Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among COVID-19 patients should fluvoxamine be used for the treatment?

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RECOMMENDATION

There is insufficient evidence to recommend the use of fluvoxamine among COVID-19 patients. (*Low certainty of evidence*)

Consensus Issues
Current evidence showed that although fluvoxamine appeared to reduce the need for emergency room visit or hospitalization, there was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, adverse events, and serious adverse events. The sample size of the two randomized controlled trials may still be too small to reach a level of significance, precluding any recommendation to be made. As of writing, there are 9 ongoing clinical trials, results of which may further elucidate on fluvoxamine's effectiveness in the treatment of COVID-19.

Key Findings

Two (2) published randomized controlled trials (RCTs) (N = 1,649) investigated on the effectiveness of fluvoxamine compared to placebo among confirmed symptomatic non-hospitalized COVID-19 patients compared. Results showed significant reduction in emergency room visits and the need for hospitalization. There was inconclusive evidence in terms of other critical outcomes such as all-cause mortality, clinical deterioration, viral negative conversion, adverse events, and serious adverse events.

Introduction

Fluvoxamine is a selective serotonin re-uptake inhibitor used to treat obsessive compulsive disorder. The anti-viral and anti-inflammatory roles of fluvoxamine have been recently studied. The potential role of fluvoxamine on the treatment of COVID-19 include a decrease in serotonin levels leading to decreased platelet aggregation, reduced mast cell degranulation thus reducing cytokine release, interference in the lysosomal activity and entry of the virus, inhibition of hyperinflammation by sigma-1 receptor affinity, and mitigation of inflammation by increasing melatonin.[1]

Common adverse reactions associated with fluvoxamine include nausea, insomnia, somnolence, headache, asthenia, dizziness, dry mouth, and vomiting. It should also be used with caution when used with other serotonergic drugs to avoid serotonin syndrome.[2]

Review Methods

A systematic search was done last October 10, 2021 to check for trials in COVID-NMA living data. Trials found in the COVID-NMA were included. Search was done in Medline, Cochrane Library, and Google scholar using free text, MeSH terms and advance search using the terms coronavirus infections, COVID-19 severe acute respiratory syndrome coronavirus 2, and fluvoxamine. Ongoing trials screening was done in various trial registries. Medrxiv, chinaxiv and biorxiv was also searched for preprints. RCTs on fluvoxamine as treatment for COVID-19 compared to placebo were included. No limits were placed on age, severity and dose. In order to compute for confidence interval, we imputed 1 if a study has no event in the treatment arm.

Results

Two (2) published RCTs (N = 1,649) evaluated the effectiveness of fluvoxamine among confirmed symptomatic non-hospitalized COVID-19 patients compared to placebo. Both trials reviewed were also included in the COVID-NMA Living Data.[3,4]

Appendix 3 summarizes the characteristics of the included studies. One study was done in the US [3] and the other was done in Brazil.[4] Study participants in both trials included confirmed COVID-19 symptomatic patients aged 18 years old and above. One of the studies [4] specified at least one co-morbidity in the inclusion criteria. Both studies excluded patients being referred for hospitalization at the start of the study.

The overall quality of evidence was rated low due to very serious imprecision on one critical outcome (clinical deterioration) and serious imprecision and inconsistency on another critical outcome (serious adverse events). Both trials have no serious risk of bias. The risk of bias summary is shown in Appendix 4. The GRADE evidence summary is in Appendix 5.

Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.99; I^2 48%; 2 RCTs, 1,649 participants) [3,4] and the need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, 1,497 participants) among symptomatic COVID-19 patients compared to placebo.[4] However, fluvoxamine had no benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27) [4], clinical deterioration at day 15 (RR 0.70, 95% CI 0.00-1.21) [3], and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04) compared to placebo.[4]

Safety

There was no significant difference on adverse events (RR 1.00, 95% CI 0.77-1.29) and serious adverse events (RR 0.49, 95% CI 0.10-2.27) between fluvoxamine and placebo. Common adverse events reported were loss of sense of smell, fatigue, body aches, cough, subjective fever, and loss of appetite. Serious adverse events reported were dehydration, exacerbation of COVID-19, respiratory failure, and pneumonia.

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US-NIH Guidelines as of October 7, 2021 [5]	There is insufficient evidence to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.
Australian Guideline on COVID-19 as of October 8, 2021 [6]	Fluvoxamine for the treatment of COVID-19 should only be used in research settings.
WHO Living Guidelines [7]	

Infectious Diseases Society of America (IDSA) [8]	No statement on the use of fluvoxamine for the treatment of COVID-19.

Research Gaps

As of October 10, 2021, there are nine (9) ongoing trials on fluvoxamine registered on *clinicaltrials.gov* and EU Clinical Trials Register. One trial is already completed and awaiting results (Appendix 8).

References

[1] Sukhatme VP, Reiersen AM, Vayttaden SJ and Sukhatme VV. Fluvoxamine: A Review of Its Mechanism of Action and Its Role in COVID-19. Frontiers in Pharmacology. 2021; 12(652688). doi: 10.3389/fphar.2021.652688

[2] Fluvoxamine maleate [package insert]. Food and Drug Administration. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021519s012lbl.pdf.

[3] Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19. JAMA Intern Med. 2020;324(22):2292-2300

[4] Reis G, dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Glob Health. 2021 Oct;S2214109X21004484.

[5] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Institutes of Health; 2021. Available from: https://www.covid19treatmentguidelines.nih.gov/

[6] Coronavirus Disease 2019 (COVID-19): Communicable Disease Network Australia National Guidelines for Public Health Units. 2021;5.1. Available from: https://www1.health.gov.au/

[7] World Health Organization. [Internet]. Therapeutics and COVID-19 Living Guidelines. [updated 2021 Sept 24]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2.

[8] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. [Internet]. Infectious Diseases Society of America 2021; Version 5.2.0. [updated 2021 Sept 21]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 7)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (5)	Uncertain (2)	Trivial		• Fluvoxamine significantly reduced the need for hospitalization (RR 0.75, 95% CI 0.57-0.99; 2 RCTs, 1,649 participants) and need for emergency room visits (RR 0.73, 95% CI 0.62-0.86; 1 RCT, 1,497 participants) among symptomatic COVID-19 patients compared to placebo. • However, fluvoxamine had no benefit on all-cause mortality (RR 0.69, 95% CI 0.38-1.27), clinical deterioration at day 15 (RR = 0.70, 95% CI 0.00-1.21), and viral negative conversion at day 7 (RR 0.70, 95% CI 0.48-1.04) compared to placebo.
Harm	Large	Small (4)	Uncertain (3)	Varies			• There was no significant difference on adverse events (RR 1.00, 95% CI 0.77-1.29) and serious adverse events (RR 0.49, 95% CI 0.10-2.27) between fluvoxamine and placebo
Certainty of Evidence	High	Moderate (1)	Low (4)	Very low (2)			• The overall quality of evidence is rated low due to very serious imprecision on one critical outcome(clinical deterioration) and serious imprecision and inconsistency on another critical outcome (serious adverse events)
Balance of effects	Favors drug (3)	Does not favor drug (2)	Uncertain (2)				• There appears to be trend towards benefit (need for hospitalization, need for ER visit) without significant harm • There is still inconclusive evidence in terms of other critical outcomes (all-cause mortality, clinical deterioration, adverse events and serious adverse events)
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate cost (7)	Negligible cost	Moderate savings	Large savings	• The local price of fluvoxamine is at P75.25 for 50mg/tab. Taken orally, two to three times a day for 10 to 15 days at a maximum dose of 300 mg/day.

							• The total cost of treatment per patient would be P 6,772.50
Certainty of evidence of required resources	No included studies (3)	Very low (2)	Low (1)	Moderate (1)	High		• The cost of fluvoxamine was quoted from a private tertiary hospital's drug price list available online
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison (2)	Favors the intervention			
Equity	Uncertain (3)	Reduced (1)	Probably no impact (1)	Increased (2)			
Acceptability	Uncertain (5)	No	Yes (2)				
Feasibility	Uncertain (3)	No	Yes (4)				

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine	October 9, 2021 8:47 PM	30	1
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND Fluvoxamine	October 9, 2021 9:29 PM	13	10
COVID-NMA Initiative	Fluvoxamine	October 9, 2021 9:18 PM	2	2
Google Scholar	Fluvoxamine AND COVID-19 AND “randomized trial” Custom range: year 2020-2021	October 9, 2021 10:47PM	108	2
ClinicalTrials.gov	COVID-19, COVID-19 Pneumonia, Investigational Trials, Fluvoxamine	October 9, 2021 11:09 PM	7	7
Chinese Clinical Trial Registry	COVID, Fluvoxamine, Randomly Sampling	October 9, 2021 11:24 PM	0	0
EU Clinical Trials Register	COVID AND Fluvoxamine	October 9, 2021 11:25 PM	1	1
Republic of Korea - Clinical Research Information Service	COVID, fluvoxamine, investigational	October 9, 2021 11:29 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	COVID AND Fluvoxamine	October 9, 2021 11:30 PM	0	0
CenterWatch	COVID AND fluvoxamine	October 9, 2021 11:32 PM	0	0
WHO database COVID-19 studies	COVID AND fluvoxamine	October 9, 2021 11:38 PM	16	2
chinaxiv.org	COVID AND fluvoxamine	October 9, 2021 11:40 PM	0	0

Medrxiv.org	COVID AND fluvoxamine	October 9, 2021 11:44 PM	18	1
Biorxiv.org	COVID AND fluvoxamine	October 9, 2021 11:46 PM	13	0

Appendix 3: Characteristics of Included Studies

Title/Author	Study design	Country	Population	Intervention Group(s)	Control	Outcomes
Lenze 2020	Double-blind, placebo-controlled, randomized trial	United States of America	≥18 years old, outpatient, confirmed, symptomatic (N = 152)	Fluvoxamine 50mg, then 100mg twice daily for 2 days, then 100mg 3 times daily through day 15	Placebo	• Clinical deterioration • Clinical Status on 7-point scale • Adverse event • Serious adverse events
Reis 2021 TOGETHER Trial	Adaptive Placebo controlled randomized trial	Brazil	≥18 years old, with acute symptomatic confirmed COVID-19, at least one additional criterion for comorbidity (N = 1,497)	Fluvoxamine 100mg twice daily for 10 days	Placebo	• Extended emergency room observation • Hospitalization • Viral clearance • Time to clinical improvement • Number of days with respiratory symptoms • Time to hospitalization • Clinical deterioration • All-cause mortality • Days in hospital or mechanical ventilator • Adverse events

Appendix 4. Study Appraisal

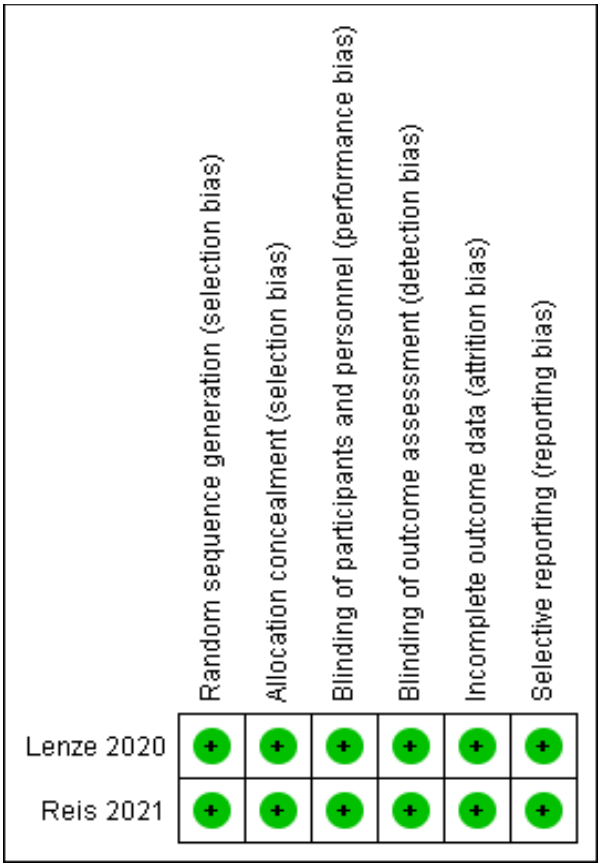

Figure 1. Risk of bias summary table

Appendix 5: GRADE Evidence Profile

Author(s): K. Relato; S.
Question: Fluvoxamine compared to standard of care in COVID-19
Bibliography: https://covid-nma.com/

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluvoxamine	Standard of care	Relative (95% CI)	Absolute (95% CI)		
Clinical Deterioration												
1	randomised trials	not serious	not serious	not serious	very serious[a,b,c]	none	1/80 (1.3%)	7/72 (9.7%)	**RR 0.07** (0.02 to 1.02)	**85 fewer per 1,000** (from – fewer to 17 more)	⊕⊕◯◯ LOW	CRITICAL
All-cause mortality at Day 28												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	17/741 (2.3%)	25/756(3.3%)	**RR 0.69** (0.38 to 1.27)	**10 fewer per 1,000** (from 21 fewer to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Need for hospitalization												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	76/821 (9.3%)	103/828 (12.4%)	**RR 0.75** (0.57 to 0.99)	**31 fewer per 1,000** (from 53fewer to 1 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Emergency room visit												
1	randomised trials	not serious	not serious	not serious	not serious	none	180/741 (24.3%)	251/756 (33.2%)	**RR 0.73** (0.62 to 0.86)	**90 fewer per 1,000** (from 126 fewer to 46 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Viral Negative Conversion												
1	randomised trials	Not serious	not serious	not serious	serious[c]	none	40/741 (5.4%)	57/756 (7.5%)	**RR 0.70** (0.48 to 1.04)	**23 fewer per 1,000** (from 39 fewer to 3 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

Adverse Events

2	randomised trials	not serious	not serious	not serious	serious[c]	none	103/821(12.5.0%)	104/828 (12.6%)	**RR 1.00** (0.77 to 1.29)	**0 fewer per 1,000** (from 29 fewer to 36 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Serious Adverse Events

2	randomised trials	not serious	serious [d]	not serious	serious [c]	none	78/821 (9.5%)	102/828(12. 3.7%)	**RR 0.49** (0.10 to 2.27)	**63 fewer per 1,000** (from 111fewer to 156 more)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanation

a. small number of events does not reach optimal information size
b. low sample size
c..wide confidence interval with possibility for benefit and harm.
d. $I^2 = 60\%$

Appendix 6: Forest Plots

Figure 1. Need for hospitalization

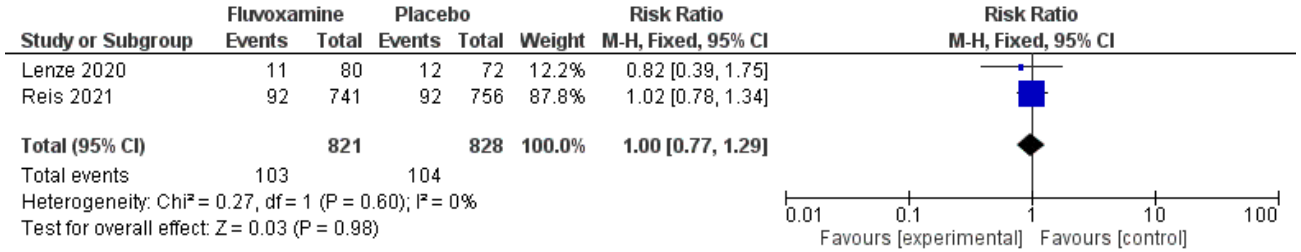

Figure 2. Adverse Events

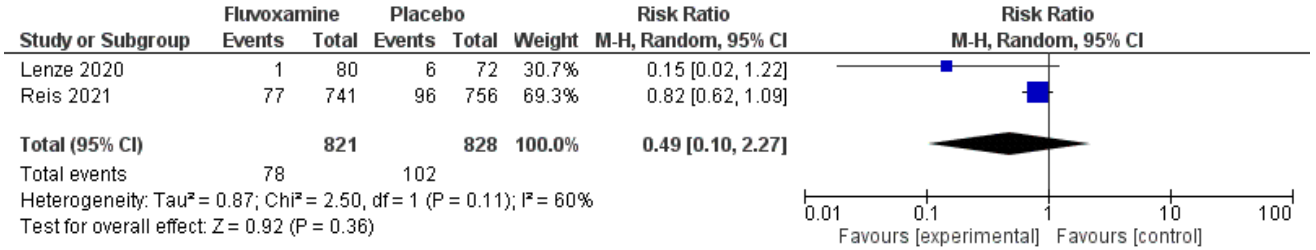

Figure 3. Serious Adverse Events

Appendix 7. Pooled Results of Trials

Outcome	Pooled/ Relative Risk	95% CI	Certainty of evidence (GRADE)
Clinical Deterioration (1 RCT, N = 152)	0.07	0.00 to 1.21	Low
All-cause mortality (1 RCT, N = 1497)	0.69	0.38 to 1.27	Moderate
Need for hospitalization (2 RCTs, N = 1649)	0.75	0.57 to 0.99	Moderate
Emergency Room visit (1 RCT, N = 1497)	0.73	0.62 to 0.86	High
Viral Negative Conversion (1 RCT, N = 1497)	0.70	0.48 to 1.04	Moderate
Adverse events (2 RCTs, N = 1649)	1.00	0.77 to 1.29	Moderate
Serious adverse events (2 RCTs, N =1649)	0.49	0.10 to 2.27	Low

Appendix 8. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Effect of fluvoxamine medicine on cytokine level of COVID-19 patients, hospitalized in ICU ward **Completed awaiting result**	Hospitalized in ICU due to COVID-19	Experimental: Fluvoxamine 50mg daily up to 300mg/week Control: Standard of care	Primary: CRP, ESR, IL-6 level upon discharge from ICU	Randomized control open label
2. Fluvoxamine for Adults With Mild to Moderate COVID-19 Suspended	Laboratory-confirmed SARS-CoV-2 patients who have mild to moderate symptoms related to COVID-19	Experimental: Fluvoxamine 50mg then 100mg twice daily until discharge or for approximately 10 days Control: Placebo	Primary: Time to clinical deterioration	Randomized placebo-control single blind
3. Fluvoxamine for Early Treatment of Covid-19 (Stop Covid 2) Recruitment completed	>/= 30 years old, not currently hospitalized, proven SARS-CoV-2 positive, currently symptomatic, one of the following risk factors for clinical deterioration: age≥40, racial/ethnic group African-American, Hispanic, or Native American or 1+ of the following medical conditions which increased risk for developing moderate-severe COVID illness: obesity, hypertension, diabetes, heart disease, lung disease, immune disorder	Experimental: Fluvoxamine 50mg once daily then 100mg twice daily approximately 15 days Control: Placebo	Primary: Time to clinical deterioration	Randomized placebo controlled double-blind
4. Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms Recruiting	>/=18 years old, flu-Like symptoms < 07 days, at least ONE enhancement criteria: 50 years; Diabetes mellitus, Systemic arterial hypertension, cardiovascular diseases, Symptomatic lung disease, Fever > 38 C at baseline, Obesity, Transplanted patients, chronic kidney disease, Immunosuppressed patients/ using corticosteroid therapy, Patients with a history of cancer Patients with important limitation of daily activities, positive rapid test for SARS-CoV2 antigen performed on occasion of the screening or patient with a positive SARS-CoV2 diagnostic test within 07 days of the onset of symptoms.	Experimental: Group 1: Fluvoxamine 100mg twice daily through day 9 Group 2: Doxazosin Group 3: Ivermectin Group 4: Peg INF lambda Group 5: Peg INF Beta Control: Placebo	Primary: Need for emergency care and clinical worsening 28 days Need for hospitalization	Randomized double blind placebo controlled
5. Effect of Combined Fluvoxamine with Favipiravir versus Favipiravir Monotherapy in Prevention of Clinical Deterioration among mild to moderate COVID-19 patients Monitoring by Telemedicine in	>/= 18 years old, confirmed COVID-19 with 1 or more of the symptoms, Asymptomatic COVID-19, accept to perform chest CT, Nasopharyngeal swab or oropharyngeal swab detected ORF1 a/b gene E gene from SARS-CoV-2 PCR with Ct	Experimental: Fluvoxamine 100mg daily for 10 days plus Favipavir Control: Favipavir	Primary: Clinical deterioration	Randomized open-label

Virtual Clinic: Open-label Randomized Controlled Trial *Not yet recruiting*	value, does not meet WHO criteria for hospitalization			
6. Fluvoxamine Administration in Moderate SARS-CoV-2 (COVID-19) Infected Patients *Recruiting*	18-70 years of age, Hospitalized patients with confirmed SARS-CoV-2 by PCR, Moderate cases (each of the followings met): showing dyspnea but not manifest respiratory distress, respiratory rate 22-29 / min; oxygen saturation at rest > 93%; with or without the need for oxygen supplementation; pneumonia on medical imaging with pulmonary infiltrates occupying ≤ 50% of the lung-fields	Experimental: Fluvoxamine 200mg daily over 74 days Control: Placebo	Primary: Time to clinical recovery	Randomized double blind placebo-controlled
7. A randomized, double-blind, placebo-controlled, adaptive-design study to assess the safety and efficacy of daily 200 mg fluvoxamine as add-on therapy to standard of care in moderate severity COVID-19 patients *Recruiting*	18-80 years of age, hospitalized patients with confirmed SARS-CoV-2, Moderate cases (at least one of the following criteria is met): dyspnea/tachypnea, respiratory rate 22-29 / min; with the need for oxygen supplementation; pulmonary infiltrates on medical imaging	Experimental: Fluvoxamine 50mg Control: Placebo	Primary: Time to clinical recovery	Randomized double blind placebo-controlled
8. ACTIV-6: COVID-19 Study of Repurposed Medications Recruiting	Age ≥ 30 years old, Confirmed SARS-CoV-2 infection within 10 days of screening, Two or more current symptoms of acute infection for ≤7 days: fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, new loss of sense of taste or smell	Experimental: Group 1: Ivermectin Group 2: Fluvoxamine 50mg twice daily for 10 days Group 3 Fluticasone Control: Placebo	Primary: Number of hospitalizations Number of deaths Number of symptoms	Randomized double blind placebo controlled
9. COVID-OUT: Early Outpatient Treatment for SARS-CoV-2 Infection (COVID-19) *Recruiting*	30 to 85 years old, positive RT PCR within 3 days, no known history of confirmed SARS-CoV-2 infection, BMI >= 25kg/m2, GFR>45ml/min within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure.	Experimental: Group 1: Metformin Group 2: Ivermectin Group 3: Fluvoxamine 50mg twice daily for 14 days Group 4: Fluvoxamine and Metformin Group 5: Metformin and Ivermectin Control: Placebo	Primary: Decreased oxygenation Emergency department utilization	Randomized double blind placebo-controlled