

# Clinical Applications of N-acetylcysteine

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## Abstract

N-acetylcysteine (NAC), the acetylated variant of the amino acid L-cysteine, is an excellent source of sulfhydryl (SH) groups, and is converted in the body into metabolites capable of stimulating glutathione (GSH) synthesis, promoting detoxification, and acting directly as free radical scavengers. Administration of NAC has historically been as a mucolytic agent in a variety of respiratory illnesses; however, it appears to also have beneficial effects in conditions characterized by decreased GSH or oxidative stress, such as HIV infection, cancer, heart disease, and cigarette smoking. An 18-dose oral course of NAC is currently the mainstay of treatment for acetaminophen-induced hepatotoxicity. N-acetylcysteine also appears to have some clinical usefulness as a chelating agent in the treatment of acute heavy metal poisoning, both as an agent capable of protecting the liver and kidney from damage and as an intervention to enhance elimination of the metals.

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## Introduction

N-acetylcysteine (NAC), a precursor of reduced glutathione (GSH), has been in clinical use for more than 30 years, primarily as a mucolytic. In addition to its mucolytic action, NAC is being studied and utilized in conditions characterized by decreased GSH or oxidative stress such as HIV infection, cancer, and heart disease. Because of its hepato-protective activity, intravenous and oral administration of NAC have been used extensively in the management of acetaminophen poisoning.

## Chemistry and Pharmacokinetics

NAC is a thiol (sulfhydryl-containing) compound which has the chemical formula  $C_5H_9NO_3S$  and a molecular weight of 163.2.<sup>1</sup> It is rapidly absorbed following an oral dose; however, extensive first pass metabolism by the cells of the small intestine and the liver results in the incorporation of NAC into protein peptide chains and the formation of a variety of metabolites of NAC. Only a small percentage of the intact NAC molecule arrives in the plasma, and subsequently in tissue.<sup>2</sup>

Only three percent of radioactively-labeled NAC is excreted in the feces following oral administration, indicating an almost complete absorption of NAC and its metabolites.<sup>3</sup> Peak concentrations of NAC typically appear in the plasma in less than one hour following oral administration.<sup>2,3</sup> The plasma half-life of free NAC is estimated to be about 2.15 hours, and

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virtually no NAC is detectable 10 to 12 hours post-administration.<sup>2</sup> Between 13 and 38 percent of a radioactive oral dose is recovered in urine within 24 hours.<sup>3</sup>

The sulfhydryl (SH) group is responsible for a great deal of the metabolic activity of NAC, while the acetyl-substituted amino group makes the molecule more stable against oxidation. Experimental results indicate that in gastric fluid most thiol-containing compounds are relatively unstable; however, in intestinal fluid only 16 percent of NAC is oxidized, while the oxidation of other thiol-containing molecules is between 75 and 100 percent.<sup>4</sup>

Researchers have estimated the oral bioavailability of the intact NAC molecule to be between four and ten percent;<sup>2,3,5</sup> however, disulfide linking to proteins,<sup>2</sup> and deacetylation of NAC in the intestinal mucosa and lumen are probably the greatest factors in this apparent low oral bioavailability of NAC.<sup>6</sup> Following an oral dose, the majority of NAC appears to be metabolized into other compounds, since, in addition to free and total NAC, concomitant increases in non-protein and protein SH groups, and small molecular weight protein-bound thiols, are found in human plasma.<sup>2,7</sup> *In vivo* experiments with animals indicate small quantities of both reduced and oxidized NAC do appear in hepatic portal vein plasma following the administration of NAC; however, cysteine and inorganic sulfite appear to be the major metabolites of NAC to arrive in the liver. Glutathione also accumulates in portal vein plasma, but to a much lesser degree.<sup>7</sup> Conversion of NAC to these metabolites most likely accounts for the majority of NAC's activity and protective effects.

### Mechanisms of Action

Most of the beneficial effects of orally-administered NAC are theorized to be a result of its ability to either reduce extracellular cystine to cysteine, or to be a source of SH

metabolites. As a source of SH groups, NAC can stimulate GSH synthesis, enhance glutathione-S-transferase activity, promote detoxification, and act directly on reactive oxidant radicals.<sup>8</sup>

Evidence, both *in vitro* and *in vivo*, indicates NAC is able to enhance the intracellular biosynthesis of GSH. In cell culture experiments, NAC promotes the uptake of cystine from the culture medium for cellular GSH biosynthesis.<sup>9</sup> *In vivo*, NAC can increase intracellular GSH levels in erythrocytes and in liver and lung cells,<sup>10</sup> and replenish GSH stores following experimental depletion.<sup>11</sup> Experimental results suggest NAC exerts a protective effect against paraquat-induced cytotoxicity by acting as a GSH precursor and by enhancing intracellular concentrations of GSH.<sup>12</sup> NAC also appears to work as an antidote for acetaminophen overdose because of its ability to act as a precursor of intracellular GSH.<sup>13</sup> Administration of a large dose of acetaminophen depletes glutathione levels and inhibits cytosolic glutathione transferase activity. Administration of NAC one hour after acetaminophen can prevent both of these effects.<sup>14</sup> Bernard et al have reported that NAC enhances red blood cell glutathione levels in patients with acute respiratory distress syndrome.<sup>15</sup>

NAC corrects the reduction in glutathione concentration and results in significant preservation of membrane fluidity and of the activities of catalase, mitochondrial superoxide dismutase and the different forms of glutathione peroxidase in biliary obstructed rats. These effects of NAC suggest it may be a useful agent to preserve liver function in patients with biliary obstruction.<sup>16</sup>

NAC appears to support the synthesis of GSH under conditions when the demand for GSH is increased, such as during the metabolism of acetaminophen; however, in the absence of increased stress on the glutathione pools, NAC might have no effect on plasma GSH. After the administration of NAC (30 mg/

**Figure 1.** Mechanisms of Action of NAC

antioxidant  
detoxification promoter  
enhances nitroglycerine effects  
glutathione synthesis promoter  
hepatoprotectant  
lowers lipoprotein (a) levels  
lowers homocysteine levels  
mucolytic

kg) to healthy volunteers, no increase in total cysteine and free and total glutathione was observed in plasma. In contrast, following the co-administration of 2 grams NAC and 2 grams acetaminophen, an increase in circulating cysteine and GSH concentrations was observed.<sup>17</sup>

*In vivo* treatment with NAC can enhance detoxification by liver and lung tissue of some direct-acting mutagens. NAC appears to exert protective effects by promoting GSH synthesis and metabolism, and by restricting the biotransformation of mutagenic/carcinogenic substances into more toxic compounds.<sup>10</sup> Although NAC does not appear to affect the concentrations of cytochromes P-450 in hepatic and pulmonary microsomes, it can stimulate cytosolic enzyme activities involved in NADP reduction (glucose 6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase), in glutathione reduction (GSSG-reductase) and in the reductive detoxification of xenobiotics.<sup>10</sup> NAC also appears to be able to increase cyclic guanosine monophosphate concentration under some experimental conditions.<sup>18</sup>

SH groups are essential for defense against reactive oxygen species. So, it is not surprising that NAC is a powerful scavenger of hypochlorous acid, and is capable of reducing hydroxyl radicals and hydrogen peroxide.<sup>19</sup> In animal experiments, NAC has been shown to be protective against oxygen toxicity to the lung caused by prolonged administration of 100 percent oxygen.<sup>20</sup>

NAC has been used successfully as a radioprotective agent and apparently exerts part of this effect by modulating cytokine concentrations. Interleukin-1, tumor necrosis factor-alpha and interferon-gamma endogenously provide protection of the hematopoietic system against radiation. *In vitro*, at low concentrations (0.6 and 6 mmol/l), NAC can significantly increase the concentration of interleukin-1 alpha and beta, and interleukin-2, while at higher concentrations (12-24 mmol/l), NAC decreases these cytokine concentrations.<sup>21</sup>

### Clinical Implications

**Respiratory:** Cotgreave et al found oral NAC was not effective in increasing levels of NAC, cysteine, or glutathione in the bronchoalveolar lavage fluid of six healthy volunteers given 600 mg of NAC daily for two weeks. However, they did find increases in protein-bound NAC and significant increases in both free and total plasma glutathione in plasma.<sup>22</sup> In contrast, Rodenstein et al administered NAC orally to patients with respiratory disorders. Their results indicate that concentrations of radioactivity in lung tissue were comparable with that of plasma. However, the percentage of free NAC, metabolites of NAC, and NAC bound in labile disulfide bridges to proteins accounted for 95 percent of the radioactivity in lung tissue, whereas the majority of radioactivity in plasma (about 64%) was incorporated into proteins.<sup>23</sup> These findings indicate NAC and its metabolites might only concentrate in lung tissue if they are required because of local disease processes.

Protective effects of NAC have been described in experimental and clinical acute respiratory distress syndrome. It appears NAC acts, in part, by replenishing the intracellular stores of GSH in activated granulocytes.<sup>24</sup> Administration has been shown to counteract the experimentally-induced increase in lung weight, development of alveolar edema,

deposition of fibrin, and increase in plasma viscosity.<sup>25</sup> Oral NAC has shown protection against inhalation of perfluoroisobutene, a pyrolysis product of polytetrafluoroethene which can cause pulmonary edema and death when inhaled.<sup>26</sup>

Oral NAC has been advocated as a mucolytic agent for use in chronic bronchitis; however, clinical results are equivocal. Miller et al investigated the effects of regular use of 200 mg three times per day for four weeks in nine patients with chronic bronchitis. No significant differences were found in lung function, mucociliary clearance curves, or sputum viscosity following treatment with NAC as compared to control or placebo measurements.<sup>27</sup> The influence of oral NAC on the exacerbation rate in patients with chronic bronchitis and severe airway obstruction was studied on 181 patients randomized to receive either NAC (200 mg three times per day) or placebo for five months in a double-blind, parallel group study. Although the outcome in the group taking NAC was better, differences did not reach statistical significance. The mean number of exacerbations was 2.1 for individuals receiving NAC and 2.6 for placebo, while the total number of days taking an antibiotic was 13.5 for the NAC group and 18.0 for the placebo group.<sup>28</sup> Parr et al gave either NAC or placebo to 526 patients suffering from chronic bronchitis for a six-month period. No statistically significant difference was found between the two groups in the number of acute exacerbations, but patients taking NAC showed a significant reduction in the number of days they were incapacitated.<sup>29</sup>

Rasmussen and Glennow investigated the clinical effect of NAC controlled-release tablets (300 mg twice per day) in chronic bronchitis. The double-blind, placebo-controlled, six-month comparison study included statistical evaluation after four and six months. During the trial, the NAC-treated group had a lower number of sick-leave days (NAC 260,

placebo 739), and exacerbation days (NAC 378, placebo 557) respectively.<sup>30</sup> Jackson et al reported NAC administration benefited symptomatology of patients with chronic bronchitis. In this multicenter, double-blind, placebo-controlled study, although improvement in subjective symptoms (sputum viscosity and character, difficulty in expectoration, and cough severity) occurred in both treatment groups, improvements in difficulty in expectoration and cough severity were greater in patients receiving NAC.<sup>31</sup>

Behr et al investigated the effect of NAC (600 mg three times per day for 12 weeks), as an adjunct to maintenance immunosuppression, on 18 patients with fibrosing alveolitis, a condition characterized by excessive oxidative stress and reduced levels of GSH in the lower respiratory tract. An increase in total and reduced glutathione were observed and pulmonary function tests improved during treatment with NAC.<sup>32</sup>

In animal models, NAC has been shown to attenuate diaphragm fatigue, possibly due to its ability to scavenge free radicals. NAC inhibits the impairment in diaphragm contractility caused by the administration of streptozotocin to rats.<sup>33</sup> Evidence indicates NAC might positively impact some aspects of human diaphragm function as well. The research of Travaline et al indicates intravenous NAC can improve contractility and attenuate low-frequency human diaphragm fatigue.<sup>34</sup>

**HIV:** In general, low cysteine and GSH levels are found in human immunodeficiency virus (HIV)-positive individuals; however, the therapeutic efficacy of NAC administration in this population is still equivocal. *In vitro*, NAC causes splenocyte proliferation and protects lymphocytes against mitogen-induced cytotoxicity.<sup>35</sup> Evidence suggest NAC enhances the immune response of peripheral blood T cells. In addition, NAC blocks the suppression of T cell mitogenesis and cytokine production by protease inhibitors such as

N-tosylphenylalanine chloromethyl ketone.<sup>36</sup> Cell culture evidence also suggests NAC supplementation can protect hematopoietic progenitor cells from zidovudine (AZT)-induced toxicity.<sup>37</sup>

Roberts et al conducted a cell culture study to determine the effects of glutathione and NAC on the cytotoxicity of neutrophils and mononuclear cells from HIV-infected patients. They found that NAC enhanced the antibody-dependent cellular cytotoxicity of neutrophils and suggested NAC "... may be beneficial to AIDS patients whose defects in leukocyte cytotoxicity may be due to glutathione depletion."<sup>38</sup>

Wu et al reported that NAC can improve the ability of cells to form T-cell colonies in individuals with AIDS and constitutional symptoms of HIV infection.<sup>39</sup> Herzenberg et al demonstrated that low GSH levels predict poor survival in otherwise indistinguishable HIV-infected subjects. They suggested that since oral administration of NAC replenishes GSH in these subjects, its supplementation might be able to improve survival.<sup>40</sup> Droge et al noted "...anecdotal observations by us and others revealed that patients with manifest AIDS may improve substantially on NAC therapy but cannot be cured....treatment of HIV-infected patients in the early stages of the disease with NAC may help to prevent the progression to AIDS."<sup>41</sup>

Akerlund et al conducted a double-blind, placebo-controlled trial to determine the effect of NAC supplementation in individuals seropositive for HIV. All subjects began the trial with a CD4+ lymphocyte cell count of more than 200 x 10<sup>6</sup>/l. Subjects received either 800 mg NAC or placebo for four months. Administration of NAC increased plasma cysteine levels to normal, and slowed the decline of the CD4+ lymphocyte count when compared to placebo.<sup>42</sup>

Akerlund et al also investigated the use of NAC in combination with trimethoprim-

sulfamethoxazole in primary *Pneumocystis carinii* prophylaxis in HIV sero-positive patients with CD4+ cell counts of less than 200 x 10<sup>6</sup>/l or an AIDS diagnosis. Although oral NAC was well tolerated, it did not replenish plasma cysteine or glutathione levels in these subjects and it did not significantly decrease the risk of adverse reactions to trimethoprim-sulphamethoxazole.<sup>43</sup>

Although further trials are needed, based upon available information it appears NAC supplementation might be a valuable component of an integrated protocol for HIV-seropositive individuals, particularly those with low GSH levels and CD4+ cell counts of more than 200 x 10<sup>6</sup>/l.

**Influenza:** Administration of NAC appears to reduce symptomatology associated with influenza and influenza-like episodes. A total of 262 subjects of both sexes were given either placebo or NAC (600 mg) orally twice daily for six months. Although frequency of seroconversion towards A/H1N1 Singapore 6/86 influenza virus was similar in the two groups, NAC treatment decreased both the frequency and severity of influenza-like episodes, and the length of time confined to bed. The authors concluded "N-acetylcysteine did not prevent A/H1N1 virus influenza infection but significantly reduced the incidence of clinically apparent disease."<sup>44</sup>

**Cancer:** The administration of NAC might have a role in the prevention of cancer and in an integrated approach to the treatment of some forms of cancer; however, information in this area is still preliminary. Experimentally-induced DNA damage can be completely blocked by NAC. Evidence also indicates NAC can protect bone marrow cells from the growth-inhibitory effects of chloramphenicol and thiamphenicol.<sup>45</sup> NAC has been shown to have antimutagenic activity towards various genotoxic agents. Administration of NAC can also reduce the incidence of experimentally-induced intestinal tumors.<sup>46</sup>

De Flora et al investigated the effect of NAC on GSH metabolism and on the biotransformation of carcinogenic and/or mutagenic compounds. *In vitro*, NAC counteracted the mutagenicity of direct-acting compounds, and at high concentrations, completely inhibited the mutagenicity of procarcinogens. *In vivo*, NAC can also inhibit the mutagenicity of a number of compounds and can inhibit the induction of tumors by some carcinogens.<sup>47</sup> NAC was not effective as a chemopreventive agent in a model of tumorigenesis by nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.<sup>48</sup>

Cell culture and animal studies have demonstrated NAC might protect normal cells, but not malignant cells, from the toxic effects of chemotherapeutic agents and radiation. De Flora et al reported combined treatment with doxorubicin and NAC, under various experimental conditions, can be highly effective, apparently working synergistically to reduce tumor formation and prevent metastases.<sup>49</sup> Experimental evidence suggested NAC pre-treatment dramatically diminished the cardiac toxicity of doxorubicin in mice. Pre-treatment with NAC increased the non-protein SH content of P388 leukemia cells nearly threefold, without negatively affecting the chemotherapeutic activity of doxorubicin against this tumor.<sup>50</sup> Evidence also indicates that although NAC could help protect against toxicity resulting from X-rays or chemotherapeutic treatment, it did not interfere with the efficient killing of tumor cells by X-rays or by bleomycin.<sup>51</sup>

Kobrinsky et al conducted a phase I trial of high-dose acetaminophen with NAC rescue on 19 patients with advanced cancer. Moderate fatigue, anorexia, and weight loss were the main toxic effects observed. Transient grade 3 liver toxicity was also noted following one treatment. A 15.8 percent partial response rate was observed.<sup>52</sup>

**Heart Disease** : NAC appears to have several possible therapeutic roles associated

with heart disease. Administration seems to positively impact homocysteine and possibly lipoprotein(a) (Lp(a)) levels, protect against ischemic and reperfusion damage, and enhance aspects of the effectiveness of nitroglycerine (NTG).

High levels of plasma Lp(a) or homocysteine are associated with an increased risk for cardiovascular disease. Gavish and Breslow administered 2 grams NAC daily for four weeks followed by 4 grams daily for four weeks to two patients with elevated Lp(a). They reported a 70 percent reduction of Lp(a) in these individuals (reduction of plasma Lp(a) from 58 to 20 mg/dl and from 59 to 18 mg/dl).<sup>53</sup> In cell cultures, NAC has been shown to lower the intracellular accumulation of homocysteine.<sup>54</sup> Wiklund et al showed administration of NAC reduces plasma homocysteine levels by 45 percent ( $P < 0.0001$ ). In their trial, NAC had no effect on plasma Lp(a) levels.<sup>55</sup> Patients undergoing maintenance dialysis often (> 75% of patients) have hyperhomocysteinemia refractory to standard B-vitamin supplementation. Bostom et al reported oral NAC supplementation (1200 mg) resulted in a 16 percent reduction in non-fasting pre-hemodialysis total plasma homocysteine.<sup>56</sup>

Experimental research and initial clinical observations indicate NAC might be useful in the treatment of ischemic and reperfusion injury in acute myocardial infarction. Because myocardial ischemia generally is characterized by a decline of cellular SH groups, reperfusion can result in oxidative damage. Under experimental conditions, infusion with NAC for 60 minutes before ischemia increased tissue content of GSH by 38 percent. The ischemia-induced decrease of GSH and protein SH was also limited by pre-treatment with NAC.<sup>57</sup>

Administration of NAC, in combination with NTG and streptokinase, was associated with significantly less oxidative stress, a trend toward more rapid reperfusion,

and better preservation of left ventricular function in patients with evolving acute myocardial infarction.<sup>58</sup> Sochman et al reported that patients treated with streptokinase plus NAC (100 mg/kg) had significantly more favorable values of the monitored parameters than those treated with streptokinase alone.<sup>59</sup>

Evidence suggests pretreatment with NAC might attenuate impaired tissue oxygenation and preserve myocardial performance in cardiac risk patients undergoing hyperoxic ventilation. Intravenous administration of NAC (150 mg/kg) was reported to slightly increase cardiac index and left ventricular stroke work index, preserve whole-body oxygen consumption, and decrease systemic vascular resistance during brief hyperoxia in cardiac risk patients. Clinical signs of myocardial ischemia, such as ST-depression, also did not occur if patients were prophylactically treated with NAC.<sup>60</sup>

NAC potentiates the coronary dilating<sup>61</sup> and anti-platelet effects of NTG<sup>62</sup> and limits the development of hemodynamic tolerance to NTG.<sup>63</sup> Horowitz et al, in a randomized double-blind study of 46 patients with severe unstable angina pectoris unresponsive to standard treatment, reported the combined intravenous administration of NTG and NAC resulted in a significantly lower incidence of acute myocardial infarction. However, since symptomatic hypotension did occur frequently in the NTG/NAC group, the authors suggested "this regimen should be used with some caution."<sup>64</sup>

NTG and NAC appear to be an effective combination for the treatment of unstable angina; however, the high incidence of side-effects (about 35%; mostly severe headaches) limits the clinical usefulness of this therapeutic strategy.<sup>65</sup>

**Cigarette Smoking:** Oral supplementation with NAC might be a prudent recommendation for smokers or individuals

constantly exposed to second-hand smoke. Cigarette smoke significantly increases the number of secretory cells in the airways of experimental animals; however, prophylactic administration of NAC inhibited cigarette smoking-induced mucous cell hyperplasia and epithelial hypertrophy,<sup>66</sup> and reduced the time required for the number of secretory cells to return to normal levels.<sup>67</sup>

Data suggests oral NAC can positively influence the activity of inflammatory cells in the bronchoalveolar space of smokers.<sup>68</sup> Oral administration of NAC (200 mg three times per day) also counteracted the cigarette-smoking-induced decline in the proportion of alveolar lymphocytes and the decreased phagocytic capacity and ability to produce leukotriene B4 of alveolar macrophages in smokers.<sup>69</sup>

**Acetaminophen Overdose:** Acetaminophen (Tylenol<sup>®</sup>, paracetamol) overdose is a common form of poisoning, capable of injuring the liver, kidneys, heart, and central nervous system. Overdose can also produce fatal results, typically in individuals who intentionally consume greater than 10 g. Liver damage usually develops within several hours of ingestion as a result of oxidation of acetaminophen to toxic metabolites such as N-acetylbenzoquinonimine. These metabolites deplete hepatic intracellular GSH stores and subsequently damage the liver. In cases of acetaminophen overdose, NAC is the antidote of choice. The mainstay of treatment for acetaminophen-induced hepatotoxicity is currently an enteral 18-dose course of NAC.

Smilkstein et al analyzed the use of oral NAC as an antidote for poisoning with acetaminophen in 2,540 patients treated with a loading dose of 140 mg oral NAC per kg of body weight, followed four hours later by 70 mg per kg given every four hours for an additional 17 doses. Eleven deaths were reported from the 2,540 patients; however, no deaths were clearly caused by acetaminophen toxicity when NAC therapy was begun within 16

hours of overdose. When given within eight hours of acetaminophen ingestion, NAC was protective regardless of the initial plasma acetaminophen concentration; however, efficacy decreased when treatment was further delayed. The authors concluded "...N-acetylcysteine treatment should be started within eight hours of an acetaminophen overdose, but that treatment is still indicated at least as late as 24 hours after ingestion. On the basis of available data, the 72-hour regimen of oral N-acetylcysteine is as effective as the 20-hour intravenous regimen..."<sup>70</sup> Delay in administering NAC after acetaminophen intoxication significantly increases the risk of mortality.<sup>71</sup>

The combination of acetaminophen and alcohol can also result in potentially fatal outcomes. Johnston and Pelletier reviewed the available literature and found that if the combination of a clear history of alcohol use and a history of acetaminophen use/abuse caused a peak aspartate aminotransferase (AST) greater than 800 U/L, the result was a mortality rate of 32 percent. In these individuals, treatment with NAC was often not effective due to delayed presentation and diagnosis.<sup>72</sup>

Experimental evidence indicates the combination of NAC and cimetidine (an H<sub>2</sub>-receptor-antagonist drug and an inhibitor of hepatic microsomal oxidative enzymes) might also have an additive effect in the treatment of acetaminophen overdose. In mice, the concomitant administration of NAC and cimetidine produced a 100 percent survival rate, reduced plasma GOT and GPT activities to within the normal range, and significantly raised hepatic GSH concentrations to values close to those measured in saline-treated control animals.<sup>73</sup>

Adverse reactions to NAC treatment are relatively common, but are rarely serious; however, anaphylactic reaction to NAC after an overdose of acetaminophen is possible. The most common adverse reactions to NAC during antidote of acetaminophen overdose are

vomiting, diarrhea, skin reactions, and headache.<sup>74</sup>

**Other Poisonings:** Acute acrylonitrile intoxication is followed by loss of consciousness, convulsions, respiratory arrest, and may end fatally. Animal experiments have demonstrated the antidotal effects of NAC after acrylonitrile inhalation.<sup>75</sup>

NAC administration appears to be beneficial in the treatment of caustic alkaline injury to the esophagus. Under experimental conditions, stricture formation was less frequent, and the severity of stenosis was decreased in animals treated with NAC.<sup>76</sup>

**Heavy Metals:** NAC appears to have some clinical usefulness as a chelating agent in the therapy of acute heavy metal poisoning. NAC has been shown to be more effective than calcium EDTA or dimercaptosuccinic acid as an agent to increase the urinary excretion of chromium and boron. NAC also appeared to reverse the oliguria associated with intoxication from these compounds. In these same experiments, NAC did not increase the excretion of lead.<sup>77</sup>

*In vitro*, NAC effectively chelates gold, silver, and mercury. In patients receiving gold injections for rheumatoid arthritis, Lorber et al found a consistent increase in gold excretion following NAC therapy. They also reported NAC was effective in correcting the gold-induced suppression of bone marrow function.<sup>78</sup> Hanson et al similarly reported a beneficial effect of NAC in a case of gold-induced aplastic anemia. A 47-year-old woman with rheumatoid arthritis developed aplastic anemia after a five-year treatment with gold sodium thiomalate. Treatment with corticosteroids, plasmapheresis and infusion of NAC resulted in complete hematologic remission.<sup>79</sup>

Evidence suggests that the ability of mercury to accumulate in the liver and kidneys might be inversely related to the supply of non-protein SH groups. NAC, a source of these groups, significantly reduces mercury content



## Figure 2. Clinical Indications For NAC Supplementation

acetaminophen toxicity  
acute respiratory distress syndrome  
cancer  
chronic bronchitis  
epilepsy (Unverricht-Lundborg type)  
heart disease  
heavy metal poisoning  
HIV infection  
influenza prevention  
Sjogren's Syndrome

in and is protective against mercury-induced damage to these organs.<sup>80</sup> NAC appears to have the ability to promote the urinary elimination of methyl mercury. Lund et al reported that, in a case of acute methyl mercury ingestion, urinary organic mercury elimination rate increased dramatically during and following hemodialysis with an infusion of NAC. They suggested "...NAC may be more effective than either D-penicillamine or DMPS for enhancing urinary organic mercury elimination."<sup>81</sup>

Under experimental conditions, NAC has been shown to be protective against arsenite<sup>82, 83</sup> and copper poisoning.<sup>83</sup> Martin et al reported a case of a man who had ingested a potentially lethal dose of sodium arsenate ant poison (900 mg) in a suicide attempt. The individual deteriorated progressively for 27 hours, while dimercaprol and other supportive measures failed to improve his condition. Based upon recommendations from the National Capitol Poison Center, Washington, D.C., intravenous NAC was added to the regimen. Four grams of NAC were administered every four hours for a total of 18 doses. Within 24 hours, the patient's clinical condition improved markedly. Within several days his serum albumin and liver-associated enzymes normalized and he was released from the hospital.<sup>84</sup>

The chelation of heavy metals utilizing NAC during pregnancy should be considered contraindicated until more information is

available. Endo and Watanabe hypothesized that since NAC is effective at chelating metals such as mercury, cadmium, and chromium, administration might ameliorate the teratogenic effects of these metals. Although their results show a reduction in the rate of dead or resorbed fetuses, they also unexpectedly found that in all experimental animals administered NAC in combination with heavy metals, the incidence of congenital malformations was distinctly elevated when compared with the groups receiving just the heavy metals.<sup>85</sup>

**Sjogren's syndrome:** NAC may also have a beneficial therapeutic effect on ocular symptoms of Sjogren's syndrome. Walters et al investigated the therapeutic efficacy of NAC (200 mg three times per day) in 26 patients with primary or secondary Sjogren's syndrome in a double-blind, cross-over trial. One patient withdrew from the trial due to central abdominal pain following each dose of NAC; however, the remaining 25 individuals completed the four-week study. Six of twenty patients reported improvement of ocular soreness ( $p = 0.004$ ) and ocular irritability ( $p = 0.006$ ) following supplementation with NAC. Halitosis ( $p = 0.033$ ) and daytime thirst ( $p = 0.033$ ) also improved following NAC supplementation.<sup>86</sup>

**Myoclonus Epilepsy:** Hurd et al reported beneficial effects of treating four siblings with progressive myoclonus epilepsy of the Unverricht-Lundborg type, with NAC (4-6 grams a day), other antioxidants, and magnesium. The patients were treated for up to 30 months and a marked decrease in myoclonus and some normalization of somatosensory evoked potentials were reported.<sup>87</sup>

**Drug and Nutrient Interactions:** Typically, the concomitant oral administration of charcoal and NAC is not recommended, since it is believed that charcoal might interfere with absorption of NAC. Although *in vitro* experiments have shown NAC can be adsorbed by activated charcoal,<sup>88, 89</sup> *in vivo* experiments indicate either no interference,<sup>90</sup>

or, with high doses of charcoal (100 g), slight reductions in NAC absorption.<sup>91</sup>

**Toxicity and Side-effects:** The LD50 of NAC is 7888 mg/kg in mice and greater than 6000 mg/kg in rats following oral doses. In animal fertility studies, no adverse affects were reported at doses up to 250 mg/kg and no teratogenic effects were observed at doses as high as 2000 mg/kg. In these same studies NAC had no adverse effects on delivery, physical development, or lactation. NAC evidenced no mutagenicity in the "Ames test."<sup>94</sup> Wong et al reported oral administration of NAC partially reduced phenytoin-induced teratogenicity and embryopathy; however, altering the route of NAC administration, or increasing the dose of phenytoin and/or NAC, enhanced phenytoin embryotoxicity.<sup>92</sup>

NAC has been safely administered during pregnancy; however, most of the evidence for its safety is a result of acetaminophen overdose. Experimental evidence indicates NAC might increase the incidence of teratogenicity when utilized for heavy metal intoxication. In general there are no adequate studies of NAC administration and pregnancy, so it should only be used when clearly indicated.<sup>93</sup>

The intravenous administration of NAC can result very infrequently in allergic reactions. These reactions have been primarily reported when NAC has been utilized for acetaminophen toxicity, generally confined to the skin, and consisting of urticaria and/or angioedema.<sup>94</sup> Large oral doses of NAC, usually given in reponse to acetaminophen overdose, can result in nausea and vomiting, gastrointestinal disturbances, rash, pruritis, angioedema, bronchospasm, tachycardia, hypotension, or hypertension, although the occurrence is rare.<sup>95</sup>

The pharmacokinetics of NAC are altered in patients with chronic liver disease. In general, these individuals tend to have increased serum concentrations and decreased ability to clear NAC from the blood stream following an intravenous dose.<sup>95</sup>

Evidence suggests that in healthy individuals, at doses as low as 1.2 g daily, NAC might actually act as a pro-oxidant and might lower GSH and increase the amount of oxidized GSH.<sup>96</sup> Because of this information, it is not recommended that clinically-relevant amounts of NAC be utilized by healthy persons who are not exposed to extreme oxidative stress.

## Conclusions

Although deacetylation of NAC in the intestinal mucosa and lumen probably limits the absorption of intact molecules of NAC, this apparent low bioavailability is misleading, since in the degradation process a variety of physiologically-beneficial, SH-containing metabolites are formed. These metabolites stimulate GSH synthesis, enhance glutathione-S-transferase activity, promote detoxification, and act directly as free radical scavengers.

NAC appears to support the synthesis of GSH primarily under conditions when the demand for GSH is increased, such as during excessive oxidative stress, or during certain disease processes. However, the chronic oral supplementation of NAC as a nutrient to enhance life extension (because of its role in replenishing GSH and acting as an antioxidant) by otherwise healthy individuals might need to be reconsidered. Since NAC appears to be most effective at enhancing GSH only in conditions when it is low, and if it can act, as some evidence indicates, as a pro-oxidant in healthy individuals, with doses as low as 1.2 grams per day, chronic daily supplementation of a therapeutic dose by healthy individuals not subject to excessive oxidative stress should be considered ill advised.

In conditions characterized by excessive oxidative stress, such as chronic exposure to cigarette smoke and heart disease, and in clinical situations where GSH levels are decreased, NAC appears to be a highly effective component of a nutritional supplementation

protocol. It is currently the “gold-standard” treatment approach for management of acetaminophen poisoning and should be investigated for its antidotal properties in other types of poisoning. NAC supplementation should also be considered as a possible addition to protocols designed to enhance elimination of heavy metals.

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