# Is N-Acetylcysteine (NAC) Effective as Psychiatric and Neurological Treatment? Where Does the Evidence Lie?

*Sabrina K. Bradbury-Segal, Ph.D.*


## ABSTRACT

N-acetylcysteine (NAC) is widely known as a nutritional supplement with antioxidant properties. Due to its role in reducing neuroinflammation, oxidative stress, and modulating neurotransmission it has received a lot of interest in treating medical conditions since the 1980s. Given that many neuropsychiatric disorders are associated with pathophysiologies that include neuroinflammation, oxidative stress, mitochondrial dysfunction, and disruptions in neurotransmission, NAC has recently received more attention for the treatment of a variety of mental health conditions. There has been favorable evidence for the use of NAC in many psychiatric and neurological disorders, including bipolar disorder, autism, Alzheimer's disease, substance use disorder (e.g., cocaine, methamphetamine, and cannabis), depression, obsessive compulsive disorder, schizophrenia, traumatic brain injury, and myoclonic epilepsy. However, to date there have been no large randomized controlled trials that focus on the use of NAC to treat mental health conditions. In this article, we evaluate previous and current research findings for the efficacy of NAC as stand-alone or adjunctive treatment for a variety of mental health conditions.


## What is NAC?

N-acetylcysteine (NAC) is the acetyl derivative of the amino acid cysteine.[1] It is widely available as an over-the-counter nutritional supplement with antioxidant properties.[2] NAC has been used across the world for the treatment of a variety of medical conditions, and is considered to be safe, and well-tolerated.[3] Oral administration of NAC has been approved by the Food and Drug Administration (FDA) for acetaminophen overdose since 1985, and in 2004 the FDA approved the intravenous form for acetaminophen overdose.[4] It has also been used to treat a variety of medical conditions, ranging from a preventative agent for atrial fibrillation,[5] to adjunct therapy for HIV-infection.[6] In the past decade, there has been growing research on the use of NAC to treat various psychiatric and neurological disorders. According to preclinical research studies, NAC may modulate pathophysiological processes that are involved in multiple psychiatric and neurological disorders. These include oxidative stress, neurogenesis and apoptosis, mitochondrial dysfunction, neuroinflammation, and dysfunction of glutamate and dopamine neurotransmitter systems.[7,8]

## Role in Oxidative Homeostasis

The use of NAC as an antioxidant precursor to glutathione (γ-glutamylcysteinylglycine; GSH) levels has been well established. [7] Glutathione is the primary endogenous antioxidant, as it neutralizes reactive oxygen and nitrogen species from the cell via both direct and indirect scavenging. Its major role, as the most abundant and ubiquitous antioxidant, is to maintain the oxidative balance in the cell. [9] Glial cells contain much higher levels of GSH than neuronal cells and support neuronal GSH production. In addition to providing cysteine for GSH production, NAC also scavenges oxidants directly, particularly via reduction of the hydroxyl radical ·OH, and hypochlorous acid.[9] Oral administration of GSH, or L-cysteine have minimal effects on brain GSH levels, however oral NAC administration results in increased

plasma cysteine levels, leading to increased plasma GSH levels.[10,11] Additionally, NAC has been shown to penetrate the blood-brain barrier and increase brain GSH levels in animal models, resulting in altered brain GSH levels.[12]

## NAC, and Mitochondrial Dysfunction

In animal models of traumatic brain injury (TBI)-induced mitochondrial dysfunction, n-acetylcysteine (NAC) significantly restored mitochondrial electron transfer, energy coupling capacity, and calcium uptake activity within 12 hours, if administered up to 1 hour postinjury.[13] Additionally, NAC administration up to 1 hour postinjury resulted in restored brain GSH levels, and mitochondrial GSH levels up to 14 days post-TBI. Timing appears to be critical, since NAC administered 2 hours postinjury did not have the same effect. Additionally, in animal models of mitochondrial complex I disease, NAC rescued animal lifespan and reduced cellular oxidative stress.[14] Since mitochondria are the major reactive oxygen species (ROS)-generating organelles in cells,[15] NAC likely has restorative effects on mitochondria, through its antioxidant properties.

## Effects of NAC on Neurotransmission

Glutamate

In addition to influence that cysteine levels have on GSH levels, and oxidative balance, alterations in cysteine levels have also shown to modulate neurotransmitter pathways, such as glutamate and dopamine.[16] Cysteine is heavily involved in the regulation of neuronal intra- and extracellular exchange of glutamate, through the cystine-glutamate antiporter, located primarily on glial cells. The dimer, cystine, is then taken up by astrocytes and exchanged for glutamate, released into the extracellular space. The free glutamate, in turn, stimulates inhibitory metabotropic glutamate receptors, reducing the synaptic release of glutamate.[17] Additionally, alterations in the neuronal GSH levels from NAC may alter glutamate levels indirectly, yet also have a direct effect on glutamatergic transmission. GSH has been shown to potentiate brain N-methyl-D-aspartate receptor response to glutamate in animals.[18,19]

Dopamine

In addition to modulating glutamate levels via the cystine-glutamate antiporter, NAC has also been shown to alter dopamine (DA) release. In animal research, NAC has demonstrated a protective effect against reductions in DA transporter levels, following repeated methamphetamine administration.[20] In a cell line study examining the effects of rotenone on midbrain dopamine neurons (mDA) as a model for Parkinson's disease, significantly more NAC-exposed mDA neurons survived after rotenone exposure. Additionally, there was significantly increased DAT binding in the caudate and putamen compared to no changes in the control group.[21] The increased levels of glutathione from NAC administration may play a role, since glutathione has also shown to increase glutamate agonist-evoked DA release in animal striatal neurons.[16]

## NAC in Neuroinflammation and Neurogenesis

Many psychiatric disorders have been associated with alterations in pro- and anti-inflammatory cytokines. For example, interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-α alterations have been reported in patients with depression, bipolar disorder, and schizophrenia.[22,23] NAC has been shown to reduce levels of IL-6 in hemodialysis patients.[24] NAC has also demonstrated reductions in TNF-α and IL-1β in animal models of various types of traumatic brain injury (TBI), and improve outcomes in lipopolysaccharide models of inflammation.[25,26,27] The reductions in inflammatory cytokines by NAC treatment may be a potential mechanism through which NAC modulates various symptoms of psychiatric disorders, either directly via inflammatory pathways, or indirectly through oxidative processes associated with neuroinflammation. Inflammation downregulates neurogenesis, through modulation of mitochondrial viability.[28] Thus, the neuroprotective properties of NAC may be related to its neurogenesis-inducing ability, which is likely related to mitochondria-protective mechanisms. NAC's antioxidant properties, in addition to these other factors, may be the underlying components that promote cell survival and growth factor synthesis (e.g., brain-derived neurotrophic factor; BDNF), ultimately resulting in neurogenesis. See Figure 1.

Figure 1.

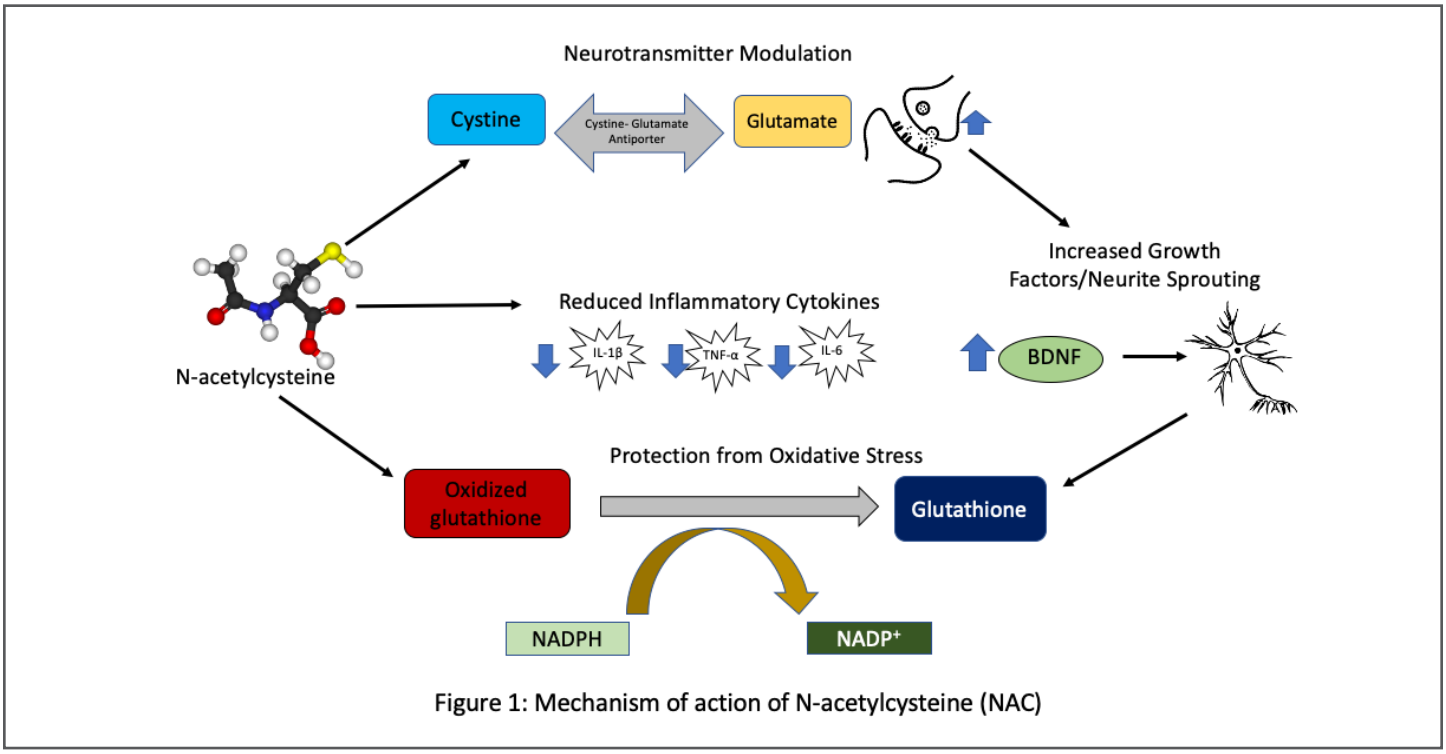


Figure 1: Mechanism of action of N-acetylcysteine (NAC)

## Treatment of Psychiatric Disorders

Bipolar Disorder

The pathophysiology that underlies bipolar disorder (BP) has not been fully elucidated, yet alterations in oxidative metabolism have been reported in patients with BP.[29] Similar to schizophrenia, changes in antioxidant levels, increased markers of lipid peroxidation, and protein carbonylation have been described. The alterations seem to be phase specific, where there is increased oxidative stress in the manic phase. This also supports reports of hyperdopaminergic states during manic episodes.[30] Additionally, there have been links found between oxidative status and duration of illness.[31] There is also evidence of a critical role of mitochondrial dysfunction in the underlying pathophysiology for BP.[31] One hypothesis suggests that BP involves a phasic dysregulation of mitochondrial bioenergetics, namely the inability to upregulate biogenesis in response to metabolic demands during depression, or to downregulate during mania.[32] Due to NAC's role in oxidative homeostasis, neurotransmission, and mitochondria restoration/ protection, it has been studied as a stand-alone or adjunct treatment for BP.

Several studies have examined the application of NAC in treating and preventing symptoms during the maintenance phase of BP.[33] In the first multicenter double-blind placebo-controlled (DBPC) study (n=75), the NAC group demonstrated a significant improvement on the Montgomery-Asberg Depression Scale (MADRS) and the Bipolar Depression Rating Scale (BDRS), compared to placebo. However, the study failed to demonstrate significant differences between the two groups in the frequency or latency to novel episodes of either depression or mania.[34] Subsequent studies conducted subgroup analyses in patients with BP. In one such study, (n=17) individuals who had experienced a major depressive episode at baseline demonstrated that NAC treatment significantly improved measures on symptom severity, functioning, quality of life, and response rate at the end of 24 weeks.[35] In a different study of patients with BP II (n=14), alterations were more pronounced for every outcome, including the Young Mania Rating Scale (YMRS) for the NAC group compared to the placebo.[36] Finally, another small subgroup analysis examined patients (n=15) with a manic or hypomanic episode at baseline and reported improvement in YMRS in the NAC group and

worsening of the BDRS in the placebo group. Additionally, more patients in the NAC group experienced complete remission, although it was not statistically significant.[37] Subsequent studies focused specifically on depressive symptoms of BP. A large 8-week open-label-run-in (n =149) to a DBPC trial focused on patients with BP and a recent depressive episode. Significant improvement in BDRS, functioning, and quality of life were reported in the NAC add-on to usual treatment group, compared to placebo,[38],[39] however the latency to a mood episode was not significantly different between the treatment and placebo group.[40] Taken together, there is evidence that NAC may be a safe and effective treatment for some of the symptoms associated with BP, yet further research is needed.

Depression

In a large, randomized trial (n=252), patients with major depressive disorder (MDD), and MADRS score ≥ 18, demonstrated improvement in multiple outcome measures in the NAC group compared to placebo add-on treatment to usual treatment for 12 weeks.[41] Additionally, in a case series of two patients with MDD, NAC augmentation revealed successful and sustained improvement of depressive symptoms.[42] Both patients had only partially responded to a trial of monoamine oxidase inhibitor (MAOI) tranylcypromine. The results suggest that NAC as an adjunctive treatment for depressive symptoms is effective for MDD, however more research is needed.

Schizophrenia

Similar to that of BP, there is increasing evidence that redox dysregulation and the resulting oxidative stress may play key roles in the pathophysiology of schizophrenia.[43] One known pathway resulting in redox dysregulation in schizophrenia is decreased levels of GSH. Given that the redox dysregulation model proposes that underlying factors in the pathophysiology of schizophrenia stem from the combined action of a GSH synthesis deficit of genetic origin, excessive oxidative stress from environmental factors during neurodevelopment, along with neuroinflammation and glutamatergic hypofunction, it is not surprising that NAC has been studied as an appropriate and effective treatment for schizophrenia.

In a large DBPC study (n=140), patients were randomized to receive either 2000mg NAC or placebo daily for the duration of the trial. The study reported significantly greater improvement in the NAC group in all qualitative measures, and some quantitative measures.[39],[44] In another small-sized DBPC study, the addition of NAC to risperidone for 8 weeks was examined, and significant improvement in the Positive and Negative Syndrome Scale (PANSS) negative and total scores were reported.[45] A case study on a 24-year-old woman with treatment-resistant schizophrenia reported that 0.6g/day of NAC for 7 days resulted in improvements in the PANSS and the Clinical Global Impression Scale (CGI-S).[46] A recent study examined the effects of 6-month NAC treatment on functional brain connectivity between regions of the cingulate cortex in patients with schizophrenia.[47] The brain areas were of interest, since they have been associated with positive symptoms and processing speed decline in patients with schizophrenia. In the pilot study, patients received either 2700 mg/day NAC (n=9) or placebo (n=11) and underwent a variety of neuroimaging tests at baseline and 6 months later. Increased functional connectivity along the cingulum, and more precisely between the caudal anterior part of the isthmus of the cingulate cortex, were observed in patients who received NAC. The researchers suggested that the changes could be due to NAC-induced increased brain glutathione levels, resulting in improved symptomatic expression and processing speed. Significant results from several studies suggest that NAC may be a safe and effective treatment for schizophrenia, however more research is needed.[47]

Autism

There have been several somewhat recent studies that have focused on NAC as a treatment for symptoms associated with autism. In a small-sized DBPC study (n=29), Aberrant Behavior Checklist Irritability (ABC-I) Subscale scores significantly decreased over the study period in the NAC group compared to the placebo group.[48] However, outcome on secondary measures was mixed. In another small DBPC study (n=40) patients who received NAC as add-on treatment to risperidone demonstrated a decrease in ABC-I compared to those who received placebo, yet they did not show a difference

in core autism symptoms.[49] Similar findings were observed in a 10-week small-sized DBPC study (n=40), where NAC adjunctive treatment to risperidone significantly improved irritability and hyperactivity subscales.[50] Only two case studies have reported improvements in core and associated autism symptoms with NAC treatment.[51],[52] The results suggest that NAC may be a promising treatment for irritability associated with autism, but that further research is needed to determine whether it is effective in treating core symptoms.

Addiction

Craving is considered a key clinical construct for assessment and treatment of substance use disorders (SUDs) in The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5).[53] Altered neurotransmitter pathways (mainly dopamine and glutamate) are heavily involved in drug seeking, elicited by cues and in craving, thus restoration of these glutamatergic and dopaminergic pathways are therapeutic targets for medication development.[7] Due to NAC's properties, it has potential as a medication for craving reduction. Animal studies have demonstrated that NAC serves as a source of cystine that promotes glutamate exchange through the cystine-glutamate antiporter in glial cells located within the nucleus accumbens.[54]

Overall, the evidence is limited for NAC as a treatment for addiction. While there have been several controlled studies for NAC on cocaine addiction with promising findings, the largest study was only positive for a small subset of participants. There have been some promising findings for cannabis as well, however these are limited due to inconsistent findings and study design approaches.[55] However, a recent review of seven randomized controlled trials (RCTs) (n=245) found that NAC was significantly superior to placebo for reducing cravings in several SUDs (e.g., methamphetamine, cocaine, nicotine).[56] This recent evidence suggests that NAC may be helpful at least in treating cravings related to SUDs. Further research is needed to fully elucidate the potential that NAC may have on specific addictions.

Alzheimer's Disease

In a DBPC trial (n=43), patients with probable Alzheimer's disease (AD) were treated with either 50mg/kg/day of NAC or placebo for 24 weeks. Those who had received NAC showed improvement in some, but not all cognitive testing.[57] A small, uncontrolled case-series (n=6) reported that 0.6g of NAC, in addition to other nutritional supplements, resulted in delayed decline in the Dementia Rating Scale (DRS) and the Clock Drawing Test (CLOX-1) and improvements in the Neuropsychiatric Inventory and AD Cooperative Study- Activities of Daily Living.[58] There have been other case reports of improvements on AD-related cognitive measures, however NAC was administered in conjunction with other supplements. Due to poor study designs and high drop-out rates, it has thus far been difficult to truly assess the efficacy of NAC in treating Alzheimer's disease, and future research with larger sample sizes is needed.

Other Psychiatric Disorders

NAC has been studied as a treatment for a variety of other mental disorders, such as anxiety, obsessive compulsive disorder, and attention deficit disorder with some promising findings, however the evidence remains inconclusive at this time, and further research is needed.

## Treatment for Neurological Disorders

Traumatic Brain Injury

NAC has been studied for the treatment of symptoms associated with traumatic brain injury (TBI), primarily because of its anti-inflammatory properties. In one DBPC study, 2g of NAC was administered within 24 hours of a blast-induced mild traumatic brain injury (mTBI) in a combat military population. NAC administration was associated with significant improvement in mTBI symptoms, neuropsychological testing results, and complete symptom resolution when compared to placebo.[59] There have been small studies or case studies that have examined the use of NAC in combination with other nutritional supplements and reported improvements in cognitive measures, etc., however more research is needed before we can understand the efficacy of NAC as a treatment for TBI.

Myoclonic Seizures

Given the role that NAC plays in the modulation of neurotransmission (e.g., glutamate), it has also been studied for the treatment of seizures in Unverricht-Lundborg Disease (ULD), a progressive, myoclonus epilepsy, however only in a handful of case studies. There has been conflicting evidence, where some report remarkable improvement in symptoms, and others observed partial or failed improvement with marked side effects. More research, and larger study designs with proper controls, are needed to better understand whether NAC is a beneficial and effective treatment for epilepsy.[7]

Summary

Taken together, NAC seems to demonstrate improvement in symptoms across a range of mental conditions, however the lack of large, controlled randomized trials makes it difficult to interpret its effectiveness or clinical application at this time. A recent review in 2015 by Deepmala and colleagues[33] was conducted to examine the most established evidence for the use of NAC for the treatment of mental conditions. A grade of recommendation (GOR) was assigned to each mental condition, based on the level of evidence (LOE) for each condition. Out of all the mental conditions, bipolar disorder is the only one that received an A. Evidence for traumatic brain injury, schizophrenia, autism, depressive disorder, and addiction received a B. Since the time of this review, there have been only a handful of case studies or pilot studies conducted on these disorders, and no large RCTs. For more information please refer to Table 1.

Table 1.

| Psychiatric/Neurologic Condition | Uncontrolled studies Positive% (positive/total) | Controlled studies Positive% (positive/total) | Grade Of Recommendation | Recommendation for treatment |
|---|---|---|---|---|
| Bipolar Disorder | 100% (1/1) | 50% (1/2) | A | Mixed |
| Addiction-cannabis | 50% (0.5/1) | 50% (0.5/1) | B | Mixed |
| Addiction-cocaine | 100% (1/1) | 50% (1.5/3) | B | Mixed |
| Addiction-methamphetamine | N/A | 25%(0.5/2) | B | No |
| Addiction- nicotine | N/A | 33% (2/6) | B | No |
| Alzheimer's disease | 100% (2/2) | 50% (0.5/1) | C | Mixed |
| Attention Deficit Disorder | N/A | 100% (1/1) | C | None |
| Autism | 100% (2/2) | 50% (1.5/3) | B | Mixed |
| Depressive disorder | 100% (1/1) | 50% (0.5/1) | B | Mixed |
| Epilepsy | 75%(3/4) | N/A | C | Mixed |
| Schizophrenia | 100% (1/1) | 50% (0.5/1) | B | Mixed |
| Obsessive Compulsive Disorder | 100% (1/1) | 75% (1.5/2) | B | Mixed |
| Traumatic Brain Injury | N/A | 100% (1/1) | B | None |

Legend: Grade of recommendation (GOR) for n-acetylcysteine (NAC) for a variety of mental health conditions by Deepmala et al. (2015), according to level of evidence.

## References


1. Arakawa M, Ito Y. N-acetylcysteine and neurodegenerative diseases: basic and clinical pharmacology. Cerebellum 2007;6(4):308–14.
2. Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci 2013;34(3):167–77.
3. LaRowe SD, Mardikian P, Malcolm R et al. Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. Am J Addict 2006;1(1);105–10.
4. Yarema MC, Johnson DW, Berlin RJ et al. Comparison of the 20-hour intravenous and 72-hour oral acetylcysteine protocols for the treatment of acute acetaminophen poisoning. Ann Emerg Med 2009;54(4):606–14.
5. Liu XH, Xu CY, Fan GH. Efficacy of N-acetylcysteine in preventing atrial fibrillation after cardiac surgery: a meta-analysis of published randomized controlled trials. BMC Cardiovasc Disord. 2014;14:52.
6. De Rosa S, Zaretsk, M, Dubs JG et al. N-acetylcysteine replenishes glutathione in HIV infection. Eur J Clin Investig 2000;30(10):915–29.
7. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci 2011;36(2):78–86.
8. Samuni Y, Goldstein S, Dean OM, Berk M. The chemistry and biological activities of N-acetylcysteine. Biochim Biophys Acta 2013;1830(8):4117–29.
9. Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of N-acetylcysteine: its reaction with hydrogen peroxide, hydroxyl radical, superoxide, and hypochlorous acid. Free Radic Biol Med 1989;6(6):593–7.
10. Holdiness MR. Clinical pharmokinetics of N-acetylcysteine. Clin Pharmacokinet 1991;20(2):123–34.
11. Lavoie S, Murray MM, Deppen P et al. Glutathione precursor, N-acetylcysteine, improves mismatch negativity in schizophrenia patients. Neuropsychopharmacology 2008;33(9):2187–99.
12. Neuwelt EA, Pagel MA, Hasler BP et al. Therapeutic efficacy of aortic administration of N-acetylcysteine as a chemoprotectant against bone marrow toxicity after intracarotid administration of alkylators, with or without glutathione depletion in a rat model. Cancer Res 2001;61(21):7868–74.
13. Xiong Y, Peterson PL, Lee CP. Effect of n-acetylcysteine on mitochondrial function following traumatic brain injury in rats. J Neurotrauma 1999;16(11):1067–82.
14. Polyak E, Ostrovsky J, Peng M et al. N-acetylcysteine and vitamin E rescue animal longevity and cellular oxidative stress in pre-clinical models of mitochondrial complex I disease. Mol Genet Metab;123(4):449–462.
15. Chen Q, Vazquez EJ, Moghaddas S, Hoppel CL, Lesnefsky EJ, Production of reactive oxygen species by mitochondria: central role of complex III. J Biol Chem 2003;278(38):36027–31.
16. Janaky R, Dohovics R, Saransaari P et al. Modulation of [3H] dopamine release by glutathione in mouse striatal slices. Neurochem Res 2007;32(8):1357–64.
17. Moran MM, McFarland K, Melendez RI et al. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. J Neurosci 2005;25(27):6389–93.
18. Ogita K, Kitago T, Nakamuta H et al. Glutathione-induced inhibition of Na+-independent and -dependent bindings of L-[3H] glutamate in rat brain. Life Sci 1986;39(25):2411–8.
19. Varga V, Jenei Z, Janaky R et al. Glutathione is an endogenous ligand of rat brain N-methyl-D-aspartate (NMDA) and 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors. Neurochem Res 1997;22(9):1165–71.
20. Hashimoto K, Tsukada H, Nishiyama S, et al. Effects of N-acetyl-L-cysteine on the reduction of brain dopamine transporters in monkey treated with methamphetamine. Ann N Y Acad Sci 2004;1025:231–5.
21. Monti DA, Zabrecky F, Kremens D et al. N-acetyl cysteine may support dopamine neurons in parkinson's disease: preliminary clinical and cell line data. PloS One 2016;11(6):e0157602.
22. Drexhage RC, Knijff EM, Padmos RC et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother 2010;10(1):59–76.
23. Dinan TG. Inflammatory markers in depression. Curr Opin Psychiatry 2009;22(1):32–6.
24. Nascimento MM, Suliman ME, Silva M et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: a placebo-controlled study. Perit Dial Int 2010;30(3):336–42.
25. Chen G, Shi J, Hu Z, Hang C. Inhibitory effect on cerebral inflammatory response following traumatic brain injury in rats: a potential neuroprotective mechanism of N-acetylcysteine. Mediators Inflamm 2008:716458.
26. Khan M, Sekhon B, Jatana M et al. Administration of N-acetylcysteine after focal cerebral ischemia protects brain and reduces inflammation in a rat model of experimental stroke. J Neurosci Res 2004;76(4):519–27.
27. Lante F, Meunier J, Guiramand J et al. Late N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation. Hippocampus 2008;18(6):602–9.

28. Voloboueva LA, Lee SW, Emery JF, Palmer TD, Giffard RG. Mitochondrial protection attenuates inflammation-induced impairment of neurogenesis in vitro and in vivo. J Neurosci 2010;30(37):12242–51.
29. Scaini G, Rezin GT, Carvalho AF et al. Mitochondrial dysfunction in bipolar disorder: evidence, pathophysiology and translational implications. Neurosci Biobehav Rev 2016;68:694–713.
30. Kunz M, Gama CS, Andreazza AC et al. Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2008;32(7):1677–81.
31. Morris G, Walder K, McGee SL et al. A model of the mitochondrial basis of bipolar disorder. Neurosci Biobehav Rev 2017;74(Pt A):1–20.
32. Andreazza AC, Kauer-Sant'anna M, Frey BN et al. Oxidative stress markers in bipolar disorder: a meta-analysis. J Affect Disord 2008;111(2–3):135–44.
33. Deepmala, Slaterry J, Kumar N, et al. Clinical trials of n-acetylcysteine in psychiatry and neurology: a systematic review. Neuroscience and Biobehavioral Reviews. 2015;55:294-321.
34. Berk M, Copolov DL, Dean O et al. N-acetyl cysteine for depressive symptoms in bipolar disorder–a double-blind randomized placebo-controlled trial. Biol Psychiatry 2008;64(6):468–75.
35. Magalhaes PV, Dean OM, Bush AI et al. N-acetylcysteine for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr 2011;33(4):374–8.
36. Magalhaes PV, Dean OM, Bush AI et al. N-acetyl cysteine add-on treatment for bipolar II disorder: a subgroup analysis of a randomized placebo-controlled trial. J Affect Disord 2011;129 (1–3):317–20.
37. Magalhaes PV, Dean OM, Bush AI et al. A preliminary investigation on the efficacy of N-acetyl cysteine for mania or hypomania. Aust NZ J Psychiatry 2013;47(6):564–8.
38. Berk M, Dean O, Cotton SM et al. The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. J Affect Disord 2011;135(1–3):389–94.
39. Berk M, Munib A, Dean O et al. Qualitative methods in early-phase drug trials: broadening the scope of data and methods from an RCT of N-acetylcysteine in schizophrenia. J Clin Psychiatry 2011;72(7):909–13.
40. Berk M, Dean OM, Cotton SM et al. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo-controlled trial. BMC Med 2012;10:91.
41. Berk M, Dean O, Cotton SM et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 2014;75(6):628–36.
42. Carvalho AF, Macedo DS, Goulia P, Hyphantis TN. N-acetylcysteine augmentation to tranylcypromine in treatment-resistant major depression. J Clin Psychopharmacol 2013;33(5): 719–20.
43. Steullet P, Cabungcal JH, Monin A et al. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: a "central hub" in schizophrenia pathophysiology? Schizophr Res 2016;176(1):41–51.
44. Berk M, Copolov D, Dean O et al. N-acetyl cysteine as a glutathione precursor for schizophrenia – a double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64(5):361–8.
45. Farokhnia M, Azarkolah A, Adinehfar F et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. Clin Neuropharmacol 2013;36(6):185–92.
46. Bulut M, Savas HA, Altindag A, Virit O, Dalkilic A. Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia. World J Biol Psychiatry 2009;10(4 Pt 2):626–8.
47. Mullier E, Roine T, Griffa A et al. N-acetyl-cysteine supplementation improves functional connectivity within the cingulate cortex in early psychosis: a pilot study. Int J Neuropsychoph. 2019;22(8):478–87.
48. Hardan AY, Fung LK, Libove RA et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. Biol Psychiatry 2012;71(11):956–61.
49. Ghanizadeh A, Moghimi-Sarani E. A randomized double-blind placebo-controlled clinical trial of N-acetylcysteine added to risperidone for treating autistic disorders. BMC Psychiatry 2013;13(1):196.
50. Nikoo M, Radnia H, Farokhnia M, Mohammadi MR, Akhondzadeh S. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. Clin Neuropharmacol 2015;38(1):11–7.
51. Ghanizadeh A, Derakhshan N. N-acetylcysteine for treatment of autism, a case report. J Res Med Sci 2012;17(10):985–7.
52. Marler S, Sanders KB, Veenstra-VanderWeele J. N-acetylcysteine as treatment for self-injurious behavior in a child with autism. J Child Adolesc Psychopharmacol 2014;24(4):231–4.
53. Sinha R, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacol 2011;218(1):69–82.

54. McClure EA, Gipson CD, Malcolm RJ et al. Potential role of N-acetylcysteine in the management of substance use disorders. CNS Drugs 2014;28(2):95–106

55. La Rowe SD, Kalivas PW, Nicholas, JS et al. A double-blind placebo-controlled trial of N-acetylcysteine in the treatment of cocaine dependence. Am J Addict 2013;22(5):443–52.

56. Duailibi MS, Cordeiro Q, Brietzke E et al. N-acetylcysteine in the treatment of craving in substance use disorders: systematic review and meta-analysis. Am J Addict 2017;26(7):660-6.

57. Adair JC, Knoefel JE, Morgan N. Controlled trial of N-acetylcysteine for patients with probable Alzheimer's disease. Neurology 2001;57(8):1515–7.

58. Remington R, Chan A, Paskavitz J, Shea TB. Efficacy of a vitamin/nutriceutical formulation for moderate-stage to later-stage Alzheimer's disease: a placebo-controlled pilot study. Am J Alzheimers Dis Other Demen 2009;24(1):27–33.

59. Hoffer ME, Balaban C, Slade MD, Tsao JW, Hoffer B. Amelioration of acute sequelae of blast-induced mild traumatic brain injury by N-acetylcysteine: a double-blind, placebo-controlled study. PLOS ONE 2013;8(1):e54163.