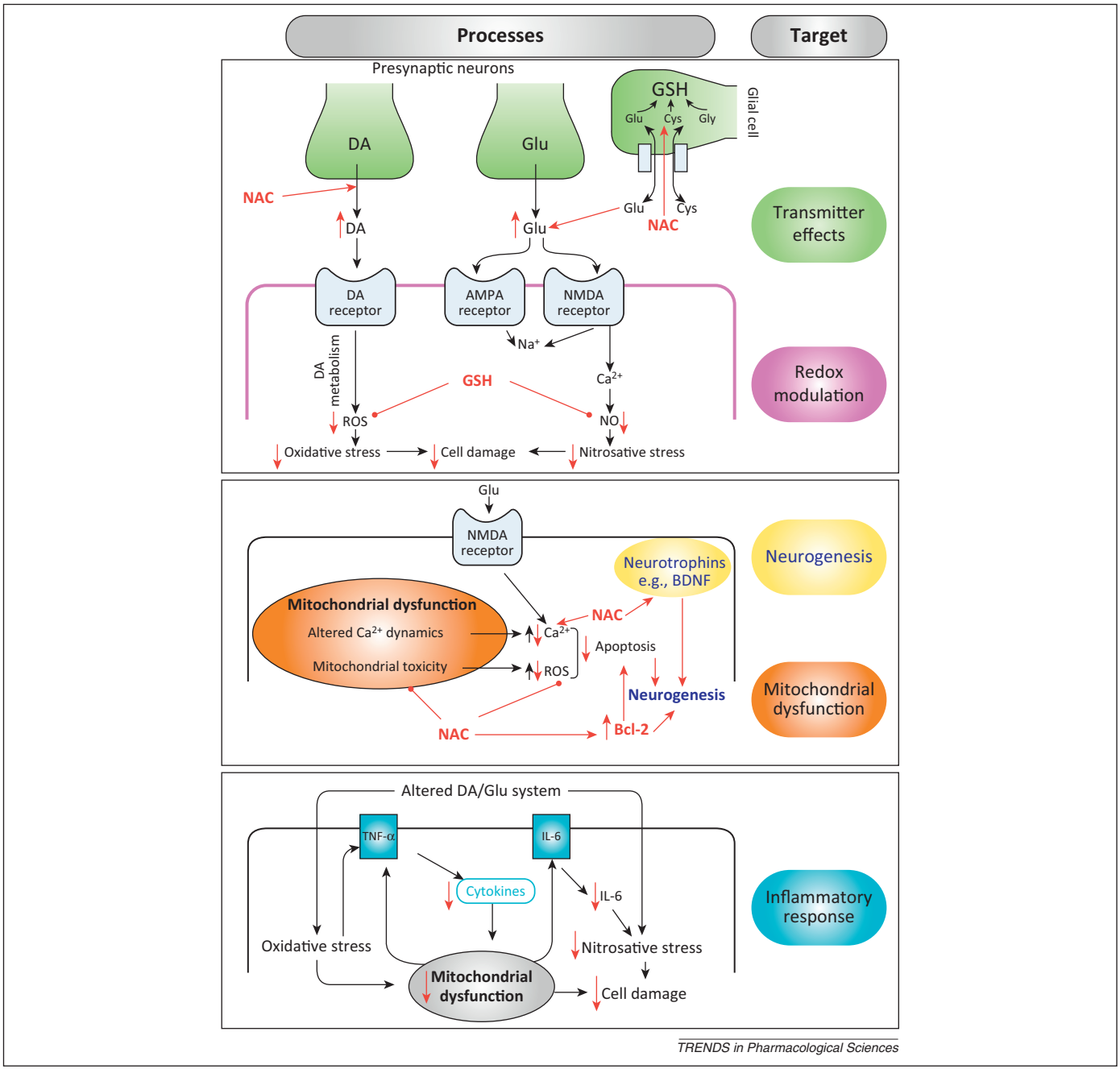

Figure 1. Pathophysiological targets of *N*-acetylcysteine (NAC). Transmitter effects: glutathione (GSH) is synthesized from three peptides: glutamate (Glu), cysteine (Cys), and glycine (Gly). Oral administration of NAC increases availability of Cys, which in turn facilitates the Cys–Glu antiporter and the production of glutathione (GSH) in glial cells. Heightened activity of the Cys–Glu antiporter also leads to increased extracellular glutamate which then acts on 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors. In addition, NAC facilitates the release of dopamine (DA). Redox modulation: GSH is the main antioxidant in the brain and scavenges reactive oxygen species (ROS) and nitrous oxide (NO), both of which are intracellular toxic byproducts of dysfunctional DA metabolism and Glu neurotransmission, respectively. Therefore, NAC induced increased GSH availability, lessens oxidative and nitrosative stressors in the brain, and this decreases cellular damage. Neurogenesis: administration of NAC has been shown to promote neurogenesis both directly, by increasing neuroprotective proteins, such as brain derived neurotrophic factor (BDNF), and indirectly by reducing apoptosis through an increase of antiapoptotic proteins, such as B cell lymphoma 2 (Bcl-2). Mitochondrial dysfunction: NAC corrects mitochondrial dysfunction by modifying calcium (Ca^{+}) dynamics within the mitochondria, and by decreasing intracellular Ca^{+}. NAC also reverses mitochondrial toxicity which in turn decreases the ROS produced by dysfunctional mitochondrial metabolism. Additionally, NAC scavenges ROS which overall inhibits apoptotic pathways. Inflammatory response: alterations to neurotransmission activate inflammatory pathways that can ultimately lead to cellular stress and mitochondrial dysfunction. NAC dampens the inflammatory response by decreasing the production of cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6).

of glutamate. The extracellular glutamate activates metabotropic glutamate receptors (mGluR2/3) on presynaptic neurons and regulates vesicular glutamate neurotransmission [11]. NAC administration can activate the cystine/glutamate antiporter through provision of additional cystine, thus modulating glutamatergic neurotransmission. Through regulation of this system NAC has been thought to show beneficial effects in psychotomimetic-induced models of schizophrenia, ameliorating behavioural deficits and reversing elevations of extracellular glutamate [12]. NAC also shows beneficial effects in animal models of cocaine addiction, suggested to be through stimulation of cystine/glutamate antiporter and presynaptic mGluR2/3 signalling [8,13].

In addition to regulation of glutamate release, NAC, via GSH or its derivatives, has the capacity to modulate NMDA activity [14–16]. Earlier studies suggested that his was through direct binding of the NMDA receptor but more recent reports focus on modulation of redox state by GSH. The NMDA receptor, along with many other cellular proteins, is regulated by subtoxic levels of oxidant species. Elevated levels of oxidising agents reduce the activity of the NMDA receptor via binding to extracellular redox-sensitive sites and depletion of GSH has recapitulated this effect [17].

Taken together, these results provide clear evidence that NAC modulates glutamatergic neurotransmission both directly and indirectly. Given the central role of glutamate signalling in multiple neuropsychiatric disorders it is likely to be that this activity of NAC is a key component of its therapeutic effect.

Dopamine

Given that dopamine has historically played a lead role in theories underpinning the pathology of many neuropsychiatric disorders (e.g., schizophrenia and Parkinson's disease), the ability of NAC to modulate dopamine is noteworthy. NAC regulation of the cystine/glutamate antiporter and mGluR2/3 as described above can also regulate dopamine release from presynaptic terminals [11]. NAC may also regulate dopamine release via modulation of the redox status of the cell, via the antioxidant effects of GSH and L-cysteine [18,19] (Figure 1). Dopamine itself is strongly prooxidant, forming hydrogen peroxide (H_2O_2) and free radicals through autooxidation and normal metabolism, and hence dysregulation of dopamine signalling is thought to be a major contributor to neurotoxicity [20]. Methamphetamine evokes strong dopamine release and drives neuronal apoptosis. NAC ameliorates the oxidative stress induced by methamphetamine production and prevents the downregulation of the dopamine transporter elicited by excessive dopamine release [21,22]. These results not only highlight the therapeutic effects of NAC but also demonstrate the importance of cystine/glutamate transport and GSH regulation of oxidative stress in dopaminergic signalling [23].

Role in oxidative homeostasis

The brain is acutely sensitive to changes in redox status. The high metabolic activity of this organ is a persistent source of oxidative species, as utilisation of O_2 by energy-generating mitochondria constantly generates oxygen free radicals [24,25]. Neurotransmitter activity also generates free radicals, with autooxidation of dopamine and excitotoxicity related to glutamatergic signalling being important sources of oxidative stress [10,20]. Neurons rely on the integrity of extensive axonal membranes for efficient information signalling, and these membranes, high in polyunsaturated fatty acids, are vulnerable to free radical damage. Compounding these factors, the levels of endogenous antioxidants in the brain are low relative to other highly metabolically active organs. At the far end of the spectrum, excessive oxidative stress can lead to neurotoxicity and cell death, but redox systems also play an important regulatory role in the modulation of enzyme activity, intracellular signalling systems, and receptors (beyond the scope of this review, but discussed in [26]). One example of this is the redox regulation of the NMDA receptor, as discussed above. Thus, even moderate perturbations of the redox balance can alter neuronal function, even in the absence of overt toxicity and neuronal damage.

Evidence for disrupted oxidative signalling in psychiatric disorders is compelling. Alterations in multiple biomarkers of oxidative stress, including enzymes involved in the production or clearance of free radical species, have been observed in attention deficit hyperactivity, bipolar disorder, autism, depression, and schizophrenia [27–29]. Markers of oxidative damage to neurons have also been observed in postmortem samples in several psychiatric diseases [30–32]. Mitochondria are a major source of free radicals in the brain as a byproduct of energy production, and dysfunction of mitochondrial function can significantly elevate oxidative stress. Alterations in mitochondrial function are observed in schizophrenia and bipolar disorder, in particular [33–35]. Interestingly, genetically mediated mitochondrial disorders are also associated with elevated incidences of psychiatric disorders, particularly mood disorders and psychosis [36].

The major endogenous antioxidant molecule in the brain is GSH, which is key to the mechanism of action of NAC. GSH reduction is ironically one of the oldest biomarkers in psychiatry, known for three-quarters of a century, and noted in studies of depression, schizophrenia, and bipolar disorder [37–46]. GSH is a very efficient redox scavenger, carrying a free thiol group which can interact directly with reactive oxygen/nitrogen species and can maintain the oxidative status of key cellular enzymes. The cycle of GSH and the reduced species glutathione disulphide (GSSG) is a critical mechanism for regulation of cellular oxidative balance.

Mice deficient in the rate-limiting enzyme for GSH synthesis show a range of behavioural symptoms reminiscent of schizophrenia and bipolar disorder, including a heightened response to psychotomimetics. Treatment with NAC reverses some of these deficits [47,48]. Similarly, experimental GSH depletion in the brain induces spatial memory deficits which are reversed by NAC [49]. GSH levels are efficiently restored by NAC [50], which acts as a donor of cysteine, the rate-limiting component of GSH synthesis. NAC is also effective in reversing the oxidative stress associated with mitochondrial dysfunction [51,52].

NAC also contributes to the maintenance of oxidative balance through the actions of the cysteine/cystine cycle. Similarly to GSH and GSSG, cysteine and cystine are coupled redox partners which help to prevent oxidative cellular dysfunction and injury [53–55]. Hence, the actions of NAC are multifold and inter-related, with the production of GSH, the cysteine/cystine cycle, and the action of the glutamate/cystine antiporter contributing to maintenance of oxidative balance and cellular function.

Interaction with inflammatory mediators

Another potential therapeutic avenue for NAC stems from its anti-inflammatory properties. Dysregulation of inflammatory pathways and cytokine levels in both the periphery and the central nervous system (CNS) are associated with

psychiatric disorders, and in particular depression. Several meta-analyses have demonstrated dysregulated production of inflammatory cytokines in depressed patients [56–58]. Patients treated with the cytokines interleukin-2 (IL-2) and interferon-α for other somatic conditions report a significantly higher incidence of depressive symptoms [59–61]. Dysregulated inflammatory pathways are thought to alter the production of neurotransmitters and key neurotrophic factors in the CNS and contribute to the pathophysiology of depression [62,63].

NAC has been shown to reduce IL-6 levels in haemodialysis patients [64] and tumour necrosis factor-α (TNF-α) and IL-1β in patients undergoing surgery [65]. NAC also suppresses production of multiple inflammatory cytokines in burn patients [66]. In rat models of both traumatic brain injury and focal cerebral ischemia, increased TNF-α and IL-1β levels were reduced following NAC administration [67,68].

Administration of lipopolysaccharide (LPS), a bacterial endotoxin, induces widespread inflammation and depressive-like symptoms in animal models [69]. However, NAC pretreatment prevents the upregulation of inflammatory cytokines in the brain in response to LPS [70]. Furthermore, sensitisation to hypoxic brain injury by LPS and markers of cerebral inflammation are prevented by NAC treatment [71]. The capacity for NAC to reduce neuroinflammation may be through inhibition of the brain inflammatory cells, the microglia. Microglia are brain macrophage-like cells which can be activated by cytokines and in turn produce inflammatory mediators, induce oxidative stress, and promote neurotoxicity [72,73]. NAC can inhibit activation, cytokine production, and oxidative species production by macrophages and microglia [74]. This effect is likely to be through both stimulation of GSH production and regulation of cystine/glutamate antiporters, regulating oxidative stress and glutamate excitotoxicity [75].

Use in psychiatry

There is a growing body of literature of potential benefit of NAC in a wide range of neuropsychiatric disorders. These are discussed briefly below and highlighted in Table 1.

Addiction

The majority of the clinical studies investigating addiction have based their rationale for using NAC on the extant literature implicating glutamatergic abnormalities in addiction [76]. Glutamatergic dysfunction has been considered a central tenet of addictive disorders since the demonstration that blockade of NMDA glutamatergic receptors inhibits sensitisation [77], and glutamate is now thought to additionally regulate dopaminergic activity in the ventral tegmental reward area. The ability of NAC to regulate glutamate availability via the activity of the cystine/glutamate antiporter highlights the potential therapeutic efficacy of this drug in treating addictive disorders. In an open-label crossover imaging study of cocaine-dependent patients NAC normalised elevated levels of glutamate, as measured by brain imaging [78].

However, there is now data from both clinical studies and animal models suggesting a role of oxidative stress in addiction [79–84], suggesting a further pathway whereby NAC may offer an alternate rational approach via promotion of GSH synthesis. In addition to the disorders listed below, NAC is also being investigated as an adjunctive treatment for alcohol dependence (ClinicalTrials.gov: NCT01214083), and a pilot randomised controlled trial (RCT) of NAC in combination with naltrexone has been conducted for the treatment of methamphetamine dependence, with a negative outcome [85].

Cannabis dependence. An open-label study of NAC (1200 mg BD) was conducted in 24 dependent cannabis users [86]. After NAC treatment, users reported reductions in days per week of use, 'number of hits', and compulsivity, emotionality, and purposefulness with cannabis use. Interestingly, objective urine cannabinoid measures did not significantly change with treatment and remained higher than the test's detection range [86]. However, a recent 8-week double-blind RCT ($n = 116$) investigated treatment with NAC (1200 mg BD) versus placebo for cannabis cessation in adolescents and found that during treatment, those receiving NAC had more than twice the odds of having negative urine cannabinoid test results than placebo, supporting its efficacy as a primary cessation therapy although in an intent-to-treat analysis [87]. Studies are continuing to explore the potential of NAC in cannabis dependence (ClinicalTrials.gov: NCT01005810, NCT01439828).

Nicotine addiction. NAC has also been studied in nicotine addiction because of its potential to restore glutamate homeostasis and modulate redox balance. In a placebo-controlled study of NAC (2400 mg/day) for tobacco cessation ($n = 29$), there was no significant difference in the number of cigarettes smoked or carbon monoxide levels between NAC and placebo groups. However, *post hoc* analysis revealed trends towards decreased number of cigarettes smoked in the NAC group after the removal of two outliers based on alcohol consumption, but this too did not correspond with decreased carbon monoxide levels [84]. In another small-scale 6-month placebo-controlled study of NAC (1200 mg/day), the detrimental biophysical aspects of smoking were examined (participants were instructed to continue their cigarette use). In the NAC group, there were decreases between baseline and endpoint in markers of DNA damage, compared with the placebo group, indicating a decrease in oxidative stress processes associated with addiction [88].

A recent pilot double-blind study investigated the effects of a larger daily dose of NAC (3600 mg) on short-term abstinence in heavy smokers. Participants received NAC ($n = 10$) or placebo ($n = 12$) over 3.5 days. Those participants receiving NAC rated the first cigarette after abstinence as significantly less rewarding than those on placebo; however, there was no significant effect of NAC on craving [78]. There are small active-placebo gaps in this genre of research, and because a relatively small number of individuals stop smoking in these cessation trials, sample sizes in the hundreds are usually needed to demonstrate efficacy. Further studies that address these limitations (see ClinicalTrials.gov: NCT00967005) are being conducted.

Table 1. Clinical trials of NAC in neuropsychiatric disorders

Disorder	Trial type	Dose of NAC	Duration of trial	Number of participants	Clinical outcome	Biomarkers	Refs
Methamphetamine dependence	Placebo-controlled RCT (NAC + naltrexone)	600–2400 mg/day (NAC) + 50–200 mg/day (naltrexone)	8 weeks	NAC + naltrexone = 14 Placebo = 17	No effect on cravings or drug use		[85]
Cannabis dependence	Open-label	1200 mg BD	4 weeks	24	Reduced use and craving	No change in urine cannabinoid levels	[86]
	Double-blind RCT	1200 mg BD	8 weeks	NAC = 58 Placebo = 58		Twofold increase in likelihood of a negative urine cannabinoid test	[87]
Nicotine addiction	Placebo-controlled RCT	2400 mg/day	4 weeks	NAC = 15 Placebo = 14	No change in number of cigarettes smoked	No change in carbon monoxide levels	[84]
	Placebo-controlled RCT	1200 mg/day	6 months	NAC = 20 Placebo = 21		Decrease in some markers of oxidative damage	[88]
	Pilot double-blind RCT	3600 mg/day	3 days	NAC = 10 Placebo = 12	Reduced rewarding stimulus after short-term abstinence, no effect on craving		[78]
Cocaine addiction	Placebo-controlled crossover study	2400 mg	2 days	13	Reduced withdrawal symptoms and craving		[89]
	Double-blind placebo-controlled crossover study	2400 mg	3 days	13	Reduced cue reactivity to cocaine-related stimuli		[90]
	Open-label trial	1200, 1800, or 3600 mg/day	4 weeks	23	Nonsignificant reductions in use		[91]
	Open-label crossover trial		Single dose	10		Normalised glutamate levels	[78]
Pathological gambling	Open-label study followed by placebo-controlled RCT	1800 mg	8 weeks, 6 weeks	27, 16 responders	Reduced gambling symptoms		[92]
Obsessive–compulsive disorder	Case report in treatment-resistant patient	300 mg daily	6 weeks	1	Reduced symptoms		[98]
Trichotillomania, skin picking	Two case reports	1800 mg		2	Reduced symptoms		[101]
	Double-blind placebo-controlled	1200 mg for 6 weeks, followed by 2400 mg for 6 weeks	12 weeks	50	Reduced symptoms		[102]
	Case report	1800 mg/day		1	Reduced symptoms		[101]
Schizophrenia	Double-blind placebo-controlled trial	1000 mg BID adjunctive	6 months	140	Reduced negative symptoms		[45]
	Case report in treatment resistance	600 mg/day			Improved symptoms		[108]
Bipolar disorder	Double-blind placebo-controlled RCT	1000 mg BID	6 months	75	Decreased depression rating scores and improvements on global functioning scale		[109]
	Open-label trial	1000 mg BID	8 weeks	149	Decreased depression rating scores and improvements on global functioning scale		[121]

Table 1 (*Continued*)

Disorder	Trial type	Dose of NAC	Duration of trial	Number of participants	Clinical outcome	Biomarkers	Refs
Autism	Double-blind placebo-controlled RCT	900 mg up to 2700 mg daily	12 weeks		Improvements in irritability, repetitive behaviours, and mannerisms		[113]
Alzheimer's disease	Double-blind placebo-controlled RCT	50 mg/kg/day	6 months	NAC = 23 Placebo = 20	Improved cognitive performance	No change in peripheral measures of oxidative stress	[115]
	Open-label trial	NAC in combination with other neutraceuticals	1 year	14	Improved cognitive performance		[60]
	Placebo-controlled trial	NAC in combination with other neutraceuticals	9 months	12	Improved cognitive performance		[117]

Cocaine addiction. Perhaps the most active area of study in addiction using NAC is cocaine addiction. In a 2-day crossover study (n = 13), participants who were abstaining from cocaine were given 2400 mg NAC or placebo. Four days later, participants were crossed over to alternative treatment arms. Although there was no between-group difference, the NAC within-group comparison identified a significant reduction in cravings, withdrawal symptoms, and self-reported use compared with baseline, a pattern not mirrored by the placebo group [89]. In a subsequent study, a similar sample was treated with 2400 mg of NAC. Using cue-reactivity slides (a paradigm assessing the propensity for people with addictions to have significant physiological and subjective reactions to drug-related stimuli), NAC decreased the amount of time spent looking at the cocaine-related slides, indicating a reduced interest and desire for cocaine [90]. In a subsequent larger open-label trial of NAC over 4 weeks, eight participants were given 1200 mg/day of NAC, a further nine participants were treated with 1800 mg/day, and six participants received 3600 mg/day [91]. Nonsignificant reductions in the number of days of use, the amount spent on cocaine, and improvements on the Cocaine Selective Severity Assessment were noted. In an open-label crossover study of ten cocaine dependant individuals, after a single administration of NAC, magnetic resonance spectroscopy was conducted. In the cocaine-dependent group, glutamate levels were discernibly reduced, and there was a trend towards decreased self-reported cocaine use and glutamate/creatine ratios in the dorsal anterior cingulate cortex [78].

Pathological gambling. In an 8-week, open-label study of 20 confirmed pathological gamblers, Grant *et al*. utilised 1800 mg (titrated dose) of NAC and found 16 completers had significant reductions in gambling behaviour [92]. A randomised trial of 13 responders was conducted over the subsequent 6 weeks using a fixed dose of 1800 mg/kg NAC or placebo. At the end of the treatment phase, only 28% of the placebo group were still considered responders, compared with 83% of the NAC group [92]. Further studies are currently being conducted to explore the potential of NAC as a therapy for gambling (ClinicalTrials.gov: NCT00967005).

Obsessive–compulsive disorder (OCD) and other compulsive disorders

The biochemical pathways and brain regions implicated in addiction and the OCD spectrum of disorders overlap considerably [93,94]. Oxidative stress has been reported in OCD and is reflected by decreased antioxidant levels [95], increased lipid peroxidation [96], and overall altered oxidative status [27] that are associated with the severity of symptoms [95]. In addition, there is evidence of glutamatergic abnormalities in OCD [97].

With respect to treatment however, there is currently a single case report of the use of adjunctive NAC 3000 mg daily in a person with partial response to selective serotonin reuptake inhibitor (SSRI) treatment for refractory OCD, a disorder known to have low placebo response rates. Scores on both the Yale–Brown Obsessive Compulsive Scale and the Hamilton Depression Rating Scale improved,

and were associated with improvements in compulsive washing and obsessional triggers [98]. Randomised controlled trials are underway (ClinicalTrials.gov: NCT01555970, NCT01172275).

Trichotillomania (obsessive pulling of one's hair; TTM) is thought to exist on a continuum with OCD [99]. There is also a hypothesised overlap between TTM and addictive disorders, given the shared role of impulsivity and dysfunctional reward pathways [100]. There are two reported case studies that have suggested benefits of NAC in TTM [101], where a titrated dose of 1800 mg of NAC reduced hair pulling.

There has been one double-blind, placebo-controlled trial of adjunctive NAC for the treatment of TTM, in which 50 individuals were treated with 1200 mg of NAC for 6 weeks, followed by 6 weeks of treatment with 2400 mg of NAC (or placebo). There was a greater improvement in the NAC group than the placebo group, separating at week 9 and persisting throughout the study [102]. There is a case report of cessation of nail biting with NAC in a person with both TTM and nail biting behaviours, in which symptoms recurred upon discontinuation but remitted once again on recommencement of NAC [101]. Further evidence for this action comes from a 6-month study primarily investigating NAC (2000 mg/day) in the treatment of mood disorders, which reported an incidental treatment concomitant finding of reduced nail biting in three participants [103]. Lastly, there is a case report of utility in skin picking with 1800 mg/day of NAC, in which both the urge to pick, and skin picking behaviours remitted [101] and therefore NAC for skin picking is currently being investigated in a RCT (ClinicalTrials.gov: NCT01063348).

Schizophrenia

In the pathophysiology of schizophrenia, glutamate is thought to play a key role, evidenced by decreased glutamate levels in the prefrontal cortex and dysfunction in glutamate metabolism [104]. Oxidative stress is also extensively documented in schizophrenia, and there are emerging links between symptom severity, diagnostic subtype, and oxidative stress [105].

A large-scale (n = 140) randomised double-blind placebo-controlled trial of adjunctive NAC 1000 mg BID in schizophrenia conducted over 6 months [106] found significant improvements in negative symptoms (including blunted affect, lack of volition, and social withdrawal), assessed by the Positive and Negative Symptoms Scale (PANSS). Specifically, there were improvements in PANSS total and general subscales and significant improvements also occurred in abnormal movements, particularly akathisia, as well as global functioning. Interestingly, benefits were lost 1 month after treatment discontinuation. Of note, in a study subsample, auditory sensory processing was assessed using mismatch negativity (MMN), as it is a marker of glutamatergic function and a potential endophenotype of psychosis. As anticipated, individuals with schizophrenia had reduced MMN at baseline compared with healthy controls, but after 8 weeks of treatment MMN normalised significantly in those on NAC [45].

In a blinded qualitative analysis of clinician observations and participant reports in this trial, participants treated with NAC showed more improvements in insight, social interaction, motivation, self-care, psychomotor stability, volition, and stabilisation of mood [107]. Finally, there is a case report of the use of NAC 600 mg/day in a young female with treatment-resistant schizophrenia, which suggested significant improvements in symptoms [108]. Other studies of NAC in schizophrenia are underway (ClinicalTrials.gov: NCT01354132, NCT01339858).

Bipolar disorder and unipolar depression

Alterations in pro- and anti-inflammatory cytokines, oxidative biology, mitochondrial function, glutamate, inflammation, and neurotrophins have been described in bipolar disorder, dovetailing the known pharmacokinetic properties of NAC [3]. A 6-month double-blind, RCT of NAC 1000 mg BID in addition to treatment as usual was conducted in 75 participants with bipolar disorder [109]. Scores on both the Montgomery–Asberg Depression Rating Scale (MADRS) and the Bipolar Depression Rating Scale (BDRS) evidenced large decreases in symptoms of depression between NAC and placebo groups at endpoint. Comparable improvements were seen on global improvement, severity, and functioning scales. A secondary analysis including those participants meeting criteria for a major depressive episode showed large effect sizes in favour of NAC for depressive symptoms and functional outcomes at endpoint [110]. Another secondary analysis of the trial examined individuals with bipolar II disorder. In the NAC group, six out of seven people attained remission of both depressive and manic symptoms, whereas only two out of seven people in the placebo group reached remission [111].

In a recent maintenance design RCT of 1000 g BID of NAC for bipolar disorder, the effect of NAC amongst 149 individuals with moderate depression was studied. Mean BDRS scores significantly reduced at the end of the 8-week open-label treatment phase. Comparable and significant improvements in functioning and quality of life were seen. Studies involving NAC for the treatment of bipolar depression are continuing [Australian and New Zealand Clinical Trials Registry (ANZCTR): ACTRN12612000830897] and the first trial of NAC in unipolar depression is nearing completion (ANZCTR: ACTRN12607000134426).

Autism

In autism, analogous to schizophrenia, dysregulation of redox biology, inflammation, and glutamate transmission have been noted [112]. Recent tantalising data on the efficacy of NAC in autism has been published [113]. In this 12-week, double-blind, randomised, placebo-controlled study of NAC, participants were initiated on 900 mg daily for 4 weeks and titrated to 2700 mg daily over 8 weeks. Of note, significant improvements on the Aberrant Behaviour Checklist irritability subscale in the NAC group have been reported, as well as on the Repetitive Behaviour Scale-Revised stereotypies measure and Social Responsiveness Scale mannerisms scores [113]. Further studies are underway (ClinicalTrials.gov: NCT00889538; ANZCTR: ACTRN12610000635066).

Alzheimer's disease and other neurodegenerative disorders

NAC impacts multiple pathways implicated in a variety of neurodegenerative disorders. In Parkinson's disease, for example, in addition to the overt impacts of altered dopamine metabolism on oxidative events, mitochondrial complex I dysfunction and dysregulated phosphorylation are reported [114], and may be potentially targeted by NAC treatment. Furthermore, there is preclinical evidence, particularly in Alzheimer's disease (AD) and Parkinson's disease models, suggesting potential benefits of NAC. Hence, a few clinical investigations of NAC as a treatment option in neurodegenerative disorders have been conducted.

Late-stage AD patients treated with 50 mg/kg/day of NAC for 6 months showed significant improvements in performance on the Letter Fluency Task and the Wechsler Memory Scale Immediate Number Recall; however, peripheral measures of oxidative stress did not change [115]. In a 12-month, small ($n = 14$) open-label trial of individuals with early-stage AD, the efficacy of a vitamin/nutraceutical formulation (NAC, folate, vitamin B6, α-tocopherol, *S*-adenosyl methionine, and acetyl-L-carnitine) was examined. Improvements were noted in the Dementia Rating Scale and Clock-drawing tests, as well as in reports from family caregivers [116]. In a similar study ($n = 12$), the same nutraceutical formulation showed more favourable cognitive endpoints compared with placebo [117]. However, given the small number of studies, and their exploratory nature, definitive conclusions are premature. Research into the potential benefits of NAC in neurodegenerative disorders is continuing (ClinicalTrials.gov: NCT01470027; NCT01427517, NCT01370954).

Concluding remarks

Given the paucity of new drug development, NAC is a promising novel therapeutic option for a diverse range of neuropsychiatric disorders. Although there is only preliminary data of the efficacy of NAC in many of these disorders, this field is rapidly expanding with additional trials [e.g., investigating personality disorder (ClinicalTrials.gov: NCT01555970)]. Most notable is the sheer breadth of disorders that NAC appears to benefit and the lack of recognition within extant diagnostic systems commensurate with its efficacy profile. Indeed, the seeming universality of NAC action is intriguing and implies that it perhaps targets downstream pathways that are common across disorders. Oxidative stress and associated mitochondrial dysfunction are plausible candidates as they too appear to lack specificity across psychopathologies. Equally, however, dysregulation of neurotrophins, inflammatory pathways, and neurotransmitters such as glutamate and dopamine have been similarly widely reported in a multitude of disorders. This is emphasised by the fact that there is extensive overlap of other treatments and biomarkers across disorders.

There are several caveats that need to be borne in mind. As the database increases, it is likely to be that the profile of efficacy of NAC will be greater in some disorders than others. The optimal dose of NAC is not clear; dose-finding studies may show equal efficacy at lower doses or greater efficacy at higher doses. Although the tolerability profile of NAC seems benign, there is as yet an insufficient evidence base for longer term use. Idiosyncratic events, such as asthma, have been shown in some studies, but not replicated, and pulmonary hypertension at very high dose has been reported in a few animal studies, but, as yet, has not been found in human studies [118]. At low dose NAC appears to be anti-epileptic [119], but at high doses seizures have been reported [120]. Hence, ongoing data collection regarding safety is necessary, concomitant with corroborating efficacy data.

Lastly, it is interesting that historically, the richest discoveries in psychopharmacology have been derived by reverse engineering the beneficial mechanisms of action of drugs discovered serendipitously. Notable examples include the monoamine oxidase (MAO) inhibitors, tricyclics, lithium, and phenothiazines. To date, two divergent hypothetical paths have converged on NAC as a potential treatment. Firstly, oxidative stress and GSH deficiency has driven the focus on NAC in schizophrenia, bipolar disorder, and depression. Superadded to this, and in parallel, addiction research has hypothesised NAC to be active via the modulation of glutamate and the cystine–glutamate antiporter [76]. However, knowing that NAC also has effects on inflammatory pathways, neurotrophins, mitochondrial function, and oxidative stress, its true efficacy profile may turn out to be due to preferential effects on any of these, or a summative interaction of influences on a variety of pathways. Unravelling these complexities has the potential to open up new avenues for the development of novel psychotropic agents.

Disclaimer statement

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