Fluoxetine to reduce the risk of morbidity and mortality with COVID-19 infection

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1. Background, Review of the Literature, Significance

Much of the morbidity and mortality with COVID-19 infection is thought to be the result of multisystem organ failure after a cytokine storm (Huang et al. *Lancet* 2020). This cytokine storm is very similar if not identical to the Secondary Hemophagochytic Lymphohistiocytosis (SHLH) seen in Severe Acute Respiratory Syndrom (SARS) also caused by a coronavirus, and includes increased levels of IL-2, IL-7, C-CSF, TNF-2, interferon-G inducible protein, MCP1 and MIP1a, all of which are driven by increased levels of IL-6. (Taraz 2013, Gobin, 2014) These findings have led to use of medications such as tocilizumab, an IL-6 receptor antagonist, to treat COVID-19 pneumonia. Fluoxetine and certain other selective serotonin reuptake inhibitors (SSRIs) have demonstrated in vitro and in vivo efficacy at reducing IL-6 and both preventing and treating hyperimmune responses associated with elevated levels of IL-6. Further, fluoxetine has a very safe therapeutic profile and could be used both prophylactically to prevent the cytokine storm with COVID-19, as well as an adjuvant treatment for critically ill patients.

In vitro and *in vivo* data demonstrate that fluoxetine and some other selective serotonin reuptake inhibitors (SSRIs) effectively reduce IL-6 to prevent hyperimmune response. In addition to SSRI use in adjuvant treatment for critically ill patients, the established safety profiles of many SSRIs allow these drugs to be used prophylactically in order to prevent cytokine storm associated with COVID-19 infections. SSRI treatment before starting antiviral therapies reduces incidence of interferon-induced depression and carries minimal side effect profiles consisting of rare dizziness (Udina et al., 2014). The SSRI fluoxetine demonstrates a particularly pronounced ability to inhibit IL-6 activation (Durairaj, Steury, & Parameswaran, 2015; Hashioka et al., 2007). This effect is mediated by non-serotonergic pathways involving NF-kB suppression and inhibition of dendritic cell antigen presentation (Branco-de-Almeida et al., 2011; D. Liu et al., 2011; R. P. Liu et al., 2014; Vollmar, Haghikia, Dermietzel, & Faustmann, 2008; Young et al., 2014). Animal models demonstrate that SSRIs protect against hyperinflammatory conditions and diseases states. In fact, pretreatment with fluoxetine frequently outperforms pretreatment with corticosteroids (Dong et al., 2016). Recently, clinical trials have demonstrated compelling relationships between SSRI treatment and cytokine levels (Amitai et al., 2016). A recent 2019 review and meta-analysis by Wang et al. echoes previous

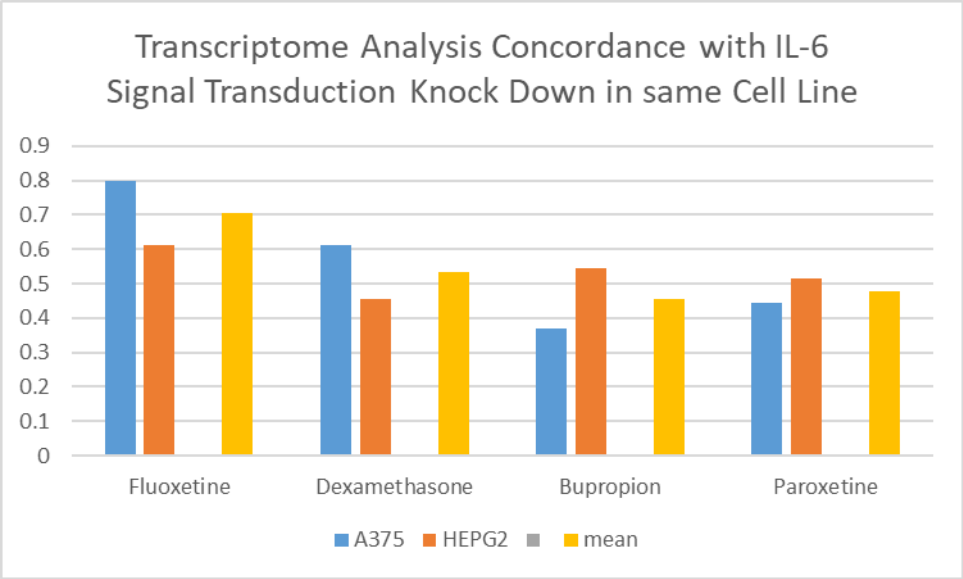
animal work and suggests that SSRI therapy indeed reduces IL-6 levels in human subjects (Wang et al., 2019).

These data are significant to COVID-19 patients at risk for pulmonary symptoms. Pretreatment with SSRIs results in decreased destructive immune reactions across a variety of animal models. In rat models of chronic obstructive pulmonary disease, fluoxetine decreases lung injury and inhibits cytokines such as TNF-a and IL-6 (Cai et al., 2017). Indeed, fluoxetine reduces inflammatory reaction in several models of human disease, providing marked decreases in reactive cytokines (Roumestan et al., 2007). In addition to decreasing expression of inflammatory cytokines, pretreatment with fluoxetine also decreases incidence of pulmonary arterial hypertension, pulmonary arterial muscularization, and extracellular matrix remodeling (Li et al., 2011). Bronchial asthma models show therapeutic effects of fluoxetine pretreatments in rats (Sherkawy, Abo-Youssef, Salama, & Ismaiel, 2018), and several studies suggest positive therapeutic efficacy may be concurrent with reduced levels of cytokines including IL-6 (Blatteau et al., 2012; Blatteau et al., 2015).

Overall, there is significant preclinical data supporting the use of SSRI's in the abrogation of harmful inflammatory side effects, such as those driving COVID19 morbidity and mortality. Furthermore, clinical data shows robust safety and efficacy profiles supporting the use of fluoxetine pretreatment interventions. At the University of Toledo Medical Campus, we are fortunate to have a leading expert on the relationship between antidepressant drugs and their anti-inflammatory therapeutic effects. Dr. Kevin Pan, who will be leading the laboratory work described in this proposal, has published extensively on the use of antidepressants to limit organ damage, decrease pro-inflammatory cytokine production, and inhibit intracellular migration of early-stage inflammatory response (Lu, Wang, Chen, Jiang, & Pan, 2020). A recent Nature publication from Dr. Pan and his team explore connections between antidepressant drug administration and cytokine signaling, providing compelling support for the use of antidepressants in inflammatory disease states. Several studies from Pan et al. indicate antidepressant use inhibits pro-inflammatory cytokine gene expression both *in vitro* and *in vivo*. Using Dr. Pan's methods, we will assay and investigate cytokine expression in our control and experimental patients while utilizing the expertise that Dr. Pan and his University of Toledo researcher team has developed on this topic.

Further evidence for the efficacy of fluoxetine in decreasing the IL-6 response that stimulates the cytokine storm in COVID-19 infection comes from an analysis comparing the transcriptomes of

cells lines treated with fluoxetine, dexamethasone (a steroid established to decrease IL-6), and 2 other antidepressants : bupropion and paroxetine to the transcriptome of the same cell line with a knock down in the IL-6 signal transduction molecule. This analysis was performed this week in the bioinformatics group in the Department of Neurosciences at University of Toledo and is illustrated below. The concordance of the fluoxetine and IL-6ST knockdown cell lines is remarkably high, averaging over 0.7 . This concordance is greater than that seen with dexamethasone treatment, the standard anti-inflammatory steroid, and is higher than 2 other commonly used antidepressants, bupropion and paroxetine.



2. <u>Objectives/Specific Aims</u>

Aim 1: Fluoxetine treatment begun early after COVID-19 infection will reduce hospitalizations, intubations, and death from COVID-19 and complications more than no medication

Aim 2: Fluoxetine will decrease intubations and mortality in patients hospitalized with COVID-19 infection greater than no medication.

Aim 3 : Fluoxetine treatment of COVID-19 infected patients will not cause significant side effects or increase morbidity and mortality compared to no medication

Aim 4. Collect blood samples from 40 subjects for future cytokine analysis: both subjects taking fluoxetine and not taking fluoxetine samples taken at baseline and weekly after study initiation.

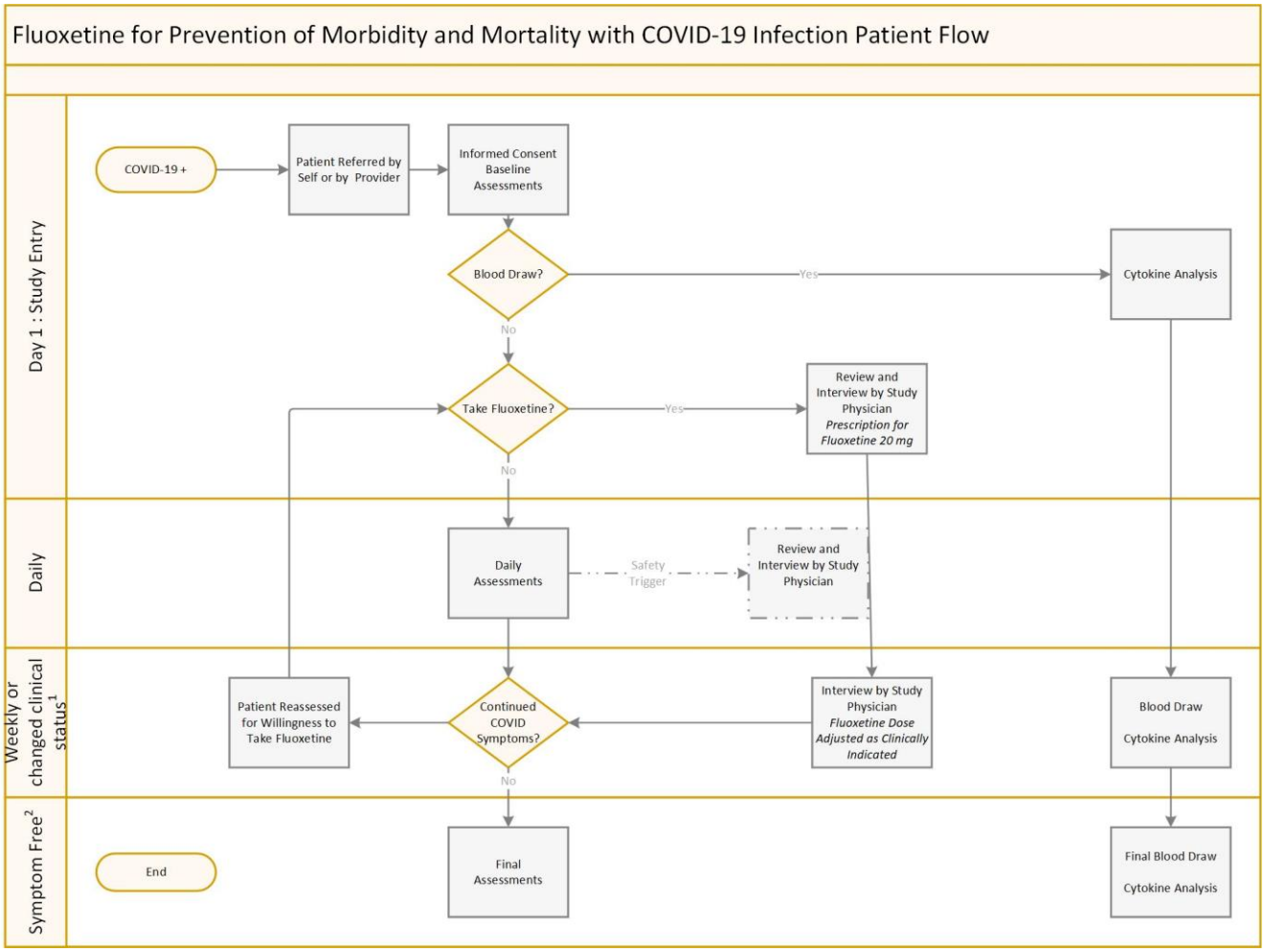
3. Methods

a) **Study Design** : Pragmatic Clinical Trial : Experimental and Observational

b) **Method of treatment assignment**

Single arm patient centered clinical trial

At study entry, participants will consent study participation via daily monitoring and will choose whether to participate in the activity monitoring, cytokine assessment and drug treatment portions of the trial. Participants who do not choose to take fluoxetine will serve as the control subjects. Additionally, patients will have the choice weekly to decide to start, continue, or discontinue the fluoxetine. See figure below :



c) **Inclusion/exclusion criteria**

Inclusion : Patients aged 18 and above, able to give informed consent

COVID-19 test positive or presumptive positive awaiting COVID testin or results by following criteria: fever, cough and shortness of breath

Overall Study Exclusion Criteria :

Unable to give informed consent

Prisoner/ institutionalized patient

Under age 18

Exclusion from Fluoxetine Arm:

Active bleeding requiring blood products

Bipolar disorder not on mood stabilizing medication*

Known allergy or hypersensitivity to fluoxetine

Currently taking the following medications : MAO I, pimozide, thioridine

Currently taking hydroxychloroquine

Pregnant or breastfeeding (pregnancy questionnaire attached)

For hospitalized patients : QTc greater than 500 ms

*Hospitalized patient may be on hydroxychloroquine if QTc<500 and the primary attending approves

Exclusion from Blood Sample Provision:

Pregnant

Self-report of under 110 pounds

d) **Justification of the number of subjects**

All power calculations were done with the clincalc program and assume a dichotomous endpoint in a two independent sample study and are based on achieving the standards of a power of 0.80 and with an alpha of 0.05. Please note, that the assumptions of fluoxetine effect size are based on the absolute most conservative values in the published literature reviewed above.

Aim 1 : Hospitalization rates

Assumptions:

1. 2/3 of patients who enter the trial will choose to take fluoxetine
2. 10% of COVID-19 + patients will progress to a clinical condition requiring hospitalization
3. Fluoxetine treatment decreases hospitalization rate by 50%

Sample Size : 312 in the no medication group and 624 in the 2 fluoxetine groups, for a total sample size of 936. This sample size is very achievable given the current coronavirus pandemic.

Prevention of Hospitalization	
Hospitalization, no medication	10%
Hospitalization, Fluoxetine	5%
Alpha	0.05
Beta	0.2
Power	0.8
Sample Size	
No medication	312
Fluoxetine, low or high	624
Total	**936**

Aim 2 : Intubation in those hospitalized

Assumptions

1. 10% of patients requiring hospitalization for COVID-19 + will progress to intubation
2. Fluoxetine treatment decreases intubation rate by 20%

Aim 2: Death in those hospitalized

Assumptions

1. 1% of patients requiring hospitalization for COVID-19 + will die during that hospitalization
2. Fluoxetine treatment decreases mortality rate by 20%

Sample Size : 3213 in the no medication group and 3213 in the fluoxetine groups, for a total sample size of 6426.These sample sizes will not be achievable in this pilot study. Data from Aims 3 and 4 will therefore be used qualitatively for the gathering of pilot data.

Prevention of intubation, death Sample Size	
No medication	3213
Fluoxetine	3213

Total	**6426**
Prevention of Intubation	
Intubation, death in no medication	10%
Intubation, death in fluoxetine	8%
Alpha	0.05
Beta	0.2
Power	0.8

e) **Study setting**

Telephone, outpatient offices, emergency department, Hospital

f) **Primary and secondary outcome measures**

Primary Outcome Measures:

Aim 1 : Rates of Hospitalization

Aim 2 : Rates of Intubation and Death

Aim 3 : Side effect profile

Secondary Outcome Measures:

Aim 1 and 2 : Depression, Anxiety, Suicidal thinking, Days of Illness, Severity of Illness

g) **Variables**

Demographic information (age, gender, medical history, co-morbidities, etc.)
Medications
Symptom profile
• Number of days of symptoms prior to testing
• Epidemiologic information from CDC/Health Department surveillance interview
• Hospital Course
Days in Hospital, Intubation, Complications

Outcome: Never hospitalized, Hospitalized, Intubation, Death

h) **Procedures, interventions, schedule**

Week/Day	**Patient Intervention**	**Setting/ Responsible Individual**	**Standard of Care**	**Research Purposes Only**
1/1	Informed Consent	Phone/ research team	------	Yes
1/1	Baseline Study Data	Phone/ research team		Yes
1	Blood Sample	Laboratory Services	Inpatient	outpatient
1	Physician Interview/ Medication Prescription	Phone/Study physician	----	Yes
Daily	Symptom/ Side effect Check In	Phone/ research team		Yes
Weekly	Physician Interview/ Medication Prescription	Phone/Study physician	----	Yes
Weekly or Change in Clinical Status*	Blood Sample	Laboratory Services	Inpatient	outpatient

*Change in Clinical Status includes outpatient to inpatient, transfer to ICU, and intubation

Procedures:

Instrument	Duration	Assessment Time Points	Frequency
Baseline Intake Form Chart Review Form 04/1/19-present *Baseline Demographics and past medical history*	30 min	Initial study entry	Once
PHQ-9	5 min	Initial Study Entry	Weekly
GAD-7	5 min	Initial Study Entry	Weekly
Columbia Screener-recent	3 min	Initial study Entry	-------
Symptom Checklist	5 min	(included in baseline)	Daily assessments
Columbia Screener – since last	3 min	-------	Daily assessments

visit			
Physician Interview/Medication Prescription	40 min	Baseline	weekly
Drug Distribution		Once, at entry	monthly
Blood Draw for future assessment of cytokine levels	60 min	Baseline	Weekly, as possible
Chart Review Followup		At study exit, one month, 3 months, 6 months and one year after study exit	See notes to left 5 data points From 4/1/19- 4/1/23

Physician Interview/Medication Prescription

Interview includes :

1) Assessment for pregnancy, contraindicated medications and review of baseline intake
2) Explanation of risks and benefits of medication : see patient handout information sheet

Blood Draw for Future Assessment of Cytokine Levels :

- Not to exceed 2 blood draws per week or a total of 50 ml total over 8 weeks time period
- Outpatient blood draws will occur only if study participants have regular clinical care blood draws until adequate personal protection equipment (PPE) is available for use in research settings. Study outpatient blood draw will occur by appointment at UTMC Emergency Department in a negative pressure room. Outpatient blood draws will not be done until there is adequate PPE available for research study purposes.
    - Study participant and phlebotomist will be equipped in full PPE.
- Inpatient blood draws will occur during normal clinical care blood draws.
- Blood samples will be stored at -80 degrees F in the hospital laboratory freezers for future cytokine analysis

Study Timeline :

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ID	Task Name	Start	Finish	Duration
1	Enroll Patients in Overall Study	4/1/2020	4/1/2021	262d
2	Enroll Patients in Fluoxetine Arm	4/1/2020	2/1/2021	219d
3	Enroll Patients in Cytokine Study	4/1/2020	10/1/2020	132d
4	Data Analysis	7/1/2020	7/1/2021	262d
5	DSMB Review 1	7/1/2020	7/1/2020	1d
6	DSMB Review 2	10/1/2020	10/1/2020	1d
7	DSMB Review 3	1/1/2021	1/1/2021	1d
8	DSMB Review 4	4/1/2021	4/1/2021	1d



4) **Planned data analysis**

Aim 1, 2, 3 : Descriptive statistics,

Compare rates of primary and secondary outcome measures in subjects receiving fluoxetine with those not receiving fluoxetine by Student t-test and Chi-square test as appropriate.

Data Safety Monitoring Board

Interim data analyses will be performed every 3 months and will be presented to a 4 member data safety monitoring board who will prepare a report on the ongoing safety of the clinical trial and consideration of early termination of the study for either benefit or harm per the guidelines of Tyson et al. 2016.

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