



# Possible Old Drugs for Repositioning in COVID-19 Treatment: Combating Cytokine Storms from Haloperidol to Anti-interleukin Agents

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Dear Editor,

We read with great interest the correspondence by Yartas Dumanli et al. (1) about the “Use of spironolactone in SARS-CoV-2 ARDS Patients”.

Since appearing in China a few months ago, the coronavirus disease 2019 (COVID-19) has become a worldwide pandemic within a short period of time. Following mild symptoms, the virus can cause pneumonia and severe acute respiratory distress syndrome (ARDS), possibly due to a cytokine storm. Antiviral agents, antimalarial agents, and macrolides are being used increasingly for the treatment of COVID-19, and results with ivermectin, an antiparasitic agent, appear to be promising. However, there is no positively proven treatment for COVID-19 (2, 3).

The severity of symptoms caused by COVID-19 are thought to be related to a cytokine storm (4), and when compared with those with mild symptoms, the level of cytokines such as interleukin (IL)-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  appears to be higher in those with severe symptoms (5). It has been reported that tocilizumab, an IL-6 receptor antagonist, has decreased the mortality of COVID-19 (6), and several centers have reported similar results with the use of similar IL-6 receptor antagonists (7, 8).

Until recently, haloperidol was the most commonly used agent in the prevention or treatment of delirium that developed in intensive care units (9, 10). Herein, we would like to consider a completely different purpose for its use. In 2005, Milbrandt et al. (11) reported that haloperidol decreased mortality of patients on mechanical ventilation and hypothesized that this was due to its effect on lowering cytokine levels and, therefore, aided in preventing a cytokine storm associated with severe disease. In line with this data, although certain texts claim the opposite, the hypothesis that haloperidol has inhibitory effects on proinflammatory cytokines may be an essential step in preventing the progression of the disease and reducing its severity. We accept that there is no certainty to recommend starting haloperidol for every patient diagnosed with COVID-19 whose treatment had commenced. However, we recommend that haloperidol be considered as an option to treat patients who develop agitation during the treatment process or agitation/delirium during the intensive care treatment process and continue to be administered routinely until proven otherwise. Of course, drug interactions must be considered.

There is still insufficient evidence for the use of either tocilizumab or other treatment agents in the treatment of COVID-19. Tocilizumab is available as an effective option in combating cytokine storm. However, this drug is not readily available all over the world. Therefore, different options must be sought, and alternatives must be put forward.

Our current strategy is to gain time by using existing drugs outside of their known indications until a definitive treatment or vaccine is found in the treatment of COVID-19. In addition to clinical studies (NCT04330638) related to the use of anti-IL agents such as anakinra, siltuximab, and tocilizumab in combating cytokine storms, studies are also being conducted with old drugs (NCT04304313) such as sildenafil, used indirectly outside of their indications. Haloperidol should also be the subject of a similar study as soon as possible.

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