N-acetyl-cysteine

N-acetyl-cysteine (NAC) is a reduced thiol compound derived from the amino acid cysteine.[1-3] NAC is rapidly converted to cysteine after absorption. A portion of NAC is de-acetylated by the aminoacylase enzyme group in intestinal epithelial cells.[4,5] Plasma cysteine levels are increased in response to oral administration of NAC, and as such, this represents an important therapeutic pathway for increasing cysteine levels.[3,6,7] NAC acts as the acetylated precursor to both the amino acid L-cysteine and to reduced glutathione.[8] Supply of cysteine precursors increases glutathione synthesis and prevents deficiency in times of nutritional or biochemical stress. Glutathione appears to be the major transportation format for cysteine in the body.[9] While cysteine is an important bioactive product from NAC, the unaltered product is also present in tissues and has a number of unique therapeutic properties.[3,7]

Peak plasma concentrations of NAC are reached within 1 to 2 hours of absorption. The plasma half-life of NAC may be considered relatively short with reports in the range of 2.5 to 6.5 hours.[2,7,10-11] Within 12 hours of administration, no detectable NAC is found in plasma tests.[7,10] While efficacy is seen in the short term, as evidenced by its use in therapeutic treatment of pharmacologically induced states of glutathione deficiency, the long term use of NAC produces biochemical changes that may positively impact health outcomes. For example, NAC contributes to the improvement of cellular redox states. Across time, the positive influence on cellular redox leads to changes in redox sensitive transcription factors, inflammatory responses and oxidative stress levels, which form the basis of biochemical changes necessary to induce functional change.[12]

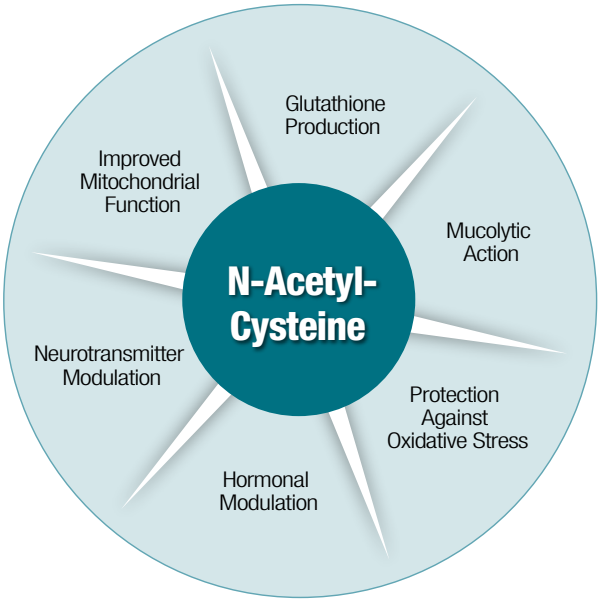
NAC has a very good safety profile whilst showing remarkable therapeutic impacts, and has demonstrated low toxicity in humans. For a 60kg person, the equivalent of 300-900g would need to be administered in order to reach a fatal dose, which is well above the daily dose range of 250mg-2g. Side effects associated with oral use are rare, the most likely being related to mild gastrointestinal upset, such as nausea or diarrhoea.[2]

N-Acetyl-Cysteine and Glutathione

One of the best known actions of NAC is the contribution to glutathione production, the efficacy of which has been clearly demonstrated. NAC is used to restore glutathione levels in cases of paracetamol overdoses and other pharmacologically induced glutathione deficiency states.[13] For example, in paracetamol overdose, reactive metabolites form protein adducts with cysteine residues. This leads to depletion of glutathione in hepatocytes. Early administration of NAC results in low to no adducts in serum samples, and when delivered either intravenously or orally within 24 hours, NAC is effective at preventing liver toxicity.[14-15]

Glutathione is the principal thiol compound found in animal cells and is a highly potent endogenous antioxidant.[9,16,17] It is a tripeptide, formed from glutamate, cysteine and glycine, and is catalysed by the action of cytosolic enzymes γ-glutamyl-cysteine synthetase and glutathione synthetase.[3,9] Glutathione plays a vital role in the maintenance of cellular homeostasis, and serious deficiency is associated with reduced cellular apoptosis and inappropriate proliferation.[9,16] Deficiency states influence cellular redox signalling, lipid peroxidation and protein-thiol decline; each of which may contribute to alterations in the cell cycle.[9,16] Glutathione has a diverse biochemical action within the body, contributing to phase II conjugation, free radical and reactive oxygen species scavenging and prostaglandin conversion.[3,9]

Figure 1.
N-acetyl-cysteine possesses varied biological activity, indicating potential for diverse therapeutic applications



Glutathione sufficiency is critical to multiple and diverse biological functions. Immune function, including the proliferation of lymphocytes, the activation of T-lymphocytes and the activation of polymorphonuclear leukocytes is only optimal during glutathione sufficient states. Similarly, spermatogenesis and sperm maturation are dependent upon glutathione sufficiency.[9] Glutathione sufficiency may support basic biochemical reactions, such as the regulation of vitamin C and E, or support more complex processes such as those involved in the inhibition of infection by influenza.[9,18]

Glutathionation is a crucial pathway for the phase II detoxification of endogenous steroids and xenobiotics.[19] This process results in detoxification of these electrophiles from cells or through bile in hepatocytes.[17] Part of the efficacy of glutathione in detoxification processes is its stability as a tripeptide; allowing it to react with highly unstable compounds. Glutathione conjugation may occur spontaneously, however it is more efficient when catalysed by glutathione-s-transferase.[20]

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BioMedica NUTRACEUTICALS

Within the brain, astrocytic glutathione release is believed to be the primary modulator of neuronal glutathione production.[6] NAC administration has been shown to act to protect astroglial function in the presence of inflammatory cytokines.[21] As cysteine is the rate limiting amino acid for glutathione production, it is important that it passes across the blood brain barrier. The passage of cysteine across the blood brain barrier has been observed in animal models following administration of NAC.[6]

N-Acetyl-Cysteine and Oxidative Stress

Oxidative stress is a term used to describe a state in which cellular environments are prone to oxygen damage. Within these environments, different redox couples predominate in oxidised forms.[1] NAC is a contributor to thiol antioxidant defence systems such as glutathione. As such, it is well placed to positively impact upon oxidative stress, quenching reactive oxygen species (ROS) through the reducing thiol group.[18] Additionally, NAC provides sulfhydryl groups that may also act as protection against reactive oxygen species.[22]

The condition of oxidative stress is well known to cause cellular damage.[1] During the interphase portion of the cell cycle, the G1/S checkpoint allows for the detection of potential errors in DNA synthesis, and the cessation of the cycle if necessary.[23] However, during oxidative stress these errors can be missed as the cell becomes more likely to rapidly progress from the G1 to the S phase.[1] Oxidative stress creates further imbalance in cellular activity. Redox switches affect a wide variety of cell functions including enzymatic activity, transcription factors, structural elements, as well as the management of protein trafficking synthesis and regulation.[1] NAC positively impacts upon the cell cycle, arresting the damaged cell at the G1 phase through the modification of the redox status of signalling proteins, and induction of cell cycle inhibitors.[22] NAC further improves functional redox switches and signalling by reducing the formation of disulfides that may contribute to abhorrent cellular signalling.[1]

N-Acetyl-Cysteine and Mucolytic Action

Mucin is a complex glycoprotein secreted by goblet cells. Once dissolved in water, mucin forms mucous which protects and lubricates surfaces of mucous membranes such as those found in the respiratory, digestive and urogenital tracts.[24] Excessive mucous production may be found in conditions such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, sinusitis, after continence-preserving urinary diversion surgery or in the female reproductive tract.[8,12,25] NAC has a reported mucolytic action, based upon the ability of the free thiol group to dehydrolise disulphide bonds.[7] This acts to decrease the viscosity of the mucous by reducing the size of mucoprotein molecules.[25]

The influence of NAC on neutrophil infiltration may also contribute to its mucolytic action. Neutrophils produce neutrophil elastase that may contribute to goblet cell degranulation.[7] NAC has been shown to influence neutrophil function, contributing to reductions in neutrophil chemotaxis, reduced neutrophil respiratory burst activity, as well as decreased IL-8 and neutrophil elastase release.[26-27]

N-Acetyl-Cysteine: Other Actions

Hepatic detoxification support: Beyond the contribution to glutathione production, NAC may support hepatic detoxification. Hepatic detoxification can cause the production of reactive oxygen intermediaries that are capable of creating free radicals and concurrent secondary tissue damage.[28] Hepatic stellate cells are primarily involved in the storage and transport of retinoids including vitamin A.[29] Oxidative stress may cause these cells to produce pro-inflammatory cytokines and excessive fibrillar collagens, potentially leading to hepatic damage.[30] NAC has a dual effect of quenching ROS through the reducing thiol group as well as inducing arrest of hepatic stellate cells at the G1 phase of their cell cycle via modification of the redox status of cysteine found in a number of signalling proteins.[16,22]

Mitochondrial support: NAC may act to improve mitochondrial oxidative phosphorylation. Animal models have demonstrated increases in complex I and complex IV activation in synaptic mitochondria, as well as increases in complex I, IV, and V-specific activities in liver mitochondria in response to NAC treatment. This could be in part due to the role of NAC in preventing oxidative damage of phosphorylation proteins and lipid peroxidation of mitochondrial membranes, although the mechanism is not clear. NAC also appears to partially prevent mitochondrial membrane depolarisation in response to tumour necrosis factor-α, and thereby may be able to prevent programmed cell death.[16]

Neurological Support: NAC has multiple potential mechanisms in the prevention of neuronal degeneration; acting to decrease oxidative damage via both glutathione activity and as a scavenger of ROS, as well as by inhibiting apoptosis and supporting mitochondrial function.[16] Redox sensitive proteins, such as N-methyl-D-aspartate (NMDA) receptors, may show altered response in glutathione deficiency states. Animal models have demonstrated hypofunction of NMDA receptors in the presence of glutathione deficiency.[11] Both glutathione and NAC have been shown to potentiate NMDA receptor function.[11]

N-Acetyl-Cysteine and Reproductive Health

NAC may be beneficial in promoting female reproductive health and assisting to improve pregnancy outcomes.[8,31,32] Further to this, NAC may assist in improving semen parameters in infertile men.[33]

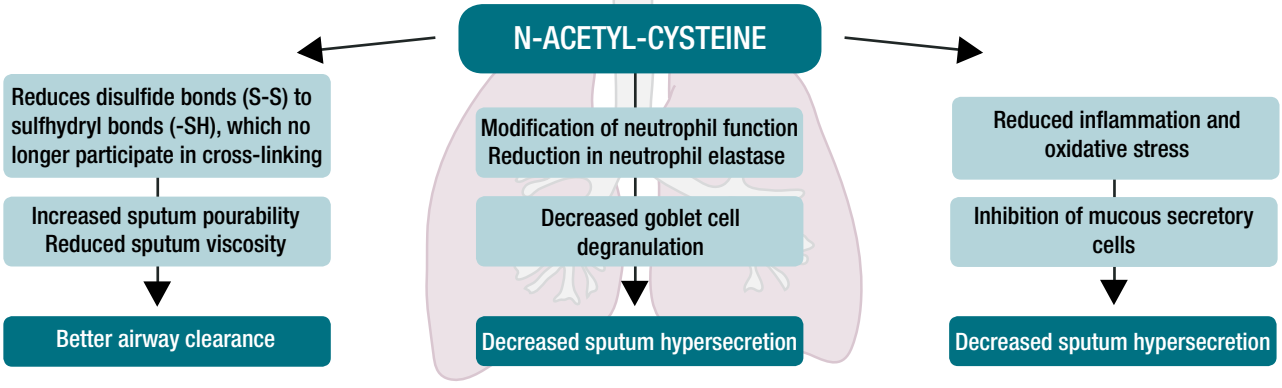
Polycystic ovarian syndrome (PCOS) is characterised by at least two of the following; oligoovulation or anovulation, hormonal elevation of androgens and/or polycystic ovaries. It occurs due to a complex multifactorial pathophysiology.[23]

Insulin secretion and insulin resistance has been noted in a large number of individuals with PCOS.[31] NAC may play a role in insulin regulation in PCOS and has demonstrated a positive effect on insulin secretion in pancreatic β-cells. In addition, glutathione is protective of insulin receptors.[31] Reductions in basal insulin levels have been noted in response to NAC administration.[32] Further to its insulin sensitising effects, NAC has been demonstrated to; reduce testosterone, DHEAs and free androgen index, as well as improve homocysteine status and lipid profiles among women with PCOS.[31,32]

Figure 2.

N-acetyl-cysteine may assist in the management of mucous hypersecretion and airway clearance[7,26,27]

Healthy respiratory flow can be encouraged by maintaining effective airway clearance and reducing mucous hypersecretion. This leads to lower adhesion of bacteria, reduced exacerbation of underlying conditions, reduced dyspnoea and improved forced respiratory flow. NAC may contribute via several mechanisms.



Cervical mucous can be an indicator of female reproductive health and likelihood to fall pregnant. Viscoelasticity varies throughout the reproductive cycle and contributes to the ease of passage of sperm.[34] As a mucolytic agent, NAC may assist with the breakdown of tenacious mucous in the reproductive tract, thereby assisting the passage of sperm through the vaginal tract.[8]

A natural result of pregnancy is an increase in oxidative stress, particularly during the first trimester as placental mitochondrial activity and blood flow establishment occurs. Failure of antioxidant defences against this increased oxidative damage may contribute to unexplainable losses early in pregnancy.[8] One study examined the impact of NAC on unexplained pregnancy losses. Comparison of a combination of 600mg of NAC with 500µg of folic acid per day against 500µg of folic acid alone, found significant increases in both successful pregnancy continuation up to 20 weeks, and successful full term deliveries in the group with NAC and folic acid combined.[8]

Oxidative stress has been implicated in the pathogenesis of idiopathic male infertility. Proposed mechanisms by which reactive oxygen species may contribute to suboptimal sperm function include damage to the membrane of the sperm or DNA damage. *In vitro* studies have shown that NAC, alone or in combination with selenium, may assist with total sperm motility and improve germ cell survival in seminiferous tubules. A 2009 double-blind placebo-controlled randomised study, investigated the effect on semen quality of 26 weeks of daily administration of 200mcg selenium orally, 600mg NAC orally, or 200mcg selenium plus 600mg of NAC orally, on 468 infertile men with idiopathic oligo-asthenoteratospermia. Total sperm count, mean sperm concentration and normal sperm morphological ratio all demonstrated statistically significant improvement in active treatment arms. Further to this, hormonal modulation was noted with slight but statistically significant improvements in serum follicle stimulating hormone (FSH), luteinising hormone (LH) and testosterone.[33]

N-Acetyl-Cysteine and Mental Health

Oxidative stress, glutamatergic dysfunction, neuronal cell damage and inflammation have all been suggested as drivers of various mental health conditions. NAC has been examined as a therapeutic intervention for numerous diagnosable mental health conditions, including schizophrenia, bipolar disorder and autism, as well as being studied in epilepsy, various addictions and obsessive compulsive disorder.[6,35-37]

Schizophrenia is associated with anatomical, functional and genetic changes that may result in various biochemical deficits. Glutathione deficiencies in the cerebrospinal fluid, prefrontal cortex and post mortem caudate region have been noted. Studies examining the efficacy of NAC in schizophrenia have identified a number of potential benefits. Negative symptoms (such as flattened affect), were improved with oral administration of 2g per day of NAC, however positive symptoms (such as thought or movement disorders) remained unaffected.[38] Auditory mismatch sensitivity is a technique used in experimental investigations of schizophrenia, and may be a proximal marker of NMDA function. Administration of 1g of NAC twice daily was shown to improve auditory cortical function in individuals with schizophrenia as studied using this parameter.[11]

In individuals with bipolar disorder, depressive symptoms appear to be positively impacted by adjunct NAC treatment. Administration of 2g of NAC daily produced significant improvement in bipolar depression symptoms in two separate studies, with one study reporting first signs of improvement at 8 weeks.[39,40] It is important to note that NAC does not however appear to reduce symptoms of mania as found in animal models.[41]

The complexity of autism spectrum disorder has resulted in multiple theoretical models being presented. Redox imbalance and glutamatergic dysfunction have been suggested as possible physiological underpinnings. NAC administration over the course of 12 weeks in a double-blind, placebo-controlled study found that there was a significant improvement in various markers of behavioural outcomes, such as irritability, hyperactivity and stereotypies.[42]

Oxidative stress has been implicated in the pathophysiology of seizures and epilepsy. In a study using mouse maximal electric shock (MES) to induce seizure activity, NAC was found to reduce seizure activity, both alone and in combination with sodium valproate.[35] High dose NAC has been reported to improve and stabilise the neurological symptoms in patients with Unverricht–Lundborg disease, a type of progressive myoclonic epilepsy in which oxidative stress has been thought to be an important factor. A series of case studies using between 4-6g per day of NAC in conjunction with medications found improvements in a variety of markers including myoclonia and various cognitive parameters.[36]

N-Acetyl-Cysteine and Biofilms

NAC may be of benefit in the disruption of biofilm. Biofilms act to protect bacteria from antibiotics and competing microbes while creating an environment in which resistant phenotypes may proliferate.[43] They occur when colonies of bacteria attach themselves to surfaces and create complex ecosystems within extracellular matrices in order to better manage environmental challenges.[44] The development and maintenance of these exopolysaccharide structures involve a vast array of bacterial signalling pathways, making it challenging to either inhibit production of biofilms or disperse them once formed.[45]

N-acetyl-cysteine has been investigated for its role in biofilm disruption. One study looked at cultured specimens from patients with a history of failed *H. pylori* eradication treatments, to determine the effect of NAC on biofilm. It was found that NAC both inhibited biofilm production and reduced existing biofilm *in vitro*. This study additionally examined the effect of 600mg of oral NAC in *Helicobacter pylori* treatment, and was shown to improve eradication when administered prior to administration of culture guided antibiotic therapy.[44]

NAC may work through a variety of mechanisms to achieve biofilm disruption. NAC has demonstrated bacteriostatic effects, including inhibition of bacterial adherence, reduction in cell viability in specific Gram-negative and Gram-positive bacteria and reductions in the rate of biofilm production.[46] Further to this, the mucolytic action of NAC may also assist with biofilm disruption. Through the dissociation of mucin disulphide bonds and other disulphide bond associated components, NAC may reduce the viscosity and thickness of the mucous layers of the biofilm.[46]

N-Acetyl-Cysteine and Respiratory Health

Glutathione and glutathione associated enzymes are critical to lung health, representing a first line defence against external agents in the lower respiratory tract. Numerous inhaled environmental chemical and physical agents, such as cigarette smoke, environmental oxidants and other pollutants and toxins, enhance the generation of reactive oxygen species within the lung. Glutathione deficiency is associated with numerous lung diseases including asthma, chronic obstructive pulmonary disease (COPD), and acute respiratory distress syndrome (ARDS).[10]

NAC has been demonstrated to positively impact upon neutrophil management in respiratory settings. Neutrophils are polymorphic phagocytes and represent the most common leukocyte in the human body.[47] In cystic fibrosis, excessive neutrophil recruitment to airways and abnormal neutrophil function is a common pathophysiological feature. The result of this is mucous hyperviscosity, increased inflammatory cytokines and an increased risk of opportunistic infection.[27] One study demonstrated that NAC at doses of 600-1000mg three times daily, reduces sputum elastase levels.[27]

Mucolytic therapy has been shown to be beneficial in the management of exacerbation rates of chronic bronchitis and COPD.[48] A review of trials using between 400-1200mg of NAC in the management of COPD showed reductions in the risk of exacerbation and hospitalisation.[12] In addition to the mucolytic action, a dose of 600mg of NAC administered twice daily over two months has been shown to reduce exhaled hydrogen peroxide levels in COPD patients, a marker of ROS production in the lung.[49] Furthermore, neutrophil recruitment to airways in COPD has been shown to increase mucous hypersecretion through increased levels of neutrophil elastase, which then causes increasing goblet cell degranulation.[7] The action of NAC on neutrophil function contributes to its overall efficacy in COPD.

N-Acetyl-Cysteine and Thyroid

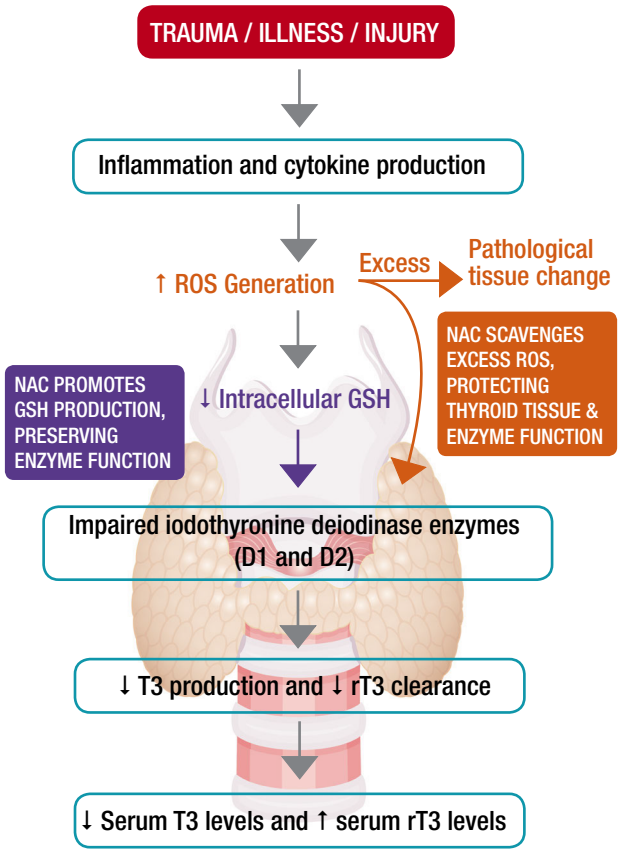
NAC may be protective of thyroid function. Reactive oxygen species are required for hormonogenesis by thyrocytes, however excessive production of reactive oxygen species can result in pathological changes to thyroid tissue that may drive autoimmune reactions.[50,51] NAC has been shown *in vivo* to reduce inflammatory reactions. The exact mechanism is unclear, but may be related to the restoration of cellular redox status for effective cell signalling pathways or the inhibition of inflammatory cytokines. NAC appears to achieve this without disrupting the minimal oxidative load required for thyroid hormone production.[51]

Further to this, NAC may assist in the balanced production of thyroid hormones. Iodothyronine deiodinases (D1-D3) are responsible for the catalysis of iodine removal from the outer D1 or D2, or inner D3 ring of thyroid hormones. Decreased function of D1 and D2 deiodinases may be noted in cases of depleted intracellular glutathione. This results in decreased triiodothyronine production (T3) and reduced reverse T3 (rT3) clearance. This contributes to imbalanced thyroid hormone levels which may be seen in conditions such as non-thyroidal illness syndrome. Further to this, all three deiodinase enzymes have an as yet undefined cofactor, with glutathione as a potential candidate for both D1 and D2 enzymes.[52]

Figure 3

The potential therapeutic impact of N-acetyl-cysteine on thyroid hormone production

NAC may balance thyroid hormone production via the promotion of glutathione (GSH) production and ROS scavenging. This may prevent impairment of iodothyronine deiodinase enzyme function.[52]



N-Acetyl-Cysteine and HIV Infection

The importance of glutathione sufficiency in HIV infection is well documented. Several studies demonstrate a direct relationship between glutathione deficiency, HIV disease progression and increased mortality. While deficiency in glutathione levels may be more marked in individuals undertaking nucleoside reverse transcriptase inhibitors (NRTI), lower levels may be due to increased oxidative stress and inflammation in response to viral infection.[13] Within the context of HIV infection, glutathione levels decrease throughout the progression of the disease particularly in erythrocytes and individual T-cell subsets.[13] Oxidative stress is known to increase activation of the HIV virus as well as contributing to DNA damage.[18] Administration of high doses of NAC (8g per day administered in multiple doses unless it was not tolerated), resulted in significant increases in glutathione levels, particularly in those individuals with severe depletion.[13]

The stimulation of nuclear factor-κB (NF-κB) by cytokines and hydroxyl radicals stimulates both gene activation in the nucleus of lymphocytes, macrophages and monocytes and the replication of HIV. The replication of the virus in turn promotes cytokine and free radical production, leading to further NF-κB production. NAC has been shown to block NF-κB activation, while glutathione has been shown to inhibit reverse transcriptase activity.[18]

Summary

The diverse actions of NAC discussed here represent a mere snapshot, and do little to elucidate the functional potential available with use. Practitioners seeking supplemental support for the management of oxidative stress, mitochondrial dysfunction, and immunological function or detoxification issues, would do well to consider NAC, particularly given its safety profile and limited side effects. While NAC has the potential to influence both biochemistry and clinical outcome relatively rapidly, it appears that long term supplementation may be required to create underlying biochemical changes that will influence overall health and wellbeing.

N-Acetyl-Cysteine Clinical Tips

Dosing: While the majority of research doses are 2g, not all individuals may be able to tolerate this dose initially and may exhibit signs of gastrointestinal upset. Clinician feedback has been that an initial dose of 250-500mg may be required, slowly increasing the dose to reach the required levels.

Timing: There is no clear indication that NAC needs to be given with or away from food to date. As NAC may interfere with mineral absorption, separate dosing of these nutrients is advised.

Medications:

- Do not use with nitroglycerin

Contraindications:

- Peptic ulcer
- Active candida infections (potential)
- Sulphur sensitivities (potential)

N-acetyl-cysteine possesses varied biological activity, indicating potential for diverse therapeutic application, including; assisting thyroid, respiratory, mental and reproductive health, imparting mucolytic action and improving antioxidant status.

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N-ACETYL-CYSTEINE LITERATURE REVIEW

CONDITION	DOSE	RESULTS	STUDY DESIGN
REPRODUCTIVE HEALTH continued			
Polycystic Ovarian Syndrome	• Arm 1 - metformin at 1.5g/day • Arm 2 - NAC at 1.8g/day	Both metformin and NAC reduced the level of fasting insulin significantly without any change in fasting glucose, glucose-insulin ratios were increased significantly. Hormonal profiles improved in both groups. Significant decreases in LH, total testosterone and free testosterone and significant increases in SHBG. Clinical manifestations of hirsuitism improved significantly in both groups compared with baseline. Total cholesterol and LDL decreased significantly after treatment with NAC.	Prospective study[56]
DETOXIFICATION			
Lead exposed workers and effect on markers of oxidative stress and glutathione metabolism	• Arm 1 - Control • Arm 2 - 200mg (1x200mg) NAC • Arm 3 - 400mg (2x200mg) NAC • Arm 4 - 800mg (4x200mg) NAC • Duration - twelve weeks while still experiencing occupational exposure	Blood levels decreased significantly in all groups receiving NAC. At 800mg, there was a significant decrease in lipofuscin levels – a marker of oxidative damage to lipids and proteins. For 400mg and 800mg doses, there was a significant increase in erythrocyte glutathione levels.	Multi-arm intervention trial of 171 male workers at zinc and lead works[57]
HIV INFECTION			
HIV	• 8g daily in divided doses	Significantly increased whole blood glutathione and CD4 cell glutathione compared to placebo.	Randomised, double-blind, placebo-controlled trial[13]
RESPIRATORY CONDITIONS			
Chronic Obstructive Pulmonary Disease	• Two NAC 600mg twice daily • Duration - 12 months duration	The GOLD classifications are the main method doctors use to describe the severity of chronic obstructive pulmonary disease (COPD). N-acetyl-cysteine treatment was found to be associated with a reduced number of exacerbations per patient year and duration of exacerbation compared to placebo. More effective in patients with GOLD II (moderate) disease than in GOLD III (serious) disease. Treatment prolonged time to first exacerbation in GOLD II patients and extended period to second and third exacerbation. Significant differences were noted by 6 month mark.	Multicentre, prospective, randomised, double-blind, placebo-controlled, parallel-group trial,1006 patients aged 40 to 80 years for 1 year; to assess whether long-term treatment with high dose NAC was useful to reduce exacerbation rates, and whether the benefits of treatment would be apparent with and without concomitant treatment with inhaled corticosteroids[58]
Chronic Obstructive Pulmonary Disease	• 600mg two times daily	Reduced exhaled hydrogen peroxide levels.	Single-blind placebo-controlled trial[48]
Idiopathic Pulmonary Fibrosis	• 600mg three times daily	In comparison to placebo, NAC significantly slows disease progression in terms of vital capacity and diffusing capacity.	Multinational, double-blind, randomised, placebo-controlled, parallel-group trial[59]
Cystic Fibrosis	• 600mg to 1g three times daily	Over the course of four weeks, treatment significantly increased GSH levels in CF blood neutrophils, significant decrease in airway neutrophil count and the number of elastase-releasing neutrophils in CF airways.	Unblinded dose-escalation tolerability and exploratory efficacy clinical trial[26]

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N-ACETYL-CYSTEINE LITERATURE REVIEW

CONDITION	DOSE	RESULTS	STUDY DESIGN
MENTAL HEALTH			
Autism	• Arm 1 - 900mg daily for 4 weeks • Arm 2 - 900mg twice daily for 4 weeks • Arm 3 - 900mg thrice daily for 4 weeks	Significant improvements in irritability, and RBS-R (Repetitive Behavior Scale – Revised) stereotypies and SRS (Social Responsiveness Scale) autism mannerisms w/ minimal adverse effects.	Pilot - Double-blind randomised placebo-controlled trial of children (aged 3.2 to 10.7 years)[41]
Autism Spectrum Disorders	• Arm 1 - 1.2g delivered in two 600mg doses alongside Risperidone • Arm 2 - Control, Risperidone alone	Reduction in irritability as measured by Aberrant Behaviour Checklist.	Randomised double-blind placebo-controlled clinical trial with two parallel groups, 40 patients[53]
Bipolar – Depression Component	• Two NAC 500mg capsules twice daily	N-acetyl-cysteine treatment was associated with a significant reduction in symptoms at treatment completion on the MADRS primary readout (least squares [LS] mean difference [95% CI]: -8.05 [-13.16c -2.95], p=0.002), paralleled by improvements in QOL and functioning measures. No significant differences between two groups for time to a mood episode and no proposed mechanism.	Double-blind placebo-controlled DSM-IV Bipolar Disorder (Type I and II) – Majority with Bipolar I diagnosis 75 patients – 58 dropped out, baseline determine by MADRS (Montgomery Asberg Depression Rating Scale) plus additional baseline testing, trial 24 weeks[38]
Bipolar	• 2g daily as two 500mg caps twice daily over 6 months	Reduction in depressive symptoms as measured by MADRS (Montgomery Asberg Depression Rating Scale). Benefit evident by end of 8 weeks.	Double-blind randomised placebo-controlled trial[38]
Negative Symptoms of Schizophrenia – Long Term	• Up to 2g/day alongside Risperidone	Significant improvement in negative symptoms in schizophrenia as measured by positive and negative syndrome scale (PANSS).	Multicenter, randomised, double-blind, placebo-controlled parallel group study of 42 patients on concurrent Risperidone treatment[54]
Schizophrenia	• 2g per day	Negative symptoms of schizophrenia, but not positive symptoms, were improved.	Double-blind randomised placebo-controlled trial[37]
Schizophrenia	• 1g twice daily	Shown to improve auditory cortical function.	A randomised, double-blind, cross-over[11]
Nicotine Dependence and Pathological Gamblers	• Between 1.2g and 3g based upon clinical assessment	When combined with behavioural therapy, NAC provided significant improvement on Fagerstrom Test for nicotine dependence after 6 weeks. During 3 month follow up, significant benefit for NAC vs placebo on measures of problem-gambling severity.	Randomised double-blind placebo-controlled 12 week study of 28 individuals undergoing BT for concurrent nicotine dependence and pathological gambling[55]
REPRODUCTIVE HEALTH			
Recurrent Unexplained Pregnancy Loss	• Arm 1 - 600mg plus folic acid at 500µg/day • Arm 2 - folic acid 500µg/day alone	The rate of successful pregnancy continuation up to 20 weeks and successful births was significantly higher in the group with NAC and folic acid compared with the folic acid only group.	Prospective controlled study[8]
Improving Sperm Parameters in Infertile Men	• Arm 1 - 200mcg selenium orally daily • Arm 2 - 600mg NAC orally daily • Arm 3 - 200mcg selenium plus 600mg of NAC orally daily • Arm 4 - Placebo • Duration - 26 weeks	Selenium and/or N-acetyl-cysteine improved semen quality. Markers showing statistically significant improvement included total sperm count, mean sperm concentration, normal sperm morphological ratio, and beneficial hormonal modulation.	Double-blind placebo-controlled randomised study including 468 infertile men with idiopathic oligo-asthenoteratospermia[33]
Polycystic Ovarian Syndrome	• 600mg three times per day	Significant reductions in total circulating testosterone levels, DHEAs, basal insulin, LDL triglyceride and homocysteine levels. Significant increases in SHBG levels and HDL levels.	Prospective study[31]