Repurposing fluvoxamine, and other psychiatric medications, for COVID-19 and other conditions

Early in the COVID-19 pandemic, repurposing some already-approved drugs was proposed for reducing the morbidity and mortality risk of those who were infected. For example, the UK RECOVERY trial demonstrated the benefits of dexamethasone for severe respiratory illness, leading to its widespread adoption by mid-2020. Many psychiatric drugs have antiviral and immune modulatory effects, and are candidates for repurposing for COVID-19 and other non-psychiatric conditions.

Fluvoxamine is a potent activator of the sigma-1 receptor (S1R), dampening cellular stress responses and leading to anti-inflammatory effects[1]. In 2020, we conducted a randomized placebo-controlled trial which demonstrated that fluvoxamine prevented clinical deterioration from COVID-19[2]. These findings were replicated in a larger study, the TOGETHER trial, which randomized 1,497 patients to fluvoxamine 100 mg twice daily or placebo for 10 days. The trial found a 32% reduction in risk for severe disease progression with fluvoxamine. Among patients who were compliant with their treatment regimen, taking at least 80% of their pills, there was a 66% reduction in risk for hospitalization with fluvoxamine, and only one death in the fluvoxamine group compared to 12 in the placebo group[3]. Fluvoxamine has now been recommended for use by several organizations, including the Ontario province in Canada. Two ongoing trials are testing fluvoxamine at a lower dose of 50 mg twice daily: the ACTIV-6 trial and the COVID OUT trial.

Based on this growing scientific evidence, as well as its safety profile and availability, we believe that fluvoxamine should be used in COVID-19 for outpatients at high risk for morbidity and mortality from complications of the infection. The recommended dose is 100 mg twice daily for 10-15 days, which can be adjusted based on tolerability. No laboratory monitoring is needed, but co-prescribed drugs should be evaluated for potential interactions, because of fluvoxamine's inhibition of cytochromes P450 (CYP) 1A2 and 2C19. Patients taking theophylline, clozapine, olanzapine and tizanidine, which are CYP1A2 substrates, should not be administered fluvoxamine in most cases. Caffeine, a CYP-1A2 substrate, should be eliminated or greatly reduced during fluvoxamine treatment. Also, for patients already taking a serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI), we would discourage adding fluvoxamine or switching to it for COVID-19 treatment.

Other potential mechanisms have been suggested for the effects of SSRIs, beyond fluvoxamine alone, including inhibition of hypercoagulable states or excess serotonin release by platelets, and functional inhibition of acid sphingomyelinase, leading to inhibition of entry and propagation of SARS-CoV-2 into cells[1]. For example, a study of adults hospitalized for severe COVID-19 found that those who were taking a medication which was a functional inhibitor of acid sphingomyelinase (including all SSRIs) were less likely to be intubated or die[4].

A study of psychiatric inpatients in New York state during the first wave of the pandemic in 2020 found that SSRIs and SNRIs, and specifically fluoxetine, showed a protective effect against COVID-19 infection[5]. Also, a study of 83,584 patients found that those who were taking SSRIs, and in particular those who were on fluoxetine or fluvoxamine, had a reduced mortality[6].

Given the time and costs of conducting large randomized controlled trials, it is tempting to use the data from these observational studies as sufficient evidence for drug repurposing. Yet, observational studies are known to suffer from biases, including confounding by indication. Although techniques exist to reduce these biases, it remains controversial to assert a drug's benefit for a new indication based purely on observational data. For example, a drug or drug class might appear to be protective against COVID-19, yet be a proxy for some other patient characteristic or behavior (e.g., social isolation because of depression). Thus, promising observational study findings will still require corroboration in randomized trials, and accomplishments such as the UK RECOVERY trial show that rapid clinical innovations are possible.

SSRIs and other antidepressants might also help with the longer-term neuropsychiatric manifestations of COVID-19. "Neuropsychiatric long COVID" refers to the fact that cognitive and psychiatric symptoms are a large proportion of the constellation of post-acute COVID-19 symptoms that are either chronic or intermittent, and are bothersome, painful and disabling. For example, the Patient-Led Research Collaborative assessed the prevalence of symptoms in 3,762 persons over 7 months post-COVID[7]. They found a preponderance of neuropsychiatric symptoms, particularly memory and cognitive dysfunction, which were experienced by over 85% of respondents, with negative impacts on daily functioning. Other common neuropsychiatric symptoms were insomnia, anxiety, depression, and occasionally hallucinations (olfactory and other).

The etiological factors involved in neuropsychiatric long COVID may include persistent SARS-CoV-2 infection and a prolonged hyper-inflammatory state, compounded by psychosocial stress. Unfortunately, there is little research to-date on the treatment of neuropsychiatric long COVID. One recent report in post-COVID depressive illness[8] found that 55/60 (92%) patients showed a clinical response after 4 weeks of SSRI treatment. This strong antidepressant benefit was seen irrespective of gender, previous psychiatric history, and SSRI type. The authors speculated that this rapid response to SSRIs could be due to their direct action on neuroinflammation, in addition to their typical antidepressant mechanisms (which remain unclear). This was a single-site, open-label study, and more research is needed regarding the efficacy of various treatments. But this study also shows an important role for psychiatrists in managing, and supervising, the long-term neuropsychiatric effects of COVID-19.

With the pandemic continuing to evolve, it will be critical to keep on answering key questions about the role of SSRIs in the treatment of acute COVID-19 illness. What is the best dose and timing of fluvoxamine, and how effective is it in combination with other treatments against COVID-19 (such as monoclonal antibodies)? Is fluoxetine, which has lower S1R affinity compared to fluvoxamine but has shown promise in preclinical and observational studies, also an effective treatment, considering that it is more widely available and easier to use? And what are the best treatments for neuropsychiatric manifestations of long COVID, and in which patients?

Given that many psychotropics are now appreciated to have widespread molecular, cellular and physiological effects, including anti-inflammatory, neuroprotective and cardioprotective, and antiproliferative, we can expect that lessons learned in testing these medications for COVID-19 will be important for other drug repurposing efforts, ranging from infectious and inflammatory diseases, to neurodegenerative diseases such as Alzheimer's disease, and cancer[9].

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Empirical severity benchmarks for obsessive-compulsive disorder across the lifespan

Obsessive-compulsive disorder (OCD) is characterized by time-consuming obsessions and compulsions that cause distress and impairment[1]. It can affect people of all ages and has a lifetime prevalence of 1-2%[2,3]. The severity of OCD is assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[4,5]. Despite extensive use of this scale for several decades, there is still uncertainty about what constitutes subclinical, mild, moderate and severe OCD.

To our knowledge, only two previous studies have attempted to calculate Y-BOCS severity benchmarks[6,7], yielding inconsistent results. Both studies were underpowered, as they included a small number of individuals in the lower and higher severity ends of the distribution, and only recruited participants from a single country or single age group.

To provide definitive severity benchmarks for OCD that can be used across the lifespan and different cultures, large multinational samples are required. Empirically supported severity benchmarks would facilitate clinical decision making, trial design, and communication between professionals, the patient community and policy makers.

The OCD Severity Benchmark Consortium collected Y-BOCS data from 5,140 individuals with a lifetime diagnosis of OCD from Sweden, Brazil, South Africa, US and India (47/53% male/female, 21/79% children/adults, age range: 5-82 years). Data were collected as part of various research projects; each of the individual studies was approved by the local ethical review board, and all participants provided written informed consent (or assent if under the age of 18) for participation.

Data from four countries were used for model development (Sweden, N=1,697; Brazil, N=936; South Africa, N=552; US, N=599; total N=3,784). Data from India (N=1,356) were used for external model validation. Experienced clinicians administered the child or adult versions of the Y-BOCS, and the Clinical Global Impression-Severity (CGI-S) scale, which constituted the benchmark measure in this study. The CGI-S is a single-item measure (score range: 1-7) of global disorder severity (in this case, OCD) that synthesizes all available information about the patient, including but not limited to current symptoms, impairment and general function[8].

An ordinal logistic regression model was trained in 80% of the data from the four countries used for model development (training dataset, N=3,027) and accuracy of the best severity benchmarks was separately evaluated in the remaining 20% of these data (holdout dataset, N=757) and in the external dataset from India. To compensate for the unevenly distributed severity classes during model development, oversampling was performed by drawing 2,500 samples, with replacement, from each severity class.

A large proportion of all participants in the training and holdout datasets were classified as having moderately severe OCD (CGI-S score of 4 or 5; N=2,577, 68.1%). The next most common severity class was mild OCD (CGI-S score of 3; N=580, 15.3%), followed by severe OCD (CGI-S score of 6 or 7; N=408, 10.8%), and subclinical OCD (CGI-S score of 1 or 2; N=219, 5.8%). In the external Indian dataset, moderately severe OCD was most common (N=502, 37.0%), followed by severe OCD (N=352, 26.0%), mild OCD (N=341, 25.1%), and subclinical OCD (N=161, 11.9%).

Spearman's rho indicated that severity class and Y-BOCS severity correlated moderately to strongly ($r=.61$, $p<0.00001$). An ordinal regression model with severity class as the dependent