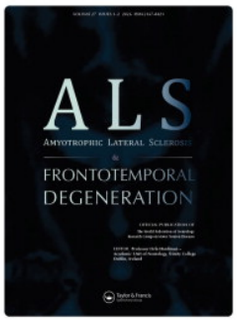

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ALSUntangled #82: N-acetylcysteine

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REVIEW ARTICLE

ALSUntangled #82: N-acetylcysteine

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Abstract

N-acetylcysteine is a thiol-containing compound and a precursor of glutathione, with mechanistic plausibility for ALS, including reducing oxidative stress, regulating neuroinflammation, and mitigating mitochondrial dysfunction. Preclinical studies have yielded conflicting results on whether N-acetylcysteine can delay the onset of motor impairment and prolong survival in ALS mouse models. Several case studies of oral or subcutaneous administration of N-acetylcysteine in patients with ALS did not demonstrate convincing benefits. Clinical trials to date have also failed to demonstrate efficacy in slowing ALS progression. While N-acetylcysteine shows theoretical promise, further research is needed to clarify its therapeutic role in ALS. At present, ALSUntangled does not support the use of N-acetylcysteine as a treatment to slow ALS progression.

Keywords: *Amyotrophic lateral sclerosis, oxidative stress, antioxidant, N-acetylcysteine*

Sandeep Yerraguntla, Bhavya Bakshi, and Keshav Chandran contributed equally to this work.

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Introduction

ALSUntangled reviews alternate and off-label treatments for people with ALS (PALS). Here, we review N-acetylcysteine (NAC), a topic for which we received 271 requests (Future Reviews - ALS Untangled®).

NAC is a synthetic derivative of amino acid L-cysteine and a precursor to reduced glutathione (GSH). GSH is a critical molecule that protects cells from oxidative stress (1), a topic ALSUntangled has previously reviewed (2). NAC has been FDA-approved as a mucolytic agent for conditions such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchitis, as well as an antidote for acetaminophen overdose. It has also been used through nebulization or direct instillation to manage thick mucus secretions in ALS patients.

Its role as a precursor to glutathione not only helps mitigate oxidative stress but also influences mitochondrial dysfunction, apoptosis, and inflammation, which are implicated in various disease processes (1). Importantly, NAC can cross the blood-brain barrier, which makes it an appealing potential therapeutic agent for neurodegenerative diseases (3). In a Parkinson's disease (PD) pilot trial, a combination of intravenous (50 mg/kg weekly) and oral (500 mg twice daily) administration of NAC for three months was associated with improvements of dopamine transporter binding and PD symptoms (4).

Herein, we review the biochemical mechanisms of NAC, relevant patient case studies, and clinical trials to critically evaluate its therapeutic potential for PALS.

Mechanistic plausibility

Antioxidant effects and glutathione synthesis

Accumulating evidence suggests that heightened oxidative stress and impaired antioxidant defenses contribute to the progressive neuronal degeneration seen in ALS (5). NAC is a thiol compound that acts as a precursor to L-cysteine, a critical substrate in the synthesis of reduced glutathione (GSH). GSH is one of the most important endogenous antioxidants that protect cells from oxidative damage by detoxifying reactive oxygen species (ROS). Among the three amino acids that form GSH—glutamate, glycine, and cysteine—cysteine is the rate-limiting component, especially during periods of oxidative stress when its intracellular concentration is limited (6). NAC supplementation replenishes cysteine levels, thereby maintaining GSH synthesis and cellular antioxidant capacity. Glutathione depletion has been proposed as a pathogenic mechanism in ALS (7). By boosting GSH levels, NAC may reduce oxidative stress and protect motor neurons from degeneration. It is worth noting that numerous antioxidants, such as vitamin C, vitamin E, combination of multiple antioxidant therapy, edaravone, and sodium phenylbutyrate/TUDCA, have all failed to modify disease progression in broad ALS population in clinical trials (8–10).

Neuroinflammation

Neuroinflammation occurs in ALS and may play a role in its progression (11). NAC has demonstrated variable effects on neuroinflammation in cell culture. In a study of lipopolysaccharide (LPS)-induced inflammation model using cultured mouse microglia cells, NAC inhibited the synthesis and secretion of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin 1β (12). However, a high dose ($\geq$30 mM) of NAC was associated with increased microglial cell death which was attributed to NAC-induced paradoxical TNF-α accumulation within cells. The findings suggest that while NAC may modulate inflammation, its effects are complex and dose dependent. The role of NAC in regulating neuroinflammation in ALS remains to be elucidated.

Mitochondrial protection

Mitochondrial dysfunction is a hallmark of ALS and other neurodegenerative disorders. It has been linked to disrupted electron transport chain activity, ATP synthesis, and increased reactive oxygen species (ROS) production, all of which contribute to cellular dysfunction (13). NAC has shown promise in protecting mitochondrial function by reducing oxidative damage and enhancing mitochondrial resilience. In a study of mice with Huntington's disease, another neurodegenerative disorder characterized by severe mitochondrial dysfunction, NAC improved mitochondrial respiratory capacity in the striatum (14). While similar studies in ALS are limited, these findings highlight NAC's potential to mitigate mitochondrial dysfunction in neurodegeneration.

ALSUntangled assigns TOE "Mechanism" grade of B as it has plausible mechanisms in regulating oxidative stress, neuroinflammation, and mitochondrial dysfunction.

Preclinical studies

NAC has been studied in human neuronal cell lines expressing wild-type (WT) SOD1 gene or $SOD1^{G93A}$, a causal ALS gene mutation. In these models, $SOD1^{G93A}$ -expressing human neuroblastoma SH-SY5Y cells exhibit increased mitochondrial ROS production compared to the cells expressing WT SOD1. NAC exposure significantly reduced ROS production in the $SOD1^{G93A}$ cells and restored

mitochondrial function to the control level. The findings suggest that the oxidative phosphorylation defects observed in G93A-transfected cells may be reversible with NAC, likely due to its ability to decrease intracellular oxidative stress (15).

NAC has also been evaluated in the $SOD1^{G93A}$ ALS mouse model. NAC was administered at a concentration of 1% via drinking water (the exact dosage is unknown) to $SOD1^{G93A}$ ALS mice at 4–5 weeks of age, before the onset of muscle weakness. The treatment delayed the onset of motor impairment and prolonged survival in $SOD1^{G93A}$ mice compared with untreated $SOD1^{G93A}$ mice (16). However, another study using NAC given orally (10 mg/mL in drinking water) or subcutaneously (0.5 mg/g) in the same mouse model failed to demonstrate similar effects (17). There were some differences between their experiment designs. In the latter study, the authors noted their $SOD1^{G93A}$ mouse line showed slower disease progression, likely due to a 30% reduction in G93A transgene copy number. They also administered NAC to much older mice (120 days old; before the onset of ALS symptoms). Whether the difference in study designs contributed to the conflicting results is unclear. However, the heterogeneity in SOD1 model behavior and sensitivity to experimental parameters substantially limits confidence in preclinical efficacy signals.

Further, another group studied intranasal delivery of NAC combined with a nanocarrier (used to facilitate drug delivery to the central nervous system (CNS)) in $SOD1^{G93A}$ mice (18). The treatment began shortly after the mice developed motor symptoms, and the results demonstrated that intranasal administration of 1 mg NAC-nanocarrier five days per week prolonged the mean survival time by 11.5 days compared to the untreated group. However, the same regimen delivered at a lower dose (0.2 mg), and intraperitoneal or intranasal administration of unmodified NAC did not affect survival. It also worth noting that the data from $SOD1^{G93A}$ ALS model may not be generalizable to other forms of ALS, which accounts for 98% of the population.

Preclinical studies of NAC (unmodified molecule) demonstrated no survival benefit in ALS mouse models and conflicting results in delaying ALS onset in these models. Therefore, ALSUntangled assigns a TOE "Preclinical" grade of U.

Cases

A remote case series study was conducted in motor neuron diseases, which included ALS and spinal muscular atrophy (SMA). The latter is a motor neuron disease caused by an *SMN* gene mutation and affects children and young adults. Upon review, no conclusion on its efficacy in slowing ALS progression can be drawn from the data for the first group of 8 patients who received a daily subcutaneous injection of 2500 mg, as the authors reported mean Norris scores and FVC values that included both ALS (4 had confirmed diagnoses) and SMA patients. The second group of 12 patients (6 had confirmed ALS diagnoses) started with 15 g of oral NAC daily, and all reported ineffective. Among them, two died, two left the study and eight completed 2500 mg daily subcutaneous injection for six months. It is unclear how many of these eight patients were ALS patients. Again, only the mean Norris score and FVC were reported (19). The same team also explored a combination of NAC and Dithiothreitol (DTT) treatment in 40 ALS patients and 11 SMA patients (20). NAC dosing, route of administration and the study outcome measures were very similar to the previous study. DTT was either added at 250 mg–500 mg to the NAC solution or given orally at 750 mg–1000 mg per day. The outcome analysis after 3–24 months showed that among 10 ALS patients who received NAC alone, 3 had a stable Norris score for >6 months; among 14 ALS patients who received NAC+DTT, 2 had a stable score for >6 months. Notably, participants were enrolled in the study regardless of their disease stages, and 7 ALS participants dropped out of the study (3 of them were due to death) and an additional 5 participants died. Given the large dropout rate and only small percentages of PALS were reported stable, we cannot draw a conclusion that NAC had any efficacy in slowing ALS progression.

Another study looked at the survival benefit of an antioxidant cocktail including NAC, vitamins C and E, DTT, and acetylmethionine in 36 PALS. They received this treatment either through subcutaneous injections, oral route, or both. There was no survival benefit when compared to historical controls (21).

In the online community PatientsLikeMe, 70 PALS reported taking NAC orally. Among 23 of the 70 PALS who provided treatment evaluations, 6 patients reported moderate to major effectiveness, but the majority reported none to slight effectiveness. There is, however, limited information regarding the effectiveness in these 6 PALS, and only one of them provided detailed benefits, including improved fatigue and slower progression.

Because none of the case studies showed benefit of NAC in slowing ALS progression, and some patients with unconfirmed diagnosis in the online ALS community reported effectiveness with limited information, ALSUntangled assigns a TOE "Cases" grade of D.

Trials

A randomized, double-blind, placebo-controlled, 12-month trial of NAC was conducted in 111

PALS three decades ago (1988–1992). Fifty-five patients were randomly assigned to the NAC treatment group, and 56 patients were assigned to the placebo group (22). Subjects self-administered NAC subcutaneously at a dose of 50 mg/kg daily or placebo fluid at home. The primary endpoints were death from all causes, permanent assisted ventilation or tracheostomy within one year of randomization. The secondary outcome measures included manual muscle strength testing, myometry, forced vital capacity, ability to perform activities of daily living, bulbar function and degree of independence. Although the 12-month survival data showed an 11% difference in favor of treatment group, this did not reach statistical significance (22). There was no significant difference in most secondary outcome measures. Importantly, it was concerning that bulbar-onset ALS participants showed more rapid deterioration of bulbar function in the treatment arm, the mechanism of which was unclear. Although rapid function decline in a subgroup of PALS after NAC treatment has not been confirmed in other studies and was not definitively related to the treatment, it is imperative to note that such therapy is not benign and may pose potential risks.

Another open-label study was conducted in 15 PALS. Data from 11 participants were reported (23). 50 mL of 5% NAC solution (the dose is equivalent to 2500 mg NAC) was infused subcutaneously via an insulin pump for 2–4 h daily, in conjunction with 300 mg of vitamin C daily. The mean duration of treatment was seven months (minimum duration was one month, and maximum duration was 12 months). Manual muscle strength testing of 42 proximal and distal muscle groups, Norris score, and forced vital capacity were assessed in these 11 participants and in a parallel untreated group of 8 ALS patients. It reported that there was no significant difference across these measures (23).

A phase 2, randomized placebo-control trial to evaluate the effectiveness of a combined therapy of NAC and EH-301 (1-(beta-D-Ribofuranosyl) nicotinamide chloride and 3,5-Dimethoxy-4′-hydroxy-trans-stilbene) in ALS will start enrollment soon in Spain.

Because one randomized placebo-controlled trial and one small open-label trial of NAC in PALS did not show benefit in slowing ALS progression, ALSUntangled assigns a TOE "Trials" grade of F.

Risks, dosing, and costs

Oral NAC was shown to cross blood brain barrier during a study in Parkinson's disease (PD) patients (3). In another PD study, 6000 mg daily oral NAC did not increase brain glutathione levels whereas intravenous NAC did, suggesting oral administration may not achieve its biological effects in the central nervous system (24). In the ALS clinical trials mentioned above, NAC was administered subcutaneously at doses of 50 mg/kg/day or 2500 mg/day. NAC was reported to cross BBB and reach a concentration of 3 mg/L in cerebrospinal fluid within 2–3 h via subcutaneous injection (22). Oral NAC up to 15 g daily was proven to be ineffective for slowing disease progression in ALS or SMA (19).

The common side effects were rash, pain, and swelling at the injection site. In the open-label clinical trial, continuous subcutaneous infusion was used over 2–4 h to minimize painful swelling due to injection (23). Reported side effects of oral NAC commonly include mild gastrointestinal symptoms such as nausea, vomiting, and diarrhea. NAC has been reported to cause severe hypotension and headaches when used concomitantly with nitroglycerin in patients with angina (25,26); therefore, co-administration of these medications should be avoided.

Based on the safety data, ALSUntangled assigns a TOE "Risks" grade of B for NAC when administered orally or via subcutaneous injection.

Oral supplementation with NAC 1000 mg daily costs $10–$20 per month. NAC solution for subcutaneous administration is not widely available, and the cost is expected to be higher than that of the oral form.

Conclusion

While NAC has theoretical therapeutic promise in ALS due to its antioxidant properties and ability to modulate oxidative stress and restore mitochondrial function, several case studies failed to show benefits, whether given orally or via subcutaneous injection, in slowing ALS progression or prolonging survival. Two clinical trials in PALS, including one randomized and placebo-controlled trial, did not demonstrate efficacy in prolonging survival or slowing functional decline. Notably, one trial demonstrated that in the bulbar-onset ALS subgroup, participants' bulbar function deteriorated more rapidly in the NAC treatment arm for unclear reasons. As such, ALSUntangled does not support the use of NAC as a treatment for slowing ALS progression.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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