CORRESPONDENCE

Comments to "Fluvoxamine and long COVID-19: a new role for sigma-1 receptor (S1R) agonists" by Khani and Entezari-Maleki

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TO THE EDITOR:

The coronavirus disease 2019 (COVID-19) pandemic causes short-term and long-term health problems in survivors after infection of SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2). A recent systematic review using 57 studies with 250,351 survivors of COVID-19 shows that the median proportion of COVID-19 survivors experiencing at least 1 PASC (post-acute sequelae of COVID-19) was 54% at 1 month (short-term), 55% at 2–5 months (intermediate-term), and 54% at 6 or more months (long-term) [1]. The most common sequelae involved neurologic symptoms (i.e., headaches, memory deficits, difficulty concentrating, cognitive impairment), psychiatric symptoms (i.e., depression, anxiety, sleep disorders), pulmonary abnormalities (i.e., dyspnea, cough, increased oxygen requirement, pulmonary diffusion abnormalities, chest imaging abnormalities), and functional mobility impairment (i.e., impairment in general functioning, mobility decline, reduced exercise tolerance). However, there are no therapeutic drugs for long-term symptoms in survivors of COVID-19.

The precise mechanisms underlying SARS-CoV-2 induced long-term detrimental effects remain unclear. Infection of SARS-CoV-2 can damage endothelial cells leading to inflammation, thrombi and brain damage. SARS-CoV-2-associated systemic inflammation leads to decreased monoamines and neurotrophic factors, and microglial activation in the brain, resulting in long-term neurological and psychiatric symptoms in COVID-19 survivors [2]. A retrospective study of Wuhan University (Wuhan, China) reported that patients with Epstein-Barr virus (EBV)/SARS-CoV-2 coinfection have about 3-fold risk of having a fever symptom than patients with SARS-CoV-2 infection alone, and that levels of C-reactive protein and aspartate aminotransferase in patients with EBV/SARS-CoV-2 coinfection were higher than those in patients with SARS-CoV-2 infection alone [3]. This report suggests that EBV reactivation may be associated with the severity of clinical symptoms after SARS-CoV-2 infection.

Interestingly, approximately 67% of patients (20/30) with long-term sequelae of COVID-19 were positive for EBV reactivation based on positive titers for EBV early antigen-diffuse IgG or EBV viral capsid antigen IgM [4]. Thus, EBV reactivation may play a role in long-term symptoms in COVID-19 survivors although further study using a large sample size is needed. The authors suggest that most of long-lasting symptoms in COVID-19 survivors following the recovery from SARS-CoV-2 infection might not be directly affected by the virus but probably result from SARS-CoV-2-associated inflammation and EBV reactivation [4].

In the issue, Khani and Entezari-Maleki proposed that fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), may be a new therapeutic drug for long-term consequences of COVID-19 survivors [5]. Fluvoxamine has been demonstrated to prevent clinical deterioration in early-stage subjects with COVID-19 [6]. In addition of serotonin transporter inhibition, sigma-1 receptor chaperone in the endoplasmic reticulum (ER) and acid sphingomyelinase might play a role in the mechanisms of beneficial action of fluvoxamine for patients with SARS-CoV-2 infection [6–8]. It is also reported that sigma-1 receptor agonists such as fluvoxamine could produce potent anti-inflammatory actions by the prevention of inositol requiring enzyme 1α (IRE1) and X-box binding protein-1 (XBP-1) pathway [9]. Collectively, it is likely that sigma-1 receptor agonists such as fluvoxamine could produce potent anti-inflammatory effects through sigma-1 receptor/IRE1/XBP-1 pathway in the ER [6–9].

Among the SSRIs, fluvoxamine was the most potent at sigma-1 receptor in the brain [6–8]. Given the link between EBV reactivation and XBP-1 [10], it is possible that the potent sigma-1 receptor agonist fluvoxamine may have beneficial effects for long-term consequences in COVID-19 survivors through sigma-1 receptor/IRE1/XBP-1 pathway [4]. Therefore, it is of great interest to examine whether fluvoxamine can improve long-term sequelae in COVID-19 survivors.

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AUTHOR CONTRIBUTIONS

YH, TS, and KH did the reference search and wrote the manuscript. All authors approved the final manuscript.

COMPETING INTERESTS

YH and TS have no conflict of interest. KH is the inventor of filed patent applications on "The use of *R*-Ketamine in the treatment of psychiatric diseases", "(*S*)-norketamine and salt thereof as pharmaceutical", "*R*-Ketamine and derivative thereof as prophylactic or therapeutic agent for neurodegeneration disease or recognition function disorder", "Preventive or therapeutic agent and pharmaceutical composition for inflammatory diseases or bone diseases", and "*R*-Ketamine and its derivatives as a preventive or therapeutic agent for a neurodevelopmental disorder" by the Chiba University. KH has also received speakers' honoraria, consultant fee, or research support from Abbott, Meiji Seika Pharma, Daiichi-Sankyo, Dainippon-Sumitomo, Taisho, Otsuka, Murakami Farm and Perception Neuroscience.

ADDITIONAL INFORMATION

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