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N-acetylcysteine: A Review of Clinical Use and Efficacy

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Abstract

N-acetylcysteine (NAC) is a derivative of the amino acid cysteine and a precursor to glutathione, the master antioxidant of the body, which makes it an important compound in detoxification processes, and it is well known for its use as an antidote to paracetamol poisoning. NAC also has direct antioxidant as well as various anti-inflammatory effects, making it a useful supplement in inflammatory conditions. NAC has been extensively used for its mucolytic properties, and research has also demonstrated its ability to interrupt biofilms.

There is evidence for benefits of NAC in diverse conditions, including respiratory infections, various mental health disorders, male infertility and polycystic ovary syndrome.

NAC is generally well tolerated but has a few potential drug interactions, and caution is advised in some underlying conditions including gastrointestinal ulceration, bronchial asthma, liver and kidney failure.

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Introduction

N-acetylcysteine (NAC) is a derivative of the amino acid cysteine with an acetyl group (CH3CO) attached to its nitrogen atom.[1] Clinically, NAC is probably best known as an antidote to paracetamol (acetaminophen) poisoning, but it is also used for a large variety of other indications, based on its antioxidant, anti-inflammatory and mucolytic effects.[2]

NAC is available as a dietary supplement and as a licensed medicine, and can be administered orally, intravenously (IV) and by inhalation.[2] In the UK, NAC is licensed for IV use in paracetamol poisoning, as eye drops in tear deficiency, and orally as a mucolytic in adults with respiratory conditions such as chronic obstructive pulmonary disease (COPD).[3] There has been controversy over the classification of NAC as a licensed medicine or a supplement in the USA, and the US Food and Drug Administration (FDA) excluded NAC from the dietary supplement definition in 2020.[4]

The focus of this white paper is the use of NAC as a dietary supplement and, unless otherwise stated, refers to an oral administration.

NAC is readily absorbed in the gastrointestinal tract, but there are contradictory research findings as to whether NAC can cross cell membranes and the blood–brain barrier directly or whether it crosses as cysteine after de-acetylation.[1]

General effects

Antioxidant

NAC contains a thiol (sulfhydryl, -SH) group that can interact with reactive oxygen species (ROS; highly reactive and therefore potentially damaging molecules).[5] However, its most important antioxidant effect is thought to be as a precursor for glutathione (GSH),[6] a tripeptide made from the amino acids glutamate, glycine and cysteine, and the body's major antioxidant. Of the three amino acids, cysteine has the lowest concentration within cells and can therefore be rate-limiting for GSH synthesis.[5] Many of the clinical benefits of NAC are based on its ability to correct or prevent GSH depletion.[2]

A 2020 meta-analysis pooled data from 12 randomised-controlled trials (RCTs) looking at the effect of NAC on biomarkers of oxidative stress, and found a significant decrease in malondialdehyde (a marker of oxidative stress)[7]. Dosages used in the studies ranged from 400 to 2000 mg per day.

A number of studies looking at various clinical benefits have also looked at the effect of NAC on GSH levels, and found increases in blood cell GSH following NAC administration.[8,9,10,11,12,13]

Anti-inflammatory

Oxidative stress plays an important role in inflammation, so the antioxidant effects of NAC confer anti-inflammatory benefits. But NAC also appears to modulate inflammation through other mechanisms, including inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB; a protein complex involved in inflammation) and pro-inflammatory cytokines.[5,14]

Many clinical trials have reported levels of anti-inflammatory markers that were summarised by two recent meta-analyses. Whilst one meta-analysis of 24 RCTs found a decrease in the pro-inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6),[15] the other (based on 28 studies) found a decrease in interleukin-8 (IL-8) when pooling all data and a decrease in IL-6 in a subset of studies using a dose of 1200 mg NAC per day or less, but no difference in CRP.[7] Dosages used in the studies ranged from 400 to 2000 mg per day.

Detoxification

The effectiveness of NAC as an antidote to paracetamol poisoning is based on its ability to restore GSH levels in the liver and to act as an alternative substrate for conjugation of toxic paracetamol metabolites.[16] GSH is also essential

for detoxifying toxic substances, including xenobiotics (chemicals foreign to the body) and heavy metals and, by increasing GSH levels, NAC is thought to play an important role in detoxification in general.[2]

Mucolytic

NAC has been used for its mucolytic (mucus-thinning) properties for decades. A number of mechanisms appear to contribute to the mucolytic and mucoregulatory benefits of NAC, including directly breaking disulphide bonds between the molecules forming the mucus with its thiol groups and reducing mucus production through its antioxidant effects (oxidative stress has been shown to increase mucus production).[17]

Biofilms

NAC has attracted interest for its potential to disrupt biofilms through its mucolytic properties.[18] A biofilm is an aggregate of bacteria in an extracellular mucus-like matrix that adheres to a surface. These biofilms can play an important role in infections as they protect pathogenic bacteria from antibacterial substances.[18] NAC has also been shown to have direct antibacterial effects, adding to its biofilm-disrupting potential.[19]

Clinical uses

Alzheimer's disease/cognitive function

Oxidative stress has been implicated in neurodegenerative conditions and impaired cognitive function and, in animal models, NAC has been shown to have a beneficial effect on cognitive function.[20]

There is one early blinded, placebo-controlled trial of NAC on its own in 43 patients with Alzheimer's disease that found NAC, 50 mg per kg bodyweight (equivalent to 3750 mg for a person weighing 75 kg) per day for 6 months, to be superior to placebo in almost all outcome measures, although not all reached statistical significance.[21] Three clinical trials, one open-label and uncontrolled,[22] one open-label and placebo controlled,[23] and one double-blind and placebo controlled,[24] investigated a multi-nutrient formulation containing NAC 1200 mg per day (other nutrients: folate, vitamin B12, alpha-tocopherol, S-adenosyl methionine and acetyl-L-carnitine) for 3–12 months in patients with Alzheimer's disease, and found significant benefits in Dementia Rating Scale and clock-drawing tests as well as in assessments by caregivers in those receiving the multi-nutrient supplement versus placebo or versus baseline.

A double-blind, placebo-controlled trial in frail elderly people without cognitive impairment found significant improvements in cognition from baseline with NAC, 1800 mg per day for 6 weeks, whilst there were no improvements in the placebo group.[25] However, the difference between the NAC and the placebo group failed to reach statistical significance. Both groups also underwent the same exercise programme.

A 2020 meta-analysis evaluated the effects of NAC on cognitive function in patients with schizophrenia.[26] Three out of the five RCTs reviewed in this meta-analysis showed improvements in at least one cognitive function outcome measure, and pooled data from three trials showed a significant improvement in working memory, whilst improvements in processing speed failed to reach statistical significance. Trials that showed benefits used dosages between 1200 and 2700 mg per day for 12–24 weeks.

One double-blind, placebo-controlled trial that investigated the effects of NAC, 2000 mg per day for 6 months, on cognition in patients with bipolar disorder (BD) found no improvements in cognitive function.[27]

Whilst evidence is limited in Alzheimer's disease, due to lack of clinical trials using NAC on its own, it is overall in favour of benefits with a dose of at least 1200 mg per day, and ideally as part of a multi-nutrient approach. NAC also appears to improve some aspects of cognition in patients with schizophrenia with a dose of at least 1200 mg per day.

Exercise performance

Intensive or prolonged exercise can result in excessive production of ROS and oxidative damage in muscles.[28] The potential benefits of antioxidants, including NAC, have therefore been studied in sports nutrition.

In 2017, a meta-analysis of seven RCTs (86 participants) found no benefits of NAC supplementation on exercise performance.[29] Since then another two small double-blind, placebo-controlled studies confirmed these results.[30,31] It is important to note that all studies were very small (maximum 18 participants), and looked at acute or short-term (up to 9 days) supplementation. A study published in 2018 established baseline GSH levels, and found that those with low GSH status at baseline also had lower physical performance, increased oxidative stress and impaired redox metabolism of erythrocytes at baseline compared with those with medium or high levels.[32] The low GSH group, but not the other two groups, experienced improved exercise performance, improved GSH status and oxidative stress with NAC 1200 mg per day for 30 days compared with placebo.

Several earlier small studies investigated NAC for other aspects of exercise physiology with mixed results,[33,34] although two studies found improvements in muscle fatigue with acute or short-term (7 days) NAC supplementation.[35,36]

Overall, the evidence does not support a benefit of NAC to enhance exercise performance, although it needs to be stressed that all studies were very small and either acute or short-term. There may be benefits for people with low GSH status at baseline.

Heavy metal toxicity

In vitro and animal studies have shown the potential of NAC to chelate (bind) and detoxify heavy metals,[37] but only a few human clinical studies have investigated NAC in heavy metal toxicity.

Gold-based drugs are sometimes used in the treatment of rheumatoid arthritis, and can cause serious side-effects. An early study compared excretion of gold through urine in 40 such patients with or without NAC, a single dose of 3000 mg by IV infusion over 6 hours, and found a 54% increase in excretion in the NAC group.[38] The same article also reports two cases with severe gold-induced bone marrow suppression who received 3000–6000 mg per day IV for 7 days and made a progressive recovery over 2 weeks.

Lead binds to thiol groups, and may therefore inactivate GSH as well as other enzymes with functional thiol groups, and has been shown to increase homocysteine levels (see below for homocysteine).[39] A RCT, including 171 workers occupationally exposed to lead, evaluated the effects of three different daily dosages of NAC, 200 mg, 400 mg or 800 mg, compared with no intervention, for 12 weeks.[39] Blood lead levels significantly decreased in all three NAC groups compared with no treatment, with no apparent effect of dose. Homocysteine levels, which were elevated at baseline, and protein carbonyl groups (a marker of oxidative stress) decreased in a dose-dependent way, with a 37% reduction of homocysteine and a 23% reduction of protein carbonyl groups with 800 mg per day.

Whilst evidence from clinical trials is limited, NAC promises to be effective at increasing heavy metal excretion, with a dose of 800 mg per day sufficient to lower blood levels of lead in exposed workers.

Helicobacter pylori eradication

Helicobacter pylori (H. pylori) is a bacterium that causes 70–80% of gastric and 95% of duodenal ulcers, and is also associated with acute and chronic gastritis and gastric cancer.[40] Usual treatment is based on triple therapy with two antibiotics and a proton pump inhibitor (PPI). However, there is a 10–20% treatment failure rate, at least in part due to antibiotic resistance. Research has shown that *H. pylori* forms a biofilm, which may prevent the antibiotics

from reaching the bacteria, and NAC, with its ability to disrupt biofilms, has therefore been investigated in a number of clinical trials alongside standard therapy.[18]

A 2019 Cochrane review of eight RCTs of NAC alongside standard treatment versus standard treatment alone or standard treatment with placebo[41] found that when pooling data from all studies, the improvement in eradication rates failed to reach statistical significance, but when only data from those five RCTs that used current eradication regimens (triple therapy in four RCTs; PPI, one antibiotic and bismuth subcitrate in the remaining study) were pooled, there was a significant 29% increase in eradication rate with the addition of NAC. Most trials in this meta-analysis used NAC, 1200 mg per day, one used 600 mg per day, and one used 1800 mg per day. The study with the highest dose found no significant beneficial effect of NAC.

In 2020 another open-label RCT of triple therapy with or without NAC, 1200 mg per day, was published, and reported that addition of NAC did not improve eradication rates.[42]

Whilst the evidence from clinical trials is mixed, overall there appears to be a benefit of NAC at a dose of 1200 mg per day alongside triple therapy.

Hyperhomocysteinemia

Elevated plasma levels of homocysteine is an independent risk factor for cardiovascular disease, as well as other chronic degenerative conditions. Homocysteine is a thiol-containing compound, 75–80% of which is bound to albumin (a blood protein). This bond can be broken by NAC and the homocysteine replaced by NAC, thus increasing free homocysteine and its clearance through the kidneys.[43,44]

A couple of uncontrolled studies in healthy volunteers showed significant homocysteine-lowering effects of acute administration of NAC, 7200 mg within 24 hours,[45] and 1200–4000 mg once,[44] with average reductions of 44% and 22%, respectively.

Beneficial homocysteine-lowering effects of NAC have also been found in a number of longer-term RCTs, with mean reductions in the range of 10–45%, depending on baseline level, patient population and dosage.[39,43,46,47,48] Dosages used have ranged from 800 to 2000 mg per day in longer-term studies (2–12 weeks), with the highest dose seeing the largest reductions in homocysteine.[48] Studies comparing different dosages also found a dose-dependent increase in reduction of homocysteine levels with increasing dose.[39,44,47] In one crossover study,[47] homocysteine levels returned to baseline when NAC was stopped for the 1-month washout period, suggesting that effects are immediate and that NAC may need to be taken continuously to help maintain homocysteine levels.

As results from clinical trials have consistently shown a homocysteine-lowering effect, NAC at a dose of at least 800 mg per day could be recommended to people with elevated homocysteine levels.

Male subfertility

Infertile men have been shown to have higher levels of ROS in semen than fertile men, and ROS have been implicated in sperm dysfunction and male infertility.[49]

Three clinical trials found significant improvements in sperm quality following supplementation with NAC, 600 mg per day, for 3–6 months. A double-blind placebo-controlled trial of NAC versus selenium versus selenium plus NAC versus placebo found significant improvements in all semen parameters with both NAC and selenium trialled singly, and additive effects when both were used together.[50] An increase of testosterone, which was associated with a decrease in luteinising hormone (LH) and follicle-stimulating hormone (FSH), was also observed with NAC and selenium, individually

and combined, in this study. Elevated levels of FSH and LH are associated with male infertility.[51] Whilst mean baseline levels for FSH and LH in study participants were within normal range, median levels were borderline high, suggesting that a considerable number of participants may have had elevated levels of LH and/or FSH.[50] Another RCT reported significant improvements in volume, motility and viscosity of semen, plasma total antioxidant capacity (TAC) and oxidative stress, but not sperm count or morphology with NAC compared with placebo.[52] An open-label, uncontrolled trial saw significant improvements in sperm motility, count, morphology and DNA fragmentation, testosterone, LH, FSH, TAC and oxidative stress.[49]

Based on the results from the above studies, the two mechanisms by which NAC may improve male fertility are thought to be its antioxidant effects as well as effects on the hypothalamus–pituitary–gonadal axis, normalising sex hormone levels.[50,52]

The evidence from the three clinical trials on NAC and male fertility suggests that 600 mg per day for 3–6 months is effective in improving sperm and semen quality, hormone levels and antioxidant status.

Non-alcoholic steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) is characterised by excessive fat accumulation in the liver, and is associated with insulin resistance, oxidative stress and inflammation. NAFLD develops in four stages, steatosis (simply a fatty liver that is thought to be largely harmless), non-alcoholic steatohepatitis (NASH; where the liver has become inflamed), fibrosis (with the formation of scar tissue) and finally cirrhosis (permanent damage that can lead to liver failure and cancer).[53] In preclinical models of NAFLD, NAC has been shown to block fat accumulation in the liver.[54]

Four open-label clinical trials have been conducted into the potential benefits of NAC in NASH: one 4-week trial of NAC, 600 mg per day, versus no treatment, found statistically significant improvements in alanine aminotransferase (ALT; a liver enzyme and marker of liver damage) in both groups, and significant improvements in aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) in the NAC group only.[55] However, the authors did not interpret this as evidence for therapeutic effects of NAC but of the fluctuating course of the biochemical parameters in NASH. A 3-month RCT of NAC, 1200 mg per day, versus vitamin C, 2000 mg per day, found significant improvements in ALT and spleen span, but not other liver enzymes or liver span with NAC, whilst improvements in steatosis grade failed to reach statistical significance.[56] Two longer-term studies, 48 and 52 weeks, respectively, found significant improvements in NAFLD/NASH activity score with NAC, 1200 mg per day, together with metformin.[57,58] The 52-week study also found improvements in a number of biochemical parameters, including glycaemic control and liver enzymes.[58]

The benefits of NAC in NAFLD are thought to be due to its antioxidant and anti-inflammatory properties with an attenuation of lipid peroxidation.[54]

Based on the above studies, NAC, at a dose of 1200 mg per day, appears to have benefits in patients with NASH, with treatment durations of 48 weeks or more and in combination with metformin.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects about 1 in 10 women, and is characterised by enlarged ovaries that contain many fluid-filled sacs (follicles) that surround the eggs, excess testosterone and irregular periods. One of the underlying causes of PCOS is thought to be insulin resistance.[59]

Fertility is commonly affected by PCOS, due to lack of ovulation, and first-line treatment for anovulation in women with PCOS is usually

clomiphene citrate (CC), but some women do not respond to this treatment (CC-resistant).[60] Fertility in PCOS has been subject to more than 10 clinical trials on the potential benefits of NAC.

In 2015, a review and meta-analysis of eight studies, including 910 women with PCOS, found that NAC increased ovulation (four trials), pregnancy (three trials) and live birth (one trial) rate by more than three times compared with placebo.[60] There was no difference in miscarriage, menstrual regulation, acne, hirsutism, change in body mass index, testosterone and insulin levels between NAC and placebo. There was also no difference in adverse effects reported and no reports of ovarian hyper-stimulation syndrome, a potentially life-threatening condition associated with drugs stimulating ovulation.[60]

Since then, several more RCTs have found that NAC, when used alongside CC or letrozole, another ovulation-stimulating drug, increased pregnancy and ovulation rates versus placebo,[61] or was as good or better than metformin[62,63,64] or L-carnitine.[65] Regimens used in these studies were 1200–1800 mg per day on days 3–7 of the menstrual cycle, for two–three cycles.

NAC has also shown benefits in improving oocyte quality and/or sex hormone levels in candidates undergoing intracytoplasmic sperm injection (ICSI).[64,66,67] The regimen used in these trials was 1800 mg per day from day 3 of the menstrual cycle to oocyte aspiration (approximately 6 weeks).

In one trial of candidates for intrauterine insemination with NAC, 1200 mg per day on days 3–7 of the menstrual cycle, improvements in number of mature follicles and pregnancy rates failed to reach statistical significance.[68]

NAC, at a dose of 1800 mg per day, has also been shown to improve glycaemic control, lipid profiles and/or oxidative stress/TAC in women with PCOS in some of the fertility studies above,[62,64,65,67] as well as in two longer-term studies of 24 weeks continuous supplementation.[69,70]

A number of possible mechanisms for the role of NAC in PCOS have been discussed in the literature. Increased intracellular GSH levels can influence insulin receptor activity thereby increasing insulin sensitivity, which in turn balances insulin and testosterone levels with a positive effect ovulation.[62] The antioxidant effects of NAC may also be responsible for the endometrial thickening observed in some trials.[63] The mucolytic action of NAC is thought to counteract the negative effects of CC on cervical mucus.[62]

Overall, the evidence shows that NAC, at a dose of 1800 mg per day on days 3–7 of the menstrual cycle, is beneficial as an add-on for women with PCOS who are undergoing fertility treatment with an ovulation-stimulating drug, such as CC. At that dose, NAC has also been shown to improve glycaemic control, hormone levels and antioxidant status in this patient group, and longer-term supplementation may therefore be beneficial.

Psychiatric disorders

Many psychiatric disorders are associated with oxidative stress, reduced antioxidant capacity and inflammation. NAC may influence inflammation directly or via its antioxidant properties, and animal studies have shown increased GSH levels in the brain following NAC administration.[71] NAC also appears to have a balancing effect on neurotransmitter dysregulation, in particular glutamate homeostasis.[71] Glutamate is the main neurotransmitter in the central nervous system, and extracellular glutamate levels are maintained by the exchange of extracellular cysteine for intracellular glutamate.[72]

Addiction

Substance use disorders (SUDs) are a major health issue, accounting for 14.5% of disability-adjusted life years according to the Global Burden of Disease Study, 2010.[72]

A 2021 meta-analysis of 16 RCTs, involving 987 patients with SUDs, found a significant decrease in craving symptoms and a significant improvement in depressive and withdrawal symptoms with NAC compared with control, whilst lower smoking frequency failed to reach statistical significance.[72] The authors reported that there was no difference in adverse events (AEs) between the NAC and control groups. Another meta-analysis of seven double-blind, placebo-controlled trials on the effect of NAC on craving specifically also found a significant reduction in craving symptoms.[73] Most individual studies were small, less than 50 participants, but there was not much heterogeneity. Dosages used ranged from 1200 to 3000 mg per day for 4 weeks to 14 months, or from 2400 to 3600 mg for short-term use (3–4 days).

A small pilot study investigated the effect of NAC on pathological gambling.[74] There was a reduction in the Yale Brown Obsessive Compulsive Scale Modified for Pathological Gambling (PG-YBO) score from a mean of 20.3 at baseline to 11.8 at the end of an 8-week open-label phase where participants received NAC, starting with 600 mg per day and increasing to up to 1800 mg per day, depending on their response. Almost 60% of subjects responded to treatment, and 13 responders were enrolled into a double-blind, placebo-controlled extension where they received either NAC, at the highest dose they had received in the open-label part of the study, or placebo. A further improvement was seen during the extension in those receiving NAC, although this failed to reach statistical significance compared with placebo, possibly due to the small numbers or due to the initial improvement being a placebo effect.

The evidence from clinical trials shows consistently that NAC can support substance use cessation, with dosages of 1200–3000 mg per day longer term. Although based on only one study, NAC could also be trialled in pathological gambling, which has similar pathophysiological mechanisms as other addictions.

Addictive behaviours have been linked to glutamate dysregulation, and the benefits of NAC are thought to be mediated by its effect on glutamate homeostasis.[72]

Autism and attention deficit hyperactivity disorder (ADHD)

The two main symptoms of autism spectrum disorder (ASD) are a deficit in social communication and/or interaction and repetitive behaviours and/or restricted interests. Dysregulation of glutamate and GABA balance and oxidative stress with a reduction in intracellular GSH are thought to be involved in the development of ASD, making NAC a prime candidate for treatment.[75]

Five RCTs have been conducted in children with ASD, and these have been summarised and evaluated in a 2021 meta-analysis. Three of the reviewed studies found significant improvements in ASD assessment scales,[76,77,78] the other two did not.[13,79] The results of the pooled data show a significant improvement with NAC in the Aberrant Behaviour Checklist (based on four studies), whilst no improvement was seen in the Repetitive Behaviour Scale (two studies), and improvements in the Social Responsiveness Scale (two studies) failed to reach statistical significance. The dosages used in the RCTs that showed benefits ranged from 600 to 2700 mg per day for 4–12 weeks.

One of the studies evaluated GSH levels and found a significant increase in blood GSH levels in the patients receiving NAC, although this study did not find significant improvements in behavioural outcomes.[13]

Although results from the five studies are mixed, the overall evidence suggests a possible benefit of NAC in children with ASD, at a dose of at least 600 mg per day for at least 8 weeks. In most studies, NAC was used alongside medication, such as risperidone.

Only one study has investigated ADHD in patients with systemic lupus erythematosus, and found NAC, at dosages of 2400 and 4800 mg per day for 3 months, to be effective in reducing ADHD scores, with a trend to the higher dose being more effective.[80] As this was quite a specific patient group, it is not possible to extrapolate these findings to the wider ADHD patient population.

Bipolar disorder

Bipolar disorder (BD) is a common psychiatric disorder, characterised by alternating depressive and manic moods, and can be a significant cause of disability and morbidity.[81] Current pharmacological treatments tend to be less effective in the depressive than the manic phase.[81] BD is associated with a dysregulation of the glutamate neurotransmitter system and with oxidative stress, and NAC has therefore received interest as an adjunct to standard treatment of depressive symptoms in BD.[82]

There are seven RCTs for the use of NAC in BD, which have been evaluated in three meta-analyses. Whilst one meta-analysis of five RCTs found no significant improvements in any of the BD scores,[81] another meta-analysis of six studies found a significant effect of NAC on Clinical Global Impression-Severity Scale (CGI-S) score, but not any other scores.[83] The third meta-analysis of six studies combined data from different scales used to assess depressive symptoms, and found a moderate but statistically significant improvement with NAC.[82] Five out of the seven studies showed some positive results, but there was significant heterogeneity between individual study results that was not explained by NAC dose, duration of treatment or severity of depressive symptoms at baseline.[82] All studies had fairly small sample sizes, the largest including 120 patients. Dosages used in trials showing beneficial effects ranged from 1000 to 2000 mg per day for 10–24 weeks.

A small open-label pilot study investigated the effects of NAC, 2400 mg per day for 8 weeks, in 15–24 year olds with depression and an increased risk of developing BD (parent with BD).[84] There were significant improvements in depressive and anxiety symptoms and CGI-S. Proton magnetic resonance spectroscopy also showed a decrease in glutamate in the left ventrolateral prefrontal cortex, although these findings were not statistically significant.

Whilst results from clinical trials are mixed, the overall evidence suggests a possible benefit of NAC in BD at dosages of 1000–2000 mg per day for at least 10 weeks.

Depression

Four double-blind, placebo-controlled trials have looked at the potential benefits of NAC in depression, other than BD.

One evaluated the benefits of NAC, 2000 mg per day for 12 weeks, with a follow-up visit after another 4 weeks, in patients with major depressive disorder (MDD).[85] Improvements seen at 12 weeks in the NAC groups were not significantly better than in the placebo group, although some secondary outcomes were significantly better in the NAC group at 16 weeks. Inflammatory markers were also evaluated in this study, but no improvements were observed in IL-6, CRP or brain-derived neurotrophic factor.[86]

Another study in patients with BD or MDD found significant improvements in depression and anxiety scales after 12 weeks on NAC, 1800 mg per day, compared with placebo; however, data for patients with MDD only were not reported in the article.[87]

A trial in patients with trichotillomania (hair pulling, see also below under obsessive compulsive disorders) found a clinically significant improvement in depressive symptoms in 44% of patients, compared with 4% in the placebo group, a statistically significant difference.[88] Patients received NAC, 1200–2400 mg per day, or placebo for 12 weeks in this trial.

In a smoking cessation study, depressive symptoms also significantly improved by 43% in patients receiving NAC, 3000 mg per day for 12 weeks, versus 11% in the placebo group.[89]

A double-blind, placebo-controlled study in veterans with post-traumatic stress disorder (PTSD) and SUD found a 48% decrease in depressive symptoms and a 32% decrease in self-reported PTSD symptoms, results that were significantly better than placebo (15% and 3%, respectively).[90] The dose used in this study was 2400 mg per day for 8 weeks, with significant improvements noted from week 3. Another study in PTSD is currently ongoing.[91]

Evidence in patients with depression without concomitant other psychiatric disorders is limited, but NAC appears to improve depressive symptoms associated with other disorders, including BD, trichotillomania, tobacco addiction and PTSD.

As with BD, the underlying mechanisms are thought to be the antioxidant properties and regulating effect of NAC on glutamate homeostasis.[92]

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD) is a common mental health disorder characterised by obsessive thoughts and compulsive behaviours. The neurotransmitter serotonin appears to play a role in the condition, but only about half of patients respond to treatment with selective serotonin reuptake inhibitors, suggesting that other mechanisms are also present.[93] Glutamatergic hyperactivity with its ensuing excitotoxicity and oxidative stress are also thought to play a role, making NAC a potential treatment option.[93]

A 2018 review and meta-analysis of five double-blind, placebo-controlled trials of NAC in OCD found that pooled data of four studies just failed to reach statistical significance for improvements in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[93] Three of the individual studies found significant improvements in Y-BOCS whilst two did not, although the latter two studies found improvements in anxiety or compulsion subscales. NAC dosages in those studies that saw benefits in Y-BOCS score ranged from 2000 to 2400 mg per day for 10–12 weeks.

A small double-blind pilot study of 11 children with OCD, aged 8–17 years, found a significant 33% reduction in the children's Y-BOCS score compared with placebo.[94] Children received 900 mg per day in the first week, 1800 mg per day in the second week and 2700 mg per day from week 3.

NAC has also been investigated in specific OCDs, including trichotillomania (hair pulling) and skin picking disorder (SPD), which can lead to serious skin infections.

A double-blind, placebo-controlled trial in adults with trichotillomania showed a significant 56% reduction in hair pulling with NAC, 1200 mg per day for 6 weeks followed by 2400 mg per day for another 6 weeks, compared with a 16% reduction in the placebo group, with improvements noticeable from 9 weeks.[88] A study in children with trichotillomania by the same team, however, found no benefits of NAC at a dose titrated from 600 mg per day to 2400 mg per day, study duration 12 weeks.[95]

A number of case reports have also been published in the literature reporting benefits in both children[96,97] and adults with trichotillomania.[96,98,99]

A double-blind, placebo-controlled trial in adults with SPD found a 39% improvement with NAC compared with placebo (21% improvement).[100] Forty-seven percent of patients in the NAC group were "much or very much improved", compared with 19% in the placebo group. Both results were statistically significantly better in the NAC group. NAC dose was titrated from 1200 mg per day to 3000 mg per day, and duration of the trial was 12 weeks. An open-label study in adult and paediatric patients with Prader-Willi syndrome (a rare genetic disorder that causes a range of

physical symptoms, learning difficulties and behavioural problems, including obsessive compulsive symptoms) and SPD also found significant benefits of NAC, 450–1200 mg per day for 12 weeks, with 25 out of 35 patients having a complete resolution of skin lesions, and the remaining 10 participants had significant improvements.[101]

A number of case reports in both adults[102,103] and children[104] have also shown benefits of NAC in skin picking. Two of these case series suggest that dosage may be of importance, with individual differences and higher doses more effective than lower ones where dose was titrated up (dosage ranges 600–1800 mg per day).[102,104] These case series also suggest that ongoing treatment may be necessary to maintain remission.[102]

One double-blind, placebo-controlled trial evaluated NAC in children and adolescents with Tourette syndrome ("tics"), which is commonly associated with OCD, but found no benefit of 2400 mg per day for 12 weeks versus placebo.[105]

Although evidence is mixed, overall the research suggests a benefit of NAC in OCDs, including trichotillomania and SPD. Dosage may need to be established for the individual, for example, starting with 600 or 1200 mg per day and titrating up to 2400 mg per day if necessary. Results have been seen from 8 weeks of supplementation.

Schizophrenia

Schizophrenia is a severe chronic psychiatric condition with symptoms including hallucinations, delusions and cognitive impairment. A key molecular target for treatment of schizophrenia is the N-methyl-D-aspartate (NMDA) receptor, a glutamate receptor and ion channel in neurons, which appears to be modulated by NAC.[106] Schizophrenia has also been associated with oxidative stress and reduced GSH levels in the brain.[26]

A 2020 meta-analysis of seven RCTs, including 440 patients with schizophrenia, found a significant improvement in Positive and Negative Syndrome Scale (PANSS) total and negative scale with NAC supplementation, especially in trials of 24 weeks or longer duration.[26] Working memory also improved in those on NAC versus controls. Dosages used in the reviewed studies ranged from 600 to 3600 mg per day for 8 weeks to 1 year, with studies using dosages of 1000–2000 mg per day showing the best responses. An open-label, uncontrolled study using 1200 mg per day for 8 weeks also found significant improvements in negative symptoms and CGI-S.[107]

Three small double-blind trials have looked at the effects of NAC on electroencephalogram (EEG) measures in patients with schizophrenia, and found significant improvements after 8 weeks with dosages of 2000–2400 mg per day.[106,108,109] It is thought that these EEG improvements may precede clinical improvements.[108]

A couple of recent double-blind, placebo-controlled, crossover studies using magnetic resonance imaging of the brain also showed significant beneficial changes with acute, single-dose (2400 mg) administration of NAC.[110,111]

Whilst duration of NAC supplementation appears to be important, another potential cause for some of the heterogeneity observed in clinical trials may be the length of time patients have been suffering from schizophrenia, with those with a history of schizophrenia for 20 years or more responding best to NAC.[112]

Overall, the evidence is in favour of a benefit of NAC for patients with schizophrenia, with most trials using a dose of 1200–2000 mg per day, and durations of at least 24 weeks appear to be necessary to see positive results.

Respiratory conditions

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterised by breathing difficulties, and includes chronic bronchitis and emphysema. It is a major cause of morbidity and mortality worldwide, especially in elderly people.[113] COPD is associated with an abnormal inflammatory response in the lungs, and with excessive mucus production and reduced mucus clearance.[113] Due to its mucolytic, anti-inflammatory and antioxidant properties, NAC is commonly used in COPD.[113]

Three meta-analyses covering 11, 12 and 13 RCTs, respectively, all found a beneficial effect of NAC in reducing the number of exacerbations by 10–25%.[113,114,115] Dosages in the included studies ranged from 260 to 1800 mg per day, with both high (> 600 mg per day) and low doses (≤ 600 mg per day) being effective. Duration of studies ranged from 3 months to 3 years, and one study found that significant benefits were only seen with a duration of at least 6 months.[113] All three meta-analyses reported that there was no increased risk of AEs with NAC compared with control.

The overall evidence is in favour of the use of NAC in COPD, and NAC is licensed in many countries as a mucolytic for patients with COPD and other airway diseases, such as cystic fibrosis.[3,116] The most commonly used dose is 600 mg per day, and long-term use is recommended.

Respiratory infections

In addition to its mucolytic, antioxidant and anti-inflammatory properties, the potential of NAC to disrupt biofilms is thought to be of benefit in acute respiratory infections.[19] Although evidence from clinical trials for its benefits is limited, NAC is commonly used in respiratory infections.

A Cochrane review from 2013 pooled data from six RCTs of NAC or carbocysteine (another mucolytic) in children with respiratory infections and found some benefit, although it was deemed to be of limited clinical relevance.[117] Only three of the studies included in this review were on NAC, but data were not divided into the separate compounds and there is no public access to the original studies that were published in 1972 and 1989, making it difficult to assess the use of NAC in this context.

A study of 120 hospitalised children with bronchopneumonia evaluated inhaled NAC versus ambroxol (another mucolytic drug), and found NAC to be superior to ambroxol, with faster recovery, shorter hospital stay and less AEs in the children receiving NAC.[118]

In a double-blind, placebo-controlled trial of 60 mechanically ventilated patients at high risk of developing ventilator-associated pneumonia (VAP), NAC significantly reduced the risk of VAP versus placebo, 26.6% versus 46.6%, and shortened intensive care unit (ICU) stay (14.4 versus 17.8 days) and hospital stay (19.2 versus 24.6 days).[119] Patients received NAC, 1200 mg per day, or placebo by nasogastric tube.

NAC also appears to be of benefit in preventing influenza. A double-blind, placebo-controlled trial of 262 subjects who were either younger than 65 years and had a chronic degenerative disease or over 65 years with or without chronic disease, but without chronic respiratory disease, received NAC, 1200 mg per day, or placebo for 6 months.[120] Participants who received NAC had a significant decrease in flu-like episodes, severity of illness and length of time confined to bed.

Although evidence from clinical trials is limited, NAC appears to be of benefit in a variety of contexts for treatment or prevention of respiratory infections, at a dose of 1200 mg per day orally (or by nasogastric tube), or as inhalation.

COVID-19

In view of the benefits of NAC in other types of respiratory illnesses and its possible ability to

stop a cytokine storm,[121] it has received much attention in the treatment of COVID-19.

In the context of the COVID-19 pandemic, a review evaluated the effectiveness of NAC in acute respiratory distress syndrome and acute lung injury, conditions similar to signs and symptoms of severe COVID-19.[122] The authors concluded that NAC may improve markers of inflammation or oxidation, systemic oxygenation, the need for/duration of ventilation, rate of patient recovery and clinical improvement score, whilst effects on length of stay, CT/x-ray images, mortality rate and pulmonary complications were inconclusive. NAC was mostly administered IV in an ICU setting.

A number of case reports and series of COVID-19 patients requiring mechanical ventilation have shown significant benefits in most patients.[121,123,124] Most of these patients received NAC IV at high doses.

However, to date, only one double-blind, placebo-controlled trial has investigated the possible benefits of NAC in severe COVID-19.[125] One-hundred and thirty-five patients were randomised to receive NAC, 21 g over 20 hours IV, or placebo. There were no significant differences in need for mechanical ventilation, time of mechanical ventilation, admission to ICU, time in ICU, or mortality between the NAC and the placebo group.

There are no clinical studies of NAC in mild to moderate COVID-19.

At present there is no evidence from clinical trials for the use of NAC in COVID-19, and more research in this area is urgently needed.

Safety

NAC is generally well tolerated. Several meta-analyses showed that there was no significantly increased risk of AEs in the NAC compared with control group in various disorders, including COPD,[113,114,115] addiction,[115] PCOS[60] and *H. pylori*.[126]

Side-effects

The following side-effects are listed for licensed oral NAC for adults:[3,116]

- Uncommon (1 in 1000 to 1 in 100): diarrhoea; fever; gastrointestinal discomfort; headache; hypotension; nausea; stomatitis; tinnitus; vomiting; allergic reactions; increased pulse rate; fever.
- Rare or very rare (less than 1 in 1000): haemorrhage.
- Frequency not known: facial oedema.

Cautions

NAC should be used with caution in patients with current or a history of gastrointestinal ulceration, bronchial asthma, liver and kidney failure.[3,116]

Drug interactions

Nitroglycerine

Concomitant administration of NAC and IV or transdermal nitroglycerine has been shown to cause severe hypotension[127] and headaches[128] in patients with angina pectoris.

Anticoagulant/antiplatelet drugs

Clinical research suggests that NAC, when administered IV, has anticoagulant and platelet-inhibiting properties,[129,130] in the context of major surgeries.

Pregnancy

NAC can cross the placenta,[131] but research into the safety of oral NAC during pregnancy is limited.

An RCT of NAC, 600 mg per day, in pregnant women with a history of preterm birth and bacterial vaginosis showed that women receiving NAC had a lower rate of preterm birth and a higher gestational age at delivery, compared with placebo.[132] No negative effects on mother or baby were reported. Another RCT evaluated the use of NAC, 2400 mg per day, in pre-eclampsia,

and found no differences in maternal or neonatal outcomes between the NAC and the placebo groups.[133]

Whilst the available evidence suggests that NAC is safe during pregnancy, in view of the scarcity of data, NAC supplementation should only be recommended to pregnant women by a suitably qualified and experienced healthcare professional.

Lactation

There are no studies reporting the safety of NAC during breastfeeding.

Children

NAC has been used safely in children and adolescents at doses of 600–2400 mg per day in a number of clinical trials,[78,94,95,105] although one RCT in autistic children reported constipation (16.1%), increased appetite (16.1%), fatigue (12.9%), nervousness (12.9%) and daytime drowsiness (12.9%), which occurred significantly more commonly in the NAC than in the placebo group.[77]

A Cochrane review of the use of NAC in children with respiratory infections evaluated the safety data from 34 clinical trials, involving 2064 children, and found NAC to be safe, although the authors note that 59 cases of paradoxically increased bronchorrhoea (increased sputum production) in infants under the age of 2 years were reported to the French pharmacovigilance system.[117,134]

Overall, NAC at a dose of 600–2400 mg per day appears to be safe for children over the age of 2 years.

Conclusion

NAC has been extensively used, both as a dietary supplement and as a prescription medication, and has been found to be generally well tolerated in adults and children. Research has been in favour of using NAC in numerous indications, including respiratory infections, various mental health disorders, *H. pylori* infection, male infertility and PCOS. These clinical benefits are thought to be mediated through its antioxidant, anti-inflammatory and mucolytic properties, its importance in detoxification processes, and potentially its ability to disrupt biofilms.

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