Evaluation of Fluvoxamine as an Effective Prophylactic, and for Treatment in Patients with COVID-19

by

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Executive Summary

• Whereas vaccines are effective at preventing disease, alternative treatments are urgently required for patients already infected with the SARS-CoV-2 virus (the virus that causes COVID-19). To date, this has relied on keeping patients alive while they build up their own immunity to fight the disease.

• It has been demonstrated that fluvoxamine has many mechanisms of action effectively treating patients with COVID-19 through all phases of the disease. These include:

a. Interfering with lysosomal trafficking of the virus;
b. Increasing melatonin levels, which collectively have a direct antiviral effect;
c. Modulating innate and adaptive immune responses;
d. Reducing histamine release from mast cells;
e. Moderating the inflammation response, thus mitigating the all so familiar cytokine storm; and
f. Reducing platelet aggregation.

• Shorter hospitalization and lower mortality rates were observed in patients treated with fluvoxamine when compared to placebo groups.

• Fluvoxamine has been prescribed to patients suffering from depression for over 25 years, with a proven safety record. It is off-patent, and is therefore readily cheap and available for off-label use for early and late treatment of patients with COVID-19.

Introduction

The fluvoxamine story started during the early days of the COVID-19 pandemic at the Sainte Anne psychiatric & neurological hospital in Paris. The observation was made that there was a higher prevalence of symptomatic and severe forms of COVID-19 infections among health care professionals (~14%) compared to patients in psychiatric wards (~4%). This unexpected observational finding in high-risk patients seemed to point to the fact that something in their regular psychiatric treatment may also be protecting them against SARS-CoV-2. Towards the end of that year, the benefits of using fluvoxamine for treating patients with COVID-19 was becoming apparent.

Fluvoxamine is a well-tolerated, widely available, inexpensive selective serotonin reuptake inhibitor that has been shown in a small, double-blind, placebo-controlled, randomized study to prevent clinical deterioration of patients with mild coronavirus disease 2019 (COVID-19). Fluvoxamine is also an agonist for activation of the sigma-1 receptor, through which it controls inflammation. There is now, a huge amount of evidence in the scientific literature outlining the mechanisms of action not only for fluvoxamine, but of other selective serotonin reuptake inhibitors that play a role in COVID- 19 treatment.

The effects of fluvoxamine include: reduction in platelet aggregation, decreased mast cell degranulation, interference with endo-lysosomal viral trafficking, modulating the inflammation process, and increasing melatonin levels. These collectively have a direct antiviral effect, and mitigate the all so familiar cytokine storm, which is a known adverse hallmark of the severe form of the disease.

Fluvoxamine's Mechanisms of Action

Originally and still is being used to treat depression and obsessive-compulsive disorder (OCD), fluvoxamine has been shown binds to the sigma-1 receptor with a highest affinity when compared with other selective serotonin reuptake inhibitors (Narita *et al*., 1996). Fluvoxamine also has the effect of increasing nerve-growth factor-induced neurite outgrowth in PC12 cells (Nishimura *et al.,* 2008). The sigma-1 receptor is a chaperone protein at the endoplasmic reticulum with anti-inflammatory properties (Ishima *et al.*, 2014). Fluvoxamine stimulates oligodendro-genesis of cultured neural stem cells and attenuates inflammation and demyelination in an animal model of multiple sclerosis (Ghareghani *et al*., 2017). Fluvoxamine's anti-inflammatory properties likely stem from its regulation of the sigma-1 receptor, which modulates innate and adaptive immune responses (Szabo *et al*., 2014), and is also an important regulator of inositol-requiring enzyme 1α-driven inflammation (Rosen *et al.*, 2019) (Figure 1).

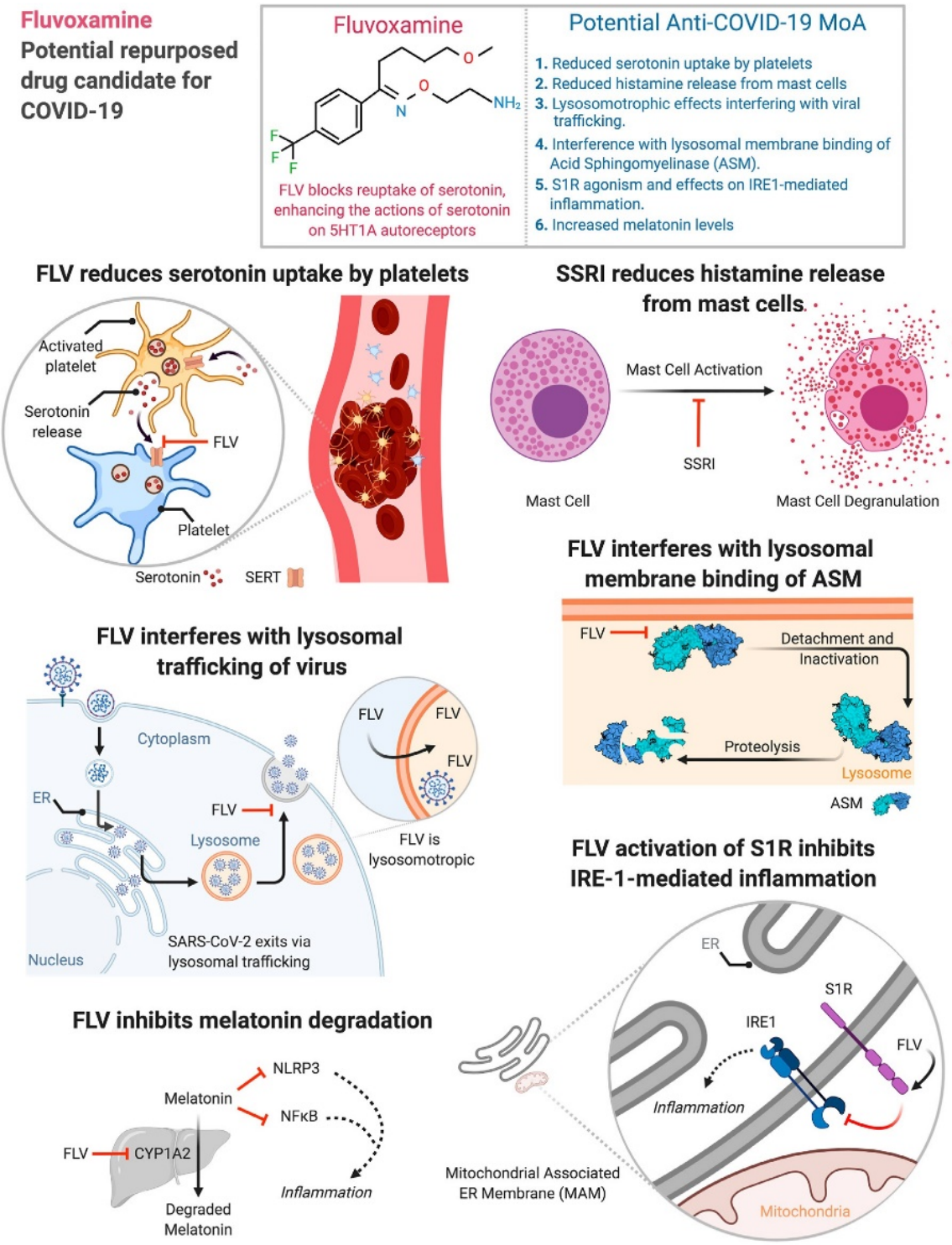

Figure 1. Potential anti-COVID-19 mechanisms of action of fluvoxamine. (Extracted from: Sukhatme, VP. *et. al.,* 2021)

All of these mechanisms of action collectively directly or indirectly have an antiviral effect, regulate coagulation and mitigate the cytokine storm, which are known hallmarks of severe COVID-19. Therefore, fluvoxamine is very effective at reducing the mortality in patients with COVID-19, as revealed in the next section.

Clinical Trials

Fluvoxamine verses placebo, a randomized clinical trial (RCT) in outpatients with symptomatic COVID-19. The participants in this limited study were randomly assigned to receive 100 mg of fluvoxamine (n=80) or placebo (n=72) 3 times a day for 15 days (Lenze *et. al.,* 2020).

Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (absolute difference, 8.7% [95%CI, 1.8%-16.4%] from survival analysis; log-rank P = .009). The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events.

Summary of results (Lenze *et al, 2020*)

	Fluvoxamine	No Treatment
Patients (n)	80	72
Hospitalization/ death rate	0%	8.3%
Significant adverse events	0	6

N=152 (p=0.01)

Fluvoxamine has the highest effect size of any approved drug for COVID-19. The best example of its efficacy was reported by (Seftel *et al.*, 2021) in Open Forum Infectious Disease in February, 2021. In a cohort of COVID-19-positive patients, many of whom were asymptomatic on study enrollment, the sicker ones were actually more likely to take FLV than those who chose observation, biasing results against the fluvoxamine group. But it didn't turn out that way. Zero percent of some 65 patients who opted for fluvoxamine required hospitalization compared with 12.5% of patients were more likely to choose fluvoxamine than observation alone (p=0.005). Two patients in the observation group required mechanical ventilation, one of whom died. At day 14, no patients in the fluvoxamine group had any evidence of on-going symptoms compared with 60% of those choosing observation alone (p>0.001).

Even months later, 10% of the observation group still had long-haul COVID-19 symptoms compared with 0% of those treated with fluvoxamine.

Table 1. Demographics and Outcomes in Prospective COVID-19 Cohort.

Group	Fluvoxamine N=65	No Therapy N=48	P-value [a]
Men	50 (59%)	35 (41%)	.66
Age, years	44 ±15	43 ±15	.74
Age >65 years	5 (7%)	2 (4%)	
Age 50-64 years	17 (26%)	15 (31%)	
Race/Ethnicity			.001
Latino	61 (94%)	34 (71%)	
White, non-Hispanic	3 (5%)	13 (27%)	
African American	1 (1.5%)	0 (0%)	
Asian	0 (0%)	1 (2%)	
Chronic comorbidity	16 (25%)	18 (38%)	.15
Diabetes	11 (17%)	4 (8%)	
Hypertension, treated	11 (17%)	17 (35%)	
Lung Disease	2 (3%)	1 (2%)	
Days for PCR confirmation	3.7 ±1.3	3.4 ±1.4	.25
Disease Status at time of testing			.064
Asymptomatic	25 (38%)	28 (58%)	
Mild	33 (37%)	24 (19%)	
Moderate [b]	16 (25%)	11 (23%)	
Respiratory Rate			
Day 1	17.7 ±2.9	17.7 ±3.4	.95
Day 7 [c]	12.9 ±1.6	15.1 ±4.1	.001
Hospitalized within 14 days	0	6	.005
ICU care and/or Death	0	2	--
Symptoms at Day 14 [d]			<0.001
None	65 (100%)	19 (40%)	
1-3	0 (0%)	15 (31%)	
4-6	0 (0%)	11 (23%)	
≥7	0 (0%)	3 (6%)	

Extracted from: Seftel *et al*., 2021

Further to these results, additional RCT's are currently being conducted to confirm these results. So far, the results are very promising. The medical doctors running the trials were very impressed with the results.
(https://www.nbclosangeles.com/on-air/common-anti-depressant-helping-fight-covid-19/2516130/)

Some of these fluvoxamine trials registered with clinicaltrials.gov with around 880 participants in the Canada and the US are expected to be completed in September 2021.

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Further information may be obtained from the following websites:

Front Line COVID-19 Critical Care Alliance: www.flccc.net

Trial SiteNews: https://trialsitenews.com/?s=Fluvoxamine

COVID-19 Early Treatment Fund: https://www.treatearly.org/fluvoxamine

Medical Education Network (MedNet): https://www.mednet.ca/en/report/oma-district-11-physicians-lounge-virtual-sessio.html