A double-blind, placebo-controlled clinical trial of fluvoxamine for symptomatic individuals with COVID-19 infection

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Study Protocol & Statistical Analytic Plan

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A double-blind, placebo-controlled clinical trial of fluvoxamine for symptomatic individuals with COVID-19 infection

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Background:

The biphasic evolution of COVID-19 infection: The clinical course of COVID-19 infection varies, with approximately 20% of individuals developing serious illness including lung damage, hypoxia, and cardiac damage. This leads to hospitalization, ICU admission, and in some cases fatality.

Many infected individuals show a biphasic evolution of the illness, in which clinical deterioration often develops during the second week of illness https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. In China, one report of 41 hospitalized patients found that 55% developed dyspnea 8 days (median; range 5-13) after illness onset https://www.ncbi.nlm.nih.gov/pubmed/31986264. Also, a data extraction of 1099 patients found the mean time from illness onset to hospital admission with pneumonia was 9 days. https://www.ncbi.nlm.nih.gov/pubmed/32109013. The first cases in Europe had the same course, with a deterioration leading to requirement of supplemental oxygen 10-11 days after the onset of mild symptoms and in spite of a decreasing viral load, and it was postulated that "the lung damage is more related to immunopathological lesions, resulting from an excessive pro-inflammatory host response, rather than to uncontrolled viral replication" https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930200-0.

Thus, many patients with COVID-19 develop lung damage resulting from excessive inflammatory responses, or "cytokine storm". These individuals often develop cardiac injury, further highlighting the short-term and long-term risks and complications from infection https://www.ncbi.nlm.nih.gov/pubmed/32169400. This cytokine storm led to recommendations to trial hydroxychloroquine which could suppress T cell activation https://www.ncbi.nlm.nih.gov/pubmed/32196083 as well as other immunosuppressive strategies https://www.ncbi.nlm.nih.gov/pubmed/32192578. Many of these drugs have significant toxicities, and to date most clinical trials have focused on individuals who already have serious to critical illness.

Sigma-1 receptor agonism as a pathway to preventing the cytokine storm: A 2019 study showed that SSRI fluvoxamine reduces damaging aspects of the inflammatory response during sepsis, and protects mice from lethal septic shock https://www.ncbi.nlm.nih.gov/pubmed/30728287. Fluvoxamine binds to the sigma-1 receptor (S1R), which regulates inflammation by inhibiting cytokine production. Fluvoxamine may also induce the S1R https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123092/. The S1R restricts the endonuclease activity of an Endoplasmic Reticulum (ER) stress sensor called Inositol-Requiring Enzyme1 (IRE1) and reduces cytokine expression, without inhibiting classical inflammatory pathways.

IRE1 is also necessary for induction of autophagy during infection of cells by a coronavirus that causes infectious bronchitis in animals https://www.ncbi.nlm.nih.gov/pubmed/31082732. S1R agonists (including fluvoxamine) also have cardioprotective effects in rodents https://www.ncbi.nlm.nih.gov/pubmed/23044468 and protective effects in other tissues https://www-ncbi-nlm-nih-gov.beckerproxy.wustl.edu/pubmed/27056295.

Repurposing antidepressants for COVID-19: A recent preprint entitled, "A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug Repurposing" argued that a key drug repurposing strategy was "modulation of the ER stress and the protein unfolding response pathway by targeting the Sigma1 and Sigma2 receptor" https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1.full.pdf.

Many antidepressants (except sertraline) are S1R agonists, and a recent article on drug repurposing has suggested SSRIs may have value in treating COVID-19 https://www.nature.com/articles/s41421-020-0153-3. SSRIs in particular are excellent candidates for drug repurposing because of their ease of use, including high safety margin, good tolerability, widespread availability, and low cost such that primary care physicians and other providers could prescribe them.

Fluvoxamine has biochemical properties favorable for repurposing as a S1R agonist against COVID-19 infection. It has the strongest S1R agonist effect of any SSRI https://www.ncbi.nlm.nih.gov/pubmed/24508523. A PET study found that a single dose of 150-200mg produced 60-63% S1R binding in brain regions (https://www.ncbi.nlm.nih.gov/pubmed/17662961). This suggests that fluvoxamine would have clinically meaningful S1R agonist effects within its clinical dosing range (up to 300mg/day is the maximum per FDA). It is also highly lipophilic and has demonstrated to have rapid, substantial intracellular uptake (http://dmd.aspetjournals.org.beckerproxy.wustl.edu/content/35/8/1325#sec-4).

Fluvoxamine also is an ideal drug for repurposing in outpatients with COVID-19. It is safe, inexpensive, and already widely available and FDA-approved. Our team has prescribed it across the age span including in older adults at maximum therapeutic doses, finding it safe and well-tolerated. Fluvoxamine does not promote QT prolongation unlike some SSRIs (https://www.ncbi.nlm.nih.gov/pubmed/30885935), and it can be rapidly initiated at high therapeutic doses. It is devoid of off-target effects, having only SSRI and S1R binding at clinically approved doses. In our review of all of the available, FDA-approved drugs that are agonists of S1R, fluvoxamine appears have the desirable combination of potent S1R agonism at clinically approved dosing, and ease of use including safety and tolerability.

These features of fluvoxamine also make it an ideal drug for a pragmatic trial in outpatients. Given risks from face-to-face contact, pragmatic fully-remote trials are a mandate. Fluvoxamine requires no therapeutic drug monitoring or baseline or follow-up laboratory testing, even in older adults. Our research group has expertise with such trials, and with secondary prevention studies (eg, https://www.ncbi.nlm.nih.gov/pubmed/31147244, https://www.ncbi.nlm.nih.gov/pubmed/23680817, https://www.ncbi.nlm.nih.gov/pubmed/16540613) with SSRIs. In fact, our ongoing antidepressant trial, OPTIMUM, has been minimally affected by the ongoing pandemic because of the ability to continue the trial fully remotely with work-from-home staff and investigators (https://www.ncbi.nlm.nih.gov/pubmed/32207542).

Summary: In the fight against COVID-19, we need a simple, benign drug that could be provided widely to outpatients early in the course of mild illness, to prevent the clinical deterioration to serious and life-threatening cardiopulmonary problems. Existing clinical trials have been appropriately focused on treating more serious cases, but with few if any focusing on this clinical space. S1R agonists – of which fluvoxamine is a particularly attractive candidate - could be given early in the course of symptomatic illness, to outpatients with mild symptoms, to decrease the excessive inflammatory response with COVID-19, and potentially prevent the evolution to more serious disease. A search (on March 28; repeated April 9) of clinicaltrials.gov and the WHO International Registry of Clinical Trials (https://www.who.int/ictrp/en/) finds no trials – yet – of fluvoxamine, or any S1R agonist.

Human Participants Involvement, Characteristics, and Design

Subject Involvement:

The proposed study is a pragmatic trial that will rapidly deliver drug/placebo and other supplies to (quarantined) patients, including thermometers, blood pressure cuffs, pregnancy tests (to confirm pregnancy exclusion in childbearing-capable females), and O2 saturation monitors. The risk pertaining to face-to-face contact is with research staff, not participants (who are already COVID-19 positive), so we will conduct the trial via a "no contact" method that will not require PPE. Because of the large, well-trained research staff in the Healthy Mind Lab, we will be able to recruit, screen, e-consent, and start intervention in each participant rapidly. All staff will be trained in COVID-19 precautions using the WHO training for health care providers (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/training/online-training) and supervised by physician faculty. The Healthy Mind Lab has extensive experience conducting clinical trials in adults including older adults, including pragmatic trials with antidepressants.

Recruitment & retention: For the present study, participants will be recruited through EPIC, physician referrers, doctor's hotlines, COVID-19 Testing Centers, and Emergency Rooms (microbiology lab). They may also be recruited, as needed, via word of mouth, referrals by colleagues, the Healthy Mind Lab website (www.healthymind.wustl.edu), flyers, and email notification. Participants will be considered eligible per the inclusion/exclusion criteria and at the PI's determination. Both genders will be enrolled without regard to race, ethnicity, or religion. Potential participants undergo screens by email and phone/videoconference.

The proposed study will require voluntary participation of individual persons and will abide by all federal regulations related to human subject protection, inclusion of women and minorities, and privacy of individually identifiable health information. As with any study that collects sensitive information, breach of confidentiality is a potential risk. To mitigate this risk, all study personnel will undergo training specific to the use of human participants in research (CITI), will be Health Insurance Portability and Accountability Act (HIPAA) and Good Clinical Practices (GCP) trained, and will be approved by the Washington University in St. Louis Institutional Review Board (IRB). Throughout the study, we will confirm plans to assure: 1) accurate, complete, and verifiable data collection and 2) the rights and well-being of human subjects will be protected, in accordance with 45 CFR 46 (Protection of Human Subjects) and, as applicable, 21 CFR part 50 (Protection of Human Subjects). Additionally, all data will be maintained strictly according to the HIPAA "two lock" policy. Only study personnel will have access to this data.

Participation in the proposed study-supported activities will be entirely voluntary and permitted only following completion of all consent-related procedures. We view informed consent as an ongoing process, and will continue the informed consent conversation with subjects throughout their participation.

Inclusion and Exclusion Criteria

Inclusion criteria:
1) men and woman age 18 and older;
2) Outpatients (living in the community)
3) Proven SARS-CoV-2 positive (per lab or physician report).
4) Currently symptomatic with one or more of one or more of the following symptoms: fever, cough, myalgia, mild dyspnea, diarrhea, vomiting, anosmia (inability to smell), ageusia (inability to taste), sore throat.
5) Able to provide informed consent.

Exclusion criteria:

1) Illness severe enough to require hospitalization or already meeting study's primary endpoint for clinical worsening.
2) Unstable medical comorbidities including, but not limited to: Severe underlying lung disease (COPD on home oxygen, interstitial lung disease, pulmonary hypertension), decompensated cirrhosis, Congestive heart failure (stage 3 or 4 per patient report and/or medical records).
3) Immunocompromised (solid organ transplant, BMT, AIDS, on biologics and/or high dose steroids (>20mg prednisone per day)
4) Already enrolled in another COVID 19 clinical trial
5) Unable to provide informed consent (eg moderate-severe dementia diagnosis)
6) Unable to perform the study procedures

Rationale for inclusion & Exclusion Criteria:Adults 18 and older who are not already medically compromised (eg severe lung disease) are at risk for developing clinical deterioration late in their clinical course. The Inclusion criteria will ensure that we collect as generalizable sample as possible of at-risk adults, while the exclusion criteria will ensure that we do not recruit individuals who are likely to need immediate hospitalization or are otherwise too medically unstable to participate in an outpatient study with remote monitoring. Older adults will be included; exclusion criteria will exclude individuals who are highly frail, medically compromised, or highly cognitively impaired.

Study Procedures, Materials, and Potential Risks

Sources of Materials

Research materials will be obtained by remote interviews, self-reports, medical records (when available), and remote self-monitoring. All materials will be obtained solely for the purposes of the research study. All data collected from the participants enrolled in the study will be stored and maintained confidentially and no identifying information, such as participant names, will be disclosed in any published documents.

Study Procedures

After passing an initial prescreening, potential participants will provide informed consent and be administered emailed, phone or videoconference-based screening assessments by trained research staff to assess the above inclusion and exclusion criteria. Participants who qualify after completing all screening assessments will then be sent or provided the study materials. This consists of study medication and self-monitoring equipment, including, as needed, a pregnancy test [for females of childbearing age not using contraception], oxygen saturation monitor, automated blood pressure monitor, and thermometer. We will finalize screening (ie confirming medical stability via oxygen saturation monitor, and vital sign measurement) prior to instructing participants to begin taking study medication, after which point (after taking first dose) they are considered "randomized", consistent with Intention to Treat principles.

Study Design

This study will randomize approximately n=152 participants. This study has an initial double-blind phase (to test the drug's effectiveness) followed by an open-label phase (to provide all participants with exposure to the drug, and allow a taper off of it for those initially taking active drug).

Assignment will be 1:1; (1) Active treatment: start and maintain fluvoxamine 100mg, three times daily. May reduce dose (or start at reduced dose) for tolerability reasons; (2) Control: placebo, three times daily. This drug vs placebo phase will last approximately 15 days and will be followed by an open-label fluvoxamine phase that will typically last 6-7 days but could last up to 15 days: 100mg two times daily for 3 days, then 50mg two times daily for 3 days, then discontinue.

Randomization will be stratified by age (we anticipate: 18-44, 45-54, 55-64 and ≥65 years, respectively, to reflect the age distribution of ascending risk for severe symptoms requiring hospitalization (https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm#F2_down) and sex. Final determination of stratification will be made by the biostatistician (Phil Miller). Stratified randomization schedules will be generated by statistician Michael Yingling.

After the randomized phase, all participants will be followed for approximately 30 days to collect clinical data (i.e., on hospitalization and other clinical outcomes). Thus, total study participation is approximately 45 days (15 days randomized, 30 days follow-up).

All enrolled participants will also be sent a longterm follow up survey which asks about persistent COVID 19 symptoms, and a PROMIS scale which asks about functioning and quality of life.

Management: To protect research staff, there will be no face-to-face contact with participants; all interactions will be fully-remote via Zoom videoconference and/or phone/text/email, as well as REDCap surveys pushed out to patients via their smartphones or other devices.

For consented participants who start protocolized treatment we will inform their relevant medical providers, such as a PCP, towards the goal of an informed and collaborative management strategy.

As this is a "prevention of clinical deterioration" study, it is anticipated that a minority (~10-15%) of participants will become hospitalized during the study, and that this will most likely occur during the randomized phase. Research staff under the physician investigators' supervision will provide support including engagement with participants' caregivers and physicians to ensure timely medical contact and emergency care (including calling 911).

If a study participant develops a decrease in oxygen saturation to less than 90% on room air on >2 readings, persistent increase in respiratory rate to >30 breaths per minute, persistent increase in Heart Rate to > 120 beats per minute, alteration in mentation, or severe worsening in shortness of breath, the research staff will direct them to seek emergency medical care at the nearest emergency department. If none of the above conditions are met, but the research staff still feel that the participant is unwell, one of the physician investigators will evaluate the participant via phone/telehealth and direct them for further care if needed. When a participant is directed to seek emergency medical care, they will be instructed to use a mask if available, and to identify themselves to EMS or to the Emergency Department staff as having been diagnosed with COVID-19.

Safety Assessments
We will assess for adverse events (including serious adverse events) daily via participant self-report during the first 15 days, and then again at the end of the study.

Outcome Assessments
As this is a prevention (of clinical deterioration) trial, the primary endpoint will be a "time to" clinical worsening analysis. Following the intention to treat principle, all participants who are confirmed to have taken at least one dose of study medication are included in the analyses.

Definition of clinical worsening: Clinical worsening is defined meeting both of the following: (1) presence of dyspnea and/or hospitalization for shortness of breath or pneumonia, plus (2) decrease in O2 saturation (<92%) on room air and/or supplemental oxygen requirement in order to keep O2 saturation >92%. A laboratory-confirmed clinical endpoint is consistent with World Health Organization clinical trial recommendations (https://www.who.int/blueprint/15-01-2020-nfr-bp-wg-clinical-trials-ncov.pdf?ua=1).

Power analysis: The below table regards the primary endpoint. It assumes 80% power, alpha=0.05, and a 20% rate of progression to serious symptoms in the placebo group. The table shows sample size required based on reduction in that rate in the active (fluvoxamine) group. With total n=152 (76 per group), we would have 80% power to find a statistically significant difference in survival curves (i.e,. time to clinical worsening) if the rate of progression with fluvoxamine is only 5% (i.e., a three-quarters reduction in the risk of clinical deterioration). This power calculation is conservative because it does not take into account the potentially improved power gained by stratification, or the enhanced power for Kaplan Meier vs. simple rates; therefore, we are likely to be sufficiently powered for a more modest treatment effect.

Treatment Response	N (each group)
.05	**76**
.06	90
.07	108
.08	131
.09	160
.10	199

We will also examine the following secondary endpoints:
1. clinical deterioration on a Likert-type scale: (1) moderate severity of illness as defined by O2 saturation <92% but no supplemental oxygen requirement; (2) O2 saturation plus supplemental oxygen requirement; (3O2 saturation <92% plus hospitalization (related to dyspnea/hypoxia); (4) the above, plus ventilator support requirement; (5) the above, plus ventilator support for at least 3 days; (6) death.
2. clinical deterioration measured by number of days: (1) requiring supplemental oxygen; (2) requiring hospitalization; (3) requiring ventilator support.
These Likert-type assessments are based on our review of current COVID-19 treatment studies. They will be collected in retrospect via patient or family report and/or medical records.

3. Total symptomatic severity during the 15 days using a continuous scale of each patient's presenting symptoms on a 0-10 Likert scale (0= symptom not present, 10= symptom is very severe). Outcomes will be collected daily, with symptomatic data collected approximately twice daily via the technique of Ecological Momentary Assessment (ie "how bad is your symptom right now?"). The most severe symptom at baseline will be the focus.This data collection and analytic technique (with frequent measurement of the symptom[s] most relevant to the individual patient) should greatly increase precision and power (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6524455/).

Data management and analysis: Data will be collected in REDCap and outcomes will be collected by blinded research staff. The study statistician, Michael Yingling, will conduct blinded (ie "treatment 1 vs treatment 2") analysis under the supervision of Phil Miller. We may conduct an interim "futility" analysis at approximately n=100 participants. The primary analysis will be survival analysis of the primary outcome (clinical worsening), while secondary endpoints (symptomatic severity) will be examined using appropriate (descriptive, Area Under the Curve (AUC), and trajectory) comparisons.

Sharing of de-identified data from this study will be critical because it will help characterize this patient population and, if positive results, would immediately lead to a potential new treatment for COVID-19. Therefore it is planned that a pre-print of the article along with de-identified data will be posted on a public repository such as arxiv (arxiv.org). This has been standard during the pandemic in order to share results as rapidly as possible.

Additional measurements:
Baseline: vital signs (pulse, blood pressure, temperature), O2 saturation, weight and height, symptoms and symptomatic severity.
Follow-up: daily vital signs, O2 saturation, adverse events (participant self-report).

Risks
Potential risks associated with study assessments
There are no risks associated with any of the assessments.

Potential risks associated with study medication
Fluvoxamine:

General comments: Fluvoxamine is an antidepressant drug that functions as a selective serotonin reuptake inhibitor (e.g., similar to escitalopram (Lexapro), fluoxetine (Prozac), sertraline (Zoloft), etc – among the most commohly prescribed drugs in the US). Its risk profile below is for chronic use in a psychiatrically ill population; the risks for short-term use in a non-psychiatric population are likely lower. The research team will carefully evaluate co-prescribed drugs as well as OTC medications and caffeine use, to mitigate drug-drug interactions. We anticipate approximately 20% of participants will be on current SSRI/SNRI use at recruitment – will include these individuals, so long as the participant can be safely switched over to fluvoxamine briefly.

Likely risks: none.

Less likely (1-10%): Nausea, Vomiting, Weight loss, Yawning, Loss of appetite, Agitation/Nervousness/Anxiety, Insomnia, Somnolence, Tremor, Headache, Dizziness, Palpitations, Tachycardia (high heart rate), Abdominal pain, Dyspepsia (indigestion), Diarrhea, Constipation, Hyperhidrosis (excess sweating), Asthenia (weakness), Malaise, Sexual dysfunction (including delayed ejaculation, erectile dysfunction, decreased libido, etc.), Xerostomia (dry mouth).

Rare (<1%): Arthralgia, Hallucination, Confusional state Extrapyramidal side effects (e.g. dystonia, parkinsonism, tremor, etc.), Orthostatic hypotension, Cutaneous hypersensitivity reactions (e.g. oedema [buildup of fluid in the tissues], rash, pruritus), Mania (elevated mood together with reduced need for sleep and increased energy), seizures, Abnormal hepatic (liver) function, Photosensitivity (being abnormally sensitive to light), Galactorrhoea (expulsion of breast milk unrelated to pregnancy or breastfeeding).

Potential risk associated with Breach of Confidentiality:
One risk of participating in this study is that confidential information may be accidentally disclosed. We will use our best efforts to keep the information about participants secure. All private information is stored in secured areas and on encrypted and password-protected servers.

Other risks:
There may also be unknown risks**.** We will adjust the informed consent process if new risks are identified.

Adequacy of Protection Against Risks
Recruitment and Informed Consent
All personnel involved in the design and conduct of the research involving human participants will receive the required education on the protection of human research participants prior to the start of this project. Procedures to recruit participants for the protocol and obtain their informed consent or assent

are conducted and supervised by the PI. Trained study staff will discuss the study, including the risks and benefits of participation, with relevant potential participants and relevant members of their treatment team to provide informed consent or assent for interested individuals. Informed consent will be obtained from all participants before any study procedures are initiated. The e-consent form, which incorporates HIPAA authorization, contains a description of the purpose and procedures, risks, procedures to minimize them, and possible benefits. Participants will be assured that participation in the study in completely voluntary, and that they are free to withdraw consent at any time and discontinue participation without prejudice to their current or future medical care. The objectives of the project, all of the requirements for participation, and any possible discomforts and risks will be clearly explained at each contact to the participants orally and in writing. All participants must sign an e-consent, indicating their consent, approved by the Washington University School of Medicine Institutional Review Board, before they can participate in the study.

Preventing Breach of Confidentiality

This project will be conducted at Washington University School of Medicine. The risks of breaching confidentiality will be strictly limited by the use of locked and restricted access to data as well as study ID numbers rather than participants' names in the database that will be created for this project. No identifiers will be included in any computer files or reports generated by this study. All personnel involved in the design or conduct of research involving the human participants will receive the required education on the protection of human research participants and will also undergo training in the psilocybin exposure protocol.

Minimizing risk:

Fluvoxamine is a commonly prescribed serotonin reuptake inhibitor which has been commonly prescribed in the US for more than 2 decades, and in this study it is provided only briefly. Therefore, moderate-severe and serious treatment-attributable AEs would be uncommon, but monitoring will include oversight by physicians with expertise in this drug class (Drs Lenze, and Nicol).