Table 4c. Fluvoxamine: Selected Clinical 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
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1]		
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 cardia arrythmia **Interventions:** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (route, dosing frequency, and duration for some patients may have differed from fluvoxamine) (n = 756) **Primary Endpoint:** • Composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19 within 28 days after randomization **Key Secondary Endpoints:** • Occurrence of COVID-19-related hospitalizations • Time to symptom resolution • Proportion of patients who were adherent to study drugs, defined as receiving >80% of possible 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 kg/m^2 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome:** • Proportion of patients who met the primary composite endpoint: 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)	**Key Limitations:** • The >6-hour emergency setting observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk for 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 emergency setting for >6 hours. • The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1], continued		
• Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	• Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	• It is difficult to define the clinical relevance of the >6-hour emergency setting observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact time to symptom resolution.
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[2]		

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 twice daily, then fluvoxamine 100 mg 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
	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.

Key: BMI = body mass index; DM = diabetes; 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; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor

References

1. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, 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;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34717820.
2. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33180097.