

POTENTIAL OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PREVENTING CLINICAL DETERIORATION OF COVID-19

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Dear editor,

The successive waves, disease occurrence following vaccinations, and newer virus strains have resulted in the COVID-19 pandemic having a massive impact on the physical and mental health of society. The disease has an unpredictable course, with manifestations ranging from mild to severe symptoms in about 20% of cases, leading to increased ICU care and health care burden (Khan et al. 2022). The body reacts to the viral infection by generating a hyperinflammatory response (cytokine storm) and a hypercoagulable state (Khan et al. 2022), which have been primarily implicated in clinical deterioration. Therefore, a useful treatment strategy would be to modify the above two risk factors using repurposed drugs.

Recently, Khan et al. (2022) have reported studies exploring Selective Serotonin Reuptake Inhibitors (SSRIs) as a disease-modifying agent in COVID-19. SSRIs can prevent disease progression due to the following favourable properties:

1: Anti-inflammatory: The beneficial effects of SSRIs in COVID-19, primarily by Sigma-1 receptor agonism, have been validated through one RCT and two observational studies (Khan et al. 2022). Additionally, SSRIs can exert anti-inflammatory actions through reduced production of inflammatory Interleukins (IL-6, IL-10), inhibition of cytokine release (TNF- α , interleukin-1 β , Interferon- γ), and increased proliferation of immune cells (Walker 2013).

2: Anticoagulant: SSRIs may decrease blood-coagulability by reducing platelet aggregation and activity. SSRIs inhibit serotonin uptake into platelets, modulate platelet surface receptors Glycogen IIb/IIIa involved in platelet activation, and upregulate glycogen synthase kinase 3-beta involved in platelet inhibition (Halperin and Reber 2007). SSRIs with the highest degree of serotonin reuptake inhibition (fluoxetine, paroxetine, and sertraline) have been useful in preventing the hypercoagulable blood state (Halperin and Reber 2007).

3: Immunomodulation and Antioxidant: Serotonin plays an important role in regulating adaptive immune responses, which get affected by stress due to COVID-19 infection. SSRIs elevate serotonin levels, reduce lipid peroxidation,

prevent the release of nitric oxide (NO) and inhibit free radical formation by neutrophils, thereby strengthening the immune system (Hamed and Hagag 2020).

4: Antiviral and Antibacterial: Recent studies on SARS-COV-2 culture models have found Fluoxetine to decrease entry and propagation of the coronavirus through impaired endolysosomal acidification and accumulation of cholesterol within the endosomes by being a functional inhibitor of sphingomyelinase (FIASMA). In vivo studies have demonstrated this action of Fluoxetine to be virus-specific and is achieved at a dose which is non-cytotoxic (Schloer et al. 2020). SSRIs also reduce the viral load by reducing chemokine and cytokine release by the infected cells, down-regulating virus-specific receptors and by inhibiting replications (Hamed & Hagag 2020). The antibacterial effects of SSRIs have also been proposed to prevent secondary or nosocomial infections in COVID-19 patients, especially on steroid therapy. Moreover, SSRIs are known to potentiate the actions of antibacterial agents against resistant strains of bacteria (Hamed and Hagag 2020).

The asymptomatic and mild COVID-19 patients reportedly develop a range of negative psychological consequences like anxiety (35.1%), depression (3.7-20.1%), post-traumatic stress disorder (7%) and stress (8%) (Sinanovic et al. 2020). SSRIs can help alleviate these anxiety and depressive symptoms and speed up the recovery process improving the global functioning of the patients.

To conclude, SSRIs can be a beneficial drug in the armamentarium against COVID-19 due to their unique anti-inflammatory, anticoagulant, antiviral and antioxidant properties. They can help prevent clinical deterioration and improve the negative psychological effects as well. The tolerability and safety of the drugs are already established, and a brief course of two-three months may be planned, taking into account the risks-benefits involved. Among SSRIs, Fluoxetine may be preferred due to its wider anti-inflammatory properties, better anticoagulation and SARS-COV-2-specific antiviral effects. Fluoxetine can safely be given to children and adults, while Sertraline in the elderly patients. However, the literature in this area is limited to only two observational, retrospective studies and one controlled trial on a small sample over a short time frame, suggesting the need for further research.

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