Title: Potential of Selective Serotonin Reuptake Inhibitors in preventing clinical deterioration of COVID-19

A short running title: Selective Serotonin Reuptake Inhibitors in COVID-19

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Abstract:

COVID-19 has an unpredictable course with substantial percentage of infected patients developing clinical deterioration and increasing health care burden. With no specific treatment or vaccination, the current search is for drugs that can limit the disease progression. Recently Fluvoxamine has been reported to have disease modifying effects in COVID-19. We suggest the hypothesis that short term routine use of Selective Serotonin Reuptake Inhibitors (SSRIs) can prevent clinical deterioration of asymptomatic or mild COVID-19 cases by the following ways: a) anti-inflammatory actions through sigma-1 agonism and reducing release of pro-inflammatory cytokines, b) anti-coagulant action by reducing platelet aggregation, c) specific antiviral and antibacterial effects, d) Immunomodulation through Serotonin pathway and anti-oxidation. The routine short term use of SSRIs can also alleviate the psychological impact of the disease. We hope our hypothesis will encourage future clinical trials to validate the routine use of SSRIs against COVID-19.

Keywords: COVID-19, SSRI, Anti-inflammatory, Anti-coagulant, Mental health

Main text:

Hypothesis:

The novel Coronavirus Infected Disease-2019 (COVID-19) outbreak was declared as a pandemic and global emergency by WHO on January 30, 2020. While we are writing this article, the highly contagious virus has already infected 85.7 million people and caused 1.85 million deaths across the globe with a massive impact on both the physical and mental health of the society (WHO, 2021). The disease has an unpredictable course with manifestations ranging from mild to severe symptoms including death. The transition from mild to severe has been reportedly 12.6 to 23.5%, leading to increased ICU care and health care burden (Yong *et al*., 2020).

Often, the body reacts to the viral infection by generating a hyperinflammatory response (including cytokine storm) (Gustine and Jones, 2021) and a hypercoagulable state (Singhania *et al*., 2020), which have been primarily implicated for the clinical deterioration. Therefore, the current search for strategies to prevent the transition from mild to severe COVID-19 aims at finding drugs that can modify the above two risk factors. The drugs routinely included in COVID-19 treatment protocols across the globe includes those with anti-inflammatory (steroids), anticoagulant (heparin, LMWH, and statins) and immunomodulatory properties (tocilizumab) (Sanders *et al*., 2020).

We herein explore the hypothesis that SSRIs have the potential to be efficacious in COVID-19 by the following favorable mechanisms of action:

1: Anti-inflammatory: The Sigma-1 Receptor (S1R), an endoplasmic reticulum chaperon protein is involved in cytokine production by interacting with the endoplasmic reticulum stress sensor inositol-requiring enzyme 1α (IRE1) [7]. A recently published double-blind, placebo-controlled

RCT conducted on non-hospitalized adult patients with COVID-19, interestingly found that Fluvoxamine at 300 mg/day for 15 days lessens the likelihood of clinical deterioration as assessed by the outcome parameters; the reduced production of inflammatory cytokines through S1R-agonism by Fluvoxamine being implicated for the findings (Lenze *et al.*, 2020).

The SSRIs have also been shown to impart anti-inflammatory actions through pathways other than S1R-IRE1 like reduced production of Interleukins (IL-6 and IL-10), inhibition of cytokine release (TNF-α, interleukin-1β, Interferon-γ), decrease proliferation of immune cells (T-Lymphocytes, Dendritic cells, Microglia, and Neutrophils) and attenuated bacterial antigen presentation (Walker, 2013). The antibacterial effects of SSRIs may be beneficial in preventing secondary infections or nosocomial infections in the COVID-19 patients, who are especially on steroid therapy. Moreover, SSRIs are known to potentiate the actions of antibacterial agents against resistant strains of S. aureus, E. coli and P. aeruginosa (Hamed and Hagag, 2020).

2: Anticoagulant: There is high evidence of SSRIs decreasing blood-coagulability by decreasing platelet aggregation and activity. SSRIs with highest degree of serotonin reuptake inhibition (fluoxetine, paroxetine, and sertraline) can be thus, useful in preventing the hypercoagulable blood state (Halperin and Reber, 2007). However, their co-administration with other anticoagulants needs close monitoring of coagulation indices particularly in patients with history of bleeding diathesis.

3: Antiviral: SSRIs, are shown to reduce viral load by reducing chemokine and cytokine release by the virus infected cells, down-regulating virus-specific receptors and coreceptors and by inhibiting replications (Hamed and Hagag, 2020). Recent studies on SARS-COV-2 culture models have found Fluoxetine to decrease entry and propagation of the virus through impaired endolysosomal acidification and accumulation of cholesterol within the endosomes. Viral entry

and propagation needs proper functioning of the plasma membrane and the endolysosomes, along with a lower luminal pH level during the final stage of lysosomal escape. Fluoxetine is a functional inhibitors of sphingomyelinase (FIASMA) which is clinically approved for broad spectrum of pathological conditions. It is capable of inhibiting SARS-COV2 infection in a dose dependent manner. 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).

4: Antioxidant and immunomodulation: Serotonin plays an important role in the regulation of adaptive immune responses, which gets affected in the stress due to COVID-19 infection. Furthermore, a lower serotonergic state is associated with greater risk for bacterial infection as well as higher oxidative damages. SSRIs elevate the serotonin levels, reduces lipid peroxidation, prevents release of nitric oxide (NO) and inhibits free radical formation by neutrophils; thereby strengthens the immune system (Hamed and Hagag, 2020).

Fig 1 compares and summarises these beneficial properties of SSRIs.

5: Benefits on the psychological impact of COVID-19: The asymptomatic and mild COVID-19 patients reportedly develop a range of negative psychological consequences like anxiety (6.33% to 50.9%), depression (14.6% to 48.3%), post-traumatic stress disorder (7% to 53.8%), psychological distress (34.43% to 38%), and stress (8.1% to 81.9%) (Talevi *et al*., 2020). SSRIs can help in alleviating these anxiety and depressive symptoms and speed-up the recovery process improving the global functioning of the patients.

The health care workers, front-liners in direct contact with the patients and law-enforcers are particularly vulnerable to the constant stress. The longer shifts under unfavorable conditions, uncertainties about the course of the pandemic and the perceived risk of infection of self and family

members have negative mental health consequences in these population (Talevi *et al*., 2020). They can be benefited by the stress modulating and anxiolytic effects of the SSRIs.

All SSRIs are comparable, having minimal drug interactions with the current disease modifying drugs routinely used for COVID-19, with safer side effect profiles, single dosing (except fluvoxamine) and reasonably lower costs.

Conclusions:

In view of the promising anti-inflammatory, anticoagulant, antiviral and antioxidant properties of SSRIs, they have the potential to become a beneficial drug in the armamentarium against COVID-19 both for preventing clinical deterioration in asymptomatic or milder cases and also for improving the negative psychological impacts of the disease. 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. However, further controlled trials in larger human population are warranted to substantiate our opinion and validate the use of SSRIs for this purpose. While evidences from a recent RCT suggests efficacy of Fluvoxamine as a disease modifying drug in COVID-19, Fluoxetine may be preferred due to its wider anti-inflammatory properties, better anticoagulation and SARS-COV2 specific antiviral effects. Fluoxetine can safely be given in children and adults while Sertraline can be considered in the elderly and those with cardiac comorbidities. However, SSRIs should be used with caution if given along with other anticoagulants.

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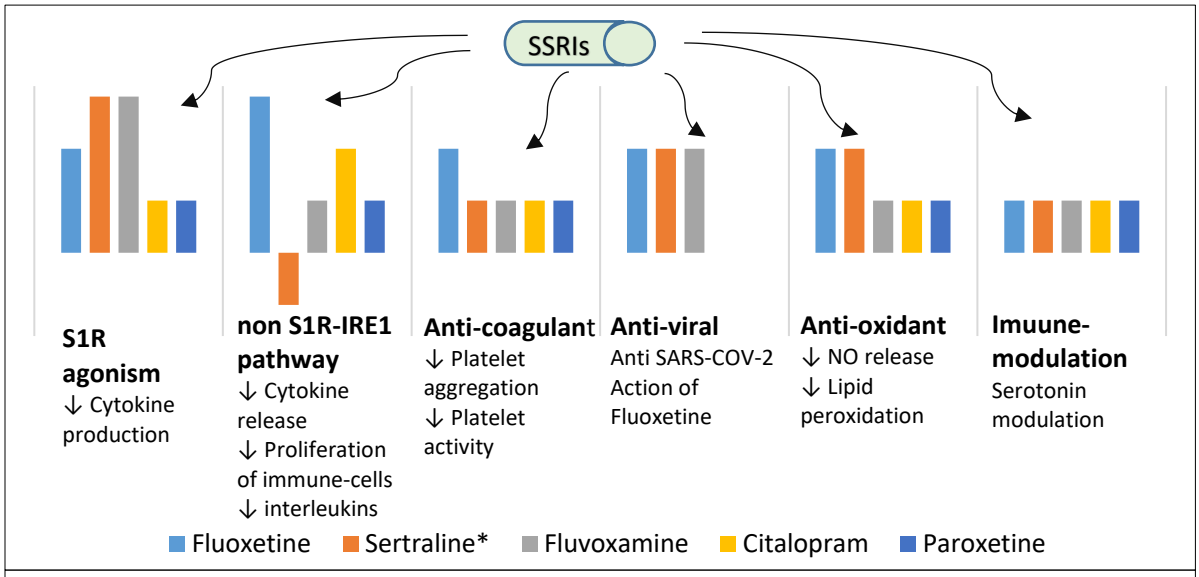
Figure Legend:

Fig 1: comparison of beneficial properties of SSRI against COVID-19
***Sertraline has S1R-antagonistic action**

Figure: (also submitted as a seperate file)



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