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MODESTUM

Letter to the Editor

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Quetiapine versus Clozapine in Treating Psychiatric Patients with Severe COVID-19: A Netosis-Based Opinion

Mohsen Khosravi [1]*

[1] Department of Psychiatry and Clinical Psychology, Zahedan University of Medical Sciences, Zahedan, IRAN
***Corresponding Author:** dr_khosravi2016@yahoo.com

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Dear Editor,

The 2019 coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to millions of confirmed cases and deaths worldwide since it became a pandemic in May 2020. Like other viral respiratory pathogens, the SARS-CoV-2 may be associated with mild to severe clinical symptoms. In severe COVID-19 patients, developed acute respiratory distress syndrome (ARDS) can lead to respiratory failure and death by causing severe acute lung injury [1]. Recent evidence has suggested that the increased neutrophil represents the severity of respiratory symptoms and a poor prognosis among COVID-19 patients [2]. Among neutrophils' well-known effector mechanisms, neutrophil-derived extracellular traps (NETs) appear to be one of the most important in COVID-19 infection [3]. NETs are web-like structures of extracellular fibers composed of double-stranded DNA, histones, myeloperoxidase (MPO), and proteinase-3. The process of NETs formation (or NETosis) is initiated with neutrophil activation via pattern recognition receptors or chemokines and continues with ROS production and calcium mobilization, activating the protein arginine deiminase-4 (PAD-4) [3,4]. Although NETs were initially reported as neutrophil microbicidal mechanisms, additional evidence suggested that NETs have double-edged-sword activities [3]. In this regard, recent studies have shown that during clinical and experimental sepsis, the concentration of NETs increases in the bloodstream, which is positively correlated with sepsis severity and biomarkers of vital organ injuries. In addition, it has been demonstrated that inhibiting NETosis using recombinant human DNase (rhDNase) or PAD-4 inhibitors can significantly reduce organ damage, particularly in the lungs, and increase the survival rate of severe septic mice [5-9]. Given the well-known similarities between key factors involved in the pathophysiology of sepsis and COVID-19 (e.g., cytokine overproduction, micro-thrombosis, and ARDS), it can be hypothesized that lung tissue damage in COVID-19 patients may be due to SARS-CoV-2-triggered NETosis [2,3]. In support of this hypothesis, recent researches have shown an increase in the concentration of NETs in the plasma and lungs of COVID-19 patients [10-12]. In detail, SARS-CoV-2 can induce apoptosis of lung epithelial cells by directly stimulating NETosis in healthy neutrophils in mechanisms dependent on the angiotensin-converting enzyme (ACE2)–serine protease axis, virus replication, and PAD-4 signaling. These findings indicate the significant role of NETosis in destroying lung epithelial cells as a part of the pathophysiology of severe COVID-19 infection. Hence, the use of NETosis stimulants can exacerbate pulmonary epithelial cell damage among COVID-19 patients [2,3]. Recently, the effect of two common second-generation antipsychotic drugs, namely quetiapine and clozapine, has been investigated on innate immune cells [4,13]. A new study on the in vitro impact of unmetabolized quetiapine on innate immune cells has shown that unmetabolized quetiapine increases formation of NETs via activated neutrophils. These results confirm the impact of quetiapine on neutrophil function, which may aggravate NETs formation and pulmonary epithelial cell damage during severe SARS-CoV-2 infection [13]. In contrast, researchers have not found any similar action in neutrophils exposed to antipsychotic clozapine [4]. Although these findings are derived from the preliminary in vitro studies, psychiatrists and other mental health professionals should be more careful about initiating or continuing quetiapine treatment in psychiatric patients with severe COVID-19 infection until the completion of information. However, regardless of other challenges of using clozapine in the COVID-19 era (such as the overlap between clozapine-induced side effects and COVID-19 symptoms and sequelae, and practical difficulties in regular laboratory monitoring), its continuation appears to be safe in psychiatric patients with severe SARS-CoV-2 infection [14-17].

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