Table 7a. Fluvoxamine: Selected Clinical Trial Data

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The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for fluvoxamine. The studies summarized below are the randomized clinical trials that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
ACTIV-6: Decentralized, Randomized, Placebo-Controlled, Platform Trial of Low-Dose Fluvoxamine in Patients With Mild to Moderate COVID-19[1]		
Key Inclusion Criteria • Aged ≥30 years • Positive SARS-CoV-2 nasopharyngeal RT-PCR result or antigen test result • ≥2 COVID-19 symptoms for ≤7 days **Key Exclusion Criterion** • Receipt of fluvoxamine in past 30 days **Interventions** • Fluvoxamine 50 mg PO twice daily for 10 days (n = 674) • Placebo (n = 614; 326 received matching placebo, 288 received placebo from another study arm) **Primary Endpoint** • Time to recovery, defined as time to third day of 3 consecutive days without symptoms **Key Secondary Endpoints** • Hospitalization or death by Day 28 • Urgent care visit, ED visit, or hospitalization by Day 28	**Participant Characteristics** • Mean age 47 years; 57% women; 81% White • 36% with BMI ≥30; 24% with HTN • 67% received ≥2 doses of a SARS-CoV-2 vaccine. • Median of 5 days from symptom onset to receipt of study drug **Primary Outcome** • Median time to recovery: 12 days in fluvoxamine arm vs. 13 days in placebo arm (HR 0.96; 95% CrI, 0.86–1.06) **Secondary Outcomes** • Hospitalization or death by Day 28: 0.2% in fluvoxamine arm vs. 0.3% in placebo arm (3 events total) • Urgent care visit, ED visit, or hospitalization by Day 28: 3.9% in fluvoxamine arm vs. 3.8% in placebo arm (HR 1.1; 95% CrI, 0.5–1.8)	**Key Limitation** • Low number of some clinical events, such as hospitalization **Interpretation** • In outpatients with mild to moderate COVID-19, fluvoxamine 50 mg twice daily for 10 days did not reduce the time to recovery or the incidence of clinical events such as hospitalization, urgent care visits, or ED visits.

Methods	Results	Limitations and Interpretation
ACTIV-6: Decentralized, Randomized, Placebo-Controlled, Platform Trial of High-Dose Fluvoxamine in Patients With Mild to Moderate COVID-19[2]		
Key Inclusion Criteria • Aged ≥30 years • Positive SARS-CoV-2 nasopharyngeal RT-PCR result or antigen test result • ≥2 COVID-19 symptoms for ≤7 days **Key Exclusion Criterion** • Receipt of fluvoxamine or other selective serotonin or norepinephrine reuptake inhibitors in past 14 days **Interventions** • Fluvoxamine 50 mg PO twice daily for 1 day, then fluvoxamine 100 mg PO twice daily for 12 days (n = 589) • Placebo (n = 586) **Primary Endpoint** • Time to recovery, defined as time to third day of 3 consecutive days without symptoms **Key Secondary Endpoints** • Hospitalization or death by Day 28 • Urgent care visit, ED visit, or hospitalization by Day 28	**Participant Characteristics** • Median age 50 years; 66% women; 73% White • 36% with BMI ≥30; 26% with HTN • 77% received ≥2 doses of a SARS-CoV-2 vaccine. • Median of 5 days from symptom onset to receipt of study drug **Primary Outcome** • Median time to recovery: 10 days in fluvoxamine arm vs. 10 days in placebo arm (HR 0.99; 95% CrI, 0.89–1.09) **Secondary Outcomes** • Hospitalization or death by Day 28: 0.2% in fluvoxamine arm vs. 0.3% in placebo arm (3 events total) • Urgent care visit, ED visit, or hospitalization by Day 28: 2.4% in fluvoxamine arm vs. 3.6% in placebo arm (HR 0.69; 95% CrI, 0.27–1.21)	**Key Limitation** • Low number of some clinical events, such as hospitalization **Interpretation** • In outpatients with mild to moderate COVID-19, fluvoxamine 100 mg twice daily did not reduce the time to symptom recovery or the incidence of clinical events such as hospitalization, urgent care visits, or ED visits.

Methods	Results	Limitations and Interpretation
COVID-OUT: Randomized Trial of Metformin, Ivermectin, and Fluvoxamine in Patients With COVID-19[3]		

Key Inclusion Criteria
• Aged 30–85 years
• BMI ≥25 or ≥23 if Asian or Latinx
• Laboratory-confirmed SARS-CoV-2 infection within 3 days of randomization
• <7 days of symptoms
Key Exclusion Criteria
• Immunocompromised
• Hepatic impairment, severe kidney disease, unstable heart failure
• Bipolar disease
Interventions
• Fluvoxamine 50 mg PO twice daily for 14 days (n = 334)
  • 159 received fluvoxamine plus placebo.
  • 175 received fluvoxamine plus metformin.
• Control (n = 327)
  • 166 received placebo plus placebo.
  • 161 received placebo plus metformin.
Primary Endpoint
• Composite of hypoxemia (SpO_2 ≤93%, as measured by a home pulse oximeter), ED visit, hospitalization, or death by Day 14
Key Secondary Endpoints
• Individual components of the composite endpoint
• Outcomes for fluvoxamine plus placebo vs. placebo plus placebo only
• Total symptom severity score
• Drug interruption or discontinuation for fluvoxamine plus placebo vs. placebo plus placebo only
	Participant Characteristics
	• Median age 43–46 years; 54% women; 82% White
	• 27% with CVD; 47% with BMI ≥30
	• 56% received primary vaccination series.
	• Mean of 5 days from symptom onset to randomization
	Primary Outcome
	• Composite of hypoxemia, ED visit, hospitalization, or death by Day 14: 24% in fluvoxamine arm vs. 25% in control arm (aOR 0.94; 95% CI, 0.66–1.36)
	Secondary Outcomes
	• Hospitalization by Day 14: 1.8% in fluvoxamine arm vs. 1.5% in control arm (aOR 1.113; 95% CI, 0.33–3.76).
	• Composite of ED visit, hospitalization, or death, excluding patients who received metformin: 9.0% in fluvoxamine plus placebo arm vs. 6.7% in placebo plus placebo arm (aOR 1.24; 95% CI, 0.54–2.87)
	• No deaths occurred in either arm.
	• No difference between arms in total symptom severity score over 14 days
	• Drug interruption or discontinuation, excluding patients who received metformin: 30% in fluvoxamine plus placebo arm vs. 25% in placebo plus placebo arm
		Key Limitation
		• In this trial, the study arms that did not include metformin were underpowered to detect differences in the primary endpoint.
		Interpretation
		• Fluvoxamine did not impact the incidence of COVID-19–related complications such as hospitalization.
		• Fluvoxamine did not impact symptom severity.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[4]		
Key Inclusion Criteria • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardiac arrhythmia **Interventions** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (n = 756; route, dosing frequency, and duration of placebo may have differed from fluvoxamine for some patients) **Primary Endpoint** • Composite of ED observation >6 hours or hospitalization for COVID-19 by Day 28 **Key Secondary Endpoints** • COVID-19–related hospitalization by Day 28 • Time to symptom resolution • Adherence to study drugs, defined as receiving >80% of possible doses • Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	**Participant Characteristics** • Median age 50 years; 58% women; 95% self-identified as mixed race • 13% with uncontrolled HTN; 13% with type 2 DM; 50% with BMI ≥30 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome** • Composite of ED observation >6 hours or hospitalization by Day 28: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CrI, 0.52–0.88) **Secondary Outcomes** • 87% of clinical events were hospitalizations. • No difference between arms in COVID-19–related hospitalizations: 10% in fluvoxamine arm vs. 13% in placebo arm (OR 0.77; 95% CI, 0.55–1.05) • No difference between arms in time to symptom resolution • Adherence: 74% in fluvoxamine arm vs. 82% in placebo arm (OR 0.62; 95% CI, 0.48–0.81) • 11% in fluvoxamine arm vs. 8% in placebo arm stopped drug due to issues of tolerability. • Mortality (ITT): 2% in fluvoxamine arm vs. 3% in placebo arm (OR 0.68; 95% CI, 0.36–1.27) • Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	**Key Limitations** • The >6-hour ED observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk of hospitalization and death. • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to fluvoxamine by route of administration, dosing frequency, or duration of therapy. • PP analyses are not randomized comparisons, and they introduce bias when adherence is associated with factors that influence the outcome. • Adherence was self-reported and not verified. **Interpretation** • Fluvoxamine reduced the proportion of patients who met the composite endpoint of COVID-19–related hospitalization or retention in an ED for >6 hours. • The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations. • It is difficult to define the clinical relevance of the >6-hour ED observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact the time to symptom resolution.

Methods	Results	Limitations and Interpretation
STOP COVID 2: Fully Remote RCT of Fluvoxamine Versus Placebo in Outpatients With Symptomatic COVID-19[5]		

Key Inclusion Criteria
• Aged ≥30 years
• Positive SARS-CoV-2 PCR result per patient self-report
• ≤7 days of symptoms
• ≥1 risk factor for clinical deterioration
Key Exclusion Criteria
• Immunocompromised
• Unstable medical comorbidities
• Significant interacting medications
Interventions
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg PO twice daily through Day 15 (n = 272)
• Placebo (n = 275)
Primary Endpoint
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoints
• Peak disease severity at any point during the 15 days post-randomization, as measured by a modified 9-point WHO scale
• Occurrence of AEs
	Participant Characteristics
	• Median age 47 years; 62% women; 27% non-White
	• 44% with obesity; 21% with HTN
	• Median of 5 days from symptom onset to randomization
	Primary Outcome
	• Clinical deterioration: 4.8% in fluvoxamine arm vs. 5.5% in placebo arm (absolute difference 0.68%; 95% CI, -3.0 to 4.4)
	Secondary Outcomes
	• Peak disease severity: 1.11 in fluvoxamine arm vs. 1.13 in placebo arm (absolute difference 0.02; 95% CI, -0.07 to 0.11)
	• GI AEs were significantly more common in fluvoxamine arm
		Key Limitations
		• Small sample size compared to other trials
		• Short follow-up period
		Interpretation
		• Fluvoxamine did not reduce the proportion of patients who experienced clinical deterioration by Day 15.

Methods	Results	Limitations and Interpretation
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[6]		

Key Inclusion Criteria
• Aged ≥18 years
• Positive SARS-CoV-2 PCR result
• ≤7 days of symptoms
Key Exclusion Criteria
• Immunocompromised
• Unstable medical comorbidities
Interventions
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg PO twice daily, then fluvoxamine 100 mg PO 3 times daily through Day 15 (n = 80)
• Placebo (n = 72)
Primary Endpoint
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoint
• Hospitalization by Day 15
	Participant Characteristics
	• Mean age 46 years; 72% women; 25% Black
	• 56% with obesity; 20% with HTN; 17% with asthma
	• Median of 4 days from symptom onset to randomization
	Primary Outcome
	• Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%)
	Secondary Outcome
	• No patients in fluvoxamine arm and 4 patients in placebo arm were hospitalized.
		Key Limitations
		• Small sample size
		• Short follow-up period
		• Ascertaining clinical deterioration was challenging because all assessments were done remotely.
		• 24% of patients stopped responding to follow-up prior to Day 15 but were included in the final analysis.
		Interpretation
		• Fluvoxamine reduced the proportion of patients who experienced clinical deterioration.
		• Due to significant limitations, it is difficult to draw definitive conclusions about the efficacy of using fluvoxamine to treat COVID-19.

Methods	Results	Limitations and Interpretation
TOGETHER: Randomized Platform Trial of Oral Fluvoxamine Plus Inhaled Budesonide for the Treatment of Early Onset COVID-19[7]		
Key Inclusion Criteria • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardiac arrhythmia **Interventions** • Fluvoxamine 100 mg PO twice daily plus budesonide 800 µg inhaled twice daily for 10 days (n = 738) • Placebo (n = 738; route, dosing frequency, and duration for some patients may have differed from treatment group) **Primary Endpoint** • Composite of ED observation >6 hours or hospitalization for COVID-19 by Day 28 **Key Secondary Endpoints** • Hospitalization by Day 28 • Health care attendance by Day 28 • Any ED visit by Day 28 • Occurrence of AEs	**Participant Characteristics** • Median age 51 years; 61% women • 42% with BMI >30; 44% with HTN; 68% with multiple comorbidities • 94% received ≥2 doses of a COVID-19 vaccine. **Primary Outcome** • Composite of ED observation >6 hours or hospitalization by Day 28: 1.8% in fluvoxamine plus inhaled budesonide arm vs. 3.7% in placebo arm (relative risk 0.50; 95% CrI, 0.25–0.92) **Secondary Outcomes** • Hospitalization by Day 28: 0.9% in fluvoxamine plus inhaled budesonide arm vs. 1.1% in placebo arm • Health care attendance by Day 28: 2.6% in fluvoxamine plus inhaled budesonide arm vs. 4.1% in placebo arm (relative risk 0.64; 95% CrI, 0.36–1.11) • Any ED visit by Day 28: 12.2% in fluvoxamine plus inhaled budesonide arm vs. 13.0% in placebo arm • Treatment-emergent AEs: 17.6% in fluvoxamine plus inhaled budesonide arm vs. 12.9% in placebo arm (relative risk 1.37; 95% CrI, 1.07–1.75) • Most AEs were grade 2.	**Key Limitation** • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to oral fluvoxamine plus inhaled budesonide. **Interpretation** • In adult outpatients with mild COVID-19, fluvoxamine plus inhaled budesonide reduced the need for ED observations >6 hours or hospitalization when compared with placebo. • The use of fluvoxamine plus inhaled budesonide did not reduce hospitalization, health care attendance, or the occurrence of any ED visit. • It is difficult to define the clinical relevance of the >6-hour ED observation endpoint and apply it to practice settings in different countries. • The use of fluvoxamine plus inhaled budesonide resulted in more AEs than placebo.

Key: AE = adverse event; BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; ED = emergency department; GI = gastrointestinal; HTN = hypertension; ITT = intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; PP = per protocol; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor; WHO = World Health Organization

References

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