N-Acetylcysteine: Multiple Clinical Applications

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_N_-acetylcysteine is the acetylated variant of the amino acid L-cysteine and is widely used as the specific antidote for acetaminophen overdose. Other applications for _N_-acetylcysteine supplementation supported by scientific evidence include prevention of chronic obstructive pulmonary disease exacerbation, prevention of contrast-induced kidney damage during imaging procedures, attenuation of illness from the influenza virus when started before infection, treatment of pulmonary fibrosis, and treatment of infertility in patients with clomiphene-resistant polycystic ovary syndrome. Preliminary studies suggest that _N_-acetylcysteine may also have a role as a cancer chemopreventive, an adjunct in the eradication of *Helicobacter pylori,* and prophylaxis of gentamicin-induced hearing loss in patients on renal dialysis. (*Am Fam Physician.* 2009;80(3):265-269. Copyright © 2009 American Academy of Family Physicians.)

Although *N*-acetylcysteine is widely known as an antidote to acetaminophen overdose,[1] it has multiple other uses supported by varying levels of evidence. These clinical applications stem from its ability to support the body's antioxidant and nitric oxide systems during stress, infections, toxic assault, and inflammatory conditions. Supplementation with *N*-acetylcysteine has been shown to increase levels of glutathione, the body's major antioxidant.[2] Glutathione is critically important for detoxifying an array of toxic substances, including xenobiotics (chemicals foreign to biologic systems), peroxide compounds, and other free radical–generating molecules. It thereby exerts a profound protective effect on cells.[3]

Of glutathione's three component amino acids (i.e., glutamate, glycine, and cysteine), cysteine has the lowest intracellular concentration.[3] Because *de novo* synthesis is the primary mechanism by which glutathione is replenished, cysteine availability can limit the rate of glutathione synthesis during times of oxidative stress.[2] By correcting or preventing glutathione depletion, *N*-acetylcysteine may ameliorate the inflammation that occurs in conditions such as chronic obstructive pulmonary disease (COPD), influenza, and idiopathic pulmonary fibrosis. In addition to its antioxidant action, *N*-acetylcysteine acts as a vasodilator by facilitating the production and action of nitric oxide. This property is an important mechanism of action in the prophylaxis of contrast-induced nephropathy and the potentiation of nitrate-induced vasodilation.[4]

COPD

N-acetylcysteine has been shown to have a positive effect on the clinical course of COPD.[2] An open-label study of 1,392 patients found that *N*-acetylcysteine reduced the viscosity of expectorated phlegm, reduced cough severity, and improved ease of expectoration in 80, 74, and 71 percent of patients, respectively, after two months of treatment.[5] The study also reported "marked improvements" in rhonchi, crepitations, dyspnea, cyanosis, and associated heart failure after one to two months of therapy.[5] In another large, open-label trial that compared *N*-acetylcysteine with a control medication, patients taking *N*-acetylcysteine experienced a decrease in the deterioration of lung function as measured by forced expiratory volume in one second (FEV_1).[6] This effect was most pronounced in patients older than 50 years. In this subgroup, the annual decline in lung function was almost 50 percent less in those taking *N*-acetylcysteine (an annual decrease of FEV_1 of 30 mL versus 54 mL in the control group).[6]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Uses of N-*acetylcysteine*	*Evidence rating*	*References*
Preservation of lung function in COPD	C	6
Prevention of exacerbation of COPD	B	5, 7
Prevention of contrast-induced nephropathy	B	16
Attenuation of influenza illness	B	18
Preservation of lung function in idiopathic pulmonary fibrosis	C	19
Treatment of infertility in women with clomiphene (Clomid)-resistant polycystic ovary syndrome	B	20, 21

COPD = chronic obstructive pulmonary disease.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

N-acetylcysteine has also been studied for its ability to prevent exacerbation of COPD. A meta-analysis of 11 double-blind, placebo-controlled trials, selected on the basis of quality criteria from 39 available studies, revealed a statistically significant difference between the number of exacerbations in patients treated with *N*-acetylcysteine and those receiving placebo.[7] Combined, these trials included 2,011 analyzable patients—996 who received *N*-acetylcysteine and 1,015 who received placebo. The number needed to treat for one patient to avoid an exacerbation was 5.8. Small improvements in FEV_1 were also reported. The rate of adverse effects, most commonly gastrointestinal, was similar to or slightly lower than that of placebo, with a number needed to harm of 198.[7]

One prominent study did not show any effect of *N*-acetylcysteine on primary end points.[8] A total of 523 patients with COPD were randomized to receive 600 mg of *N*-acetylcysteine per day or placebo and were followed for three years. Although the primary end points of exacerbation rate and deterioration of FEV_1 were not notably different between the groups, functional residual capacity did improve in the *N*-acetylcysteine group, and the exacerbation rate was much improved in patients not taking inhaled steroids.[8]

Contrast-Induced Nephropathy

Approximately 10 million procedures using radiologic contrast material are done in the United States annually.[9] The occurrence of contrast-induced nephropathy ranges from approximately 2 percent in patients with creatinine levels below 1.5 mg per dL (130 µmol per L) to 20 percent in patients with levels above 2.5 mg per dL (220 µmol per L). Patients with diabetes and all patients with creatinine levels higher than 2.0 mg per dL (180 µmol per L) are at high risk.[10] Contrast-induced nephropathy is also associated with dramatically increased mortality and morbidity that persists after hospital discharge, regardless of the need for renal dialysis.[10]

In 2000, a positive trial using *N*-acetylcysteine as prophylaxis for contrast-induced nephropathy was published in a high-profile journal,[11] initiating a burst of research activity that to date has resulted in more than 20 randomized controlled trials (RCTs) and 13 meta-analyses.[12-15] Seven of the meta-analyses determined that *N*-acetylcysteine is beneficial for preventing contrast-induced nephropathy, five determined that the data are inconclusive, and one determined that *N*-acetylcysteine is ineffective in preventing renal dialysis.[12-15] Although meta-analyses are considered the gold standard for evidence in clinical medicine, the RCTs for contrast-induced nephropathy available to date are heterogeneous clinically (i.e., differences in study design, patient populations, intervention protocols, and primary outcomes) and statistically (i.e., variation in the trial results is higher than expected by chance alone), limiting the conclusions that can be drawn from them.[15]

One recent trial studied 354 patients undergoing primary angioplasty for acute myocardial infarction.[16] Patients were randomized to placebo, standard-dose *N*-acetylcysteine (600-mg bolus intravenously before angioplasty, followed by 600 mg orally twice daily for four days), or to double-dose *N*-acetylcysteine (1,200-mg bolus intravenously, followed by 1,200 mg orally twice daily for four days). Patients in the *N*-acetylcysteine groups had marked dose-dependent reductions of contrast-induced nephropathy (35 percent in the control group, 15 percent in the standard-dose *N*-acetylcysteine group, and 8 percent in the high-dose *N*-acetylcysteine group [$P < .0001$]). In addition, in-hospital mortality was markedly reduced by *N*-acetylcysteine ($P = .03$), as was the combined end point of death, acute renal failure requiring dialysis, and the need for mechanical ventilation during the acute phase of myocardial infarction ($P = .002$).[16] This protocol *(Table 1[16])* is the only one to date showing a mortality benefit.

Because of the dichotomous research findings, prophylaxis of contrast-induced nephropathy with *N*-acetylcysteine is not considered standard care. Nevertheless, use

Table 1. One Protocol for Preventing Contrast-Induced Nephropathy in Patients Undergoing Coronary Angiography and Angioplasty

Dosing
Before the procedure, administer a 1,200-mg intravenous bolus of *N*-acetylcysteine
After the procedure, administer a 1,200-mg oral dose of *N*-acetylcysteine twice daily for 48 hours
Hydration
After the procedure, administer 1 mL of normal saline per kg per hour for 12 hours (reduced to 0.5 mL per hour in cases of overt heart failure)

Information from reference 16.

of *N*-acetylcysteine has increased based on its demonstrated safety and the potential effectiveness of specific protocols.[17]

Influenza

Compared with placebo, *N*-acetylcysteine dramatically attenuated influenza illness in a population of frail older adults who participated in a double-blind randomized placebo-controlled study over a six-month period.[18] The 262 participants were randomized to receive either *N*-acetylcysteine in a dosage of 600 mg twice daily or placebo, beginning before and continuing through the 1991 to 1992 influenza season. Although both groups had similar rates of seroconversion to A/H1N1 Singapore 6/86 virus, patients taking *N*-acetylcysteine were much less likely to have clinical influenza illness (29 percent of the *N*-acetylcysteine group versus 51 percent of the placebo group; $P = .0006$). In addition, episodes of clinical influenza illness that occurred in *N*-acetylcysteine-treated patients were, on average, much less severe. Cell-mediated immunity continually improved in the *N*-acetylcysteine group as a whole, whereas immunity in the placebo group remained unchanged.[18]

Idiopathic Pulmonary Fibrosis

In a study of 155 patients with idiopathic interstitial pulmonary fibrosis randomized to *N*-acetylcysteine (600 mg three times daily) or placebo, those receiving *N*-acetylcysteine showed notably less deterioration in lung function over one year, as measured by vital capacity and single-breath carbon monoxide–diffusing capacity (a decrease of 9 versus 24 percent; $P = .02$).[19] In addition, those patients receiving *N*-acetylcysteine had fewer adverse effects caused by bone marrow toxicity from the azathioprine (Imuran) that both groups received as part of standard care (4 versus 13 percent; $P = .03$).[19]

Polycystic Ovary Syndrome

N-acetylcysteine may ameliorate insulin resistance. In a double-blind RCT, 1,200 mg of *N*-acetylcysteine or placebo was added to the clomiphene (Clomid) regimen of women with polycystic ovary syndrome and clomiphene-resistant infertility.[20] In the group receiving *N*-acetylcysteine, clinically and statistically significant increases in both ovulation and pregnancy occurred.[20] These results have been replicated in a subsequent trial.[21]

Other Indications

N-acetylcysteine may play a role in preventing post-surgical complications. One study on the prevention of acute renal failure after cardiac surgery showed a trend in favor of patients treated with *N*-acetylcysteine that did not reach statistical significance ($P = .06$), whereas subgroup analysis of the patients placed on cardiopulmonary bypass (90 percent of the sample) revealed that those treated with *N*-acetylcysteine had a marked reduction in acute renal failure ($P = .03$).[22] Another small study of 22 patients revealed that *N*-acetylcysteine may be useful in preventing pulmonary complications in patients undergoing esophagectomy for cancer.[23]

N-acetylcysteine may also suppress colon polyps,[24] and has an additive effect when used as an adjunct to standard therapy in the eradication of *Helicobacter pylori*.[25] In addition, a small study found that *N*-acetylcysteine may decrease the risk of ototoxicity in patients on hemodialysis who are receiving gentamicin.[26]

Adverse Reactions and Drug Interactions

At dosages of 1,200 mg twice daily or lower, *N*-acetylcysteine is well tolerated. At these dosages, side effects are unusual, but may include nausea, vomiting, diarrhea, transient skin rash, flushing, epigastric pain, and constipation.[27] At the much larger dosages used to treat acetaminophen overdose, *N*-acetylcysteine is often poorly tolerated, with side effects such as headache, tinnitus, urticaria, rash, chills, fever, and anaphylactoid reactions (pseudoanaphylaxis).[27] *N*-acetylcysteine strongly potentiates the effect of nitroglycerin and related medications, and caution should be used in patients receiving these agents in whom it may cause hypotension.[4]

How Supplied

As an over-the-counter supplement, *N*-acetylcysteine is available in 500- to 1,000-mg capsules. The strength most commonly available is the 600-mg capsule (Pure

Table 2. Select Brands of *N*-Acetylcysteine

Brand	*Strength*	*Formulation*
Pure Encapsulations (on request, provides assay results from a third-party independent laboratory)	Available in 600 mg and 900 mg	Capsule
Acetadote	200 mg per mL	Solution for intravenous administration

Table 3. Key Points About *N*-Acetylcysteine

Effectiveness	Widely used as antidote for acetaminophen overdose[1]
	Prevention of exacerbation of COPD; solid evidence from multiple RCTs and meta-analyses[5,7,8]
	Prevention of contrast-induced nephropathy; conflicting evidence, but better quality RCTs appear to show definite benefit[16]
	Attenuation and prevention of influenza illness in frail older adults; good evidence from a single well-done RCT[18]
	Decreased rate of lung function deterioration in idiopathic pulmonary fibrosis; good evidence from a single well-done RCT[19]
	Increased rates of ovulation and pregnancy when given with clomiphene (Clomid) in PCOS; solid evidence from two well-done RCTs[20,21]
Adverse effects	Rare at dosages of 1,200 mg twice daily or less; mostly gastrointestinal
Interactions	Caution in patients taking nitroglycerin and related medications because of potentiation of vasodilatory action[4]
Dosages	Prophylaxis against COPD exacerbation: 600 mg to 1,200 mg daily in divided doses[7,8]
	Prevention of contrast-induced nephropathy in patients with coronary angioplasty (Table 1)[16]
	Attenuation of influenza illness: 600 mg twice daily before and throughout influenza season[18]
	Decreased deterioration of lung function in idiopathic pulmonary fibrosis: 1,800 mg in divided doses[19]
	Adjunct to clomiphene in PCOS: 1,200 mg per day in divided doses[20,21]
Cost*	$12 to $15 per month, depending on brand and dosage
Bottom line	Safe and inexpensive supplement

COPD = chronic obstructive pulmonary disease; PCOS = polycystic ovary syndrome; RCT = randomized controlled trial.

**—Estimated retail price of one month's treatment based on information obtained at www.drugstore.com (accessed March 10, 2009).*

Information from references 1, 4, 5, 7, 8, 16, and 18 through 21.

Encapsulations). In addition, an intravenous preparation (Acetadote) to treat acetaminophen overdose is available.[28] Select brands of *N*-acetylcysteine are listed in *Table 2*.

Bottom Line

N-acetylcysteine is a safe, inexpensive, and well-tolerated antioxidant with a well-defined mechanism of action. Because of the highly favorable risk/benefit ratio and the low rate of adverse events, physicians might consider use of *N*-acetylcysteine in select patients to diminish exacerbation of COPD symptoms; reduce the risk of contrast-induced nephropathy; attenuate influenza illness; decrease the rate of deterioration of pulmonary function in idiopathic pulmonary fibrosis; and serve as an adjunct to clomiphene in the treatment of infertility in women with polycystic ovalyceury syndrome. Key points about *N*-acetylcysteine are summarized in *Table 3*.[1,4,5,7,8,16,18-21]

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