Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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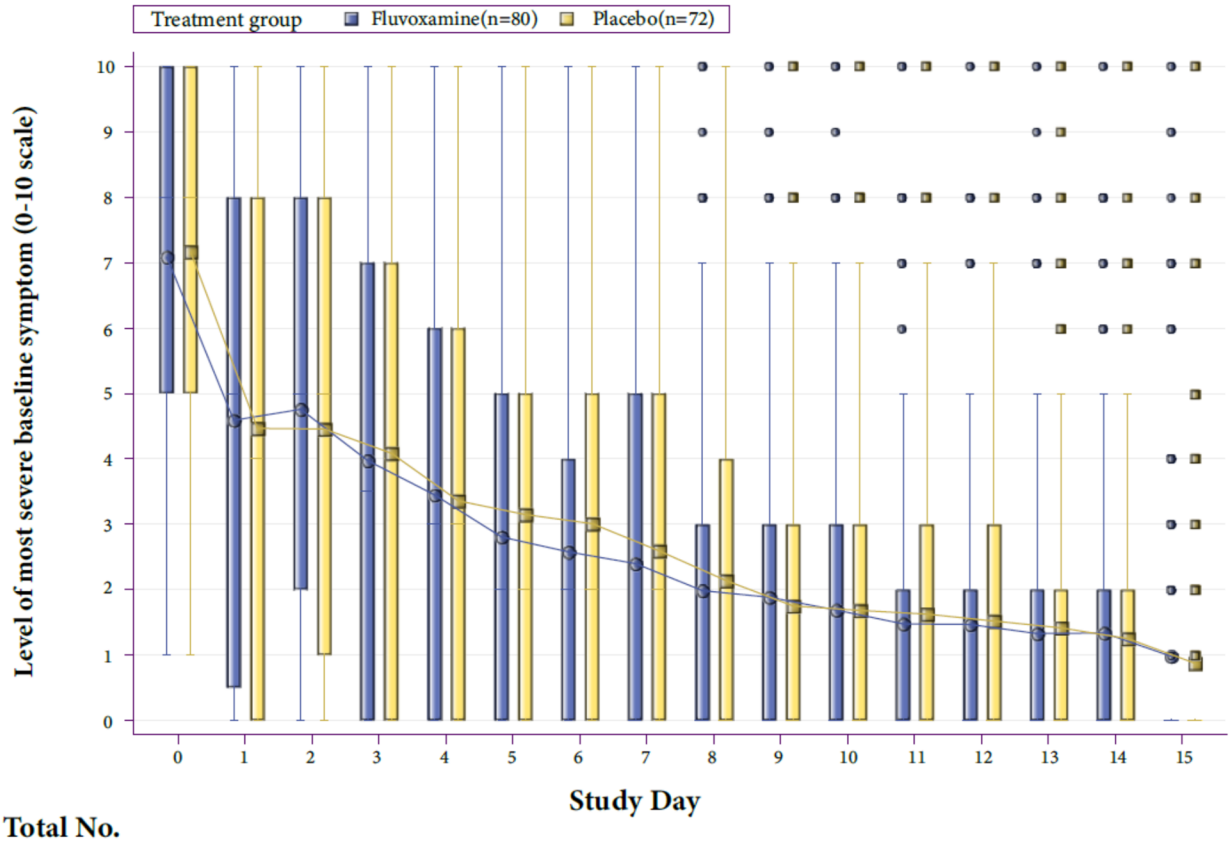
eFigure 1. Improvement in most severe baseline COVID-19 symptom
This box and whiskers plot shows the highest daily score for each participant of their most severe baseline symptom. We did not pursue this examination further because the curves showed no substantial differences and because the baseline most severe symptom was heterogeneous across participants (see Table below) and therefore did not adequately capture overall symptom burden.



Total No.																
Fluvoxamine	80	78	72	75	72	74	68	66	66	64	64	62	60	61	58	49
Placebo	72	72	67	64	63	61	59	60	58	54	55	56	52	53	50	47

Note: patients who met the primary endpoint were not dropped if they continued surveys. Study day 0=day of randomization.

Most severe COVID-19 symptom at baseline, by group (data are from Table 1)

Most severe symptom at baseline[a], No (%)	**Fluvoxamine (n=80)**	**Placebo (n=72)**
Loss of smell	26 (32.5%)	18 (25%)
Fatigue	17 (21.3%)	18 (25%)
Body aches	9 (11.3%)	13 (18.1%)
Cough	9 (11.3%)	1 (1.4%)
Subjective fever	8 (10%)	4 (5.6%)
Loss of appetite	3 (3.8%)	8 (11.1%)
Chills	3 (3.8%)	6 (8.3%)
Shortness of breath	2 (2.5%)	1 (1.4%)
Loss of taste	2 (2.5%)	2 (2.8%)
Nausea	1 (1.3%)	1 (1.4%)

[a] per patient self-report

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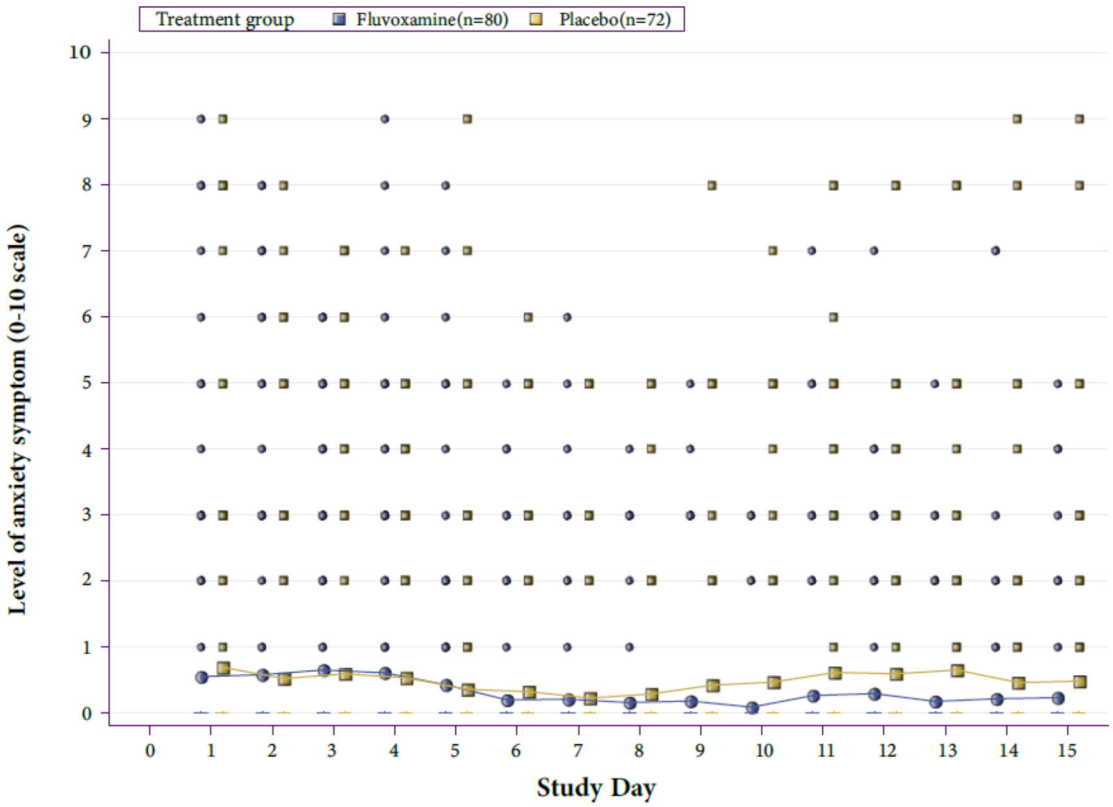
eFigure 2. Anxiety ratings in the fluvoxamine vs. placebo groups during the 15-day RCT
To determine whether fluvoxamine (an SSRI that is FDA-approved for treating anxiety disorders) produced any effect on anxiety, we tracked anxiety on a 0-10 scale twice daily during the 15 day RCT. Below is shown a box and whiskers plot of mean anxiety symptoms of time (highest score for participant on each day)



Participant No. /day															
Fluvoxamine	67	71	72	71	70	65	62	60	58	56	55	53	54	53	49
Placebo	59	63	61	58	57	56	55	54	52	50	52	47	48	47	47

Note: anxiety was not assessed at baseline (day 0).

Note: The boxplot at the bottom of the figure was not shown because most assessed values were "0"; hence, then non-zero symptom scores appeared to be far-outliers in the graph.

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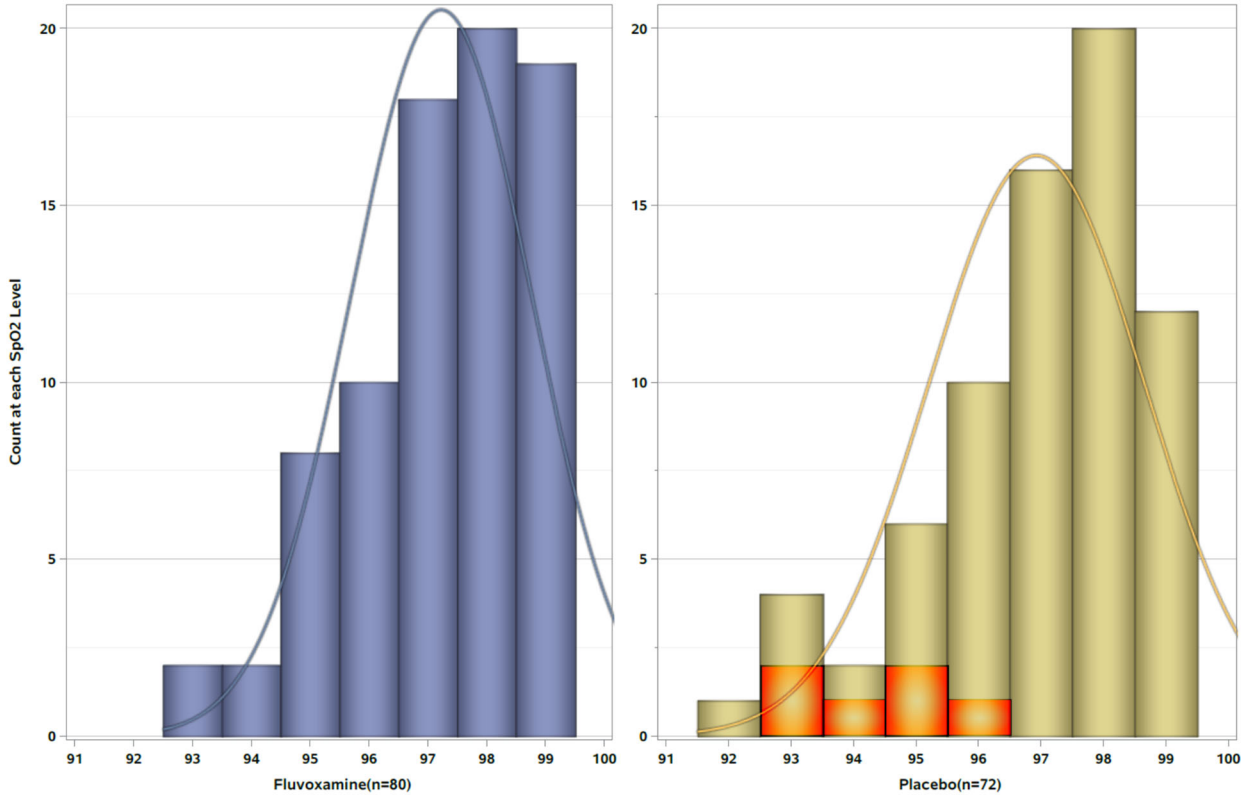
eFigure 3. Distributions of baseline oxygen saturation in the fluvoxamine and placebo groups and clinical deterioration as a function of baseline oxygen saturation
Shown are bell curve distributions of the baseline (day 0) oxygen saturation score in the two groups. In the placebo group, the six cases of clinical deterioration are marked in orange: 6/23 (26%) of those with baseline oxygen saturation ≤96% deteriorated, vs. 0/49 (0%) of those with baseline oxygen saturation >96%. In the fluvoxamine group, the corresponding numbers were 0/22 and 0/58. Table 1 shows the median baseline oxygen saturation in the two groups which was not significantly different (97% fluvoxamine, 97% placebo)



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eTable. Clinical deterioration findings ranked on study-specific 7-point (0-6) ordinal scale of clinical deterioration (prespecified secondary endpoint) and the World Health Organization (WHO) nine-point (0-8) ordinal scale for clinical improvement (post-hoc analysis)

Outcomes	Fluvoxamine group (n=80)	Placebo group (n=72)
Clinical deterioration, No (%)		
0=None	80 (100%)	66 (91.7%)
1=O_2 sat <92% but no supplemental O_2	0 (0%)	2 (2.8%)
2=Above + supplemental O_2 needed	0 (0%)	0 (0%)
3=Above + hospitalization needed	0 (0%)	3 (4.2%)
4=Above + ventilator needed (<3 days)	0 (0%)	0 (0%)
5=Above + ventilator needed (≥3 days)	0 (0%)	1 (1.4%)
6=Death	0 (0%)	0 (0%)
Total participants with values >0	0 (0%)	6 (8.3%)

Note: these data are also in Table 2; they are included here for direct comparison to the WHO scale below.

Outcomes	Fluvoxamine group (n=80)	Placebo group (n=72)
WHO scale, No (%)[a]		
0-1=uninfected or ambulatory	80 (100%)	66 (91.7%)
2=limitation of activities	0 (0%)	2 (2.8%)
3=hospitalized, no O_2 needed	0 (0%)	0 (0%)
4=hospitalized, O_2 needed	0 (0%)	3 (4.2%)
5=non-invasive vent or high-flow O_2	0 (0%)	0 (0%)
6=ventilator needed	0 (0%)	1 (1.4%)
7=ventilator+additional organ support	0 (0%)	0 (0%)
8=Death	0 (0%)	0 (0%)
Total participants with values >1	0 (0%)	6 (8.3%)

[a] only an approximate crosswalk can be made to the WHO scale because our study did not collect virological outcomes (necessary to distinguish between 0 and 1 on the WHO scale) and rated clinical deterioration, not improvement.

Note: WHO scale for clinical improvement found at p6 of https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

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eResults 1. Summaries of the six participants who showed Clinical Deterioration (all Placebo, all who were hospitalized were also considered SAEs)

Note: an age range, rather than exact age, is given to protect participant identity

1. **Low oxygen saturation plus shortness of breath:** A 35-39 year-old, white, Hispanic male participant entered the study with a reported baseline oxygen saturation of 95% and a shortness of breath rating of 0 out of 10. He reported low oxygen saturation on the Day 7 morning survey of 90% as well as a shortness of breath rating of 5/10. Study staff called the participant and a re-check on the pulse oximeter showed an oxygen saturation of 91%. The participant went to the ER, where his oxygen saturation and shortness of breath reportedly improved and he was discharged home. Clinical deterioration occurred 12 days after symptom onset.

2. **Low oxygen saturation plus shortness of breath:** A 30-34 year-old white, non-Hispanic male entered the study with a baseline oxygen saturation of 93% and a shortness of breath rating of 7 out of 10. The participant reported oxygen saturation of 90% and shortness of breath at 6/10 on the Day 6 Evening Survey. On the Day 7 Morning Survey he reported oxygen saturation of 91% with shortness of breath at 6/10. Study staff called him and he said that when he re-checked, his oxygen was 89% so he called his PCP. His PCP had him check again while she was on the phone with him and his oxygen saturation was 91%. His PCP told him to go to the ER if his oxygen saturation dipped below 90% again. Clinical deterioration occurred 10 days after symptom onset.

3. **Acute on chronic respiratory failure with hypoxia and hypercapnia:** A 55-59 year-old black, non-Hispanic female entered the study with an oxygen saturation of 94% and a shortness of breath rating of 0/10. She began study medication that evening. The following morning she recorded an oxygen saturation of 75% on her Morning Survey, though shortness of breath score remained at 0/10. Study staff called and asked her to re-check. Her oxygen saturations remained low at 75% and she complained of weakness and dizziness. She was advised to go to the ER. Records state that in the ambulance she had an oxygen saturation of 74% and received supplemental oxygen. A chest x-ray showed bilateral infiltrates. She was admitted and hospitalized a total of 21 days. During that hospital stay, she was intubated and on a ventilator for 10 days. No other organ support (e.g., pressors, renal replacement therapy, ECMO). Clinical deterioration occurred 3 days after symptom onset.

4. **Pneumonia-bilateral, multifocal**: A 30-34 year-old black, non-Hispanic female entered the study with a baseline oxygen saturation of 95% and a shortness of breath rating of 0/10. On her Day 4 evening survey, she reported an oxygen saturation of 90% and a shortness of breath rating of 4/10. Her Day 5 morning survey showed an oxygen saturation of 91% and shortness of breath at 5/10. Study staff tried calling multiple times without success. The participant recorded a Day 5 evening survey with an oxygen saturation of 89% and 6/10 shortness of breath. Staff was finally able to reach her the morning of Day 6 and recommended she call her PCP or go to the ER. After some hesitancy the participant went to the ER that same day and was subsequently hospitalized. A chest x-ray showed bilateral, multi-focal pneumonia. Records indicate that her room air oxygen saturation when admitted ranged from 89-92%, and she was given supplemental oxygen (2L/minute). She was hospitalized for 4 days. Clinical deterioration occurred 10 days after symptom onset.

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5. **Exacerbation of COVID symptoms (nausea/vomiting/fever/low oxygen saturation)**: A 55-59 year-old white, non-Hispanic female entered the study with a baseline oxygen saturation of 93% and a shortness of breath score of 0/10. The participant reported on her Day 4 Morning survey an oxygen saturation of 94% with 0/10 shortness of breath, but moderate to severe symptoms of nausea, vomiting, diarrhea and a fever. She went to the ER and was admitted later that day. Imaging revealed pneumonia. Records indicate that when on room air, her oxygen saturations during admission were in the 80s, so she received supplemental oxygen (3L/minute) up until the last day of her hospitalization. She was admitted a total of 6 days. Clinical deterioration occurred 8 days after symptom onset.

6. **Exacerbation of COVID symptoms (nausea/fever/pneumonia)**: A 65-69 year-old black, non-Hispanic male entered the study with an oxygen saturation of 96% and a shortness of breath rating of 0/10. The participant reported an oxygen saturation of 95% on his morning and evening Day 2 surveys, but a shortness of breath score of 5/10 in the morning and 8/10 in the evening. The following day he was admitted to the hospital for fever and nausea. He underwent a chest x-ray which showed opacities. He was hospitalized a total of 8 days, and received supplemental oxygen for 3 of those days to keep oxygen (5L/minute) at or above 92%. Clinical deterioration occurred 6 days after symptom onset.

Additional Serious Adverse Events during 15-day RCT (that did not meet endpoint criteria).

Placebo group:

1. **Exacerbation of COVID symptoms (nausea, vomiting, chest pain**): A 50-54 year-old black, non-Hispanic female participant did not send survey data for Day 2, but went that day to the ER for nausea, vomiting and chest pain. She was then admitted to the hospital for 2 days. Oxygen saturation at admission was 97% and does not appear to have gone under 92%. She was not given supplemental oxygen during her admission. Chest x-ray showed pneumonia of both lungs.

2. **Flank Pain**: Same participant (same person as immediately above) went to ER with flank pain and was hospitalized for one day. Her oxygen saturation stayed above 92% and she did not receive any supplemental oxygen.

Fluvoxamine group:

1. **Dehydration**: A 70-74 year-old white, non-Hispanic male participant called an ambulance after feeling weak and faint on Day 3. His oxygen saturations on both surveys that day were 94%. He was admitted to the hospital for dehydration for 2 days. His oxygen saturation did not drop <92% and he was not given supplemental oxygen. There was also no disruption of study medication.

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Additional details of adverse events in both groups

One fluvoxamine participant was hospitalized for dehydration (serious adverse event), but they never had an oxygen saturation measurement below 92%. One fluvoxamine participant had both shortness of breath and gastroenteritis (counted as one non-serious adverse event). Ten other fluvoxamine participants had only one simple non-serious adverse event (only one symptom/problem reported per event). One of these ten participants reported shortness of breath as their non-serious adverse event, but never had an oxygen saturation measurement below 92%. Two placebo group participants had only one non-serious adverse event (chest pain or vomiting). One placebo group participant had three separate non-serious adverse events (pneumonia, vomiting, migraine headache). Two placebo group participants had an event with low oxygen saturation and shortness of breath without need for hospitalization (non-serious adverse events, but met criteria for clinical deterioration). One of these had worsening shortness of breath without low oxygen saturation as an earlier non-serious adverse event. One placebo group participant had four separate non-serious adverse events (nausea/vomiting, shortness of breath, pneumonia, chest tightness), then had an exacerbation of COVID19 symptoms with hospitalization for nausea, vomiting, and chest pain (serious adverse event) plus a second hospitalization for flank pain (second serious adverse event), but never had oxygen saturation below 92%. One placebo participant had exacerbation of COVID symptoms with hospitalization for nausea, vomiting, fever, low oxygen saturation, and pneumonia (serious adverse event). One placebo participant had no shortness of breath but was hospitalized for acute on chronic respiratory failure with hypoxia and hypercapnia, and had bilateral infiltrates on chest x-ray (serious adverse event). One placebo participant had hospitalization for bilateral multi-focal pneumonia with shortness of breath and low oxygen saturation (serious adverse event). One placebo participant was hospitalized for exacerbation of COVID symptoms with nausea, fever, and pneumonia with requirement of supplemental oxygen to maintain oxygen saturation above 92% (serious adverse event).

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eResults 2. Additional hospitalizations/ER visits during 30-day post-RCT observation period

Placebo group:

1. **Chest pain:** A 45-49 year-old white, non-Hispanic female participant went to the Emergency Room complaining of chest pain and light-headedness. This occurred 27 days after the end of the double-blind phase. She was discharged home after treatment for costochondritis COVID-19 sequela. A chest x-ray was clear and no respiratory problems or hypoxia were noted.

Fluvoxamine group:

1. **Headache:** A 40-44 year old white, non-Hispanic female was hospitalized for a headache 2 days after completing the RCT phase of the study, and approximately 11 days after discontinuing study medication (took fluvoxamine for 6 days in the RCT). She was hospitalized for 3 days and the differential diagnosis was migraine vs. post-COVID headache. No respiratory problems or hypoxia were noted.

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