*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# N-acetylcysteine

**Evidence Summary**

Evidence is strong for protection of peripheral organs such as in people undergoing cardiac surgery or those with COPD/bronchitis; evidence is mixed and weaker for neuroprotection.

**Neuroprotective Benefit:** A nutraceutical formulation containing N-acetylcysteine among other compounds has shown some pro-cognitive benefits in AD patients and older adults, but the evidence for N-acetylcysteine alone is much weaker.

**Aging and related health concerns:** N-acetylcysteine supplementation is protective in patients undergoing heart surgery and those with COPD, but no studies have tested whether it prevents age-related diseases.

**Safety:** N-acetylcysteine supplementation is generally regarded as safe for most people when taken at standard doses.

**What is it?** N-acetylcysteine is a precursor of L-cysteine, which in turn is a component of the endogenous antioxidant glutathione, a tripeptide composed of glutamate, cysteine, and glycine. Glutathione (GSH) plays an important role in antioxidant activities, redox (oxidation-reduction reaction)-regulated cell signaling, and immune responses [1]. The ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) is often used as a measure of oxidative stress. Because cysteine availability is a limiting factor for GSH synthesis, N-acetylcysteine can protect from oxidative stress by maintaining or increasing GSH levels. In addition to being a component of glutathione, the thiol group (S-H) in N-acetylcysteine confers free radical scavenging properties as it interacts with reactive oxygen species such as hydroxyl radical (*OH) and hydrogen peroxide ($H_2O_2$).

N-acetylcysteine is currently used to loosen thick mucus in people with cystic fibrosis or chronic obstructive pulmonary disease (COPD). It is also used as an antidote to acetaminophen and carbon monoxide poisoning.

**Neuroprotective Benefit:** A nutraceutical formulation containing N-acetylcysteine among other compounds has shown some pro-cognitive benefits in AD patients and older adults, but the evidence for N-acetylcysteine alone is much weaker.

*Types of evidence*:

- 1 meta-analysis based on 22 RCTs in schizophrenia patients
- 3 other RCTs that tested the effects of N-acetylcysteine on cognitive function
- 2 controlled trials in AD patients, one using N-acetylcysteine and the other using a nutraceutical formulation containing N-acetylcysteine
- 1 clinical trial testing a nutraceutical formulation in patients with mild cognitive impairment
- 1 clinical study in Parkinson's disease patients evaluating N-acetylcysteine levels in the cerebral spinal fluid after oral administration
- Numerous laboratory studies

*Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?* No studies have looked at prevention of cognitive decline or dementia in humans with NAC alone. In a placebo-controlled trial of 34 people with mild cognitive impairment, daily consumption of a nutraceutical formulation containing 600 mg of N-acetylcysteine (along with folate, alpha-tocopherol, vitamin B12, S-adenosyl methionine, and acetyl-L-carnitine) for 6 months was associated with improvement in dementia rating scale and preservation of executive function [2]. However, no direct statistical comparisons were made between the nutraceutical treatment group and the placebo group,

making the results less conclusive. In a randomized controlled trial of 93 community-dwelling adults, treatment with the same nutraceutical formulation for 3 months was associated with improved verbal learning and executive function compared to baseline [3]. Patients receiving the placebo showed no improvement. Both the placebo and nutraceutical groups improved further during a 3-month open-label extension of the formulation. Also, performance declined to baseline following withdrawal of the treatment, and statistically improved when participants resumed the formulation. It is currently unknown which of the compounds are responsible for these positive effects, and whether the compounds have additive or synergistic effects.

Some studies have tested the effects of N-acetylcysteine alone, but in people with psychiatric disorders. In a double-blind randomized controlled trial of 46 bipolar disorder patients, N-acetylcysteine (2000 mg/d) treatment for 6 months did not result in any significant differences in cognitive measures including digit span, word learning, trail making, and verbal fluency when compared with the placebo group [4]. There were also no within-group differences between baseline and after N-acetylcysteine treatment. A Cochrane meta-analysis examined 22 RCTs of various supplements purported to improve cognitive symptoms in people with schizophrenia [5]. It concluded that the trials were not adequately powered and that evidence for cognitive protection with N-acetylcysteine is limited.

*Human research to suggest benefits to patients with dementia*: People with mild cognitive impairment and Alzheimer's disease have lower glutathione levels and GSH/GSSG ratios in red blood cells [6]. In a double-blind randomized controlled trial of 106 AD patients, 3 or 6 months of the nutraceutical formulation (same as above) resulted in significant improvements in the dementia rating scale and executive function compared to the placebo group [7]. During the 6-month open-label extension, both groups improved or maintained cognitive performance.

In contrast, a clinical trial specifically testing N-acetylcysteine in 43 patients with probable AD reported that N-acetylcysteine (50 mg/kg/day) for 6 months failed to significantly alter cognitive measures (MMSE) [8]. However, the N-acetylcysteine group showed significant benefit on letter fluency task compared to placebo at 6 months and there were trends toward improvement in memory. While the treatment effect favored the N-acetylcysteine group for most tasks, letter fluency task was the only task that showed statistical significance.

*Mechanisms of action for neuroprotection identified from laboratory and clinical research*: Numerous studies in rodents have shown that N-acetylcysteine has pro-cognitive and neuroprotective effects. N-

acetylcysteine is a membrane-permeable cysteine precursor that does not require active transport via the alanine-serine-cysteine system [1]. N-acetylcysteine crosses the blood-brain-barrier in both humans and rodents [9; 10]. A single infusion of N-acetylcysteine (150 mg/kg) increased blood and brain glutathione concentrations in people with Parkinson's disease, Gaucher disease, and healthy controls [11]. Brain glutathione concentrations were measured using 7T magnetic resonance spectroscopy, and GSH/GSSG redox ratios were measured from blood samples.

Chronic administration of N-acetylcysteine (100 mg/kg, s.c.) improved cognition in a mouse model of accelerated aging (SAMP8 mice) [9]. In a mouse model of AD (streptozotocin-induced AD), N-acetylcysteine treatment (50 mg/kg/day, p.o.) prevented cognitive impairment and the decrease in glucose uptake in the hippocampus [12].

An amide form of N-acetylcysteine (N-acetylcysteine amide; NACA) is thought to have high permeability through cellular and mitochondrial membranes, with increased central nervous system bioavailability [13]. In a rat model of traumatic brain injury, NACA treatment for 15 days significantly improved cognitive function and cortical tissue sparing when compared to N-acetylcysteine treatment or vehicle [14]. NACA also reduced oxidative damage (HNE levels) at 7 days post-injury. NACA maintained levels of mitochondrial glutathione and mitochondrial bioenergetics. No clinical studies have tested NACA yet, but it may be more promising than N-acetylcysteine.

*APOE4 interactions:* Unknown.

**Aging and related health concerns:** N-acetylcysteine supplementation is protective in patients undergoing heart surgery and those with COPD, but no studies have tested whether it prevents age-related diseases.

*Types of evidence:*

- 8 meta-analyses or systematic reviews, 4 in cardiac surgery patients, 2 in COPD patients, 1 in nephropathy, and 1 in chemotherapy-induced peripheral neuropathy
- 4 clinical trials that are not in the meta-analyses, 2 in cancer patients, 1 in sarcoidosis patients, and 1 in normo- and hyper-lipidemic people
- Numerous laboratory studies including 1 lifespan study in *C. elegans*

***Heart surgery/Postoperative complications:*** BENEFIT. Three meta-analyses have shown that N-acetylcysteine administration (i.v. bolus followed by infusion) is protective in heart surgery patients.

The most recent 2016 meta-analysis based on 29 clinical trials in cardiac surgery patients reported that N-acetylcysteine administration was associated with a significantly reduced incidence of atrial fibrillation (OR=0.55, 95% CI, 0.40-0.77), acute kidney injury (OR=0.77, 95% CI, 0.62-0.95), and mortality (OR=0.39, 95%CI, 0.16-0.93) post-surgery [15]. The other meta-analyses reported similar findings with reduced incidence of postoperative atrial fibrillation (ORs, 0.56 and 0.62) [16; 17] and reduced all-cause mortality (OR=0.40, 95% CI, 0.17-0.93) [17].

***Bronchitis/COPD:*** BENEFIT. Chronic obstructive pulmonary disease (COPD) is an obstructive lung disease characterized by long-term diminished airflow and increased sputum production. Two meta-analyses have shown that N-acetylcysteine is protective in patients with bronchitis or COPD. The most recent 2015 meta-analysis of 13 clinical studies including 4,155 patients reported that patients treated with N-acetylcysteine had significantly fewer exacerbations of chronic bronchitis or COPD (RR, 0.75, 95% CI, 0.66-0.84), though this protective effect was more pronounced in patients without evidence of airway obstruction [18]. Another meta-analysis including 11 clinical studies reported that long-term N-acetylcysteine treatment (4 months to 3 years) reduced both the total number of exacerbations (RR = 0.59, 95% CI, 0.47 to 0.74) and the proportion of patients with at least one exacerbation (RR = 0.76, 95% CI, 0.59 to 0.98) [19]. These trials suggested that high-dose N-acetylcysteine (more than 600 mg daily) may be protective, but the effects of lower doses (under 600 mg/day) remain uncertain.

***Homocysteine:*** BENEFIT/INCONCLUSIVE. High levels of the amino acid homocysteine are common in people over 65 and have been linked to a wide variety of age-related problems including dementia, stroke, and coronary artery disease [20]. In a double-blind randomized controlled trial of 82 people, N-acetylcysteine treatment (1.8 g/day from Fluimucil capsules) for 4 weeks significantly lowered plasma concentrations of homocysteine by -11.7% ± 3.0% (placebo: 4.1% ± 3.6%) while increasing those of cysteine by 28.1% ± 5.7% (placebo: 4.0% ± 3.4%). N-acetylcysteine also significantly decreased systolic and diastolic blood pressure. It is worth noting that no direct comparisons were made between the N-acetylcysteine group and the placebo group. Also, N-acetylcysteine-treated people had higher baseline homocysteine levels and blood pressure, making the results less conclusive.

***Lifespan:*** BENEFIT. In male mice, but not in female mice, treatment of N-acetylcysteine started at 7 months of age increased total and maximum lifespan [21]. Doses used were 5 g/L in drinking water (low dose) and 10 g/L (high dose). Both doses increased total lifespan in male mice. In both males and females, both doses caused a sudden drop in body weight followed by continued slower-rate decline in weight such that at 900 days these mice weighed comparably to mice that underwent dietary restriction. Water consumption decreased with treatment and after accounting for this and the weight

loss, the final N-acetylcysteine doses for males were 250 mg/kg/day for the low dose and 421 mg/kg/day for the high dose.

In *C. elegans*, N-acetylcysteine significantly extended both the mean (by 30.5%) and maximum lifespan (by 8 days) [22]. N-acetylcysteine supplementation also increased the total number of progeny produced. Expression of stress-responsive genes (sod-3 and hsp-16.2) increased significantly following N-acetylcysteine. N-acetylcysteine appears to promote longevity in *C. elegans*, possibly through increased resistance to environmental stressors.

**Safety:** N-acetylcysteine supplementation is generally regarded as safe for most people when taken at standard doses.

*Types of evidence:*

- 3 meta-analyses, 1 based on 41 RCTs in patients with sepsis, 1based on 22 RCTs in schizophrenics, and 1 based on 13 clinical studies in people with bronchitis or COPD
- 6 clinical trials, 2 in AD patients, 1 in people with MCI , 2 in patients undergoing cardiac surgery, and 1 in patients with cystic fibrosis

*Details*: N-acetylcysteine is generally regarded as safe and is well-tolerated for most adults. A meta-analysis based on 13 clinical studies including a total of 4,155 bronchitis/COPD patients reported that N-acetylcysteine supplementation for up to 3 years does not increase the risk of side effects (RR, 0.94, 95% CI, 0.88-0.99) [18]. In a double-blind randomized controlled study of 21 patients with cystic fibrosis, N-acetylcysteine at doses of up to 2800 mg/day was well-tolerated and deemed safe [23]. The nutraceutical formulation used in older people and those with mild cognitive impairment was also well-tolerated and no serious adverse events were reported for any of the 300+ participants [2; 7; 8].

However, some safety concerns have been raised in patients with serious health conditions. In a large meta-analysis of 41 RCTs including 2,768 patients with systemic inflammatory response syndrome or sepsis, late application (more than 24 hours after the onset of symptoms) of N-acetylcysteine was associated with cardiovascular instability [24]. A double-blind randomized controlled trial of 177 patients with renal insufficiency who were undergoing cardiac surgery reported that N-acetylcysteine treatment (100 mg/kg bolus followed by 20 mg/kg/hr infusion) was associated with a significantly greater blood loss and 1.6 more units of blood transfusion (95% CI, 0.4-3.1 units) [25]. Another double-blind randomized controlled trial of 20 patients undergoing surgery for abdominal aortic aneurysm reported that N-acetylcysteine was associated with anticoagulant and platelet-inhibiting properties,

with decreased prothrombin time and prolonged coagulation time [26]. These risks should be taken into account when N-acetylcysteine treatment is considered for patients with increased bleeding risk.

*Drug interactions*: N-acetylcysteine should not be administered with nitroglycerin, as the combination can cause severe hypotension [27] and severe headache [28]. N-acetylcysteine interacts with inhaled insulin (Afrezza™, Exubera™) and may affect the absorption of insulin into the blood stream (drugs.com).

**Sources and dosing:** A nutraceutical formulation that showed some cognitive benefits in older adults and those with mild cognitive impairment contained 600 mg of N-acetylcysteine among other compounds (folate, alpha-tocopherol, S-adenosyl methionine, acetyl-L-carnitine) [2; 3]. Much higher doses have been used in cardiac surgery patients (e.g., 50-150 mg/kg i.v. bolus before surgery followed by infusions at lower doses) to reduce the incidence of postoperative atrial fibrillation [16; 17].

N-acetylcysteine is available as a dietary supplement typically containing 600 mg per capsule. Because N-acetylcysteine can be oxidized by air, the quality of N-acetylcysteine supplements will partly depend on its packaging. PharmaNAC™ guarantees that their supplements contain pure N-acetylcysteine—each tablet is wrapped at the time of manufacture in a foil-plastic-paper to protect it from oxidation.

**Research underway:** Several clinical trials are ongoing. A clinical trial is testing whether intravenous (once per week) and daily oral N-acetylcysteine treatment supports brain function in patients with Parkinson's disease (NCT02445651). This study is estimated to be completed in March 2017. Another trial is testing whether N-acetylcysteine affects inflammatory and oxidative stress biomarkers in patients with tobacco use disorders and bipolar disorder (NCT02420418). This study is not yet open for participant recruitment. And a phase III study is testing whether N-acetylcysteine (oral) and/or isotonic bicarbonate (i.v.) prevents serious adverse outcomes following angiographic procedures (NCT01467466). Finally, another clinical trial is testing the role of N-acetylcysteine as an adjuvant to opioid treatment in patients with chronic neuropathic pain (NCT01840345). This study is currently recruiting participants. A few clinical trials testing the effects of N-acetylcysteine on cognitive functions are planned in Australia as well, one in noncardiac surgical patients (post-anesthesia) [29] and another in schizophrenia patients [30].

**Conclusion:** Alzheimer's disease patients have decreased glutathione levels and increased oxidative stress [6; 31]. There is rationale to correct these disturbances, but many traditional antioxidant therapies have failed in clinical trials likely, in part, due to low bioavailability. N-acetylcysteine is an

attractive compound as it is a precursor and component of the endogenous antioxidant glutathione in addition to being a free radical scavenger. While N-acetylcysteine crosses the blood-brain-barrier, low bioavailability is a concern like other antioxidants. One promising avenue of research may be to explore derivatives of N-acetylcysteine such as NACA (amide form), which has been reported to have higher permeability through cellular and mitochondrial membranes with increased central nervous system bioavailability compared to N-acetylcysteine [13]. NACA has shown some promising neuroprotective effects in a rodent model of traumatic brain injury [14] but no studies have tested it in humans yet. Safety and efficacy trials of NACA are warranted. In order to monitor target engagement and treatment response to N-acetylcysteine or its derivatives, glutathione levels in the brain can be measured using magnetic resonance spectroscopy. Peripheral levels of GSH and GSH/GSSG ratios can also be measured from blood samples.

Search terms:

Pubmed, Google: N-acetylcysteine

- + cognitive, + Alzheimer's, + dementia, + clinical trial, + double-blind, + meta-analysis, + Cochrane, + lifespan, + cancer, + ApoE

Clinicaltrials.gov: N-acetylcysteine

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