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The Effect of Fluvoxamine and Metformin for Fatigue in Patients With Long COVID

An Adaptive Randomized Trial

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Background: Postacute sequelae of SARS-CoV-2, or long COVID, presents a major therapeutic challenge, with fatigue being a prevalent and debilitating symptom.

Objective: To assess the efficacy of fluvoxamine and metformin for long COVID fatigue.

Design: Randomized, placebo-controlled, adaptive trial. (ClinicalTrials.gov: NCT06128967)

Setting: Outpatient sites in Brazil.

Participants: 399 adults with fatigue persisting 90 or more days after confirmed SARS-CoV-2 infection.

Intervention: Participants were randomly assigned to fluvoxamine (100 mg twice daily), metformin (750 mg twice daily), or matching placebo for 60 days.

Measurements: The primary outcome was change in Fatigue Severity Scale (FSS) score.

Results: Fluvoxamine showed a significant reduction in fatigue compared with placebo at day 60 (mean difference, −0.43 [95% credible interval {CrI}, −0.80 to −0.07]), with a sustained effect at day 90 (mean difference, −0.58 [CrI, −0.98 to −0.16]). Fluvoxamine also improved quality-of-life scores with high posterior probability. Metformin showed no significant benefit. Adverse events were less frequent with fluvoxamine (20.0%) than with metformin (28.8%) or placebo (29.7%). Grade 3 and higher adverse events were rare across all groups.

Limitations: The 90-day follow-up period limits conclusions about the durability of treatment effects, and the exclusive focus on fatigue as the primary outcome does not address other prevalent long COVID symptoms, leaving fluvoxamine's broader therapeutic utility uncertain.

Conclusion: Fluvoxamine, but not metformin, may be an effective treatment for reducing fatigue and improving quality of life in patients with long COVID.

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Postacute sequelae of SARS-CoV-2 infection, or long COVID, poses a substantial and ongoing global health burden, affecting millions of people after resolution of acute COVID-19 illness (1, 2). Fatigue is among the most prevalent and debilitating symptoms, often persisting for months and impairing quality of life (3–6). Despite the increasing recognition of long COVID's social and economic effects, therapeutic options remain limited (7–9).

Current management is largely supportive, relying on multidisciplinary care models focused on symptom relief (10, 11). The underlying mechanisms are multifactorial, involving possible persistent viral antigens, immune dysregulation, endothelial dysfunction, and mitochondrial impairment (12, 13). This complicates therapeutic development and highlights the need for targeted interventions addressing the biological drivers of long COVID (14, 15).

Metformin, a commonly prescribed antihyperglycemic agent, has recently shown promise in preventing onset of long COVID in a randomized trial when used during acute infection (16, 17). Beyond its metabolic role, metformin exhibits anti-inflammatory and mitochondrial-modulating effects, making it a plausible candidate for treatment of fatigue-related symptoms (18).

Fluvoxamine, a selective serotonin reuptake inhibitor with σ-1 receptor agonism, has shown anti-inflammatory properties and reduced hospitalization risk in acute

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Summary for Patients
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Supplemental material

COVID-19 across multiple trials (19, 20). Its central nervous system activity and immunomodulatory effects offer a possible mechanistic rationale for use in neurocognitive and fatigue-related manifestations of long COVID (21).

Although observational studies and small trials have suggested potential therapeutic options for long COVID, robust evidence from randomized controlled trials is scarce (22). To address this evidence gap, we conducted a multicenter, randomized, placebo-controlled, adaptive trial to evaluate the efficacy of metformin and fluvoxamine in reducing fatigue in adults with long COVID.

METHODS

Study Design and Participants

We conducted a multicenter, randomized, placebo-controlled, adaptive trial (REVIVE-TOGETHER) to evaluate the efficacy of metformin and fluvoxamine for the treatment of fatigue associated with long COVID. The trial was conducted at 22 participating outpatient sites in Brazil between October 2023 and February 2025. Participants were recruited at outpatient clinics and were introduced to the research team after initial eligibility screening.

Eligible participants were adults (aged ≥18 years) with a single index episode of SARS-CoV-2 infection confirmed by laboratory testing or, where testing was not available, by clinician diagnosis or self-report and with new or worsening fatigue persisting 90 to less than 365 days after the acute illness. Inclusion required moderate to severe fatigue (mean Fatigue Severity Scale [FSS] score ≥4) and symptoms that the investigator judged not to be attributable to another identifiable cause.

Key exclusion criteria included active acute SARS-CoV-2 infection, preexisting myalgic encephalomyelitis/chronic fatigue syndrome or non–SARS-CoV-2–related dysautonomia, diabetes and severe anemia (hemoglobin level <8 g/dL), recent stroke, Lyme disease, recent illicit drug use (other than marijuana), pregnancy or breastfeeding, current metformin use, contraindications to metformin or medications likely to cause chronic fatigue, and uncontrolled comorbid psychiatric disorders (including depression or anxiety) associated with significant symptoms or requiring prohibited medications. Additional exclusion criteria are detailed in the protocol (available at Annals.org).

Randomization and Masking

Participants were randomly assigned in a 1:1:1 ratio to fluvoxamine, metformin, or matching placebo using a centralized, web-based randomization system stratified by site with variable block sizes. Placebo tablets were manufactured to be indistinguishable from active medications in appearance, packaging, and schedule; no separate matching algorithm beyond randomization was used. Study medications were administered orally twice daily for 60 days. Participants, site personnel, investigators, and outcome assessors were blinded to treatment allocation. Participants with diabetes who were receiving long-term metformin therapy were not eligible for the metformin group and were enrolled only in the fluvoxamine or placebo group. Participants receiving long-term metformin assigned to the placebo group were excluded from comparisons with the metformin group.

Interventions and Follow-up

Participants received oral metformin extended-release (750 mg twice daily), oral fluvoxamine (100 mg twice daily), or oral matching placebo for 60 days. Study drugs were dispensed at the baseline visit, with adherence monitored via pill counts and self-report at each follow-up. Concomitant medications were recorded throughout the study.

Outcomes

The primary outcome was change in FSS score from baseline to day 60. The FSS is a validated 9-item self-reported measure of fatigue severity, with each item scored on a 7-point Likert scale; the total score is calculated as the mean of the 9 item scores (range, 1 to 7), with higher scores indicating greater fatigue. The trial was powered to detect a 0.45-point reduction in FSS score, informed by prior work with the FSS in chronic fatigue–related conditions (23).

Secondary outcomes included change in FSS score at day 90; quality of life, assessed by the 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L) at days 30, 60, and 90; longitudinal analysis of FSS score over time; and recovery (defined as recorded FSS score <3). Safety end points included incidence of adverse events and serious adverse events.

Safety Monitoring

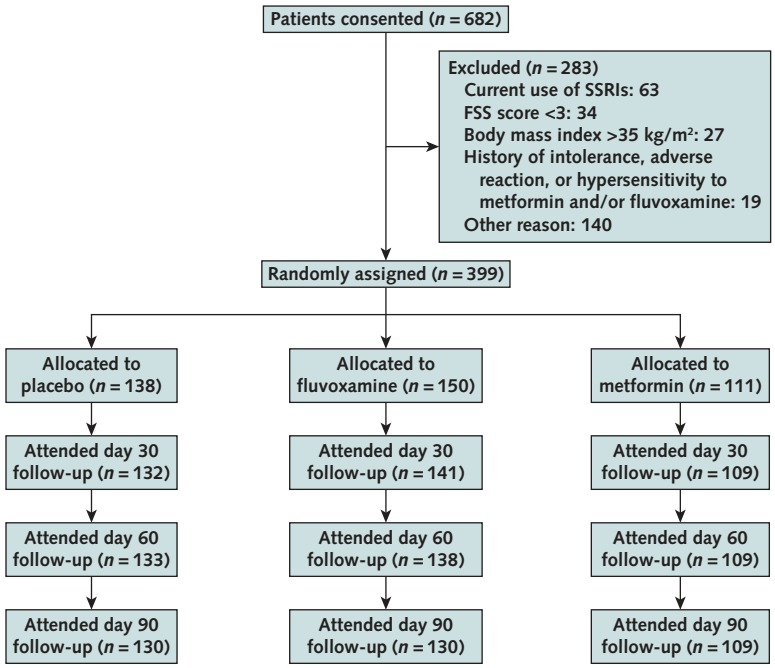
Safety assessments were conducted at all follow-up visits and included physical examination, vital signs, and structured adverse event queries. Adverse events were graded using the Common Terminology Criteria for Adverse Events, version 5.0 (24). Serious adverse events were defined per standard regulatory criteria.

An independent data safety and monitoring committee (DSMC) performed periodic safety and efficacy reviews based on prespecified interim analyses. The DSMC had authority to recommend trial modification or discontinuation. All serious adverse events and end points were reviewed by a blinded adjudication committee to ensure consistency across study sites.

Statistical Analysis

The trial followed a Bayesian adaptive design that included early stopping rules due to both futility and established treatment efficacy; details are provided in the statistical analysis plan and the adaptive trial report (both available at Annals.org). Primary analyses were done within each treatment group using a Bayesian

Figure 1. Flow of patients through the trial.



All patients completed their allocated duration. FSS = Fatigue Severity Scale; SSRI = selective serotonin reuptake inhibitor.

linear model with the default weakly informative treatment effect prior distributions implemented in the R brms library (25). Models were adjusted for baseline FSS score, site, age, and sex. Missing data were addressed using multiple imputation by chained equations with 20 imputations, implemented in the R mice package (26). The imputation model included all analysis variables, treatment group, and time indicators. For each imputed data set, we derived an independent posterior sample using the Markov chain Monte Carlo (MCMC) method. These posterior samples were then pooled by combining all MCMC draws across imputations, and Bayesian inferences (posterior means, credible intervals [CrIs], and probabilities) were derived (27). Detailed annotated code is provided in the **Supplement** (available at Annals.org).

Efficacy was expressed as posterior probability of superiority relative to placebo. Interim analyses were scheduled at 25%, 50%, and 75% of the target sample size; 2 of 4 planned analyses were conducted. Adaptive stopping criteria for efficacy and futility were prespecified. For the dichotomous outcome of recovery (FSS score <3), we fit a Bayesian logistic regression model and obtained risk ratios via regression standardization. Bayesian Tobit regression was used to analyze EQ-5D-5L utilities, which are bounded at 1.0 and showed clear clustering at the upper bound (28).

In an exploratory sensitivity analysis to test whether FSS score reduction was driven by improvement in depression symptoms alone, we fit a regression model for day 60 FSS score that included an interaction term between treatment assignment and baseline anxiety/depression dimension of the EQ-5D-5L. In addition, we modeled the anxiety/depression dimension itself as an ordered outcome at days 30, 60, and 90 using proportional odds regression, adjusted for baseline anxiety/depression and all prespecified covariates.

Longitudinal trajectories of FSS score over days 0 to 90 were analyzed using a Bayesian linear mixed model with a random intercept for each participant and time modeled as days since randomization, and inference was conducted on the treatment-by-time interaction to test the departure of the treatment trajectories from that of the placebo group.

All models were adjusted for baseline FSS score, site, age, and sex, except for the longitudinal model where baseline FSS scores were used as time 0 observations. Results were summarized using posterior means and 95% CrIs. In addition, prespecified subgroup analyses assessed potential heterogeneity of the day 60 treatment effect by age (<50 vs. ≥50 years), sex, vaccination status (0 vs. ≥1 dose), obesity, and diabetes (**Supplement Figures 4** and **5**, available at Annals.org).

All analyses followed CONSORT (Consolidated Standards of Reporting Trials) reporting standards and were conducted on the intention-to-treat population. Statistical analyses were performed using R, version 4.4.2 (R Foundation for Statistical Computing), including the gsbDesign library for adaptive design evaluation (29). Ethical approval was obtained from

Table 1. Characteristics of Patients in Each Treatment Group of the Trial

Characteristic	Treatment Group*		
	Fluvoxamine (*n* = 150)	Metformin (*n* = 111)	Placebo (*n* = 138)
Sex, *n (%)*			
Female	115 (76.7)	92 (82.9)	118 (85.5)
Male	35 (23.3)	19 (17.1)	20 (14.5)
Median age (range), *y*	44.0 (19.0–75.0)	45.0 (18.0–85.0)	44.0 (18.0–70.0)
Smoking status, *n (%)*			
Smoker	16 (10.7)	10 (9.0)	18 (13.0)
Former smoker	16 (10.7)	13 (11.7)	15 (10.9)
Nonsmoker	118 (78.7)	88 (79.3)	103 (74.6)
Missing	0 (0)	0 (0)	2 (1.4)
Median screening FSS score (range)	5.60 (3.00–7.00)	5.60 (3.00–7.00)	5.90 (3.10–7.00)
Ethnicity, *n (%)*			
Hispanic or Latino	150 (100)	111 (100)	135 (97.8)
Not Hispanic or Latino	0 (0)	0 (0)	1 (0.7)
Missing	0 (0)	0 (0)	2 (1.4)
COVID-19 vaccine doses, *n (%)*			
0	77 (51.3)	41 (36.9)	56 (40.6)
1	4 (2.7)	0 (0)	1 (0.7)
2	10 (6.7)	13 (11.7)	12 (8.7)
≥3	59 (39.3)	57 (51.4)	69 (50.0)
Median time since most recent episode (IQR), *d*	870 (511–1120)	692 (462–1090)	708 (403–1040)
Missing, *n (%)*	4 (2.7)	1 (0.9)	3 (2.2)
Obesity, *n (%)*	30 (20.0)	25 (22.5)	40 (29.0)
Diabetes, *n (%)*†	11 (7.3)	2 (1.8)	9 (6.5)
Hypertension, *n (%)*	32 (21.3)	29 (26.1)	36 (26.1)
Cardiovascular disease, *n (%)*	2 (1.3)	0 (0)	1 (0.7)
Lung disease, *n (%)*	0 (0)	1 (0.9)	0 (0)
Cancer, *n (%)*	0 (0)	1 (0.9)	3 (2.2)
Any risk factor, *n (%)*	95 (63.3)	78 (70.3)	95 (68.8)

FSS = Fatigue Severity Scale.
* Imbalance in treatment groups is due to adaptive design and early cessation of the metformin group.
† The metformin group was reserved for persons not already receiving this drug.

relevant institutional review boards, and all participants provided written informed consent before enrollment.

Role of the Funding Source

The funder had no role in the design, conduct, analysis, or submission of the study.

RESULTS

We enrolled a total of 399 participants between 18 October 2023 and 10 February 2025 and randomly assigned them to fluvoxamine (*n* = 150), metformin (*n* = 111), or placebo (*n* = 138) (**Figure 1**). The DSMC recommended stopping the metformin group after the first interim analysis for futility on 18 September 2024 and stopping the fluvoxamine group for superiority on 19 February 2025.

Baseline characteristics were well balanced across groups (**Table 1**). The median age was 44 years (range, 18 to 85 years). Median screening FSS scores ranged from 5.6 to 5.9 across groups.

Table 2 reports the primary end point (change in FSS score from baseline to day 60). Fluvoxamine reduced fatigue compared with placebo, with a mean treatment effect (difference in change from baseline relative to placebo) of −0.43 points (95% CrI, −0.80 to −0.07 points) and a 99.0% posterior probability of superiority. This benefit was sustained at day 90 (secondary end point), with a mean difference of −0.58 (CrI, −0.98 to −0.16) and a 99.7% probability of superiority (**Supplement Figure 1**, available at Annals.org). Metformin showed no evidence of benefit (day 60 treatment effect, −0.03 [CrI, −0.42 to 0.37; probability, 56.0%]; day 90 treatment effect, −0.04 [CrI, −0.47 to 0.38; probability, 57.8%]). **Supplement Figure 3** (available at Annals.org) shows the longitudinal effects over days 0 to 90, with item-specific plots shown in **Figure 2**.

For secondary outcomes (**Table 3**), fluvoxamine improved EQ-5D-5L scores at day 30 (0.10 [CrI, 0.05 to 0.15]), day 60 (0.06 [CrI, 0.01 to 0.11]), and day 90 (0.07 [CrI, 0.00 to 0.14]), with posterior probabilities of superiority of 100.0%, 98.8%, and 98.2%, respectively. Metformin showed a small improvement at day 30 but not at later time points.

Recovery (FSS score <3) was more frequent with fluvoxamine than placebo, with standardized risk ratios of 1.48 at day 30, 1.36 at day 60, and 1.19 at day 90 (posterior probability of superiority at day 90 was 99.6%). For metformin, risk ratio CrIs included 1.0 at all time points.

Prespecified subgroup analyses (**Supplement Figures 4** and **5**) assessed heterogeneity of the day 60 treatment effect on FSS score by age (<50 vs. ≥50 years), sex, vaccination status (0 vs. ≥1 dose), obesity, and diabetes. For metformin, subgroup-specific estimates were generally close to the overall null effect and were imprecise, with CrIs spanning no effect across all strata. For fluvoxamine, subgroup-specific estimates were consistently in the direction of benefit, with overlapping CrIs across strata and no meaningful effect modification.

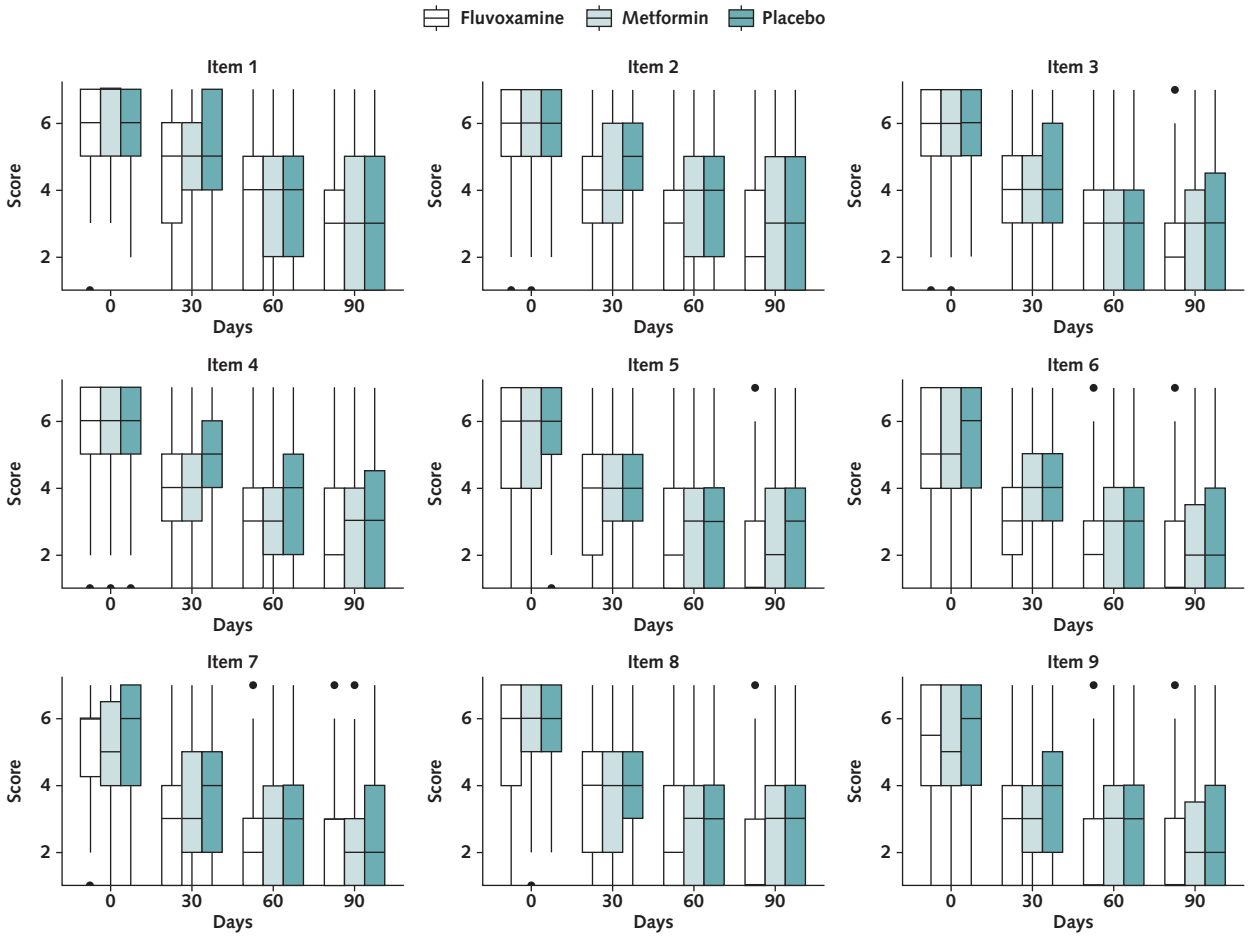
In exploratory analyses examining whether baseline anxiety/depression modified the treatment effect on fatigue, we found no evidence of interaction (treatment-by-baseline anxiety/depression interaction term centered

Table 2. Recovery (FSS Score <3) at 30, 60, and 90 Days

Day	Product	Risk Ratio (95% CrI)	Posterior Probability of Superiority, %
30	Metformin	1.11 (0.66–1.74)	61.3
	Fluvoxamine	1.48 (0.96–2.23)	96.2
60	Metformin	1.09 (0.83–1.41)	72.8
	Fluvoxamine	1.36 (1.08–1.71)	99.6
90	Metformin	0.96 (0.78–1.17)	33.5
	Fluvoxamine	1.19 (1.00–1.41)	97.8

CrI = credible interval; FSS = Fatigue Severity Scale.

Figure 2. Box plots of the distributions of the individual items comprising the FSS score at days 0, 30, 60, and 90, by treatment group.



FSS = Fatigue Severity Scale.

near zero, with the 95% CrI crossing zero). When the EQ-5D-5L anxiety/depression dimension was modeled as an outcome, fluvoxamine showed high posterior probabilities of improvement at days 30, 60, and 90 (≥97.6% at all time points), whereas metformin did not show consistent benefit (**Supplement Figure 1**).

Safety profiles were favorable across all groups. Adverse events occurred in 20.0% of participants in the fluvoxamine group, 28.8% in the metformin group, and 29.7% in the placebo group (**Table 4**). Grade 3 or higher adverse events were rare and occurred at similar frequencies across groups. Serious adverse events were uncommon, and no treatment-related deaths occurred.

Discussion

In this randomized, placebo-controlled, adaptive trial in Brazil, fluvoxamine reduced fatigue severity compared with placebo among adults with long COVID–related fatigue as measured by the FSS at day 60, with sustained benefit through day 90. Improvements in health-related quality of life, assessed via the EQ-5D-5L, were also observed across all time points. These findings suggest that fluvoxamine may have a beneficial role in the clinical management of fatigue in long COVID, although the condition encompasses a broad range of clinical manifestations beyond fatigue alone.

Quality-of-life improvements, assessed using the EQ-5D-5L, were consistent with the findings of

Table 3. Treatment Effect at 30, 60, and 90 Days on the Secondary Outcome of Improvement in Quality of Life (EQ-5D-5L)

Day	Product	Treatment Effect (95% CrI)	Posterior Probability of Superiority, %
30	Metformin	0.05 (0.00 to 0.11)	97.7
	Fluvoxamine	0.10 (0.05 to 0.15)	100.0
60	Metformin	0.01 (−0.04 to 0.07)	68.3
	Fluvoxamine	0.06 (0.01 to 0.11)	98.8
90	Metformin	−0.03 (−0.10 to 0.04)	20.0
	Fluvoxamine	0.07 (0.00 to 0.14)	98.2

CrI = credible interval; EQ-5D-5L = 5-level EuroQol 5-dimensional questionnaire.

Table 4. Adverse Events, by Severity

Product	Patients, *n*	Adverse Events, *n (%)*				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Placebo	138	0	9 (6.5)	37 (26.8)	2 (1.4)	1 (0.7)
Metformin	111	0	6 (5.4)	43 (38.7)	0 (0.0)	0 (0.0)
Fluvoxamine	150	0	5 (3.3)	27 (18.0)	4 (2.7)	0 (0.0)

reductions in fatigue. Fluvoxamine showed sustained benefit across all time points, with effect estimates ranging from 0.06 to 0.10 and posterior probabilities of superiority between 98.2% and 100.0%. The concordance between the disease-specific fatigue reduction and broader health-related quality-of-life improvement supports the clinical relevance of the observed treatment effects. Rather than implying modification of underlying long COVID pathophysiology, the observed benefits may reflect improvements in overall well-being, symptom perception, or functional capacity.

However, this trial was not designed to evaluate whether these effects are causally linked or mediated through specific biological pathways. Given the association of depression with fatigue, we should note that patients with a diagnosis of major depressive disorder or those taking antidepressant medications were excluded from this trial. However, participants with depressive symptoms (in the absence of a formal major depressive disorder diagnosis) were not excluded, reflecting the real-world comorbidity of mood symptoms in long COVID. This design choice was intentional as persons with long COVID have varying degrees of mood symptoms (30), and excluding people with depressive symptoms would have biased the sample. We did not assess whether the observed reduction in fatigue reflects improvement in depression (major disorder or symptoms) or effects mediated through nonmood pathways relevant to the pathophysiology of long COVID. We acknowledge that fatigue is a multidimensional symptom that occurs independent of depression and is associated with nonpsychiatric conditions such as postviral syndromes, inflammatory disorders, and chronic fatigue syndrome. Clarifying these relationships will require future studies incorporating structured psychiatric assessments and biological measures.

We report effect sizes and posterior probabilities instead of less informative binary statistical significance to support the interpretation of clinical importance. The estimated mean differences in FSS score were clinically meaningful in magnitude, and a higher proportion of fluvoxamine-treated participants achieved an FSS score below 3 at days 60 and 90. Although CrIs around some subgroup estimates were wide, the overall pattern of results consistently favored fluvoxamine. In contrast, metformin did not show a consistent or sustained therapeutic effect on fatigue. Although a modest signal for improved quality of life was observed at day 30, this effect diminished by days 60 and 90, and the posterior probability of superiority also decreased. This trial does not support treatment with metformin for long COVID fatigue. This contrasts with a study suggesting a lower risk for developing long COVID symptoms when metformin is taken during acute SARS-CoV-2 infection (17). Similarly, trials of antiviral therapy, including nirmatrelvir–ritonavir, have shown inconsistent effects on the development of long COVID symptoms, as exemplified by the STOP-PASC trial (31). Other candidate therapies, such as low-dose naltrexone, aripiprazole, and sulodexide, are under investigation. In a recently published clinical trial evaluating nicotinamide riboside versus placebo, no significant improvement was observed in cognition, fatigue, sleep, or mood (23, 32). These findings underscore ongoing uncertainty about effective treatment for long COVID and highlight the need for rigorously designed randomized trials.

Strengths of this study include the randomized, placebo-controlled, adaptive design; high participant retention; and validated outcome measures. The Bayesian analytic framework offered clinically interpretable probabilities of treatment benefit even under adaptive conditions, while decision boundaries were derived to still meet frequentist type I error rate requirements. The platform trial design, implemented under a master protocol, allowed efficient evaluation of multiple therapeutic agents, although no additional interventions were introduced during the study period.

Several limitations merit consideration. Although the trial was conducted across multiple clinical sites, all participants were enrolled in Brazil, potentially limiting generalizability to other populations with long COVID. Fatigue was measured by the FSS, a validated and widely used tool. However, as a self-reported measure, it may be influenced by participant expectations, mood, or other subjective factors. This trial did not assess biological correlates of response, such as inflammatory or metabolic biomarkers or self-reported measures of depression, which could have helped to elucidate mechanistic pathways. Long COVID is a heterogeneous condition with diverse clinical presentations; although fatigue is a common symptom, it is not the only symptom. Finally, early stopping of the trial, as recommended by the DSMC, reduced precision, particularly for metformin, such that clinically important benefit cannot be excluded. For fluvoxamine, the observed effect favored benefit, but uncertainty remains.

In summary, this trial offers support for fluvoxamine in reducing fatigue severity and improving quality of life in people with long COVID and should lead to

further investigation in a broader, phenotype-informed therapeutic framework. Future trials should incorporate standardized assessments of depression, anxiety, at baseline and follow-up, alongside inflammatory and metabolic biomarkers, to clarify mechanisms and identify subgroups most likely to benefit.

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Author contributions are available at Annals.org.

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