

Medical Uses of N-Acetylcysteine

Subjects: Medicine, General & Internal

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N-acetylcysteine (NAC), a plant antioxidant naturally found in onion, is a precursor to glutathione. It has been used as a drug since the 1960s and is listed on the World Health Organization (WHO) Model List of Essential Medicines as an antidote in poisonings. There are numerous other uses or proposed uses in medicine that are still in preclinical and clinical investigations. NAC is also used in food supplements and cosmetics. Despite its abundant use, there are projections that the NAC global market will grow in the next five years; therefore, the purpose of this work is to provide a balanced view of further uses of NAC as a dietary supplement. Although NAC is considered a safe substance, the results among clinical trials are sometimes controversial or incomplete, like for many other antioxidants. More clinical trials are underway that will improve our understanding of NAC applicability.

Keywords: N-acetylcysteine ; acetylcysteine ; pharmacology ; physiology ; dietary supplements ; aging ; sports

1. Introduction

N-acetylcysteine (also known as N-acetyl-cysteine, NAC) is a precursor to the amino acid L-cysteine and consequently the antioxidant glutathione (GSH) ^[1]. It is most notably found in plants of the *Allium* species, especially in the onion (*Allium cepa*, 45 mg NAC/kg) ^{[2][3]}. The sulfhydryl group (–SH) within the NAC molecule directly scavenges reactive oxygen species (ROS) ^[4], modulates the redox state of the N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (neurotransmitter effect) ^[5], and inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) to modulate cytokine synthesis (anti/pro-inflammatory effect) ^[6]. Unlike GSH itself, NAC has better oral and topical bioavailability ^{[7][8]}. Even though it has been used for more than 50 years, there are still many controversies surrounding it as a medicine as well as a dietary supplement.

2. Medical Use of NAC

NAC has been an established drug since the 1960s; it is on the World Health Organization's List of 40 Essential Medicines ^[9] and is available as an inexpensive generic drug. It has been classically used in paracetamol overdose ^[10] and as a mucolytic ^[11], as well as to combat the toxicity of various substances that can cause generation of free radicals, such as carbon monoxide and x-ray contrasts ^[12]. The NAC products currently approved by Food and Drug Administration (FDA) are listed in **Table 1**. NAC is also used in the complementary treatment of neurological and neuropsychiatric disorders ^{[5][11]}. One death due to an anaphylactic reaction was described following an intravenous (IV) injection of 150 mg/kg of NAC in a 40 year old asthmatic woman in 2002. At comparable IV doses, vomiting was also reported in 11% of patients ^[13]. However, oral NAC seems to be associated with very few side effects and is considered to have an excellent safety profile ^[11]. One case of angioedema after oral NAC administration was described in 1997 ^[14]. Clinical studies have revealed benefits of NAC also in non-alcoholic steatohepatitis ^[15], arterial hypertension of diabetic etiology ^[16], chronic obstructive pulmonary disease (COPD) ^{[17][18]} and chronic bronchitis ^[19], substance abuse disorders ^[20], recurrent unexplained pregnancy loss ^[21], male infertility ^[22], polycystic ovary syndrome ^[23], diabetic retinopathy, age-related macular degeneration, and cataract and dry eye syndrome ^[4]. In total, 300 clinical studies (291 clinical trials) of NAC are listed in ClinicalTrials.gov ^[24] in April 2019 (**Table 2**). The most common disorders that were investigated by listed interventional trials with NAC (without the currently active studies) included renal disorders (48 trials) with an emphasis on radiocontrast nephropathy prevention, chronic kidney disease, and renoprotection during surgery; and neurological and psychiatric disorders (36 trials), leading with Parkinson's disease, schizophrenia, bipolar, autistic, and behavioral disorders. Schizophrenia, for instance, has been linked to mitochondrial abnormalities, glutathione deficiency, and increased oxidative stress in the brain. Negative and general symptoms in schizophrenia may be reduced after 8–24 weeks of adjunctive treatment with NAC ^[25] in neuropsychiatric disorders and are discussed in greater detail in a recent review ^[26]. Addictive disorders (23 trials) are also a common target, with alcohol, tobacco, cocaine, cannabis, and other types of dependence. The NMDA receptors that NAC modulates may be involved in addiction ^[27], and at least three reviews discuss the use of NAC in addictive disorders ^{[20][28][29]} and emphasize the reduction of cravings for the substance

in question. Among other commonly investigated uses of NAC were applications in gastrointestinal and pulmonary diseases. The majority of the 54 currently active interventional studies are investigating the role of NAC in addictive disorders, mental health, and neurodegenerative diseases, followed by cancer/cancer treatment side-effects, cardiovascular diseases, and surgery complications/trauma.

Table 1. Overview of Food and Drug Administration FDA-approved N-acetyl-cysteine (NAC) drugs and their indications.

Route	Administration	Strength	No.*	Medical Condition/ Therapy Type	Indication
Injectable	Intravenous	200 mg/mL (6 g/30 mL)	7	Poisoning/ antidote	Acetaminophen overdose reduction; Prevention of acute hepatic injury; Hepatic injury from repeated supratherapeutic ingestion.
Effervescent tablet	Oral	500 mg 2.5 g	1		
Solution	Oral	10% 20%	3	Bronchopulmonary disorders/ Adjuvant therapy	Abnormal, viscid, inspissated mucous secretions in chronic** and acute*** bronchopulmonary disease; Pulmonary complications of cystic fibrosis; Tracheostomy care; Pulmonary complications associated with surgery;
Solution	Inhalation	10% 20%	3		Use during anesthesia; Post-traumatic chest conditions; Atelectasis due to mucous obstruction and diagnostic bronchial studies****.

*: Number of drugs, currently on the market. **: Chronic bronchopulmonary disease: chronic emphysema, emphysema with bronchitis, chronic asthmatic bronchitis, tuberculosis, bronchiectasis, and primary amyloidosis of the lung. ***: Acute bronchopulmonary disease: pneumonia, bronchitis, and tracheobronchitis. ****: Diagnostic bronchial studies: bronchograms, bronchspirometry, and bronchial wedge catheterization.

Table 2. NAC clinical trials registered at ClinicalTrials.gov [24]. The number of studies is displayed according to the study status, tested medical conditions of currently active studies, tested medical conditions in completed studies, study phase and tested medical conditions of currently active studies, study phase, and tested medical conditions of completed studies.

Status	Count
Completed	159
Not yet recruiting	14
Active	54
Withdrawn/terminated/suspended	24
Unknown status	40
Grand Total	291
Medical Conditions (Active Studies)	Count
Addiction	12
Cancer/chemotherapy side effects	5
Cardiovascular diseases	5
Gastrointestinal diseases	4
Genetic disorders	1
Graft/stem cell complications/trauma	4
Infectious diseases	1
Metabolic diseases	1
Neuro/psychiatric disorders	12

Obstetrics	2
Poisoning antidote	1
Pulmonary diseases	1
Surgery complications/trauma	5
Grand Total	54
Medical Conditions (Completed Studies)	Count
Addiction	17
Blood disorders	4
Cancer/chemotherapy side effects	2
Cardiovascular diseases	10
Dermatologic disorders	2
Gastrointestinal diseases	15
Genetic disorders	1
Infectious diseases	3
Metabolic diseases	8
Muscle disorders	1
Neuro/psychiatric disorders	24
Obstetrics	11
Ophthalmological diseases	5
ORL	5
Other	4
Poisoning antidote	2
Pulmonary diseases	13
Renal disorders	31
Surgery complications/trauma	1
Grand Total	159
Phase/Medical Conditions (Active Studies)	Count
Early Phase 1	5
Addiction	2
Metabolic diseases	1
Neuro/psychiatric disorders	1
Pulmonary diseases	1
Not Applicable	10
Cardiovascular diseases	2
Gastrointestinal diseases	1
Graft/stem cell complications/trauma	1
Neuro/psychiatric disorders	4
Obstetrics	1
Surgery complications/trauma	1
Phase 1	4

Addiction	1
Cancer/chemotherapy side effects	1
Neuro/psychiatric disorders	1
Poisoning antidote	1
Phase 1 Phase 2	3
Cancer/chemotherapy side effects	2
Gastrointestinal diseases	1
Phase 2	13
Addiction	6
Cancer/chemotherapy side effects	1
Gastrointestinal diseases	1
Genetic disorders	1
Graft/stem cell complications/trauma	1
Infectious diseases	1
Neuro/psychiatric disorders	2
Phase 2 Phase 3	3
Addiction	1
Graft/stem cell complications/trauma	1
Obstetrics	1
Phase 3	8
Cancer/chemotherapy side effects	1
Cardiovascular diseases	3
Neuro/psychiatric disorders	2
Surgery complications/trauma	2
Phase 4	8
Addiction	2
Gastrointestinal diseases	1
Graft/stem cell complications/trauma	1
Neuro/psychiatric disorders	2
Surgery complications/trauma	2
Grand Total	54
Phase/Medical Conditions (Completed Studies)	Count
Early Phase 1	3
Addiction	1
Blood disorders	1
ORL	1
Not Applicable	18
Cardiovascular diseases	1
Gastrointestinal diseases	3
Metabolic diseases	3

Neuro/psychiatric disorders	2
Obstetrics	2
Pulmonary diseases	2
Renal disorders	5
Phase 1	22
Addiction	3
Cancer/chemotherapy side effects	1
Cardiovascular diseases	1
Gastrointestinal diseases	2
Neuro/psychiatric disorders	4
Ophthalmological diseases	4
ORL	1
Other	4
Pulmonary diseases	1
Renal disorders	1
Phase 1 Phase 2	12
Addiction	2
Blood disorders	1
Infectious diseases	1
Metabolic diseases	3
Neuro/psychiatric disorders	2
Obstetrics	2
Renal disorders	1
Phase 2	47
Addiction	8
Blood disorders	1
Cancer/chemotherapy side effects	1
Cardiovascular diseases	4
Dermatologic disorders	1
Gastrointestinal diseases	2
Genetic disorders	1
Infectious diseases	1
Metabolic diseases	1
Muscle disorders	1
Neuro/psychiatric disorders	14
Obstetrics	1
Ophthalmological diseases	1
ORL	1
Pulmonary diseases	2
Renal disorders	7

Phase 2 Phase 3	8
Gastrointestinal diseases	1
Obstetrics	1
ORL	1
Renal disorders	5
Phase 3	20
Addiction	2
Blood disorders	1
Cardiovascular diseases	2
Dermatologic disorders	1
Gastrointestinal diseases	4
Infectious diseases	1
Obstetrics	2
Pulmonary diseases	2
Renal disorders	5
Phase 4	29
Addiction	1
Cardiovascular diseases	2
Gastrointestinal diseases	3
Metabolic diseases	1
Neuro/psychiatric disorders	2
Obstetrics	3
ORL	1
Poisoning antidote	2
Pulmonary diseases	6
Renal disorders	7
Surgery complications/trauma	1
Grand Total	159

ORL: Otorhinolaryngology.

The suspended, terminated, or withdrawn studies listed in ClinicalTrials.gov are in **Table 3**. Termination reasons, such as no improvement and opposite results, are recorded in only 3 out of the 23 trials. Insufficient funds and insufficient recruitment are the major termination/ suspension/ withdrawal reason [24]. There are a few reports of the NAC study premature termination in the literature. High doses of NAC did not improve respiratory health in patients with COPD and chronic bronchitis; the study was prematurely terminated [30]. The decision was based on a potential safety issue, as it was reported that NAC and vitamin E, given orally, induced lung cancer in mice. This finding was reproduced in cell lines from human and mice lung tumors [31]. Additionally, there was no indication of improvement of COPD/chronic bronchitis in the 23 patients that received 1800 mg NAC twice daily for 8 weeks compared to the equal number of subjects receiving placebo [30]. Results of a 24-week oral NAC supplementation of cystic fibrosis patients revealed that NAC recipients maintained their lung function without a significant effect on the biomarkers of neutrophilic inflammation [32]. Another trial was prematurely terminated in 2018 due to the absence of between-group differences in the rates of contrast-associated acute kidney injury; there was no noticeable benefit of the oral NAC on the contrast-associated acute kidney injury prevention, no noticeable improvement on the need for dialysis, persistent kidney injury or death in subjects at high risk of renal complications because of angiography [33]. Similar conclusions were reached from the “Acetylcysteine for contrast-induced neuropathy” trial [34].

Table 3. Medical conditions investigated by withdrawn, terminated, and suspended studies listed by ClinicalTrials.gov [24]. Listed: number of trials listed at ClinicalTrials.gov [24]; Phase: study phase; N/A: not applicable.

Status/Medical Condition	Listed	Phase	Termination Reason
SUSPENDED	4		
Autoimmune Disorders			
Systemic Lupus Erythematosus	1	1 2	Short of funds
Cardiovascular Diseases			
Cardiovascular Disease Renal Insufficiency, Acute Cardiopulmonary Bypass	1	4	Opposite result
Infectious Diseases			
Hepatitis C	1	N/A	Short of funds
Metabolic diseases			
Insulin Resistance Metabolic Syndrome	1	N/A	N/A
TERMINATED/	15		
Addiction			
Acetaminophen Overdose	1	3	Insufficient enrollment
Prevention of Hangover Using NAC	1	N/A	Insufficient enrollment
Cancer/Chemotherapy Side Effects			
Bone Marrow Suppression Brain and Central Nervous System Tumors Drug/Agent Toxicity by Tissue/Organ Long-term Effects Secondary to Cancer Therapy in Children	1	1	N/A
Malignant Ovarian Endometrioid Tumor Malignant Ovarian Serous Tumor Recurrent Fallopian Tube Carcinoma Recurrent Ovarian Carcinoma Recurrent Primary Peritoneal Carcinoma	1	2	Slow accrual
Gastrointestinal Diseases			
Acute Liver Failure Fulminant Hepatic Failure	1	4	Insufficient enrollment
Drug Induced Liver Injury	1	N/A	2 sepsis cases after steroid admin.
Genetic disorders			
Cystic Fibrosis	1	4	Insufficient enrollment
Infectious Diseases			
<i>Helicobacter pylori</i> Infection	1	1 2	Efficacy of eradication: 2 out of 31
Metabolic diseases			
Type 2 Diabetes Mellitus Hypertension	1	4	N/A
Neuro/Psychiatric Disorders			
Borderline Personality Disorder Self-Injurious Behavior	1	2	Poor subject compliance
Bulimia Nervosa	1	2 3; 3	No meaningful improvements
Obsessive-Compulsive Disorder	1	2	Insufficient enrollment
Pulmonary Diseases			

Status/Medical Condition	Listed	Phase	Termination Reason
COPD Chronic Bronchitis	1	N/A	PI's discretion
Renal Disorders			
Chronic Kidney Failure	1	N/A	N/A
Surgery Complications/Trauma			
Ischemic Reperfusion Injury Insufficiency; Hepatic, Postoperative Liver Tumour	1	2	N/A
WITHDRAWN/	4		
Cancer/Chemotherapy Side Effects			
Ovarian Carcinoma, Stage 3 or 4 Epithelial Ovarian Carcinoma Primary Peritoneal Carcinoma	1	1	No funding for the cost of NAC
Gastrointestinal Diseases			
Liver Failure Liver Failure, Acute Drug Induced Liver Injury Prevention and Control Fever	1	N/A	Short of funds
Neuro/Psychiatric Disorders			
Autistic Disorder Seizures Irritability	1	N/A	No eligible subjects located
Posttraumatic Stress Disorder	1	2	Cancelled research project
Grand Total	23		

Pre-clinical studies imply that NAC could have more uses in supportive care and preventing human disease. Examples include Alzheimer's disease [35][36], asthma [37], inflammatory bowel disease [38], influenza [39], intrauterine growth retardation [40], obesity and insulin resistance [41][42][43][44], ischemic cardiovascular disease [45][46], heavy metal toxicity [47][48], diabetic neuropathy [49], and age-related memory impairment [50]. Due to its capacity to break down biofilms and improve antibiotic permeability, it is promising as an adjuvant antimicrobial drug [51]. Several pre-clinical studies have also demonstrated that NAC supplementation leads to life extension and diminished effects of aging, in invertebrates [52][53][54][55] as well as mammals [56] and in human breast epithelial stem cells [57]. Such findings have yet to be replicated in humans. This is likely not solely due to NAC's radical scavenging activity but also at least in part to telomerase activation and apoptosis inhibition [58], as is evidenced also by its capacity to delay oocyte aging [59]. However, antioxidants have the potential to either lengthen or shorten lifespan, depending on the dose and redox balance [60].

The role of NAC in the prevention and treatment of cancer is controversial, and it is discussed in more detail in the original manuscript. NAC has also attracted considerable attention as a sports supplement that can reduce muscle fatigue, improve athletic performance, and aid muscle recovery [61]. Although NAC is a well-known antioxidant and an old generic drug with several established clinical applications, more potential uses are still inadequately investigated. One of the main challenges of NAC as a medicine and a supplement is its broad range of effects and applications, far too few of which are well studied, in spite of a large effort in conducting preclinical and clinical trials.

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