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LETTER TO THE EDITOR

# Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19

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## Abstract

Although several considerations have been raised suggesting a beneficial effect of N-acetyl cysteine (NAC) for the treatment of severe acute respiratory syndrome coronavirus 2 infection, there is currently no clinical evidence that NAC truly prevents coronavirus disease 2019 (COVID-19), reduces the severity of the disease, or improves the outcome. Appropriately designed clinical trials are warranted to prove or disprove a therapeutic effect of NAC for COVID-19 patients.

**Key Words:** N-acetyl cysteine; SARS-CoV-2; COVID-19; Reactive oxygen species; Cytokines



**Core tip:** N-acetyl cysteine (NAC) is a well-known antioxidant and anti-inflammatory agent that has been considered beneficial in the treatment for coronavirus disease 2019 (COVID-19). Although previous studies in patients with chronic lung disease, chronic heart disease, immune-mediated disease, viral infections, and malignancy have shown promising results, there is currently no clinical evidence that NAC prevents COVID-19, alleviates the severity of COVID-19, or improves the overall outcome of COVID-19 patients.

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## TO THE EDITOR

With interest, we read the review article by Dominari *et al*[1] about the putative therapeutic effect of N-acetyl cysteine (NAC) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients. The authors raise several arguments in favour of a beneficial effect of NAC for coronavirus disease 2019 (COVID-19), discuss preliminary results about ongoing studies with NAC in COVID-19, and conclude that the results of available trials are not clear. The study is appealing but raises the following comments and concerns.

We do not agree with the notion that NAC is an agent for curing SARS-CoV-2 infections[1]. There are several arguments against the antiviral effect of NAC. First, NAC is primarily an antioxidant and a precursor of reduced glutathione (GSH) that replenishes GSH stores[2]. NAC reduces oxidative stress as it scavenges and neutralises reactive oxidative species, such as OH, HOCl, or $RO_2$[3]. Thus, NAC is approved as a preventive/therapeutic agent in disorders associated with GSH depletion, as an antidote in paracetamol intoxication, and as a mucolytic agent[2]. Since SARS-CoV-2 infections are associated with oxidative stress, NAC can, at best, reduce oxidative stress and thus reduce secondary effects of the infection[2]. Although NAC additionally has an anti-inflammatory effect by reducing cytokine production *via* blocking of matrix metalloproteinase (MMP)-1, MMP-4, intracellular adhesion molecule 1, nuclear factor B, NF-E2-related factor 2, and tryparedoxin-1b[2], NAC cannot neutralise the virus and cannot reduce the virus load. Thus, NAC may have, at best, a complementary but no curative effect in SARS-CoV-2 infections as all infections are associated with increased oxidative stress and cytokine activation. Second, there are no reports that NAC is capable of reducing viral load, preventing infection, alleviating severity of COVID-19, or reducing mortality. Third, many patients are regularly taking NAC for the treatment of bronchitis, bronchiolitis, pneumonia, asthma, or chronic obstructive pulmonary disease. However, there are no indications that patients regularly taking NAC have a decreased risk of SARS-CoV-2 infection, or that morbidity or mortality of SARS-CoV-2 infection in these patients is lower compared with that in patients not taking NAC. Fourth, NAC did not prevent the presence of SARS-CoV-2 in sputum[4]. Arguments in favour of a promising role of NAC in the management of COVID-19, however, are that it generally enhances immunocompetence[5] and that it inhibits the replication of the influenza virus H5N1 [6]. A potential beneficial effect of NAC for treating COVID-19 may also derive from its capacity to increase glutathione, improve T-cell responses, and modulate inflammation[7-12]. Currently, a protocol for using NAC together with heparin has been developed[13] but no results have yet been published. Since several studies concerning the role of NAC in COVID-19 are under way, final conclusions about its contribution for treating COVID-19 cannot be reliably drawn. Future studies may demonstrate that NAC can reduce replication of SARS-CoV-2. Overall, agents that appear beneficial theoretically need to be thoroughly investigated by appropriately designed clinical trials for their putative beneficial effect. This is particularly the case for anti-COVID-19 agents, as there is strong pressure from healthcare authorities, industry, and the global community to provide a safe and effective cure of this global threat that currently influences all segments of social, economic, scientific, and political life. Effective and safe agents are needed as several drugs that were proposed to be beneficial at the beginning of the pandemic turned out to be harmful or inefficient, such as chloroquine, azithromycin and tocilizumab.

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