Cell Stress and Chaperones (2022) 27:3–4
https://doi.org/10.1007/s12192-021-01246-w

LETTER TO THE EDITOR

Heme oxygenase agonists—fluvoxamine, melatonin—are efficacious therapy for Covid-19

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Received: 8 November 2021 / Revised: 12 November 2021 / Accepted: 15 November 2021 / Published online: 30 November 2021

To the editor:
In the spring of 2020, we proposed in this Journal, *CSAC*, that heme oxygenase (Hsp 32) agonists had the potential to treat Covid-19 (Hooper 2020). As the second anniversary of the Covid-19 pandemic approaches, clinical studies are emerging demonstrating efficacious therapies. In particular, fluvoxamine and melatonin both have retrospective and prospective studies which demonstrate reduced mortality, need for hospitalization, length of hospital stay, and symptoms of Covid-19 infection.

A large population study of Covid-19 infected patients ($N = 189{,}987$) in New York City found that intubated infected patients ($N = 791$) who were treated with melatonin ($n = 112$) had one-eighth the mortality of ventilated patients not taking the supplement (Ramlall et al. 2020). Another retrospective study reported that melatonin therapy was associated with a 64% reduced likelihood of testing positive for Covid-19 (Zhou et al. 2020). A blinded study of Covid-19 infected patients found that melatonin supplementation was associated with reduced Covid-19 symptoms—shortness of breath, cough, fatigue—and half the hospitalization rate compared to treatment with a placebo (Farnoosh et al. 2021). A review of other melatonin Covid-19 intervention studies found consistent efficacy in improving clinical outcomes (Gholizadeh et al. 2021).

Fluvoxamine is an antidepressant medication belonging to the selective serotonin receptor inhibitor (SSRI) class. A Brazilian randomized placebo-controlled study of 1497 Covid-19 infected out-patients reported that ten days of fluvoxamine therapy reduced tertiary hospitalization by one-third compared to placebo. Patients that were able to adhere to the fluvoxamine had only one death compared to twelve in the placebo group (Reis et al. 2021). An outpatient trial done in the US found no clinical deterioration (defined by increased shortness of breath, need for hospitalization, pneumonia, oxygen saturation less than 92% on room air or need for supplemental oxygen) among 80 patients receiving fluvoxamine versus six cases among 72 patients receiving placebo (Lenze et al. 2020).

Both melatonin and fluvoxamine increase HO-1 (Anderson et al. 2015). Fluvoxamine's binding to the sigma 1 receptor activates HO1 (Almási et al. 2020). HO1 has anti-inflammatory activity and limits tissue damage from reactive oxygen species. Covid-19 infection itself can further block HO-1 activity (Fakhouri et al. 2020). Low HO-1 conditions like diabetes, obesity, and aging have chronic low-grade inflammation and increase vulnerability to severe Covid-19 infections with a high mortality (Hooper 2020).

Long Covid-19 syndrome fits into a category of post-viral illness and is associated with depression, fatigue, chest pain, gastro-intestinal symptoms, headache, and tachycardia. We proposed a decade ago that post-viral syndromes reflect a chronic low stress response state (Hooper et al. 2012). Relevantly, SSRIs, including fluvoxamine, markedly improved post Covid19 depression (Mazza et al. 2022). However, intervention studies with HO1 agonists in the treatment of long Covid-19 have not been published.

Both melatonin and fluvoxamine are inexpensive, readily available and have a good side-effect profile. Wide spread therapy with these agents for Covid-19 infection is warranted.

Declarations

Competing interests The authors declare no competing interests.

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