Review Article

N-acetylcysteine and coronavirus disease 2019: May it work as a beneficial preventive and adjuvant therapy? A comprehensive review study

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Background: Coronaviruses are major pathogens of respiratory system causing different disorders, including the common cold, Middle East respiratory syndrome, and severe acute respiratory syndrome. Today's global pandemic coronavirus disease 2019 (COVID-19) has high mortality rate, with an approximate of 20% in some studies, and is 30–60 times more fatal than the common annual influenza, However, there is still no gold standard treatment for it. N-acetylcysteine (NAC) is a well-known multi-potential drug with hypothetically probable acceptable effect on COVID-related consequences, which we completely focused in this comprehensive review. **Materials and Methods:** PubMed, Scopus, Science Direct, and Google Scholar have been searched. Study eligibility criteria: efficacy of NAC in various subclasses of pathogenic events which may occur during COVID-19 infection. Efficacy of NAC for managing inflammatory or any symptoms similar to symptoms of COVID-19 was reviewed and symptom improvements were assessed. **Results:** Randomized clinical trials introduced NAC as an antioxidant glutathione analog and detoxifying agent promoted for different medical conditions and pulmonary disorders to alleviate influenza and reduce mortality by 50% in influenza-infected animals. The beneficial effects of NAC on viral disorders, including Epstein–Barr virus, HIV and hepatitis, and well-known vital organ damages were also exist and reported. **Conclusion:** We classified the probable effects of NAC as oxidative-regulatory and apoptotic-regulatory roles, antiviral activities, anti-inflammatory roles, preventive and therapeutic roles in lung disorders and better oxygenation functions, supportive roles in intensive care unit admitted patients and in sepsis, positive role in other comorbidities and nonpulmonary end-organ damages or failures and even in primary COVID-associated cutaneous manifestations. Based on different beneficial effects of NAC, it could be administered as a potential adjuvant therapy for COVID-19 considering patient status, contraindications, and possible drug-related adverse events.

Keywords: Acute respiratory distress syndrome, adjuvant therapy, anti-inflammatory, anti-oxidant, anti-viral, comprehensive review, coronavirus, COVID-19, N-acetylcysteine, organ failure, prevention, pulmonary, respiratory, treatment

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INTRODUCTION

According to the WHO, severe acute respiratory syndrome (SARS)-coronavirus, Hemagglutinin Type 1 and Neuraminidase Type 1 (H1N1) Influenza, and Middle East respiratory syndrome (MERS)-Coronavirus caused epidemics in the past 20 years. Coronaviruses are major pathogens of respiratory diseases causing different diseases, including the common cold, MERS, and SARS. The current pandemic of COVID-19 began from Wuhan, China.[1-8] The clinical spectrum of COVID-19 involves asymptomatic and pauci-symptomatic conditions, including dry coughs, malaise, fever, dyspnea, respiratory failure requiring mechanical ventilation in intensive care units (ICUs), multi-organ and systemic manifestations as sepsis, septic shocks, and multiple organ dysfunction syndrome (MODS).[1-4] Approximately

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one-third of the patients require ICU hospitalization, and literature suggests a mortality of 15%.[5] Mortality was reported as approximately 49.0% in critical patients with comorbid cardiovascular disease, hypertension, diabetes, chronic respiratory diseases, or cancer.[5] The mild type of COVID-19 was observed in 81% of the cases presenting with nonpneumonia and mild pneumonia, the severe type in 14% with dyspnea and a respiratory frequency of at least 30/min, a maximum blood oxygen saturation (SpO_2) of 93%, PaO_2/FiO_2 of below 300 and/or pulmonary infiltrates of over 50% in 24–48 h and the critical type in 5% with respiratory failure, septic shocks or multiple organ failure (MOF) and/or MODS.[1-8] Despite the desirable clinical course of the disease in the majority of the patients, a sudden exacerbation of clinical conditions with rapidly worsening respiratory failure and MODS/MOF has been reported. The WHO recommends PCR on paired upper and lower respiratory tract samples for diagnosing COVID-19.[1-3]

No specific antiviral treatments or vaccines have been yet recommended or approved for COVID-19. The National Institute for Allergy and Infectious Diseases has announced the first phase of a trial on a novel coronavirus immunization in Washington. The treatment is symptomatic, and oxygen therapy is the main intervention in patients with severe infections. Mechanical ventilation may be required in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shocks. Intubation, protective mechanical ventilation, high-flow nasal oxygen therapy, and NIV are used in respiratory failure. Respiratory and organ function support is mandatory in complex clinical pictures of MOD. Hemoperfusion and extracorporeal membrane oxygenation should be considered in the patients with refractory hypoxemia under lung-protective ventilation or with poor outcomes of prone ventilation. Although no antiviral treatments have been approved, alpha-interferon and lopinavir/ritonavir have been proposed. Although both chloroquine and hydroxychloroquine inhibit SARS-CoV-2 *in vitro*, the seemingly more potent antiviral activity of the latter is beneficial in COVID-19. Tocilizumab, an IL-6 inhibitor, has been proposed in patients with severe COVID-19. Remdesivir, an RNA polymerase inhibitor with *in vitro* activities against multiple RNA viruses such as Ebola, can contribute to the prophylaxis and treatment of coronavirus infections. Given the lack of evidence, the application of systemic corticosteroids to treating viral pneumonia and acute respiratory distress syndrome (ARDS) is controversial; methylprednisolone was, however, reported as useful. Moreover, antibiotics should not be unselectively or inappropriately administered. As an optimal antiviral intervention, prolonged viral shedding can be applied for a median duration of 20 days in survivors and permanently in fatal cases to isolate infected patients. Accurately evaluating potential medications in terms of effectiveness and safety is crucial for determining the mechanisms through which they target the pathogenic course of COVID-19.[1-3,9,10] Human pathogenic coronaviruses bind to target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. This expression is substantially increased in patients with Type 1 or 2 diabetes treated with ACE inhibitors and angiotensin II type 1 receptor blockers (ARBs). Treating hypertension with ACE inhibitors and ARBs also causes the upregulation of ACE2. Thiazolidinediones as a diabetes treatment and ibuprofen can also increase ACE2. Diabetes and its medications and ACE inhibitors and ARBs used in hypertension therefore increase the ACE2 expression and the risk of COVID-19. ACE2-stimulating drugs used to treat diabetes and hypertension can also increase the risk of developing severe and fatal COVID-19. Patients with cardiac diseases, hypertension, and diabetes treated with ACE2-increasing drugs, who are at higher risks for severe COVID-19, should be therefore monitored for ACE2-modulating medications, including ACE inhibitors and ARBs. Furthermore, antihypertensive calcium channel blockers are recommended in these patients.[11]

As an acetylated variant and precursor of L-cysteine, a scavenger of free radicals, especially oxygen radicals, a strong antioxidant in certain conditions, a nutritional supplement and the cause of glutathione biosynthesis and elevation, N-acetylcysteine (NAC) is commonly used as a specific antidote for acetaminophen overdose and medical conditions related to glutathione synthetase deficiency. NAC exerts its therapeutic effects in hepatotoxic acetaminophen overdose through several mechanisms, and functions as a precursor for the substrate (l-cysteine) in the synthesis of hepatic glutathione depleted through acetaminophen conjugation. N-acetylcysteine alleviates the clinical symptoms of cystic fibrosis through the cysteine-mediated disruption to disulfide cross-bridges in the glycoprotein matrix in mucus. Glucuronidation and sulfation (>90%) at therapeutic doses mainly contribute to acetaminophen metabolism. Below 5% of the drug oxidized by CYP450 isoforms, mainly CYP2E1, produces a toxic metabolite, namely N-acetyl-p-benzoquinone imine (NAPQI), as a precursor of cell injury. Glutathione can normally detoxify these minuscule quantities of NAPQI in the liver and prevent tissue damage. In acetaminophen overdose, glucuronidation and sulfation pathways are saturated, and the more significant CYP450 pathway produces more toxic metabolites, which depletes glutathione reserves and causes their accumulation and tissue injury through binding to

cellular macromolecules.[12-17] The anti-oxidative activity of NAC is attributed to fast reactions with free radicals and restitution of glutathione; nevertheless, NAC by itself should not be considered a strong antioxidant, as its strength depends on the targeted replenishment of glutathione in deficient cells, which improves its efficacy in certain circumstances, including inflammatory processes and oxidative stress.[12-17]

We know that, there are not any specific virus-targeted gold standard therapies for COVID-19 infection. Most of the proposed drugs are immunomodulators for regulating virus-host associated cytokine and inflammation storms. Many of the immunomodulators have immunosuppressant characteristics which may not work properly in a setting of a viral disorder.[1-3]

NAC is an immunomodulators without immunosuppressant characteristics.[12,13]

N-acetylcysteine (NAC) is a multi-potential drug with a wide variety of use in different medical conditions especially with its anti-inflammatory, anti-oxidative, and respiratory supportive effects like positive effect on respiratory outcomes such as ARDS and other end-organ failures.[12,13]

Hence, the aim of this study was classification of probable effects of NAC in many categories of COVID-19-associated consequences.

MATERIALS AND METHODS

Although this study covered a wide topic therefore hard to be written as a systematic review article, we managed to write it to some extent in a systematized and well-classified search and manner.

Eligibility criteria

Inclusion criteria comprised all studies about COVID-19 symptoms and pathogenesis and all studies about N-acetylcysteine mechanisms and applications and efficacy of NAC in various subclasses of pathogenic events which may occurs during COVID-19 infection.

For this review, humans or animal studies which focused on NAC for managing inflammatory or any symptoms similar to symptoms of COVID-19, were reviewed and symptoms improvement were assessed. The exclusion criteria consisted of all publications not meeting the above and non-English literature.

Information sources

Databases PubMed (http://ncbi.nlm.nih.gov/pubmed), Scopus (http://www.scopus.com), Science Direct (https://www.sciencedirect.com), and Google Scholar (https://scholar.google.com/) have been searched for the evidence.

Search strategy

The search was performed by keywords COVID-19, corona viruses, COVID-19 symptoms, novel coronavirus, coronavirus pneumonia, coronavirus disease, inflammation symptoms and their synonyms. N-acetylcysteine and their synonyms, and N-acetylcysteine with each subclass searched separately. Search was not limited to the entries to any condition. The search started and completed on April 22, 2020. The period of search was any articles published until April 22, 2020.

Study selection

Endnote® X8 (Clarivate Analytics, Philadelphia, USA) was used for study screening and data extraction. 900 articles assigned to the inclusion and exclusion groups. In the first step, the titles and abstracts of articles were read. Moreover, if accepted has evaluated to second step; 400 article went to the full-text screening; the authors read the full-text and executed the final inclusion articles based on the highest level of evidence.

RESULT

Study selection

From 400 articles 111 article met inclusion criteria at final and their data were used for this review.

Results of individual studies

COVID-19 is categorized by respiratory features as follows:[1-3] nonsevere/critical cases divided into uncomplicated mild cases presenting with symptoms of upper respiratory tract viral infections, including mild fever, sore throat, dry coughs, malaise, nasal congestion, headache, and muscle pain.

- Moderate pneumonia cases presenting with respiratory symptoms, including coughs and shortness of breath or tachypnea in children without symptoms of severe pneumonia
- Severe pneumonia cases whose moderate fever, if any, is associated with severe dyspnea, respiratory distress, tachypnea (over 30 breaths/min) and hypoxia (SpO_2 <90% on room air)
- ARDS cases whose diagnosis requires clinical measures and ventilation. Characterized by an emerging serious respiratory failure or the worsening of an already-diagnosed respiratory dysfunction, ARDS is classified by the degree of hypoxia (PaO2/FiO2) as severe, i.e., PaO_2/FiO_2 ≤100 mmHg, moderate, i.e., 100 mmHg < PaO_2/FiO_2 ≤200 mmHg, and mild, i.e., 200 mmHg < PaO_2/FiO_2 ≤300 mmHg in the nonventilated

patients or in those managed through noninvasive ventilation (NIV) using positive end-expiratory pressure or continuous positive airway pressure (CPAP) ≥5 cmH_2O.

In the cases of unavailable PaO_2, $SpO_2/FiO_2 \leq 315$ can suggest ARDS. Despite the need for excluding nonpulmonary origins such as cardiac failure and fluid overload, the clinical scenario and ventilator data can suggest pulmonary edema in some cases. Sepsis can occur as a life-threatening organ dysfunction due to dysregulated host responses to COVID-19 emerging as severe dyspnea and hypoxemia, renal impairment with reduced urine output, tachycardia, altered mental status and functional alterations of organs expressed as laboratory data of hyperbilirubinemia, acidosis, high lactate, coagulopathy, thrombocytopenia, and the associated hypotension in septic shocks.[1-3,18-22]

Accidental findings obtained from histopathological evaluations of the lung in COVID-19 patients suggested edema, important proteinaceous exudates as large protein globules, vascular congestion comorbid with inflammatory clusters of fibrinoid materials, multinucleated giant cells and pneumocyte hyperplasia. Lung histopathological evaluations in autopsy also suggested bilateral diffuse alveolar damage with cellular fibromyxoid exudates. Moreover, desquamated pneumocytes and hyaline membrane formation, suggesting interstitial mononuclear inflammatory infiltrates, were also reported in ARDS dominated by lymphocytes. Cytopathic effects with no obvious intranuclear or intracytoplasmic viral inclusions could also be identified as multinucleated syncytial cells with atypically enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm and prominent nucleoli in intra-alveolar spaces.[1,23]

COVID-19 can cause pneumonia and damage other organs and systems, including the heart, liver, kidney, blood, and the immune system. MOF, shocks, ARDS, heart failure, arrhythmias, and renal failure can eventually cause death. Basic treatments, including antivirals, antibiotics, oxygen therapy, and glucocorticoids, were administered for the pneumonia observed in 22% of the patients classified as type A. Individual evaluations should be performed and specific treatment plans, including antihypertensives, hypoglycemic, and continuous renal replacement therapy, be developed to monitor serious comorbidities and manage different degrees of pneumonia in 55% of the patients classified as Type B. The unsatisfactory effects of early treatments on Type A or the aggravation of original comorbidities in Type B, both causing MOF, can turn into the critical disease classified as Type C (23%).[24]

Potential risk factors, including old age, high sequential organ failure assessment scores, and D-dimer over 1 μg/mL, can assist clinicians with the early-stage identification of patients with poor prognoses. Age, comorbidities, lymphocytopenia, elevated alanine aminotransferase, D-dimer, creatine kinase, high-sensitivity cardiac troponin I, prothrombin time, and disease severity were found associated with ICU admission.[10]

The critically ill patients with SARS-CoV-2 pneumonia are quite likely to die within 1–2 weeks of ICU admission. Patients aged over 65 with comorbidities and ARDS are also at higher risk of death.[25]

The ARDS risk and the associated mortality increase with reductions in immunologic responses caused by aging. High fever can be associated with both the development and improved outcomes of ARDS.[9]

Mechanisms of N-acetylcysteine

N-acetylcysteine replenishes glutathione reserves by providing cysteine as an essential precursor of glutathione production, binds to toxic metabolites, scavenges free radicals, increases mitochondrial ATP production and oxygen delivery to tissues, and alters the microvascular tone to increase the blood flow and oxygen delivery to the liver and other vital organs. NAC is therefore a vital agent with oxidative-regulatory and apoptosis-regulatory effects.[12-17]

Patients with malnutrition, alcoholism, or cirrhosis and those using drugs that metabolized through CYP2E1 such as isoniazid are vulnerable to decreased glutathione reserves.[12]

NAC available at a 20% concentration in 30-mL vials and oral NAC available at 10% and 20% concentrations in 10-mL vials require dilution before IV administration. Six hundred milligram of IV NAC can be administered every 8 h in surgical patients and ICU patients with toxic epidermal necrolysis.[26,27]

Major complications of oral NAC include nausea, diarrhea, flatus, gastroesophageal reflux, and vomiting, which occurs in one-third of the patients. Oral NAC can also induce gastrointestinal bleeding in patients with gastrointestinal ulcers or varices.[20] IV NAC can cause anaphylactoid reactions in approximately 18% of patients, including 6% with mild reactions, 10% with moderate, and about 1% with severe reactions, including bronchospasm and hypotension. More commonly observed anaphylactoid reactions at low hepatotoxic acetaminophen levels can be explained by decreases in histamine release from mast cells and mononuclear cells by the ingested acetaminophen. More commonly observed bronchospasm in patients with reactive airway diseases, including asthma, require

bronchodilating agents. NAC should be immediately stopped and anti-histamines and IV fluid be administered rather than vasopressors for hypotension in anaphylactoid reactions. N-acetylcysteine therapy can be re-administered more slowly after the reaction resolution or used as an alternative oral medication in the case of persistent reactions. IV NAC can cause false-positive urine ketones and false increases in international normalized ratios, which normalize once infusion stops. The initial dose of IV NAC should be monitored in assessing anaphylactoid reactions potentially requiring prompt interventions. IV NAC is not recommended in patients with heart failure or cardiomyopathy, who are at risk for hypervolemia.[12] In overall, NAC is safe without any common or serious side effect or interaction, but in heptic encephalopathy, asthma, fluid overload, and gastric hemorrhage, should not be use also the charcoal, ifosfamide and insulin inhalation (rapid acting, may adversely interact with NAC.[12]

Nebulized N-acetylcysteine plays mucolytic, anti-inflammatory, and antioxidant roles in respiratory diseases, including chronic obstructive bronchopulmonary disease (COPD) and cystic fibrosis. The administration routes of NAC include topical, oral, and IV in different medical indications and research on its therapeutic efficacy and ideal doses and most effective mode of delivery of these indications is ongoing.[26-40]

The applications of NAC include:[12-17,26-40]

- Acetaminophen (paracetamol) overdose
- Cystic fibrosis
- Mucolytic agent
- Preventing and treating pulmonary diseases, including ARDS, bronchitis, COPD, pneumonia, and idiopathic pulmonary fibrosis (IPF)
- Antineoplastic agent and cancer chemoprevention
- Psychiatric disorders, including bipolar disorder, schizophrenia, and depression
- Gastrointestinal disorders, including H. Pylori infections, and hepatorenal syndrome
- Infertility, including clomiphene-resistant polycystic ovary syndrome
- Necrotizing enterocolitis
- ICU patients with sepsis, cardiac injuries, MOF, and lung injuries
- Hematological diseases, including sickle cell disease
- Neurologically improving comatose patients with carbon monoxide poisoning
- Preventing contrast-induced nephropathy and thrombosis, i.e., kidney damage during imaging or after heavy surgeries, including coronary artery bypass
- Alleviating preexisting influenza
- Prophylaxis of gentamicin-induced hearing loss in patients undergoing hemodialysis
- Early stages of toxicity induced by nonacetaminophen drugs, alcohol, and pesticides
- Inflammatory and critical systemic disorders.

Preventing and treating dermatologic conditions, including toxic epidermal necrolysis, drug hypersensitivity syndrome, trichotillomania, excoriation disorder, onychotillomania, ichthyosis, contact dermatitis, atopic dermatitis, melasma, pseudoporphyria, connective tissue disorders, wounds, and alopecia as well as protecting against radiation-induced damage including radiation dermatitis, photoaging and photocarcinogenesis

The global demand for NAC as a plant antioxidant in onion is growing, especially in nutritional supplements and cosmetics. Randomized clinical trials (RCTs) suggest controversial and inconclusive evidence for this seemingly safe substance as in the case of other antioxidants. A systematic review and meta-analysis reported increasing side effects with the dose of NAC. Decisions should be therefore made considering the advantages and potential disadvantages.[41,42]

In addition to exerting anti-inflammatory and antioxidant effects, NAC alters neurotransmitter levels, inhibits the proliferation of fibroblasts and keratinocytes and causes vasodilatation. As systemic and topical forms, NAC is used in dermatologic applications.[26-28,35-41] Systematic reviews and meta-analyses in RCTs confirmed the safety, tolerability profile, and effectiveness of NAC in wound healing, photoprotection, pseudoporphyria, xeroderma pigmentosum, onychophagia, systemic sclerosis, Type-I lamellar ichthyosis, toxic epidermal necrolysis, eczema, trichotillomania, acne vulgaris, and bullous morphea.[43]

DISCUSSION

Summary of evidence

In the USA, influenza annually causes approximately 30,000 deaths and infection of 30 million people. The initially found mortality of the currently spread RNA coronavirus in China and all over the world is globally 1%–2% and 2.92% in the USA, which is much higher than that of the common flu, i.e., 0.05%–0.1%, compared to a case fatality of 2.3% in confirmed cases of COVID-19. The real mortality founded to be higher in further investigations of the pandemic. COVID-19 is 30–60 times more fatal than the annual flu,[1-8] as recent evidence suggests an approximate mortality of 20%.[5]

Both influenza and coronavirus cause inflammatory storms in the lungs, which cause organ failure, ARDS and death. Certain medications can reduce lung inflammations caused by RNA viruses and boost the associated Type I interferon

responses as the body's primary mechanism of producing antiviral antibodies to fight viral infections.[1,18-22]

The approved treatments for influenza are generally costly, ineffective, and complicated. Flu vaccines are effective in around half of the cases. Safer and more effective alternatives are therefore required for treating influenza. The management complication of COVID-19 caused by failing to yet propose specific targeted therapies requires serious assessments of potential treatments.[1-3]

RCTs suggest NAC with multiple potential medical applications reduces the influenza duration by 2–4 days and its severity. Nutraceuticals, including spirulina, glucosamine, β-glucans, and N-acetylcysteine, were found to reduce mortality by 50% and the infection severity in influenza-infected animals. The beneficial effects of NAC on other viral disorders, including HIV, Epstein–Barr virus and hepatitis, are highlighted in literature.[12,13,29-33,44-52]

NAC is a glutathione analog antioxidant promoted for treating a wide range of diseases such as pulmonary disorders, including IPF, ARDS, bronchitis, COPD, and pneumonia, which significantly increase mortality in COVID-19 patients. The potential benefits and effectiveness of NAC in coronaviruses are not addressed in literature.

The preventive and therapeutic effects of NAC on COVID-19 and its consequences include:

Oxidative-regulatory and apoptotic-regulatory roles

The anti-oxidative activity of NAC is attributed to fast reactions with free radicals and restitution of glutathione; nevertheless, NAC by itself should not be considered a strong antioxidant, as its strength depends on the targeted replenishment of glutathione in deficient cells, which improves its efficacy in certain circumstances, including inflammatory processes and oxidative stress.[12,13]

NAC regulates the activity of Group I metabotropic glutamate receptors (mGlus) in neuroprotection and neurotoxicity, reduces oxidative stress and increases cell survival. NAC can target the group I mGlus activation in treating Parkinson's disease. Significantly-reduced local induction of bax and caspase 3 and significantly increased the reduced local production of bcl-2 by N-acetylcysteine suggest its effectiveness in protecting the lungs against lipopolysaccharides.

NAC induces apoptosis via mitochondriadependent pathways rather than endoplasmic reticulum stress in H9c2 cells, and exogenous glutathione of NAC does not alter oxidized milieu in the endoplasmic reticulum. NAC causes anti-apoptotic molecule Bcl-2 to significantly reduce apoptosis induced by pro-necrotic concentrations of certain cytotoxic drugs, including cisplatin.[14-17]

Antiviral activities

Influenza A

An animal model of lethal influenza confirmed the effectiveness of combination therapy by demonstrating the effect of NAC in only 20% of cases due to its suboptimal dose and a survival increase of 60% with oseltamivir as an antiviral medicine and 100% with a combination of NAC and oseltamivir.[44]

Evaluating virus replication and virus-induced pro-inflammatory responses in H5N1-infected A549 lung epithelial cells found 5–15 mM NAC to reduce H5N1-induced cytopathogenic effects, virus-induced apoptosis, 24-h postinfection viral yield, pro-inflammatory molecules produced, i.e., CXCL8, CXCL10, CCL5, and interleukin-6, and monocyte migration towards the supernatant of the cells. The antiviral and anti-inflammatory mechanisms of NAC inhibited the activation of oxidant sensitive pathways, including transcription factors NF-κB and p38 mitogen-activated protein kinase. The effects of the pharmacological inhibitors of NF-κB (BAY 11-7085) and p38 (SB203580) resembled those of NAC on H5N1-infected cells. A combination of SB203580 and BAY 11-7085 raised inhibitory effects on virus replication and production of pro-inflammatory molecules in monotherapies. NAC inhibits H5N1 replication and H5N1-induced production of pro-inflammatory molecules.[45] NAC was found unable to alter the course of a fatal influenza pneumonia caused by inoculated murinized swine H1N1 influenza viruses. The inhibitory effects of NAC on swine virus reported *in vitro* were significantly lower than on other strains. NAC is not considered a universal treatment for influenza pneumonia given its strain-dependent effects on influenza viruses.[46] Although NAC was found to limit lung inflammation, viral growth and the virus-caused damage *in-vitro*, its antiviral activity significantly depended on the influenza A strain. These yet-unclear inter-strain variations can be related to the activation level of NF-κB required for the virus to achieve its infectious cycle.[47]

Epstein–Barr virus

Given that NAC slows down the progression of pathology by reducing leukocyte recruitment to sites of inflammation, it can alleviate chronic inflammatory pathologies, including postviral diseases.[48]

HIV

Given the reduction in intracellular glutathione levels of circulating T cells in HIV-infected patients, glutathione-replenishing drugs, including NAC can help

treat HIV. The difference between NAC and many other antiviral drugs lies in its ability to inhibit the host-mediated stimulation of viral replication in normal immune responses, which extends latency. Inhibiting inflammatory cytokines as mediators of cachexia by NAC supports its effectiveness in alleviating the deleterious effects of late-stage AIDS.[49,50]

HIV-seropositive patients with CD4 lymphocyte cell counts of over 200 × 10^6 randomly received 800 mg of NAC or placebo for 4 months in a double-blind placebo-controlled trial. Low cysteine plasma levels, high free radical activity in neutrophils in the presence of autologous plasma measured with the nitroblue tetrazolium test, and increased tumor necrosis factor (TNF)-alpha levels were observed in the HIV patients before the treatment. Cysteine plasma increased to normal levels and TNF-alpha levels and the drop rate of CD4 + lymphocyte counts decreased in the NAC group compared to in the placebo group after the treatment. NAC did not affect the radical production by neutrophils, although it decreased the decline in CD4+ cells.[51]

Hepatitis virus

An RCT recruited 13 females and 28 males hospitalized with acute viral hepatitis (AVH) and administered placebo capsules in controls and 200 mg of oral NAC three times daily in the experimental group to determine the efficacy of NAC, which was found ineffective in the time necessary for ALT normalization, total bilirubin, and length of stay. Despite its innocuous effects on AVH patients, NAC was not recommended for treating icteric AVH.[52] These findings can be explained by the low dose of oral NAC administered.

Preventive and therapeutic roles in pulmonary disorders

Idiopathic pulmonary fibrosis

Well-designed studies found insignificant differences in complications and mortality between two groups and NAC to reduce disease progression based on PaO_2 and improve pulmonary dysfunction based on forced-vital-capacity (FVC) and diffusion capacity of lung for carbon monoxide (DLCO) compared to in controls, which confirmed the efficacy, tolerability and safety of the treatment. Furthermore, subgroup analysis found combination therapy for IPF with NAC more effective than NAC monotherapy and oral NAC safer than inhalation. This review and meta-analysis provided valuable evidence that can be applied to clinically treating IPC with NAC.[53-62]

Chronic obstructive pulmonary disease

NAC has been frequently found with anti-oxidative, anti-inflammatory, and positive mucolytic effects on COPD. Given the controversial findings on NAC effects on COPD outcomes, including exacerbation and changes in lung function, a systematic review and meta-analysis found NAC ineffective in exacerbation, forced expiratory volume in 1 s, FVC, and inspiratory capacity and long-term administration of NAC effective in decreasing the COPD exacerbation risk.[63-71]

NAC was found to moderately and significantly affect aspergillosis and bacterial pulmonary infections, respectively.[72,73]

Pneumonia

Ventilator-associated pneumonia (VAP) is characterized by mortality, morbidity, and prolonged stay in ICUs. As part of the pathogenic mechanism of community-acquired pneumonia (CAP), oxidative stress significantly relates to inflammation. Alleviating oxidative stress appears to decrease pulmonary damage. Research suggests no adverse NAC-associated events and significantly higher frequencies of complete recovery from VAP in NAC groups compared to in controls. NAC was found safe and effective in preventing and postponing VAP and improving its complete recovery in a selected high-risk ICU population. Investigating CAP patients showed insignificant differences in plasma superoxide dismutase activity and CT scores between controls and a group receiving NAC. Malondialdehyde and TNF-α decreased and total antioxidant capacity increased using NAC, which exerted no adverse effects on CAP patients. Moreover, NAC can reduce oxidative and inflammatory damage in pneumonia patients.[74,75]

Acute respiratory distress syndrome

Compelling evidence suggests antioxidants and omega-3 fatty acids cause insignificant differences in all-cause mortality between adult groups with ARDS. The effect of immuno-nutrition with omega-3 fatty acids and antioxidants on ventilator days, ICU stay, and oxygenation at day 4 should be confirmed given the flimsy evidence available. Immuno-nutrition-associated adverse events should also be clarified given that confidence intervals might increase the risk of cardiac, gastrointestinal, and total adverse events. NAC reduces ICU stay despite its ineffectiveness in mortality and its limited effect on ARDS.[76-83]

Supportive roles in intensive care units

Vitamin and high-dose trace element supplementation can improve outcomes in critically ill patients, especially those at increased risks of death. NAC can only be recommended for treating paracetamol poisoning, and its effect on other disorders is still being evaluated. High doses of NAC did not improve patient outcomes and increased the inflammation risk and serum creatinine.[84-87]

Sepsis

Investigating septic patients showed insignificant differences in mortality between NAC groups and placebo

groups. NAC did not significantly affect lengths of stay and mechanical ventilation and incidence of organ failures. Neither the early application of NAC nor its application 24 h after developing symptoms, which related to cardiovascular instability, prevented oxidation inflammatory responses. NAC therefore appears ineffective in hemodynamic instability, including sepsis and septic shocks.[87-91]

Role in comorbidities and nonpulmonary end-organ damage or failure

Heart

NAC is a nontoxic and safe antioxidant with mild adverse effects at high doses, including dizziness, hypotension, chest pain, bronchospasm, pruritus, rash, flushing, nausea, and vomiting. As an acetaminophen antidote, it appears to prevent cardiovascular disorders. Despite suggesting beneficial effects for NAC, literature contains controversies over its dose, time of administration, and duration of treatment in cardiovascular disorders. NAC has great potential for protecting diabetic heart at risks for myocardial infarction by inhibiting oxidative stress. The potential effects of NAC on ischemia and nonischemic-associated cardiac damage have attracted the attention of researchers; nevertheless, its administration during cardiac surgeries caused statistically-insignificant reductions in clinical outcomes. Large multi-center placebo-controlled RCTs are recommended for determining the effect of NAC on mortality in these settings.[92-94]

Hypertension

Research suggests ineffectiveness of NAC in blood pressure and surrogate markers for cardiovascular injury in nondiabetic patients with chronic kidney disease. In contrast, NAC combined with ACEIs was found to significantly decrease systolic and diastolic blood pressure, although ACEIs alone were ineffective in blood pressure. Systolic blood pressure decreased by 7 mmHg on an average.[95,96]

Diabetes mellitus

NAC can positively affect glutathione peroxidase in patients with Type II diabetes. NACl treatment with faster and more prolonged effects significantly improved cardiac function and decreased fibrosis. In cardiac fibroblasts, NAC blocked cardiac fibroblast proliferation and hyperglycemia-induced collagen synthesis. The present findings suggest NAC can protect diabetics against diabetic cardiomyopathy through inhibiting the ROS production and fibrosis, which should be investigated in future research.[97,98]

Nephropathy

The preventive effects of NAC resembled those of VC and NAC plus VC in patients with contrast-induced nephropathy (CIN) undergoing contrast administration. In contrast to ascorbic acid (VC) and NAC plus VC, NAC significantly lowered serum creatinine levels. NAC plus statins plus IV saline appears the most effective in preventing CIN after coronary angiography (CAG). NAC plus IV saline can also protect from short-term all-cause mortality. None of these medications have, however, effectively reduced dialysis and major adverse cardiovascular events (MACE).[99]

Liver failure

Nonparacetamol induced

Despite the numerous positive findings, currently available scarce evidence is not compelling in terms of determining the role of NAC in nonparacetamol drug-induced liver injuries.[100]

Paracetamol-induced

NAC is a standard medication for liver injuries associated with acetaminophen. Despite reporting similar hepatotoxicity for IV and oral NAC in literature, comparisons should be drawn. Although disentangling the effects of dose and duration from those of route is difficult, the present findings suggest similar hepatotoxicity rates for IV and oral administration of NAC.[101]

Other organs

NAC is popular for its antitoxic properties in ototoxicity and acetaminophen poisoning. Evidence suggests the safety and otoprotective impact of NAC co-administered with aminoglycoside. The effect of concomitant NAC treatment on patients receiving aminoglycosides as part of multidrug-resistant tuberculosis treatment is recommended to be investigated.[102]

Given its oxidative regulatory and immune-regulatory effects and facilitation of oxygenation and circulation, a large body of literature was recently assigned to the efficacy of NAC in neurologic and psychiatric conditions, burns, and CO poisoning.[103-105]

There are documented with quality studies on efficacy of NAC in the treatment of viruses which target respiratory system and the related acute injuries such as ARDS (importantly by the drug's antioxidant and immunomodulatory roles), it is especially true about influenza (strains A and B) and respiratory syncytial virus (RSV) so that this drug has been highly recommended in the setting of influenza pandemic.[106-108]

Based on this review, there are many special probable therapeutic effects of NAC on COVID-19 and its consequences such as respiratory outcomes and other end-organ failures. We classified the probable effects of NAC in many categories such as oxidative-regulatory and

apoptotic-regulatory roles, antiviral activities, preventive and therapeutic roles in pulmonary disorders and better oxygenation, Supportive roles in ICUs and sepsis, positive role in comorbidities, and nonpulmonary end-organ damage or failure. NAC could be administered as a potential adjuvant therapy for COVID-19 considering patient status, contraindications and possible drug-related adverse events. Oral NAC may be recommended as a preventive or therapeutic agent for disease-related outcomes in stable nonseptic and nonintubated patients.

In the last update of this comprehensive review, we found the first rapid review on the evidence for effectiveness of NAC in treating COVID-19 that published on April 14 in CEBM of Oxford University, which resulted in us be so pleasured that our hypothesis may be supported by other experts. In this review the authors had been focused on previous data of clinical trials justified use of NAC in COVID-19 like its use in influenza, bronchopulmonary disorders, and pneumonia[109] and also found other two studies focused on applicability of NAC usage in cytokine storm, dyspnea and ARDS related to COVID-19. This review is the most holistic study on the efficacy of NAC in various aspects of COVID-19.

Limitations and recommendations

In the present study, there is no RCT that has used NAC in COVID-19 patients. In the latest search update of the article, three studies were found that their researchers agreed on the effect of NAC in COVID-19 patients.[109-111]

In addition, the field of COVID is of interest of the authors of this study and the author have been focused on other multi-potential drugs and specific manifestation of COVID and COVID in patients with specific disorders.[112-114]

Some clinical and therapeutic features of COVID-19 and its final sequels may become more clear and evident during time especially about nonrespiratory symptoms such as cutaneous signs and some of them could be targeted by NAC such as severe adverse cutaneous reactions that needs more focus in future studies.[26,27,113,114] In our medical field, dermatology, some cosmetic procedures and nonemergent surgeries could be postponed and some disorders may be managed by drugs that are effective for dermatologic diseases also be a potential preventive strategy for probable COVID in this pandemic area and NAC is among such drugs.[113,115,116]

CONCLUSION

Given the special probable therapeutic effects of NAC on COVID-19 and its consequences, respiratory outcomes and other end-organ failures, NAC could be administered as a potential adjuvant therapy for COVID-19 considering patient status, contraindications, and possible drug-related adverse events. Oral NAC is recommended as a preventive or therapeutic agent for disease-related outcomes in stable nonseptic and nonintubated patients. In this review, we classified the probable effects of NAC in many categories such as oxidative-regulatory and apoptotic-regulatory roles, antiviral activities, preventive and therapeutic roles in pulmonary disorders and better oxygenation, supportive roles in ICUs and sepsis, positive role in comorbidities and nonpulmonary end-organ damage or failure and even in primary COVID-associated cutaneous manifestations. IV NAC is recommended in case the efficacy is found valuable and significant. Analytical case–control studies and RCTs also finally systematically review of evidence are recommended for assessing NAC effects on COVID-19 outcomes.

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Conflicts of interest

There are no conflicts of interest.

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