Review Article

Int J. Pharm. Drug. Anal, Vol: 11, Issue: 1, 2023; 17-30

International Journal of Pharmaceutics and Drug Analysis

Content Available at www.ijpda.com ISSN: 2348:8948

PHARMACOLOGICAL APPLICATIONS AND PHARMACOKINETIC MODIFICATIONS OF N-ACETYLCYSTEINE

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Received: 08 Jan 2023 Revised: 25 Feb 2023 Accepted: 20 Mar 2023

Abstract

NAC, an acetylated cysteine compound, is a proteinogenic acid. Being a glutathione recurs or NAC is rather unique because of the multifaceted chemical properties of the cysteinyl thiol group of the molecule. This critical review focuses on the pharmacological applications and pharmacokinetic modifications of NAC to provide a better understanding. NAC was earlier used as a mucolytic agent in various respiratory illnesses and is now widely used as the specific antidote for acetaminophen overdose. In course of time, it has proven to be beneficial in many conditions such as HIV infection, COPD exacerbations, heart diseases, treatment of pulmonary fibrosis, Alzheimer's, and Parkinson's disease; helps in the prevention of contrast-induced kidney damage during procedures, etc. Preliminary studies also suggest NAC maintains a major role as cancer chemo protective, adjunct in the eradication of Helicobacter pylori, prophylaxis of gentamicin-induced hearing loss in patients, and also found to have some clinical usefulness as a chelating agent in the treatment of acute heavy metal poisoning. Despite its beneficial traits with limited side effects, bioavailability remains a major concern. Hence different pharmacokinetic modifications of NAC like N-acetyl cysteine amide (NACA), N-acetyl-L-cysteine ethyl ester (NACET), Liposomal-N-acetyl cysteine, Effervescent tablet of N-acetyl cysteine, Acetyl cysteine oral inhalation, etc may ameliorate this major drawback. As a result, to develop a more well-designed and reliable indication; to optimize the dose of NAC, larger controlled trials with longer follow-up sections is demanded in the future. Thus, this review brings forward comprehensive knowledge about the possibilities to introduce NAC as a protective and tolerable medication for these various conditions.

Keywords: N-Acetyl Cysteine, NAC-applications, Pharmacokinetic Modifications-NAC.

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DOI: https://doi.org/10.47957/ijpda.v11i1.535

Produced and Published by

South Asian Academic Publications

Introduction

N-acetyl-L-cysteine is the N-acetylated analogue of cysteine [1]. It is an a minothiol and a synthetic precursor of intracellular cysteine and GSH, making it a valuable antioxidant [2].N-Acetyl-l-cysteine, often known as NAC, was first used as a mucolytic in The 1960s to reduce the viscosity of aberrant respiratory tract secretions in a variety of trachea bronchial and broncho pulmonary illnesses, including cystic fibrosis [3]. The molecule was determined to be sufficiently stable after acetylation of the l-cysteine N-terminus [4]. It has a well-known safety profile and its toxicity is rare depending on the mode of administration and large doses. NAC is approved by the Food and Drug Administration (FDA) and listed as an essential drug by the World Health Organization (WHO) [5]. NAC is widely accessible as an over-the-counter nutritional supplement in various countries, such as the United States, Canada, and Australia, due to its antioxidant qualities and economic value as a nutraceutical [6].For almost 35 years, NAC has been used as an antidote in the treatment of acetaminophen over dose, a well-

known and widely approved antidote [7]. It has also been shown that NAC protects against paraquat toxicity [8].

N-Acetyl-L-Cysteine and Cysteine

Cysteine is a non-essential amino acid produced intra cellularly from methionine and serine [9]. Cysteine serves as a precursor for protein synthesis and thereby as a building block for protein synthesis. Cysteine is also used by cells in the formation of the tri peptidegluta thione (GSH), which is involved in the cellular detoxification of xenobiotic compounds [10]. GSH acts as an antioxidant, protecting cells and tissues from the damaging effects of various reactive oxygen species [11]. The primary purpose of both NAC and cysteine is to enhance intracellular free sulfhydryl group (free-SH) levels and provide a substrate for GSH production which in turn mediates various physiologically essential functions listed for NAC.

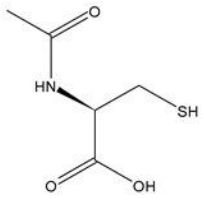
One of the primary reasons why NAC is preferred over cysteine in vivo experimental systems is that NAC is not easily oxidized in the intestinal fluids, whereas cysteine is rapidly oxidized and transitioned to cystine, whose uptake demands exchange with glutamate, resulting in glutamate deficit from the cells. It hasbeen demonstrated that in the intestinal fluid, 75–100% of thiol groups besides NAC are oxidized, but only 16% of NAC is oxidized under such conditions [12]. As a result, NAC is primarily absorbed in the reduced state and promptly converted to cysteine, leaving only at race of intact NAC in the plasma [13]. The accelerated oxidation of cysteine in the intestinal fluid has been reported.

Biochemical Properties of NAC:

NAC's biological action is ascribed to its sulfhydryl (thiol) group, whereas its acetyl-substituted amino group protects it against oxidative and metabolic events [14,15]. The acetylgroup makes cysteine extra water-soluble and aids in the absorption and distribution of orally consumed cysteine. The acetyl group also decreases the reactivity of the sulfhydryl group, making NAC less toxic and more resistant to oxidation than cysteine [16]. NAC is therefore amembrane-permeable aminothiol that can act as a sulfhydryl group donor and a forerunner to intracellular cysteine and glutathione. The necessity to provide decreased sulfhydryl moieties to influence the rupture of disulfide bridges within the glycoprotein network of mucus prompted the use of NAC as a mucolytic.

Chemical Structure of NAC

N -Acetyl-l -cysteine, having a molecular weight of 163.2 g/mol, is made by acetylating l-cysteine hydrochloride monohydrate by acetic anhydride in an alkaline aqueous medium. NAC is also endogenously produced, with an estimated circulating concentration of 80 nM [17].



Structural Modifications and Formulations of NAC

N-Acetylcysteine Amide (NACA)

A modified form of N-acetylcysteine, N-acetylcysteine amide (NACA) which is also known asAD4 contains an amide group in place of the carboxyl group of NAC, which gives the compound a neutral charge and enhances hydrophobicity and lipophilicity. This minor modification can enhance the efficacy of NACA as compared to NAC [18][19]. The design andsynthesis were based on the possibility that neutralizing the carboxyl group would aid in its passage through cell membranes. From one recent study, it was evident that the membrane permeation capacity of NACA is more than the NAC and also could reload intra cellular GSH in RBCs, by disulfide exchange with oxidized glutathione (GSSG). Hydrolyzed NACA can give cysteine which can boost endogenous glutathione production. This compound also crosses the BBB, scavenge free radicals, chelate copper, protect red blood cells from oxidative stress, and ease Myelin Oligodendrocyte Glycoprotein (MOG)-induced experimental autoimmune encephalo myelitis in multiple sclerosis mouse model [18] [20].

Radicals avenging power

Due to the many deleterious effects of radicalsin biologicalsy stems, free radicals cavengingis a very important property of an antioxidant. From a study, it was found that at a lower concentration, the radical scavenging properties of NACA and NAC were similar (25.9%and21.8%,respectively)andathigherconcentrations ,NACAhasahigherradicalscavengingability,ascomparedt oNAC(88.2%and56.5%,respectively). A feasible reason for the lowered ability to scavenge radicals at a higher concentration by NAC may be due to the saturation kinetics of the reaction [18]. A compound reducing power is a supporting feature or its antioxidant activity. These properties are mainly connected with the presence of reduct ones, which exhibit antioxidant action by breaking the chain reactions by donating a hydrogen atom. From the study, it was found that the

reducing power of NACA is greater than NAC [20]. From studies at lower concentrations of NAC was shown to have the best H2O2 scavenging activity andat the highest concentration used, NACA showed greater scavenging activity than NAC. The short-lived hydroxyl radicals are free radicals that can be highly deleterious to cellmembranes and other biomolecules. Therefore, OH scavenging is necessary to protect cells from oxidative damage. From the study hydroxyl, radical scavenging capacity was found to be NAC >NACA [18].

N-Acetyl-L-Cysteine Ethyl Ester (NACET)

The esterified form of NAC is N-acetyl-L-Cysteine ethyl ester (NACET). NACET is quickly absorbed in rats after oral administration but reaches very low concentrations in plasma, dueto its a unique feature that is it rapidly enters into the cells where it is trapped being changed into NAC and cysteine., NACET was able to increase the glutathione content of most tissues examined, brain included, and to protect from paracetamol intoxication after the oral treatment. It also has a unique feature to accumulate in human erythrocytes and acts as a potent protector against hydroperoxide-induced oxidative damage. NACET is a good candidate for oral use as an H2S producer, as it increases circulating hydrogen sulphide (H2S), with clear advantages over NAC [21].

Chemical properties

NACET is a white powder at room temperature with a melting point of about 44ºC. It is freely soluble in water and organic solvents. The reactivity of the SH group of NACET is found to be about 10 times higher than that of NAC. From the determination of the octanol/water distribution coefficients (log D) for NAC and NACET, the log D value was 5.4for NAC and 0.85 for NACET. The higher log D of NACET impressively indicates that esterification of the carboxyl group of NAC by ethanol drastically increases the lipophilicity of the molecule. The esterification of NAC is associated with a considerable increase in the reactivity of the SH group toward the electrophile DTNB [21].

Pharmacokinetics of N-acetylcysteine and NACET

Both reduced and oxidized forms of NAC and NACET can be found in plasma. In pharmacokinetic research, the sum of all of these forms, namely tNAC and tNACET, was taken into account. Oral administration of NAC or NACET to rats at identical doses resulted in comparable Cmax values but differing Tmax values in the study. tNACET attained relatively low plasma concentrations after intravenous administration of similar doses to rats and dissipated quickly from the plasma compartment. NAC infusion resulted in extremely high levels of tNAC in the plasma compartment, which gradually vanished. The oral bioavailability of NAC was judged to be only 4.8 ±1.2 percent based on the AUCs measured and the dosages utilized, but 58.5± 8.8 percent for NACET. NACET readily enters the cells, where it is rapidly metabolized to NAC and Cys, according to the isolated organ experiments [21] [22].

Effects compared on GSH levels with N-acetylcysteine or NACET

In the study, rats were treated per or twice a day with NAC, NACET, or vehicles with relatively high drug doses (50 mg/kg of NAC or an equivalent dosage of NACET). After 2 weeks an increase of GSH was obtained in some tissues, namely the brain, liver, kidney, testis, and heart only for NACET, whereas NAC was unable to elicit the same effect. Upon NACET treatment, g-Glu-Cys was higher in some tissues with increased GSH content [21].

Other important effects

In vivo production of H2S from cells can be stimulated primarily by increasing cellular stores of Cys that can function as a substrate of CSE (cys tathionine g-lyase, one enzyme of the trans sulphuration pathway). The circulating levels of H2S after oral administration of two equivalent doses of NAC and NACET given twice withinan8-hinterval time between were compared and was found that plasma H2S concentration increased immediately after NACET administration but not upon NAC administration [21]. From the study, it was found that indicators of liver damage, namely GOT/AST, GPT/ALT, and LDH, were consistently lower in the NACET group in acute poisoning experiments when the utility of NACET to prevent paracetamol-induced toxicity was tested [29].

Liposomal-N-Acetylcysteine

Intracellular delivery and extending the retention of entrapped agents inside the cell arefacilitated by liposomes. When the efficacy of conventional N-acetylcysteine (NAC) and liposomal-NAC (L-NAC) against PQ-induced cytotoxicity was compared, it was discovered that pretreatment of cells with L-NAC was more effective than the conventional drug in reducing PQ-induced cytotoxicity, as indicated by the biomarkers used in the study[23]. In a studyto determine whether a NAC-loaded liposomal formulation is more effective than the conventional NAC in shielding against acute acetaminophen-induced hepatotoxicity, it was found that in reducing APAP-induced hepatotoxicity, treatment of animals with Lipo-NAC was significantly

more effective than free NAC. From histological evaluation the APAP caused periacinar hepatocellular apoptosis and/or necrosis of hepatocytes around the terminal hepatic venules and is reduced by NAC treatment, the degree of reduction being greater for Lipo-NAC [24].

Effervescent Tablet of N-Acetylcysteine

Due to high dose, taste problems of NAC, and stability problems; it is difficult to formulate in film-coated tablets or as syrup. Effervescent tablets act as an alternative dosage form. Before administration, these tablets are dissolved or dispersed in water. Since these are administrated in liquid form, they are easily swallowed so they are preferred over tablets or capsules [25]. Internal route administration may have some pharmacokinetic advantages as it produces higher NAC concentrations in the liver but due to first-pass metabolism, oral administration gain slower serum on cent rations [26]. Even though the bioavailability of effervescent NAC and oral solution NAC are not different; Effervescent NAC tablets appear to be more palatable and acceptable to patients. One other advantage of effervescent NAC tablets is the preparation ease for practitioners and patients outside the emergency department in selected cases [27].

Acetylcy steine Inhalation

NAC can be administered orally, intravenously, viaaerosol, or by intra peritoneal injection. But inhalation therapy has advantages like lower dosage, more rapid onset, and fewer side effects due to the direct effects on the airways. Acetylcysteine inhalation can be used along with other treatments to reduce chest congestion due to thick or abnormal mucous secretions in people with lung conditions including asthma, emphysema, bronchitis, etc. It acts by thinning the mucusin the air passages, making it easier to cough up the mucus and clear the airways [26]. In a study, NAC inhalation provide patients with good respiratory tract conditions, which supported early recovery and 12-month survival. Compared with oral or IV administration, inhalation medication is delivered by special devices through which that can rapidly and directly act on the airways to allow high local drug concentrations and limit the systemic impact. So, it can be concluded as preoperative and intra operative NAC inhalation may reduce the incidence of PPCs and may improve patient outcomes after liver transplantation [28].

Pharmacological Applications of NAC

NAC in psychiatry

Alzheimer's:

Alzheimer's disease (AD) is a complex disease with numerous physiological, metabolic, and neurochemical aspects. Inhibition of cytoxidase assembly potentiates the increase in oxidative and apoptotic (Bax and caspase 9) markers in aged and AD fibroblasts, demonstrating that mitochondria are important players in oxidative stress. Although active therapy of Alzheimer's disease with NAC alone fails to cure the condition, it shows promise for lowering oxidative stress in the disease. It has been discovered that combining Lipoic acid with NAC provides greater protection against oxidative stress caused by age and Alzheimer's disease. NAC, as a cysteine donor, keeps intracellular glutathione levels up and may prevent neuronal mortality by preventing cell cycle entry, increasing free radical surveillance, and preserving mitochondrial function[30][31]. When compared to untreated animals, aged rats treated with NAC demonstrated a minor improvement in brain-specific mitochondrial energy production efficiency, mostly with NAD-dependent substrates, as well as a decrease in carbonyl protein content thrills of brain systolic fraction. As a result, NAC protects the brain from oxidative stress, apoptosis, and inflammation [32].

Anxiety:

In one study, a 17-year-old teenage patient with selective serotonin reuptake inhibitor-resistant generalized anxiety disorder and social phobia was given NAC as a prospective anxiety treatment. This study found that after 8 weeks of treatment with NAC at doses of1200 mg/day for 4 weeks and 2400 mg/day for the remaining 4 weeks, symptoms improved significantly. The patient did not experience any side effects as a result of the treatment [34]. Another case study reported significant improvement in a 17-year-old male with generalized anxiety disorder and social phobia who had previously failed multiple selective serotonin reuptake inhibitors and cognitive behavioral therapy after 8 weeks of treatment with NAC, as evidenced by a drop in CGI-S from 5 to 2 after 8 weeks of treatment with NAC [33].

Behavioral addictions

NAC has shown to be beneficial in the treatment of behavioral addictions such as cocaine addiction, cannabis addiction, nicotine addiction, and pathological gambling. Studies reveal that NAC cures drug-induced synaptic damage and lowers relapse in animal models leading to the identification of a permanent disturbance of glutamatergic neurotransmission in animal models of cocaine, heroin, alcohol, and nicotine relapse. NAC

reduced drug-seeking behavior in these trials by restoring synaptic plasticity at glutamatergic inputs to the basal ganglia. One of the most important studies in this field employed various doses of NAC, ranging from 0.6 to 3.6 g per day, and discovered that low doses of NAC were insufficient to induce the required rise in extracellular glutamate. High doses, on the other hand, may have proved harmful, resulting in increased extracellular glutamate levels and indiscriminate stimulation of other glutamate receptors rather than the desired stimulation of mGluR2/3. The best dose of NAC for treating addictions has yet to be discovered. Nonetheless, the discovery that 2.4 g of NAC restored glutamate levels in cocaine-dependent patients'd ACC may serve as a temporary benchmark [34][35] [36].

Attention deficit/hyperactivity

With a lifetime prevalence of 5.9-8.7%, ADHD is a prevalent childhood-onset condition. ADHD can have a significant impact on a child's social, academic, and family life. ADHD patients are more prone than the general population to suffer from a variety of comorbid medical and psychological problems. Early diagnosis of attention deficit disorder and its responsiveness to NAC may aid in the prevention of neuropsychiatric consequences, as well as a decrease in disease activity and fatigue in SLE patients.[34][37].

Autism

Autism spectrum disorders (ASDs) are a group of developmental disorders marked by consider blesocial impairment, language and communication difficulties, repetitive and stereo typed behaviors, and interests. Recent research suggests that the pathophysiology of autism inchildren may be influenced by an imbalance of oxidative stress and antioxidative defense systems. The viability of administering oral NAC in the treatment of behavioral abnormalities in children with ASDs has been investigated based on this concept [34]. N-acetylcysteine may provide cystine, which is a precursor for glutathione (GSH), a key antioxidant in the brain. There is a case report of a youngster with autism whose symptoms were significantly reduced after taking 800 mg of N-acetylcysteine three times a day. His social contact expanded dramatically. During the two-month experiment, the social impairment score on a visual analogue scale dropped from 10 to 6. The number of hostile actions dropped from ten to three. This example demonstrates that N-acetylcysteine may help with autism symptoms. [38].

Bipolar disorder

Changes in antioxidant levels, as well as elevated indicators of lipid peroxidation and protein carbonylation, have been seen in patients with bipolar disorder (BD). These appear to be state-related, with mania accompanied by increased oxidative stress. This is in line with descriptions of manic episodes causing hyper dopaminergic states. Furthermore, there were connections between oxidative state and sickness duration [34]. In people with bipolar disorder who are suffering significant depressive episodes, a 24-week randomized clinical trial comparing adjunctive NAC to placebo was conducted. Throughout the trial, data on symptomatic and functional outcomes were gathered. For this report, seventeen people were available. At the end of the study, very high effect sizes in favor of NAC were discovered for depressive symptoms and functional outcomes. At the end of the study, eight of the ten NAC patients had a treatment response, while just one of the seven placebo participants did. These findings suggest that additive NAC may be beneficial for bipolar disorder and major depressive episodes [39].

Depressive disorder

Because oxidative stress and abnormalities of glutamate neurotransmission are implicated in the pathophysiology of major depressive disorder (MDD), there is renewed interest in the potential function of NAC in its therapy. A major randomized controlled trial (n=252) inpeople with MDD and a MADRS score of 18 found only modest support for NAC as a novel augmentation option for treating MDD, with the NAC-treated group showing improvement only in secondary end measures compared to the placebo group. In two patients with MDD who had only partially reacted to a trial of the monoamine oxidase inhibitors (MAOI) tranylcypromine, a case series revealed effective and sustained relief of depressive symptoms with NAC augmentation [34].

Obsessive-compulsive and related disorders

Obsessive-compulsive and related disorders are a collection of debilitating psychiatric disorders in which the role of glutamate dysfunction in the underpinning neurobiology is becoming well established. Selected serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants are common pharmaceutical therapies for obsessive-compulsive disorder (OCD). N-acetyl cysteine (NAC) is a glutamate modulator with a promising therapeutic effect. During a 12-week open trial, a 58-year-old female OCD patient was treated with fluv oxamine (300 mg daily) and found improvement by supplementing with NAC, which was titrated from 600

mg to 3 g/day. The patient's Y-BOCS (Yale-Brown Obsessive Compulsive Scale) score decreased significantly, along with improved control of compulsive washing and obsessional triggers, which were maintained during a 2-month follow-up [34].NAC appears to be extremely well-tolerated, with minimal adverse effects reported. Intestinal effects appear to be the most common symptom-flatulence (which ceased after two weeks of NAC supplementation), headache, skin rash, diarrhea and nausea, and vomiting of mild-moderate intensity [40]

Trichotillo mania

Trichotillo mania is a condition in which people pull their hair out repeatedly, resulting in substantial hair loss. Patients with this illness experience a lot of tension before the hair-pulling and a lot of relief afterward. SSRIs are a pharmacological therapeutic option; however, their usefulness has been questioned. Clomipramine has also been shown to be moderately beneficial when compared to placebo; however, the advantages do not always last. Glutamatergic dysfunction has been implicated in the pathophysiology of this condition, prompting research into glutamatergic modulators, including NAC, as potential add-on therapy. NAC works by restoring extracellular glutamate levels in the nucleus accumbens, which are thought to be involved in the etiology of obsessive behaviors, including trichotillomania. Several case reports in adults, including one case of a severe, treatment-resistant type of the illness, indicated increased hair growth after using NAC at a mean dosage of 1400 mg/die [34] [41].

Excoriation, or skin-picking, disorder

Excoriation, or skin-picking, the disorder is defined by recurring, uncontrollable skin picking that results in skin lesions and is linked with considerable discomfort and functional impairment, according to the DSM-5. Patients with Prader-Willi syndrome are also prone to picking at their skin. The pathophysiology of compulsive or habitual behaviors has been linked to glutamatergic dysfunction. Glutamate levels in the nucleus accumbens appear to affect reward-seeking behavior in preclinical studies. Glutamate manipulations also affect extra dimensional set-shifting (a type of cognitive flexibility), and these effects appear to be mediated via the nucleus accumbens. N-acetylcysteine, a cysteine prodrug and antioxidant, increases extracellular glutamate levels in the nucleus accumbens, perhaps through a process in which inhibitory metabotropic glutamate receptors are activated, reducing synaptic glutamate release. Restoring extracellular glutamate concentration in the nucleus accumbens may thus prevent compulsive behaviors from resurfacing [42].

Nail Biting

The effectiveness of NAC on nail-bitinghabits is only supported by a small amount of research. *Berket al.* showed better reduced nail-biting frequency in two women 46 and 44 years old, as well as a male 46 years old, both of whom had bipolar disorder and were engaged in the previously mentioned bipolar disorder treatment program. After 2 weeks of therapy supplementation with 2000 mg/day of NAC, the 46-year-old female patient ceased biting, the 44-year-old female after 4 months of NAC treatment (same dose), and the 46-year- old male patient after 7 months[34] [43].

Schizophrenia

Schizophrenia is a debilitating psychiatric illness associated with positive and negative symptoms as well as significant impairments in cognition. Cognitive dysfunction is the most devastating cluster of symptoms seen in schizophrenia. NAC-mediated increases in antioxidant defense may have a direct impact on cognition. NAC has the potential to be a helpful treatment for schizophrenia's cognitive symptoms. The most apparent method they act is by boosting GSH levels in response to NAC administration, which leads to a reduction in oxidative stress, an increase in glutamatergic modulation of N –Methyl-D aspartate receptor system, and, as a result, neuroprotection of cognition-related neuronal networks. These networks' neuroprotection is expected to occur across multiple domains, and it could involve a cascade effect of reduced inflammation and calcification, which leads to improved neuronal function [34] [44].

Paracetamol Poisoning

In the treatment of paracetamol poisoning, N-acetylcysteine (NAC) is an efficient antidote. When given within 8-10 hours of intake, intravenous acetylcysteine was successful in preventing severe liver damage, renal failure, and mortality caused by paracetamol overdosage. In individuals with plasma paracetamol concentrations over the therapeutic line, intravenous acetylcysteine is indicated if treatment begins within 15 hours after intake. Patients who have taken more than 7-5 g paracetamol in the last eight hours, on the other hand, should be treated right away without waiting for the plasma paracetamol result [45]. Asthma should be regarded as a risk factor for developing NAC adverse effects. The adverse effects, on

the other hand, are easily treated, and there is no reason to deny NAC to any patient suffering from paracetamol toxicity [46].

NAC in HIV therapy

Several researchers have linked glutathione (GSH) depletion and the production of reactive oxygen intermediates (ROIs) to the regulation of the human immunodeficiency virus (HIV). In chronic and acute infection scenarios, N-acetylcysteine (NAC) suppresses HIV expression and replication in normal peripheral blood mononuclear cells. The ability of NAC to block viral activation by ROIs, which form in response to inflammatory cytokines, is linked to its antiviral properties. HIV-positive people's circulating T cells had reduced levels of intracellular GSH. Because GSH is the key protective factor against the establishment of ROIs, the observed decrease is due to chronic oxidative stress caused by continual exposure to high levels of inflammatory cytokines. NAC is different from many other antiviral drugs in that it stops the host from stimulating viral replication as a result of normal immune responses, potentially lengthening latency. It also inhibits the action of inflammatory cytokines that can cause cachexia, potentially reducing the detriment a wasting associated with late-stage AIDS [47].

NAC in lung diseases

Idiopathic pulmonary fibrosis (IPF) is a chronic inflammatory interstitial lung disease characterized by alveolar macrophages and neutrophils accumulating in the lower respiratory tract, parenchymal damage, and alveolar wall fibrosis. Inflammatory cells in the lungs produce excessive levels of highly reactive oxygen radicals. Oral administration of NAC, a glutathione precursor, boosted lung glutathione levels in animal models and people with lung tumors. At least in BALF, oral NAC treatment increased inadequate glutathione levels. Oral NAC treatment enhanced lung glutathione levels without causing any short-term side effects. Importantly, there were no indicators of enhanced alveolar-capillary barrier permeability as a result of increased inflammatory activity after NAC therapy. Oral NAC therapy may be a sensible way to correct glutathione deficit in the lower respiratory tract of individuals with IPF, restoring, at least partially, the compartment's impaired antioxidant capacity and controlling fibro blast growth [48].

NAC as Mucolytic Agent

NAC is a thiol reducing agent that is derived from cysteine. In several nations, NAC is commonly utilized as a mucolytic drug. It has been shown to lower the viscosity of purulent sputum in both CF and chronic bronchitis patients, improving pulmonary secretion clearance through ciliary action or cough. NAC converts the disulfide bond (S-S) to a sulfhydryl bond (-SH), which is no longer involved in cross linking and so lowers mucus elasticity and viscosity. In vitro investigations of NAC's effect on sputum viscosity show that it has a dose-dependent effect: the higher the concentration of NAC given, the lower the viscosity. NAC had equal effects on purulent and nonpurulent sputum in both types of sputum. Other in vitro experiments found that NAC's mucolytic activity decreased when the pH of the solution increased from 5.5 to 8.0. NAC, on the other hand, has several drawbacks, particularly when used topically or in aerosol [49].

NAC in COPD

COPD is a disease characterized by a lack of airflow that is not completely reversible. The air flow restriction is usually progressive and dies linked to an aberrant inflammatory response in the lungs in reaction to irritating particles or gases, which is predominantly induced by cigarette smoking. COPD not only affects the lungs, but it also has systemic effects such as chronic inflammation and oxidative stress. Both of these processes are tightly intertwined, trapping patients in a vicious cycle of inflammation and oxidative stress. Oral NAC has been employed as a mucolytic drug in the treatment of a variety of lung ailments. It's also been studied as a drug that could reduce oxidative stress and inflammation in COPD patients, resulting in better lung function and a lower rate of exacerbation and hospitalization. [50].The antioxidant and anti-inflammatory qualities of NAC are founded on a consistent number of in vitro and in vivid demonstrations, and fresh knowledge about the drug' useful engagement in the most intimate pathways involved in triggering and maintaining respiratory inflammation is constantly emerging. COPD's inflammatory nature has already been established, implying that oxidative stress is intimately linked to the inflammatory process. Furthermore, in COPD patients, the level of reactive oxygen species (ROS) in the lungs is gradually increasing. NAC can interfere with the processes that underpin COPD pathogenesis, and it does so by lowering the level of oxidants in the respiratory system. As a result, NAC's antioxidant and mucolytic effects suggest that it could be a valuable supplement in COPD treatment. Even though a recent study found that NAC can improve the efficiency of anti

muscarinic bronchodilators often used in COPD patients [51].

Cystic Fibrosis

Patients with C Fare frequently prescribed nebulized NAC to facilitate the expectoration of sputum by lowering its tenacity to slowdown the deterioration of lung function in people with cystic fibrosis [52]. Inhalation of Nacystelyn, a lysine salt of NAC, has been demonstrated to be well tolerated by CF patients and to result in a dose-dependent reduction in sputum viscoelasticity and solid content [53]. Since the sputum barrier has been widely recognized as a key hurdle to airway gene and medication delivery, this combination of mucolytics /nanoparticle-coating method has important therapeutic implications for CF and probably other lung disorders defined by excess mucus formation[54].In vitro, NAC depolymerizes disulfide linkages, resulting in a considerable decrease in mucous and mucopurulent sputum[55]. Because of its quickabsorption and delayed elimination, it causes high plasma and lung tissue concentrations when takenorally [56]. In the bronchialmucous, however, only traces of NAC may be seen [57].

According to *Tirouvanziam et al's* study, N-acetylcysteine was taken orally in large amounts (0.6 to 1.0 g three times daily, for 4 weeks) which was shown to be safe and significantly reduced sputum ela stase activity (P 0.006), the most accurate predictor of CF pulmonary function. As a result, high-dose oral N-acetylcysteine can balance redox and inflammatory abnormalities in CF patients [58]. A single-center, randomized, double-blinded, placebo-controlled phase II clinical study was conducted by *Dauletbaev et al.* investigated the effects of a12-week NAC treatment with low-dose (700 mg/daily) and high-dose (2800 mg/daily) on clinical parameters, extracellular glutathione concentrations in induced sputum and blood, and inflammatory markers in induced sputum in CF patients[59].

Diagnostic aid in postoperative and intra cheotomy Inhalational burns are a major challenge for otolaryngologists across the world on how to treat patients in this acute context in a systematic, evidence-based manner. *Miller et al*. found that the use of nebulized N-acetylcysteine, as well as other medicines including heparin sulfate and albuterol sulfate, enhanced survival due to N-acetylcysteine-induced mucolysis inpatients that needed mechanical ventilation. The effects of these medications result in a reduction in the amount of time a patient spends on mechanical breathing, as well as a drop in morbidity and mortality, as well as a decrease in the expense of medical treatment [60]. The impact of NAC inhalation following orthotopic liver transplantation (OLT) onpostoperative pulmonary problems was investigated by *Li X et al* in a prospective randomized controlled clinical study (PPCs). The incidence of early PPCs, as well as the consequences, such as the survival rate, were studied. After OLT, atomization inhaled NAC dramatically decreased the occurrence of PPCs. In essence, perioperative NAC inhalation has the potential to minimize the occurrence of PPCs andenhance patient outcomes following OLT. In the research of *Weinbroum et al.,* NAC reduces liver ischemia-reperfusion (I/R) and protects the lungs from hepatic I/R damage [28].

NAC in Kidney and Bladder Diseases

In radio contrast induced kidney disease

A major cause of hospital-acquired acute renal failure is radio contrast nephropathy (RCN).To investigate the efficacy of NAC on the prevention of RCN in patients with pre-existing chronic renal disease, *Alonso et al* did a meta-analysis of group data gathered from previously published trials (CKD). Blinded and un blinded randomized controlled trials were conducted in persons 18 years and older with pre-existing CKD. NAC was found to beefficacious in avoiding RCN in adult patients with pre-existing CKD who had iodinated radio contrast material injected intravenously. Despite the paucity of cost-effectiveness studies, NAC is affordable and has few side effects, therefore it should be prescribed to people who a reat high risk for RCN **[**61].

Cyclo phosphamide induced hemorrhagic cystitis

Cyclophosphamide (CP) is an oxaza phosphorine nitrogen mustard alkylating drug used to treat chroni candacute leukemias, lymphoma, myeloma, and cancers of the breast and ovary. However, when it comes into contact with certain enzymes, it is metabolized into active substances that can damage the uro the lium and cause severe cardiac toxicity. The effectiveness of the NAC in the prevention of hemorrhagic cystitis was demonstrated in a rat model. Preventive therapy with N-acetylcysteine resulted in bladder protection in 33% of theanimals, compared to 60%in the group that did not receive themedicine **[**62].

N-Acetylcysteine (NAC) was found to be protective against CP-induced cardiotoxicity in ratsby *Mansour et al.* A considerable rise in serum aminotransferases, creatine kinase (CK), lactate dehydrogenase (LDH) enzymes, asymmetric dimethylarginine, and tumor

necrosisfactor—and a significant decrease in total nitrate/nitrite—was seen after CP (NOx). NAC hasbeen shown to have a variety of therapeutic effects, including increased cyclic guanosinem onophosphate levels, platelet aggregation inhibition, sulfhydryl group donation to regenerate endothelial-derived relaxing factors, and decreased IL-8 and TNF-α production[63].NAC (200 mg/kg, i.p.) treatment for 5 days before CP attenuates all of the metabolic alterations caused by CP. These findings show that NAC reduces CP-induced cardio toxicity by suppressing oxidative and nitrosative stress while also retaining anti oxidant enzyme activity. The current study's findings suggest that NAC pre-treatment protects against CP-induced cardio toxicity by reducing oxidative and nitrosative stress and maintaining anti oxidant enzyme activity [64].

Limitation of N-Acetyl Cysteine

Adverseeffect: N -acetylcysteine is probably safe for most adults when taken by mouth. N-acetyl cysteine isa prescription medicine that has been approved by the FDA. Dry mouth, nausea, vomiting,and diarrhea are all possible adverse effects. It has a strong odor that some people find difficult to bear [65]. When taken as a prescription drug, N-acetyl cysteine is likely safe for most adults when breathed. But there are some side effects including bacterial pneumonia, cough, and sore throat were the most common side effects of inhaled NAC[66][67]. NAC can elicit aphylactoid reactions such as flushing, urticaria, angioedema, bronchospasm, and other respiratory symptoms when given intravenously, or a combination of these symptoms [68] [69].

The use of NAC is safe during pregnancy when administered orally or inhaled. It hasn't shown any harm to the fetus. It can be used for treating acetaminophen toxicity during pregnancy with lesser side effects by administering intravenously [70]. NAC causes bronchospasm in Asthma patients if administered orally or intravenously [71]. It slows down blood coagulation and hence not be used before or during surgery due to the risk of excessive bleeding. So, NAC is contraindicated for bleeding disorder patients due to delay in coagulation [72].

Interaction

Nitroglycerin's capacity to expand blood vessels and improve blood flow was enhanced by the co administration of N-acetyl cysteine. This could make more susceptible to adverse symptoms like headaches, dizziness, and light headedness [73]. When patients take too much acetaminophen or other drugs, activated charcoal is occasionally used to prevent toxicity. Taking N-acetyl cysteine with activated charcoal is effective in preventing poisoning [74]. Likewise, Chloroquine's anti malarial effects may be reduced by N-acetyl cysteine [75]. The N-acetyl cysteine may help to reduce blood pressure hence it has antihypertensive activity. When N-acetyl cysteine is taken with blood pressure drugs, blood pressure may drop too low [76]. Blood coagulation may be slowed by N-acetyl cysteine so; it acts as an anti platelet drug. Taking N-acetyl cysteine alongside other blood-thinning drugs may raise the risk of bruising and bleeding [77]. Fungistatic action of N-Acetylcysteine on Candida albicans biofilms and interaction with antifungal agents has been observed [78].

Future Perspectives

N-acetylcysteine (NAC) is a precursor to glutathione, a plant antioxidant. It has been used as a medicine since the 1960s, and it is on the WHO's model list of Essential Medicines as an antidote for poisonings. There are various other medical uses or prospective uses that are still being researched in preclinical and clinical settings. NAC is also utilized in cosmetics and food supplements, anti-aging supplements for de generative processes [79]. It has traditionally been used to treat paracetamol overdose [80], as a mucolytic [81], and to counteract the toxicity of several compounds that can produce free radical formation, such as carbon monoxide and x-ray contrasts. It is used in the treatment of neurological and neuropsychiatric disorders. The action of NAC as a precursor to the antioxidant glutathione justifies its use in psychiatric illnesses. NAC affects glutamatergic, neurotrophic, and inflammatory pathways as a precursor to the antioxidant glutathione [82].

NAC and dimethylarginine will improve endothelial function in hypertensive individuals with type 2 diabetes by reducing oxidative stress and increasing Nitric oxide production [83]. Management of COPD furthermore, as a mucolytic medication, may clean the airways by lowering sputum viscosity, resulting in less dyspnea and improved lung function [81]. The current review will concentrate on N-acetylcysteine (NAC), a safe and well-tolerated glutamatergic agent, as a promising prospective pharmacotherapy for the treatment of SUDs in a variety of drug addictions [84].Diabetic retinopathy, cataracts, dry eye syndrome recurrent unexplained pregnancy loss, male infertility,

polycystic ovary syndrome, age-related macular degeneration, and more than 200 different clinical studies related to NAC are enlisted in clinicaltrail.gov in April 2019 [79].

In a recent meta-analysis, the performance of NAC as a sports supplement is reviewed in detail. However, NAC supplementation has been demonstrated in certain studies to significantly improve athletic performance during repeated bouts of intermittent activity (up to 50%), particularly in athletes who can generate more ROS in their muscles during exercise. When muscles are in a pre-fatigued state, the advantages of NAC appear to be even greater [85]. N acetyl cysteine (NAC) is a viable treatment drug for COVID-19 because of its pharmacological properties and possible capabilities in slowing the infection's progression [86].

Conflict of Interest

Authors are declared No Conflict of Interest

Acknowledgement

Not Applicable

Author Contribution

All Authors Contributed equally

Ethical Considerations

Not Applicable

Inform Consent

Not Applicable

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