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REPORT

The Overlooked Compound That Saves Lives

By Julius Goepp, MD

N-ACETYL CYSTEINE

For more than three decades, a safe, low-cost compound has provided millions of people relief from the coughing, wheezing, and thick phlegm associated with cold and flu. Of course, pharmaceutical companies long ago co-opted it for profit by incorporating it into various patented drugs.

The sad consequence is that most aging individuals have never heard of it. Even many doctors remain unaware of its potential role as a frontline defense against some of today's most deadly public health threats, including:

- ***Acetaminophen toxicity and acute liver failure:*** the number one cause of acute liver failure in the United States.[1]
- ***Influenza:*** whose victims are primarily aging individuals—***three quarters*** of all flu-related deaths occur in the elderly.[2]
- ***Chronic obstructive pulmonary disease:*** the fourth-leading cause of death in the United States (includes **emphysema** and **chronic bronchitis**).[2]
- ***Helicobacter pylori:*** the bacterial culprit behind stomach ulcers, and a potentially lethal pathogen closely linked to malignant gastric cancer, the second most *frequent* cause of cancer death worldwide.[3]

Fortunately, renewed clinical interest in its broad-spectrum benefits is yielding fresh data on promising interventions for this safe, effective compound.

In this article, you will discover the latest research on ***N-acetyl cysteine*** (NAC), a readily available, inexpensive amino-acid derivative with four decades of scientific validation. You will learn of its role in restoring intracellular levels of one of the body's most powerful antioxidant defenses, ***glutathione*** (GSH). You will also find out how **600-1,800 mg** of NAC daily may act as an effective intervention against a constellation of chronic, degenerative diseases, including impaired glucose control and cancer.

AN UNDERUTILIZED INTERVENTION

NAC is a slightly modified version of the sulfur-containing amino acid cysteine. When taken internally, NAC replenishes intracellular levels of the natural antioxidant glutathione (GSH), helping to restore cells' ability to fight damage from reactive oxygen species (ROS).

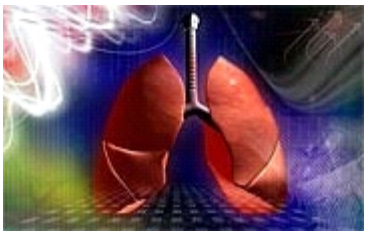
NAC has been used in conventional medicine for more than 30 years, primarily as a mucolytic (mucous-thinner) inhaled to manage conditions such as cystic fibrosis, in which mucous is abnormally thick and tenacious. While there is little in the scientific literature to support its use as an inhalant, NAC administered in this form remains highly popular among experienced pulmonary speclialists.[4,5]

NAC given intravenously or orally, on the other hand, saves lives every year as a treatment for acute poisoning with acetaminophen-containing pain-relieving drugs. Acetaminophen is sold as Tylenol® and combined with other drugs to create analgesic compounds, including Vicodin® and Percocet®.[6] Overdoses with acetaminophen are the number one cause of acute liver failure in the United States.[6-8] Too much acetaminophen overwhelms the body's glutathione reserves, which creates widespread and irreversible liver damage. NAC quickly restores protective levels of glutathione, averting catastrophe.[7]

Beyond this particular application, NAC has remained a relatively obscure and poorly understood compound until quite recently. Scientists all over the world are now beginning to understand just how vital glutathione metabolism really is, and how many

disease states involve glutathione deficiency.[9] According to Stanford University's Dr. Kondala R. Atkuri, "NAC has been used successfully to treat glutathione deficiency in a wide range of infections, genetic defects and metabolic disorders, including HIV infection and COPD. Over two-thirds of 46 placebo-controlled clinical trials with orally administered NAC have indicated beneficial effects of NAC measured either as trial endpoints or as general measures of improvement in quality of life and well-being of the patients."[9]

MULTITARGETED REGULATION OF GENE EXPRESSION



Much of NAC's beneficial activity derives from its capacity to modulate expression of genes for myriad signaling molecules in the inflammatory response.[10-12] NAC inhibits expression of pro-inflammatory cytokines following exposure to bacterial cell components and infection with influenza A virus.[13,14] NAC suppresses the "master signaling molecule" nuclear factor-kappaB (NF-kB), which in turn prevents activation of multiple inflammatory mediators.[15,16] NAC also regulates the gene for COX-2, the enzyme that produces pain- and inflammation-inducing prostaglandins in a wide array of chronic conditions.[17]

NAC's ability to replenish the intracellular glutathione supply and mitigate oxidative damage is a separate and equally powerful mechanism that affords protection against DNA damage and cancer development, even in smokers.[18] NAC's inhibition of inflammatory cytokine production is another mechanism credited with cancer reduction in various body tissues.[19]

Gene expression modifications induced by NAC may also help reduce the acute oxidant-provoked inflammatory response following exercise, making vigorous activity safer and even more beneficial.[20] Finally, obesity-associated insulin resistance, which arises from production of inflammatory signaling molecules in fat cells, can be sharply mitigated by NAC through regulation of their genes.[21,22]

The recent explosion of scientific evidence for NAC's multi-targeted health benefits is matched only by the willful ignorance of the mainstream medical community. Some even question its safety, despite nearly 40 years of use in a variety of clinical conditions, which have established the safety of this compound, even at very high doses and for long-term treatments.[18] One study demonstrated the safety of 1,800 mg per day for 142 days, while another study demonstrated the safety of 2,800 mg per day for 3 months.[23]

Here is a selection of the most compelling information about NAC from the global scientific community—information that should convince even skeptical mainstream physicians.

WHAT YOU NEED TO KNOW: N-ACETYL CYSTEINE'S BROAD-SPECTRUM BENEFITS

- Long relegated to infrequent use in unusual circumstances, the amino acid-derived compound N-acetyl cysteine (NAC) has drawn increased scientific attention.
- NAC replenishes levels of the intracellular antioxidant glutathione (GSH), which is often deficient with advancing age and in chronic illness.
- NAC also regulates expression of scores of genes in the pathways that link oxidative stress to inflammation.
- These dual effects give NAC a unique role in the prevention and treatment of many common diseases, both acute and chronic.
- NAC can protect against avian influenza and more common seasonal flu symptoms.
- NAC reduces the frequency and duration of attacks of chronic obstructive pulmonary disease (COPD) and may slow the clinical course of idiopathic pulmonary fibrosis (IPF).
- NAC protects tissues from the effects of exercise-induced oxidative stress, adding value and safety to your workout.
- NAC improves insulin sensitivity in people with some of the most difficult-to-treat metabolic disorders.
- NAC blocks cancer development at virtually every step in the process, and through multiple mechanisms, making it an important cancer chemopreventive agent.
- NAC fights the stomach infection Helicobacter pylori on two fronts, inhibiting the organism's growth while reducing production of inflammatory cytokines that can lead to gastritis and cancer.
- Though most individuals gain benefits from 600-1,800 mg/day, clinical studies have found that doses of up to 2,000 mg/day are safe and effective. A recent study demonstrated the safety of 2,800 mg/day for 3 months in patients with COPD.[23]

POTENT INFLUENZA PROTECTION

H5N1 influenza, or bird flu, is a lethal and potentially pandemic infection that produces the massive release of inflammatory mediators aptly called the “cytokine storm.”24 Other more common forms of influenza also act by triggering massive cytokine releases that inflame vulnerable lung tissue. In early 2010, it was discovered that NAC offers dual protection against bird flu. It inhibits both virus replication and expression of pro-inflammatory molecules in cells infected with H5N1 virus, holding out the promise of effective protection in the event of a global avian flu pandemic.[13]

NAC has also proven effective against seasonal influenza and flu-like illnesses. In a large study of older adults who took 600 mg twice daily for 6 months, only 25% of those experienced influenza-like episodes, compared with 79% in the placebo group.[25] Even those with flu symptoms experienced a significant reduction in illness severity and length of time confined to bed. All subjects tolerated the treatment well. The study’s lead author, Dr. Silvio de Flora, commented that “Administration of N-acetyl cysteine during the winter, thus, appears to provide a significant attenuation of influenza and influenza-like episodes, especially in elderly high-risk individuals.”[25]

Influenza is a complex disease with multiple targets, most notably inflicting damage to lung tissue through extreme oxidative stress and inducing genes for a large variety of inflammatory mediators.26,27 At the microscopic level the destruction is vivid. The influenza virus causes such intracellular turmoil that the term “cell boiling” has been used to describe the devastation.[28] But pretreatment of cells with NAC significantly offsets these effects, reducing the oxidative and inflammatory burden within lung tissue through multiple mechanisms.[26,28-30]

NAC has now been shown to protect laboratory mice from lethal influenza infection, synergistically enhancing the effects of several common antiviral medications.[31,32] And a nutrient mixture containing NAC, green tea extract, certain amino acids and micronutrients had powerful antiviral effects in cultured cells, rivaling those of prescription flu drugs such as amantadine and oseltamivir (Tamiflu®).[33,34] The NAC-based mixture actually affected viral replication for a longer period than did the drugs.[34]

In the words of prolific medical theorist Mark F. McCarty, “The most foolproof way to promote survival in epidemics of potentially lethal influenza is to target… intracellular signaling pathways which promote viral propagation or lung inflammation.”[30] McCarty goes on to cite NAC’s benefits as a multitargeted supplement with precisely those attributes. NAC at doses of 600 mg twice daily may significantly reduce the risk of a devastating bout of influenza.

NAC AND PULMONARY ARTERIAL HYPERTENSION: A REAL RISK?

N-acetyl cysteine (NAC) produces numerous beneficial effects in many human tissues both by supporting natural antioxidant systems and by favorably affecting expression of genes involved in the inflammatory response.

A 2007 study in laboratory mice, however, has raised a theoretical concern that chronic NAC administration in those animals might produce a condition called pulmonary arterial hypertension.[76] Here is a review of that study and some reassuring facts:

THE ISSUE

Pulmonary arterial hypertension (PAH) is an elevation in blood pressure in the arteries leading from the heart to the lungs. It is one of the consequences of *chronic hypoxia* (lack of sufficient oxygen) that occurs in a number of chronic cardiovascular and pulmonary (lung) diseases. It also arises in people with obstructive sleep apnea.[77-79] It is a rare condition, but when it occurs it can be difficult to detect and may be fatal if untreated.[79] Its causes remain unclear, but they seem to involve signaling molecules produced during hypoxia; some of those molecules include those involved in detecting and responding to oxidative stress.[80]

THE CONCERN

Scientists at the University of Virginia School of Medicine were studying the molecular signaling involved in hypoxia-related development of PAH when they observed what seemed to be a concerning finding: mice treated with NAC over periods of 3 weeks were developing PAH that mimicked the effects of chronic hypoxia.[76] The scientists were not studying the effects of NAC itself; they were simply using it to measure other nitrogen-related transfer reactions in blood. And the doses they used correspond to a human dose of about **20 grams** (20,000 mg) per day—far above any known supplement recommendation. Nevertheless, parts of their report were cited in one commentary as raising “the concern that chronic NAC therapy may induce similar vascular pathology in patients.”[81]

Is this a realistic concern, or is it a laboratory anomaly? Here’s the evidence to date.

THE EVIDENCE

The Virginia team's mouse study was published in 2007. Now, nearly 3 years later, there has not been a single additional publication connecting NAC therapy with PAH in either animals or humans. In reality, a substantial amount of science both before and after the 2007 report suggests just the opposite—that NAC may be instrumental in reducing, not increasing, the oxidant-induced blood vessel changes that occur in PAH. Here are the highlights:

- In one of the original animal studies demonstrating that oxidative stress contributes to development of PAH induced by hypoxia, NAC actually reduced the heart and lung changes that lead to PAH, in part by reducing toxic peroxide molecules.[80]
- NAC, given before and at the beginning of experimental hypoxia, was effective at preventing PAH, including deadly heart muscle changes, in laboratory rats.[82]
- NAC protects experimental animals' lungs from the acute lung injury caused by a variety of mechanisms involving hypoxia, oxidant stress, and inflammation, through its joint antioxidant and anti-inflammatory actions.[83,84]
- A study of human volunteers revealed that NAC supplements at **1,800 mg/day** *increased* the healthy respiratory response to hypoxia,[85] which normally declines strongly with age and may contribute to PAH.[86] Although this study was cited by the Virginia group as supporting their concern about NAC inducing PAH, no such evidence is presented in the human study, and in fact the authors conclude that NAC treatment "may be useful for elderly subjects and for patients who have other conditions with an oxidative shift… such as coronary heart disease and malignant diseases."[85]

THE RECOMMENDATION

There have been no further publications supporting this one-time observation made in an animal model using doses 10-20 times those suggested for long-term human supplementation. No human study has uncovered any evidence for a similar effect in humans. By contrast, there have been numerous studies demonstrating human benefit from NAC supplementation at moderate doses (1,200-1,800 mg per day) over the course of nearly 4 decades. At this point the known benefits of NAC appear to outweigh any potential risks. As with all supplementation, people should communicate clearly with their healthcare providers about how supplements and medications might work jointly to influence their health.

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LUNG DISEASE DEFENSE

Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and chronic emphysema, is a rapidly growing problem with global impact.[35] COPD is the result of years of oxidative damage to delicate lung tissue, with resultant chronic inflammatory changes.[36] The disease is worsened by air pollution and cigarette smoking, but is by no means limited to people with those exposures. Over time, victims' damaged airways may become colonized with dangerous bacteria, leading to chronic infection and still more inflammation in a vicious cycle. Current treatment consists mainly of anti-inflammatory steroids and lung-opening medications used in asthma, with the addition of antibiotics when infection threatens.

With its ability to reduce oxidative stress and simultaneously quash chronic inflammatory changes, NAC is emerging as a game-changing therapy in COPD. A randomized pilot study of adults with acute exacerbation of chronic bronchitis and positive bacterial culture in the sputum demonstrated that 600 mg of NAC twice daily led to a near doubling of the rate of bacterial eradication compared with standard therapy, while reducing the number and duration of acute exacerbations and improving quality of life.[35] NAC treatment of patients with moderate-to-severe COPD improved their physical performance on lung function tests, especially after exercise.[37]

Patients with advanced COPD frequently require low-dose oxygen therapy because of their lung damage. In many cases, however, oxidative stress induced by the disease has already rendered them glutathione deficient, so they have diminished protection against ongoing oxidation.[38] NAC administration at doses of 1,200-1,800 mg/day along with low-dose oxygen powerfully counteracts this oxidative stress. At doses of 1,800 mg per day, it has been shown to completely prevent further protein oxidation.[38] A dose of 600 mg twice daily over a 2-month period rapidly reduced exhaled hydrogen peroxide, a measure of oxidative burden in COPD sufferers.[39]

In one study utilizing a dose of just 600 mg per day for 10 weeks, NAC disrupted the molecular relationship between oxidative stress and inflammation, protecting lung tissue.[36] When NAC is added to inhaled corticosteroids, still further reductions in inflammatory parameters are found.[40]

Emphysema can be the unfortunate endpoint of advanced COPD, with lung tissue breaking down and losing much of its ability to exchange oxygen and carbon dioxide. Animal studies show that NAC attenuates COPD-related lung damage and emphysema by supporting expression of important protective genes in the cells lining the lung.[41]

Another devastating chronic lung condition called idiopathic pulmonary fibrosis (IPF) also involves increased oxidative burden and a deficiency of glutathione in lung tissue and fluids.[42] This progressive disease has a poor prognosis, even when treated with standard corticosteroids and powerful prescription anti-inflammatory drugs.[43,44] The median survival is only about 3 years regardless of therapy.[45]

Oral NAC supplements now offer a ray of hope for IPF sufferers. NAC significantly increases lung glutathione levels in both animal and human studies of IPF.[42,46] Given as an aerosol treatment, NAC may delay disease progression, and at doses of 600 mg three times daily preserves lung vital capacity and gas exchange better than standard therapy alone.[43,44]

In summary, evidence suggests that NAC may offer benefits at doses of 600 mg 2-3 times daily for people who have, or are at risk for, chronic lung conditions such as COPD and IPF (idiopathic pulmonary fibrosis).

REDUCE EXERCISE-INDUCED OXIDATIVE STRESS

Health-conscious people know that regular moderate exercise is vital to maintaining the integrity of the human body. Of course, everything has its price, and the rapid increase in metabolic activity during exercise produces some unwanted side effects.[20] These include an increase in oxidative stress that can overwhelm the body's antioxidant defense mechanisms and lead to tissue damage and abnormal activity of certain immune system cells.[47,48] Exercise also increases plasma levels of inflammatory cytokines such as TNF-alpha and various interleukins.[49] The solution, of course, is not to reduce your exercise regimen, but rather to look for ways to optimize the way your body handles those metabolic challenges.

NAC, with its powerful antioxidant and gene-regulating powers, is an excellent means of maintaining good exercise performance and limiting the damage caused by oxidative stress in the process. Supplementation with NAC (2,000 mg daily for 3 days, followed by 800 mg prior to exercise) in strenuously exercising adults lowered key interleukin levels to undetectable amounts and abolished the exercise-induced TNF-alpha response.49 And in patients with severe COPD, NAC supplementation improved exercise endurance time by 25% compared with placebo, while significantly reducing levels of oxidative molecules released by stimulated immune cells.[50] NAC supplementation also dramatically curtailed production of oxidized proteins in this group of highly oxidant-stressed chronically ill patients.

In vigorously exercising men, 1,800 mg per day of NAC prevented the expected decline in intracellular antioxidant levels and increased activity of the enzyme responsible for recycling and restoring glutathione to normal levels, protecting cells from oxidative stress.[51] And in mice, NAC supplementation significantly protected brain tissue against exercise-induced oxidative changes.[52] NAC also preserves normal levels of vital lymphocytes, which can decline after vigorous exercise.[48,53-55]

Regular supplementation with NAC at up to 1,800-2,000 mg per day may be an effective means of optimizing exercise performance while minimizing the effects of exercise-induced metabolic stress.

BRING GLUCOSE LEVELS UNDER CONTROL

Oxidative stress and inflammation are closely linked to insulin resistance and rising blood glucose levels. These effects are not limited to those with diabetes, but in fact are found even in obese, non-diabetic people and those with metabolic syndrome.[56] There are multiple steps in the cascade of events leading from oxidation to damaged insulin receptors and insulin resistance, so it makes sense to seek a supplement that can target many of those steps independently.[57,58] NAC is emerging as one such

multi-targeted supplement.[56]

Over time, chronic high blood sugar initiates a downward spiral by helping generate advanced glycation end-products (AGEs) that then impair normal responses to insulin, perpetuating elevated sugar levels. NAC reverses those effects in laboratory models.[22] Increasing blood sugar levels in laboratory animals triggers a pro-inflammatory response in fat tissue—also effectively reduced by NAC.[21] In an experiment that recreates a common human dietary trend, rats were given a diet high in the sweetener fructose, which produced increased blood pressure, plasma insulin levels, and triglyceride levels. Yet all of these dangerous physiological alterations were inhibited by NAC.[59]

Human studies of NAC to improve insulin sensitivity have recently appeared, especially in a group of people typically very difficult to treat. Profound insulin resistance is seen in women with polycystic ovary syndrome (PCOS), along with a variety of other metabolic disturbances. One study showed that NAC at 1,200 mg per day along with 1,600 mg of the amino acid arginine promoted a trend toward normal ovulatory cycles and substantially improved insulin sensitivity.[60] A short-term study showed that 1,800 mg of NAC daily helped improve insulin sensitivity in women with PCOS.[61]

Virtually all Americans consume too many calories and are at risk for at least some degree of insulin resistance. Daily supplementation with NAC at 1,200 to 1,800 mg per day may help to reduce the impact and slow the damage wrought by AGEs.

CANCER PREVENTION

The strong and growing links between oxidative stress, inflammation, and cancer make NAC a natural go-to compound for cancer chemoprevention. True to form, NAC has multiple anti-cancer activities acting at multiple targets to provide layers of cancer protection against a large variety of cancer types. NAC induces programmed cell death (apoptosis) in multiple types of human cancer cells.[62] In human gastric cancer cells, NAC not only induces apoptosis, but also stops DNA synthesis, preventing cancer the cells from replicating.[63] In melanoma cells, NAC inhibits NF-kB, preventing expression of signaling molecules needed by the cancer for growth.[64] NAC inactivates and promotes destruction of c-Src, a chemical control molecule that is overproduced in many human cancers, providing a completely unique means of slowing or stopping tumor development.[65] Finally, NAC protects DNA from breakage induced by ionizing radiation, but does not prevent cell destruction by radiation.[66] That's a vital finding because it means that NAC might allow radiation therapy to effectively kill cancer cells while minimizing the risk of so-called secondary cancers that could otherwise arise as side effects of the radiation.

Animal studies strengthen the case for NAC still further. NAC protects mice from cigarette smoke-induced lung cancers and other lung changes, a finding with enormous implications not only for current smokers but for ex-smokers and people exposed to second-hand smoke.[67] NAC protects rats from chemically-induced liver cancers immediately following tumor initiation.[68] This early interference with cancer development bodes well for NAC as a chemopreventive agent in the many human toxin-related cancers.

Human studies are similarly encouraging, even in the most challenging patient groups such as smokers. A randomized, double-blind chemoprevention trial of NAC 600 mg twice daily for 6 months vs. placebo in otherwise healthy smokers showed a significant reduction in formation of damaged or oxidized DNA segments, telltale early markers of cancer development in lung fluid.[69] The same study also demonstrated reductions in abnormal, pre-cancerous cell changes in the mouths of supplemented smokers. These effects support the scientists' conclusion that NAC can reduce tobacco smoke carcinogenicity in humans.

Colon cancer is another malignancy with strong links to oxidative stress and inflammation. Preliminary studies in humans show a 40% reduction in colorectal polyps in patients given 600 mg per day of NAC, compared with controls.[70] In a group of people with a previous history of pre-cancerous colonic polyps, 800 mg per day of NAC for 12 weeks significantly reduced the proliferative index, indicating a decreased risk of colon cancer.[71]

Supplementing with 600-1,200 mg per day of NAC appears to be an entirely appropriate means of adding to your general cancer-prevention strategy.

GASTRITIS, ULCERS, CANCER, AND HELICOBACTER PYLORI

Helicobacter pylori is a bacterium that colonizes various regions of the stomach and upper part of the small intestine. *H. pylori* infection produces major oxidative stress on tissues already vulnerable to extremes of pH and other chemical challenges, and the resulting inflammation produces pain and promotes development of gastric and esophageal cancers.[19] NAC is an obvious candidate for fighting *H. pylori* infections, both because of its powerful ability to interfere with the oxidant-inflammation connection, and also because of its potential to break down some of the gastric mucous layer beneath which the organism hides.[72]

NAC fights *H. pylori* in at least two ways. It markedly inhibits growth of H. pylori both in culture dishes and in live mice, helping to

reduce the total load of organisms present.[72] But NAC also powerfully regulates gene expression in stomach lining cells, reducing hydrogen peroxide production induced by H. pylori, and decreasing activation of NF-kB and subsequent release of inflammatory cytokines.[19,73] In human trials NAC improves eradication rates of *H. pylori* produced by standard treatment with antacids and antibiotics, when given at doses of **1,200 mg** per day.[74,75]

People who have gastritis or gastroesophageal reflux disease (GERD) may be infected with *H. pylori* and may benefit from supplementation with **1,200 mg** per day of NAC, especially during co-treatment with drugs to eradicate the organism.

SUMMARY

N-acetyl cysteine is a broad-spectrum compound traditionally under-utilized in conventional medicine. A burst of new clinical research reveals that NAC exerts dual effects, functioning both as a powerful antioxidant that replenishes cellular antioxidant systems (glutathione in particular) and also as a potent modulator of gene expression, regulating inflammation at multiple, fundamental levels. It has been shown to be an effective intervention against influenza, chronic lung diseases, cancers, insulin resistance, and gastritis caused by *H. pylori.* NAC's further value is shown in its ability to mitigate otherwise inevitable metabolic and immunological disturbances caused by exercise.

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

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