Vortioxetine for Cognitive Impairment in Major Depressive Disorder During Post-COVID Syndrome:

Real-World Evidence

Hernan F. Guillen-Burgos, MD, MSc; Juan F. Galvez-Florez, MD; Sergio Moreno-López, PhD; Juan-Manuel Anaya, MD, PhD; Angela T.H. Kwan, MSc; and Roger S. McIntyre, MD, FRCPC

Abstract

Objective: To compare the effectiveness of vortioxetine versus escitalopram and sertraline as a treatment in individuals with major depressive disorder (MDD) and post-COVID syndrome (PCS).

Methods: This is a prospective, open-label, comparative effectiveness study in individuals with new-onset MDD as PCS outcome. The study was carried out in 1 clinical site. Individuals who had a history of confirmed SARS-CoV-2 infection, who met World Health Organization–defined criteria for PCS, and who met new-onset of MDD criteria according to *DSM-5-TR* were included. Participants that were eligible were assigned to receive vortioxetine at 10–20 mg/d, escitalopram 10–20 mg/d, or sertraline 50–200 mg/d over 8 weeks. The primary and secondary outcomes were changes from baseline to end point in Digital Symbol Substitution Test (DSST) and Montgomery-Asberg Depression Rating Scale (MADRS) or Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a (PROMIS 7a), respectively. Data were collected during January 2022 and December 2023.

Results: 140 participants were assigned to received vortioxetine (n = 70), escitalopram (n = 36), or sertraline (n = 34). Participants assigned to vortioxetine exhibited significant changes in DSST scores from baseline to end point compared to escitalopram or sertraline (least squares [LS] mean differences, 8.25; 95% CI, 6.25–10.25; $P < .001$; LS mean differences, 8.00; 95% CI, 5.95–10.06; $P < .001$, respectively). Participants in the vortioxetine treatment group reported significantly greater changes in total MADRS scores from baseline to end point compared to escitalopram or sertraline (LS mean differences, −4.06; 95% CI, −4.92 to −3.20; $P < .001$; LS mean differences, −3.94; 95% CI, −4.83 to −3.06; $P < .001$, respectively).

Conclusion: Vortioxetine has a significant procognitive effect. Antidepressant effects and improvement in fatigue symptoms (PROMIS 7a) also were observed.

J Clin Psychiatry 2025;86(2):24m15387

Author affiliations are listed at the end of this article.

Post-COVID syndrome (PCS), or long COVID, is a multisystemic complication that usually occurs 3 months after a SARS-CoV-2 infection, persists for at least 2 months, and cannot be explained by an alternative diagnosis.[1] The incidence of PCS ranges from 10% to 70%, depending on the definition, with most estimates at approximately 20%.[2]

PCS encompasses symptoms across multiple organ systems with differing pathology.[3] Cognitive impairment and neuropsychiatric disorders are among the most common enduring and debilitating findings in individuals with persistent post-COVID symptoms.[4–7] In this context, mood disorders have been shown to have an increased risk after SARS-CoV-2 infection in both retrospective and prospective studies.[5,8,9]

Mood disorders are the leading mental illnesses worldwide, contributing to a higher burden of disease and an increased risk for disability and suicide.[10] According to different studies, cognitive decline and mood alterations reduce quality of life and may contribute to the burden of disease attributable to PCS.[11] However, there are no approved or established therapeutic options to manage cognitive impairment comorbid with mood disturbances in individuals who have experienced PCS. Although antidepressants, such as the multimodal agent vortioxetine, have recently been developed with proven

Scan Now

See supplementary material for this article at Psychiatrist.com

Editor's Note

We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at psychiatrist.com/contact/goldberg.

Clinical Points

- Post-COVID syndrome (PCS) is associated with cognitive impairment and mood disorders, yet treatment strategies are underexplored. This study highlights vortioxetine as a promising option, addressing an urgent need for evidence-based interventions in this population.
- Vortioxetine showed superior efficacy in improving cognitive function and depressive symptoms compared to SSRIs in patients with PCS-related major depressive disorder (MDD). Clinicians might consider it a first-line treatment option for managing these dual challenges.
- Elevated inflammatory markers during SARS-CoV-2 infection may predict better responses to vortioxetine. Future treatments for PCS-related MDD should incorporate biomarker-based stratification for optimized outcomes.

effects on the recovery of cognitive function in individuals with major depressive disorder (MDD),[12,13] the effects in PCS have not been evaluated using real-world data in large samples.

A recently published randomized controlled trial (RCT) showed that vortioxetine may improve cognitive function in individuals with PCS and elevated[11] CRP levels at baseline. Additionally, this study demonstrated significant improvements in depressive symptoms and health-related quality of life.[11] Therefore, the effect of vortioxetine in individuals with PCS may be associated with a better response in those with an activated immune response or a robust immune-inflammatory response during SARS-CoV-2 infection.

In this context, we conducted a prospective, comparative effectiveness study of vortioxetine compared to 2 selective serotonin reuptake inhibitors (SSRIs), escitalopram and sertraline, as treatment for individuals with MDD and PCS.

MATERIALS AND METHODS

Design and Settings

This is a prospective, open-label, comparative effectiveness study of vortioxetine vs 2 SSRIs, escitalopram and sertraline, over 8 weeks in individuals with new-onset MDD as PCS outcome. The study was carried out in 1 clinical site (Center for Clinical and Translational Research, Colombia) during January 2022 and December 2023. Sample size was calculated according to effect sizes of vortioxetine on Digital Symbol Substitution Test (DSST) cognitive function in MDD, which have been estimated around Cohen *d* of 0.2–0.5.[11,13]

Participants

A cohort of COVID-19 survivors derived from a teaching hospital affiliated to the Center for Clinical and Translational Research with new onset of MDD, and subjective cognitive complaints as PCS sequelae were recruited for study assessments. A prescreening visit considered a cutoff point of Montgomery-Asberg Depression Rating Scale (MADRS) ≥26 as positive for moderate-to-severe symptoms of depression. Then, participants with the following inclusion criteria were eligible: adults aged 18–64 years with new-onset MDD diagnosed within 12 months of recovering from SARS-CoV-2 infection. Participants who were included met World Health Organization–defined criteria for PCS evidenced by physical, mental, or cognitive subjective complaint occurring within 3 months after acute SARS-CoV-2 infection and additionally met criteria for new onset of MDD according to *DSM-5-TR* evaluated with the Structured Clinical Interview for *DSM-5* (SCID-5-CV). Participants were excluded if they had pre-existing neurological or psychiatric conditions that may cause cognitive impairment, adjustment disorder, substance use disorders, any medication for a general or mental disorder that may affect cognitive function, dyslexia, intellectual disability disorders, pregnancy or breastfeeding, previous history of mania or hypomania, seizures, or active suicide ideation or behavior. Participants with autoimmune disease were also excluded. For our recruitment strategy, the outreach methods included targeted advertisements, referral networks within healthcare systems, and community-based awareness campaigns.

Participants that were eligible were assigned according to clinical judgment by a psychiatrist to receive vortioxetine at 10 mg/d during weeks 1 and 2, and 20 mg/d from weeks 3–8, or escitalopram 10 mg/d during weeks 1 and 2, and 20 mg/d from weeks 3–8, or sertraline 50 mg/d during weeks 1 and 2, and 100–200 mg/d from weeks 3–8. For participants with intolerance to higher doses, down-titration according to clinical judgment was permitted.

Clinical Assessments

A screening visit was performed to identify possible eligible participants. This visit consisted of SCID-5-CV, medical evaluation, and clinical laboratory testing. Individuals who fulfilled the eligibility criteria were allocated by a psychiatric judge to initiate vortioxetine, escitalopram, or sertraline at the previously mentioned dosages. The baseline assessment was completed at visit 1, and from week 8 onward, clinical assessments were conducted every 2 weeks. Participants completed the clinical assessments according to the study protocol.

Clinical scales used during this study were the DSST, Perceived Deficits Questionnaire–Depression (PDQ-D), Montgomery-Asberg Depression Rating Scale (MADRS), Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a (PROMIS 7a), and Columbia-Suicide Severity Rating Scale (C-SSRS).

DSST is a cognitive test that requires individuals to match symbols to numbers according to a key located at the top of the page. The participants select the corresponding symbol as fast as possible. The number of correct symbols within 90 seconds is recorded. This test has been used widely to detect a range of cognitive operations.[14] Previously, DSST has been used in clinical studies evaluating vortioxetine's effect in MDD.[11–13] Therefore, the DSST was selected due to its sensitivity in assessing attention, processing speed, and executive functioning, key domains commonly impaired in PCS. As a brief yet reliable tool, it minimizes participant burden while capturing meaningful cognitive changes.

The PDQ-D is a 20-item brief patient-rated scale to assess subjective cognitive complaint in individuals with MDD.[15] PDQ-D has been validated with an excellent internal consistency in the subscales (Cronbach α: .81–.96).[15]

The MADRS is a widely used clinician-rated measure of depressive severity.[16,17] Previously, MADRS has been used in RCT evaluating vortioxetine in MDD.[13] The MADRS has been validated in Colombia with and excellent internal consistency with a Cronbach α of 0.92.[18]

The PROMIS 7a evaluates a variety of self-reported symptoms, ranging from minor subjective fatigue to severe. A standardized score with a mean of 50 and a standard deviation (SD) of 10 is created by rescaling the raw score using the T-score. Higher t-score values represent worse fatigue symptoms, and lower t-score values represent better fatigue symptoms. PROMIS has been used to evaluate post-COVID symptoms.[19] The short form for adults to evaluate fatigue (PROMIS 7a) has demonstrated good internal consistency reliability (Cronbach α = .84).[20]

Primary Outcome

Change from baseline to end point (Week 8) in DSST score was considered as the primary outcome.

Secondary Outcome

Changes from baseline to end point (Week 8) in MADRS score and PROMIS 7a were considered as secondary outcomes.

Safety and Tolerability

Assessments included vital signs, physical examination, routinary clinical laboratory test, and reported adverse events. Suicidality was evaluated with the C-SSRS. The C-SSRS is a tool that uses 4 constructs (severity ideation, intensity ideation, behavior, and lethality).[21]

Cytokine Panel

Data regarding cytokine panel were obtained from the registry of COVID-19 survivors collected in the Center for Clinical and Translational Research for research purposes. Briefly, upon admission to the hospital during acute SARS-CoV-2 infection, blood samples were collected to measure routinary laboratory test and cytokines profile levels. Serum was obtained after centrifugation for 10 min at 2,000 rpm, and each serum sample was stored at −80°C until processing. A Human ProcartaPlex TM Multiplex Immunoassay Mix & Match of 7 – Plex based on magnetic beads was selected to detect serum proteins (Invitrogen, Whatman, Massachusetts). These analytes included interleukin (IL)-1 β, IL-4, IL-6, IL-8, IL-13, IL-17 α, and TNF-α. Undiluted samples were processed following the manufacturer instructions. Then, the analytes were analyzed using the Luminex 100/200 TM (ThermoFisher Scientific, Luminex Corporation 12212 Technology Blvd. Austin, Texas). All samples and standards were measured in duplicate. Primary data were analyzed using Xponet Software (Luminex, Austin, Texas).

Ethical Consideration

The study protocol was approved by Universidad Simon Bolivar Ethics Committee (protocol number: CEI-USB-CE-0324-00-00). All participants accepted and provided a written informed consent to participate. The study follows the Good Clinical Practices, Declaration of Helsinki, Belmont Report, and CIOMS.

Statistical Analysis

All statistical analyses were performed using Stata/SE version 18.0, with two-sided tests of significance conducted at an α level of 0.05. Results are reported with 95% confidence intervals (CIs) to provide measures of precision and reliability. The study follows the STROBE recommendations of equator network for observational studies.[22] A *t* test was used to compare hypothesis testing for continuous variables. An intent-to-treat analysis (ie, all assigned participants) was used to assess baseline-to-end point changes in the DSST, MADRS, and PROMIS 7a total scores.

The primary and secondary outcomes analyses were conducted using mixed-effects model for repeated measures (MMRM) analysis with treatment, visit, gender, age, and treatment-by-visit interaction included as covariables to examine the baseline-to-end point change in the mean score of DSST-measured cognitive function and MADRS-measured depressive symptoms. PROMIS 7a was also included as a secondary outcome and was measured using MMRM analysis. We employed MMRM for analyzing longitudinal data, as it accounts for missing data under the missing-at-random assumption and allows for flexibility in modeling changes over time. To ensure robustness, sensitivity analyses were performed, including adjustments for age, sex, and baseline severity of cognitive impairment. To address missing data in primary outcome analyses, the last observation carried forward method was used as an imputation model. This conservative approach ensures that missing values are replaced by the most recent available data point, maintaining the integrity of the

Table 1.

Baseline Characteristics in a Sample of PCS With MDD (n = 126)

Variable	Vortioxetine (n = 63)	Escitalopram (n = 33)	Sertraline (n = 30)	*P* value
Baseline characteristics				
Age (years), mean ± SD	40.3 ± 11.3	41.3 ± 13.7	40.0 ± 13.6	.878
Gender (male), n (%)	35 (55.6)	22 (66.7)	17 (56.7)	.559
Baseline CRP, mean ± SD	3.1 ± 2.8	2.9 ± 2.6	2.7 ± 3.1	.191
BMI (total score), mean ± SD	33.7 ± 5.2	33.0 ± 6.0	34.1 ± 4.6	.903
DSST (total score), mean ± SD	55.8 ± 4.2	55.3 ± 4.3	54.9 ± 6.0	.471
MADRS (total score), mean ± SD	27.5 ± 1.5	27.3 ± 1.6	27.6 ± 1.4	.816
CGI-S (total score), mean ± SD	4.98 ± 0.8	5.03 ± 0.9	5.1 ± 0.84	.313
PROMIS 7a (total score), mean ± SD	71.6 ± 12.6	69.7 ± 14.9	72.6 ± 10.5	.927
Prior interleukins during SARS-CoV-2 infection				
IL-1B, mean ± SD	62.1 ± 37.7	59.4 ± 39.7	62.7 ± 35.6	.913
IL-4, mean ± SD	63.3 ± 28.3	60.4 ± 30.8	64.4 ± 26.1	.904
IL-6, mean ± SD	23.9 ± 9.6	22.9 ± 10.5	24.3 ± 8.9	.923
IL-8, mean ± SD	65.2 ± 25.2	62.3 ± 28.2	66.3 ± 22.6	.917
IL-13, mean ± SD	20.7 ± 10.8	19.8 ± 11.4	21.0 ± 10.2	.920
IL-17, mean ± SD	42.9 ± 19.2	41.0 ± 21.0	43.5 ± 17.6	.916
TNF-α, mean ± SD	38.5 ± 16.9	37.2 ± 19.4	38.7 ± 14.0	.904

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impression-Severity, CRP = C-reactive protein, DSST = Digit Symbol Substitution Test, IL = interleukin, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, PCS = post-COVID syndrome, PROMIS 7a = Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a, TNF = tumor necrosis factor.

dataset while avoiding biases introduced by loss to follow-up. An unstructured covariance matrix was used to account for within-subject correlation. Between-group effect sizes were calculated with a least squares mean analysis to estimate the change from baseline to 8 weeks by both treatment and visit. Additionally, response rate (≥50% reduction in MADRS) and remission (MADRS ≤10) were obtained.

Adverse events were collected and reported as absolute and relative values. Plots were generated with ggplot2 packages in R free software.

RESULTS

There were no statistical significant differences between groups with respect to baseline sociodemographic and clinical characteristics of individuals with PCS and MDD, as shown in Table 1. Of the 215 participants enrolled who met prescreening, 140 (65.1%) were assigned to received vortioxetine (n = 70), escitalopram (n = 36), or sertraline (n = 34). During the 8-week open-label treatment period, 7 participants for vortioxetine, 3 participants for escitalopram, and 4 participants for sertraline dropped out for different reasons. None presented lethal adverse effects. The complete recruitment and enrollment summary is shown in Supplementary Figure 1.

Effectiveness

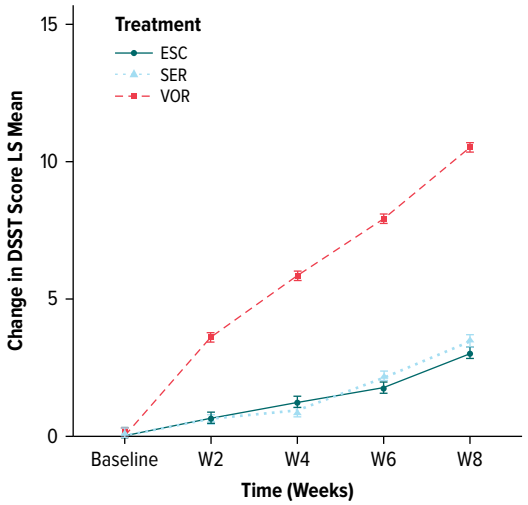
Primary end point. An adjusted MMRM analysis was conducted on 126 participants with PCS and MDD administered treatments according to the 3 groups. Participants assigned to vortioxetine exhibited significantly changes in DSST scores from baseline to week 8 compared to escitalopram or sertraline (LS mean differences, 8.25; 95% CI, 6.25–10.25; $P < .001$; LS mean differences, 8.00; 95% CI, 5.95–10.06; $P < .001$, respectively) (Figure 1). The baseline-to-end point mean change for DSST-measured cognitive function was −10.49 ± 0.10, $P < .001$ for vortioxetine. For escitalopram, it was −3.00 ± 0.32, $P < .001$, and for sertraline, it was −3.43 ± 0.28, $P < .001$ (Table 2).

Secondary end point. For MADRS-measured depressive symptoms, a significant treatment × time interaction ($\chi^2 = 242.4$, $P < .001$) was observed after adjusting for the covariables described above. Significant group ($\chi^2 = 107.6$, $P < .001$) and time ($\chi^2 = 2{,}624$, $P < .001$) effects were also observed. In this sense, participants' depressive symptoms improved over time and at significantly different rates within each treatment group (Figure 2). Participants in the vortioxetine arm reported significant changes in MADRS scores from baseline to week 8 compared to escitalopram or sertraline (LS mean differences, −4.06; 95% CI, −4.92 to −3.20; $P < .001$; LS mean differences, −3.94; 95% CI, −4.83 to −3.06; $P < .001$, respectively) (Figure 2). The baseline-to-end point mean change for MADRS-measured depressive symptoms was 11.31 ± 0.07, $P < .001$ for vortioxetine. For escitalopram, it was 6.36 ± 0.25, $P < .001$, and for sertraline, it was 6.00 ± 0.17, $P < .001$ (Table 2).

For PROMIS 7a-measured fatigue symptoms, a significant treatment × time interaction ($\chi^2 = 113.2$, $P < .001$) was observed after adjusting for the covariables described above. Significant group ($\chi^2 = 100.1$, $P < .001$) and time ($\chi^2 = 645.3$, $P < .001$)

Figure 1.

Changes in LS Mean Score of DSST in Individuals With PCS and MDD



Abbreviations: DSST = Digit Symbol Substitution Test, ESC = escitalopram, LS = least squares, MDD = major depressive disorder, PCS = post-COVID syndrome, SER = sertraline, VOR = vortioxetine.

effects were also observed. In this sense, participants' fatigue symptoms improved over time and at significantly different rates within each treatment group (Supplementary Figure 2). Participants in the vortioxetine arm reported significant changes in PROMIS 7a scores from baseline to week 8 compared to escitalopram or sertraline (LS mean differences, −8.02; 95% CI, −9.92 to −4.50; $P < .001$; LS mean differences, −6.46; 95% CI, −7.83 to −4.90; $P < .001$, respectively) (Supplementary Figure 2). The baseline-to-end point mean change for PROMIS 7a-measured fatigue symptoms was 30.02 ± 0.27, $P < .001$ for vortioxetine. For escitalopram, it was 21.35 ± 0.25, $P < .001$, and for sertraline, it was 22.95 ± 0.27, $P < .001$.

Safety

The total of participants who reported treatment adverse events was 17.46% (11 participants) for vortioxetine, 18.2% for escitalopram, and 26.7% for sertraline. Of those who reported adverse effects in the vortioxetine, escitalopram, or sertraline groups, nausea was the most common (45.5%, 50.0%, 37.5%, respectively), followed by dizziness (36.3%, 33.3%, 25.0%, respectively), dry mouth (27.3%, 16.7%, 25.0%), diarrhea (18.2%, 0%, 12.5%), and constipation (1%, 0%, 0%, respectively).

Response Rate and Remission

After 8 weeks of treatment, the rate of response in vortioxetine arm was 81% and remission rate was 36.5%. For escitalopram, the response rate was 33.3% and remission rate was 12.1%, and for sertraline, the response rate was 30% and remission rate was 16.6% (Supplementary Figure 3).

DISCUSSION

To our knowledge, this is the first prospective, open-label, head-to-head, real world comparative effectiveness study comparing vortioxetine to other first-line SSRIs in individuals with depressive symptoms as a PCS outcome. Our results highlight a significant change in cognitive function as primary outcome (DSST) and reduced depressive symptoms as secondary outcome (MADRS) at week 8 in participants treated with vortioxetine compared to escitalopram or sertraline. Also, our findings show an improvement in psychosocial function mediated by fatigue. Finally, the antidepressant response rate and remission rates of symptoms were higher in the vortioxetine group than in the SSRI groups.

A recent RCT published by the authors showed that vortioxetine improved cognitive function and depressive symptoms compared to placebo group using CRP levels as a moderator.[11] In this sense, the hypothesized biological model of cognitive dysfunction in PCS mediated by immune-inflammatory dysregulation indirectly supports the notion that vortioxetine's anti-inflammatory and immunomodulatory effects may contribute to its mechanisms of action.[23] Our sample evidenced higher mean levels of pro-inflammatory cytokines during previous SARS-CoV-2 infection; therefore, individuals with a prior activated immune response in the context of COVID-19 who develop MDD as a PCS outcome may experience greater improvements in cognitive function and depressive symptoms when treated with vortioxetine compared to SSRIs.

As depression is a common symptom during PCS,[2] and cognitive dysfunction has previously been established in MDD,[12,24–26] a common treatment approach is the use of SSRIs in PCS depression. A prospective study that evaluated SSRIs' efficacy in PCS depression showed that SSRIs have a rapid antidepressant effect in most of these individuals.[27] SSRI treatment may have a positive effect on cognition measures among depressed participants as shown in a meta-analysis published by Prado et al.[28] Nevertheless, vortioxetine, a multimodal antidepressant, has demonstrated efficacy in adult patients with MDD according to several studies.[29–31] Also, the efficacy of vortioxetine for cognitive function and depressive symptoms has been demonstrated in RCT published previously.[12,13,32] However, there are no head-to-head studies comparing vortioxetine vs other antidepressants in long COVID–associated depression. Notwithstanding, vortioxetine has been shown to be effective in MDD with other medical comorbidities, eg, diabetes mellitus, cardiovascular disease, Alzheimer disease, and Parkinson disease.

Table 2.
Mean Changes in Primary and Secondary Outcomes in Individuals With PCS and MDD Treated With Vortioxetine vs Escitalopram vs Sertraline

	Week 2		Week 4		Week 6		Week 8	
Outcome	Mean change	*P* value	Mean change	*P* value	Mean change	*P* value	Mean change	*P* value
Vortioxetine (n = 63)								
DSST	−3.57 ± 0.15 [−3.87 to −3.26]	<.001	−5.80 ± 0.13 [−6.05 to −5.53]	<.001	−7.88 ± 0.14 [−8.18 to −7.59]	<.001	−10.49 ± 0.10 [−10.69 to −10.28]	<.001
MADRS	5.55 ± 1.91 [5.17 to 5.93]	<.001	6.60 ± 0.13 [6.33 to 6.87]	<.001	9.65 ± 0.13 [9.37 to 9.92]	<.001	11.31 ± 0.07 [11.16 to 11.47]	<.001
PROMIS 7a	10.63 ± 1.03 [10.01 to 11.03]	<.001	15.57 ± 1.51 [14.63 to 15.98]	<.001	23.27 ± 1.01 [22.20 to 23.35]	<.001	30.02 ± 0.09 [29.05 to 31.03]	<.001
Escitalopram (n = 33)								
DSST	−0.63 ± 0.08 [−0.80 to −0.46]	<.001	−1.12 ± 0.15 [−1.43 to −0.80]	<.001	−1.75 ± 0.25 [−2.27 to −1.24]	<.001	−3.00 ± 0.32 [−3.65 to −2.34]	<.001
MADRS	2.51 ± 0.31 [1.86 to 3.16]	<.001	3.54 ± 0.31 [2.89 to 4.19]	<.001	4.42 ± 0.26 [3.89 to 4.95]	<.001	6.36 ± 0.25 [5.84 to 6.87]	<.001
PROMIS 7a	7.34 ± 1.96 [6.54 to 8.02]	<.001	11.02 ± 1.34 [10.41 to 11.38]	<.001	17.03 ± 1.46 [16.00 to 18.17]	<.001	21.35 ± 1.38 [20.53 to 21.93]	<.001
Sertraline (n = 30)								
DSST	−0.56 ± 0.09 [−0.75 to −0.37]	<.001	−0.93 ± 0.15 [−1.25 to −0.60]	<.001	−2.06 ± 0.28 [−2.65 to −1.47]	<.001	−3.43 ± 0.28 [−4.01 to −2.84]	<.001
MADRS	2.50 ± 0.36 [1.76 to 3.23]	<.001	3.53 ± 0.25 [3.00 to 4.05]	<.001	4.70 ± 0.28 [4.12 to 5.27]	<.001	6.00 ± 0.17 [5.63 to 6.36]	<.001
PROMIS 7a	9.30 ± 1.01 [8.93 to 10.02]	<.001	13.67 ± 0.07 [13.04 to 13.99]	<.001	18.76 ± 1.33 [17.54 to 18.93]	<.001	22.95 ± 1.09 [22.00 to 23.36]	<.001

Abbreviations: DSST = Digit Symbol Substitution Test, IL = interleukin, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, PCS = post-COVID syndrome, PROMIS 7a = Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a.

Our findings suggest a robust improvement after 8-week treatment with vortioxetine when compared to escitalopram or sertraline. Preclinical studies have reported that vortioxetine mediates the pro-inflammatory response in hippocampus in rodent models with a cognitive and depressive-like behavior.[33] Vortioxetine increased levels of mRNA and the expression of genes related with transcription factors, signal transduction, neuroplasticity, and neurotransmission, especially in neuroanatomical area of hippocampal in mice models.[34–36] In these animal models with visuospatial memory impairment and depressed-like behavior, vortioxetine but not fluoxetine, another SSRI, decreased depression-like behavior, which is consistent with the clinical findings that elderly patients have a lower response to SSRIs.[37]

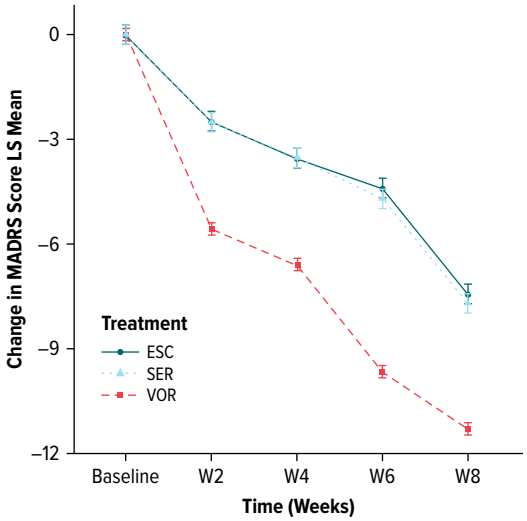
Other in vitro electrophysiological studies have observed that vortioxetine enhances synaptic transmission inducing long-term potentiation and counteracted the 5-HT–induced spontaneous inhibitory postsynaptic currents in hippocampal pyramidal neurons, unlike sertraline, which does not achieve this effect.[38] Another important preclinical findings regarding cognitive impairment attributed to vortioxetine and not to SSRIs such as escitalopram is reversed memory impairment in rats depleted of 5-HT.[39,40]

Additionally, the relationship between inflammation, MDD, and PCS has garnered significant attention, as emerging evidence suggests that inflammatory processes may play a crucial role in the pathophysiology of both MDD and PCS. Inflammation has been implicated as a key factor in the pathophysiology of MDD, with numerous studies indicating that elevated levels of pro-inflammatory cytokines correlate with depressive symptoms.[41–43] In the context of COVID-19, the viral infection triggers a robust immune response characterized by a cytokine storm, which can lead to increased levels of inflammatory markers such as IL-6 and tumor necrosis factor-α (TNF-α).[44–46] These inflammatory markers have been shown to be elevated not only during the acute phase of the infection but can persist in the post-acute phase, contributing to the development of depressive symptoms in survivors[3,47–52]

Research has demonstrated that the severity of depressive symptoms in individuals with PCS is proportional to the levels of systemic inflammation measured during the acute infection.[49,50] Consistent with these findings, we identified high levels of pro-inflammatory markers in the acute phase in individuals without diagnosed mental illness during hospitalization for SARS-CoV-2, including higher levels of CRP at the baseline. This suggests that the inflammatory response elicited by COVID-19 may have long-lasting effects on mental health, particularly in those who develop new-onset MDD following their recovery from the virus.

Figure 2.

Estimated MADRS LS Mean from Baseline to End-Point (Week 8) Comparing Vortioxetine (10–20 mg/d) vs Escitalopram (10–20 mg/d) vs Sertraline (50–200 mg/d)



Abbreviations: ESC = escitalopram, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, SER = sertraline, VOR = vortioxetine.

The neurobiological mechanisms linking inflammation and depression are complex and multifaceted. Inflammatory cytokines can disrupt neurotransmitter systems, particularly serotonin and dopamine, which are critical for mood regulation.[27,53] The activation of the indoleamine 2,3-dioxygenase (IDO) pathway, induced by pro-inflammatory cytokines, leads to increased conversion of tryptophan to kynurenine, thereby reducing serotonin availability.[53] Additionally, chronic inflammation may impair neuroplasticity and neurogenesis, processes that are vital for emotional resilience, further exacerbating depressive symptoms.[54]

Available research evidence provides compelling evidence that vortioxetine exerts anti-inflammatory effects on human monocytes and macrophages.[23] This study demonstrated that vortioxetine led to an increase in the gene expression of peroxisome proliferator-activated receptor gamma (PPARγ) in resting monocytes and both macrophage populations. PPARγ is known for its anti-inflammatory properties and plays a critical role in the differentiation of monocytes into macrophages, promoting an anti-inflammatory phenotype.[55,56] Furthermore, vortioxetine was found to induce a negative trend in the expression of TNF-α, a pro-inflammatory cytokine, suggesting that vortioxetine may help mitigate inflammatory responses in these immune cells.[23]

Fatigue is a common residual symptoms of depression. Also, fatigue appears as a symptomatic criterion as part of a MDD diagnosis according to *DSM-5-TR*.[57] However, fatigue is overlapping in several physical and mental disorders.[58,59] In acute and PCS, fatigue accompanied the course of the illness and persistent after 24 months of previous infection.[4] Previous analyses have elucidated that vortioxetine improves psychosocial functions in persons with PCS mediated by improvement measures of fatigue.[60] In our analysis, we show that vortioxetine improves PROMIS 7a scores with a tendency to obtain after 8 weeks better results. Therefore, vortioxetine may improve depressive cognitions and physical performance in MDD as a sequela of PCS.

Finally, response and remission rates were higher in the group treated with vortioxetine (Supplementary Material Figure 3). This finding is interesting due to the mixed evidence regarding the reduction of depressive symptoms between vortioxetine and other antidepressants.[61] Although the benefit of vortioxetine in the cognitive symptoms of MDD was observed, as well as the better functionality demonstrated and greater tolerability, a more accurate image of the multidimensional nature of MDD and the significance of taking into account these factors in the effectiveness of interventions in each of the dimensions may be obtained by combining various domains (such as mood and physical symptoms, cognition, functionality, and quality of life) in the clinical and research measurements.

The observed cognitive improvements with vortioxetine may partially reflect its superior antidepressant effects compared to SSRIs, given the close interplay between mood and cognition in PCS. However, vortioxetine's unique pharmacological profile, including modulation of glutamatergic neurotransmission and enhancement of neuroplasticity, supports an independent pro-cognitive effect. Prior studies have reported cognitive benefits in nondepressed populations, further suggesting a direct mechanism.[62–64] Future studies should explore these effects using mediation analyses to distinguish antidepressant-driven changes from primary cognitive improvements.

There are many other factors that may influence the interpretation of our study findings. For example, variations in baseline cytokine levels, pre-existing medical conditions, and differences in COVID-19 severity across participants could partially influence treatment outcomes. Although a robust statistical model was employed to balance key covariates, residual confounding cannot be fully excluded due to the study's nonrandomized design.

Future research should aim to replicate and expand upon these findings, with a focus on RCTs that explore the role of biomarkers, such as cytokine profiles, in mediating treatment outcomes for PCS-related MDD. These findings underscore the importance of stratifying patients based on inflammatory biomarkers to optimize treatment efficacy and guide personalized therapeutic

approaches in PCS-related MDD. Future investigations should prioritize integrating biomarker-based selection criteria and long-term evaluations of vortioxetine's efficacy in diverse PCS populations.

Our study has several strengths: (1) it used a sample calculation according to the expected effects for the outcomes, (2) it compared the effectiveness of the treatments head-to-head considering 3 domains associated with MDD, (3) it used robust estimates and explanatory statistical models for prospective follow-up studies, (4) it used standardized clinical scales to obtain information related to outcomes as well as adverse effects, and (5) it had a reduced information bias due to a low rate of dropouts during the follow-up. The limitations that this study faces are as follows: (1) a small sample for the comparison arms; (2) the nonrandomization of participants for each of the interventions, which increases the risk of selection bias; (3) most participants had higher baseline values associated with the cytokine profile during acute SARS-CoV-2 infection; a robust comparison could not be performed with participants without a high immune response during COVID-19 that would clarify whether the effect of vortioxetine was sustained in the group with a cytokine profile within normal ranges; (4) the lack of a comparator group of PCS patients without MDD limits the ability to isolate inflammatory contributions unique to MDD; and (5) no measures of functionality were included beyond the Patient-Reported Outcome Measurement obtained through PROMIS 7a.

CONCLUSIONS

Vortioxetine, a multimodal antidepressant, is an effective option as first-line treatment in new-onset MDD after SARS-CoV-2 infection. Measure of cognitive function and depressive symptoms improved to a greater extent with vortioxetine when compared to escitalopram or sertraline in PCS participants with MDD. Physical symptoms such as fatigue also significantly improved to a greater extent than the comparator. Future studies are necessary to replicate and extend the findings observed in our real-world study.

Article Information

Published Online: May 5, 2025. https://doi.org/10.4088/JCP.24m15387

Submitted: April 15, 2024; accepted February 27, 2025.

To Cite: Guillen-Burgos HF, Galvez-Florez JF, Moreno-López S, et al. Vortioxetine for cognitive impairment in major depressive disorder during post-COVID syndrome: real-world evidence. *J Clin Psychiatry* 2025;86(2):24m15387.

Author Affiliations: Universidad Simón Bolívar, Centro de Investigaciones en Ciencias de la Vida, Center for Clinical and Translational Research, Barranquilla, Colombia (Guillen-Burgos); Universidad El Bosque, Faculty of Medicine, Center for Clinical and Translational Research, Bogotá, Colombia (Guillen-Burgos, Galvez-Florez); Pontificia Universidad Javeriana, Department of Psychiatry and Mental Health, Hospital Universitario San Ignacio, Bogotá, Colombia (Guillen-Burgos); Faculty of Medicine, Universidad de Los Andes, Bogotá, Colombia (Moreno-López); Universidad de la Costa, Faculty of Medicine, Barranquilla, Colombia (Anaya); Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Kwan); Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Ontario, Canada (Kwan); Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada (Kwan); Department of Psychiatry, University of Toronto, Toronto, ON, Canada (McIntyre).

Corresponding Author: Hernan F. Guillen-Burgos, MD, Centro de Investigaciones en Ciencias de la Vida, Center for Clinical and Translational Research, Universidad Simón Bolívar, Carrera 54 # 64-22, Barranquilla, CO (hernan.guillen@unisimon.edu.co).

Relevant Financial Relationships: Dr Guillen-Burgos has received research grant support from the Ministry of Science, Technology, and Innovation (MinCiencias) in Colombia; UKRI in the United Kingdom; and speaker fees from Roche, Pfizer, Abbott, GSK, and Synergy R&D. **Dr Galvez-Florez** is a full-time employee for Zerenia Clinics Bogotá, Colombia. **Dr McIntyre** has received research grant support from the CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute and speaker/consultation fees from Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie, and Atai Life Sciences. **Dr McIntyre** is a CEO of Braxia Scientific Corp. The other authors declare no conflicts of interest.

Funding/Support: This research was supported by an internal grant from the Universidad Simón Bolívar (Barranquilla, Atlántico, Colombia) and the Center for Clinical and Translational Research (Barranquilla, Atlántico, Colombia) awarded to Dr. Guillen-Burgos. Materials for this study were provided by Universidad Simón Bolívar.

Role of the Funder: The funding organizations had no role in the design of the study, data collection, data analysis, interpretation of results, manuscript preparation, or the decision to submit the article for publication.

Supplementary Material: Available at Psychiatrist.com.

References

1. World Health Organization. A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus, 6 October 2021. 2021.
2. Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol*. 2023;21(3):133–146.
3. Anaya JM, Rojas M, Salinas ML, et al. Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev*. 2021;20(11):102947.
4. Kim Y, Bae S, Chang H-H, et al. Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. *Sci Rep*. 2023;13(1):11207.
5. Taquet M, Luciano S, Geddes JR, et al. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 2021;8(2):130–140.
6. Guillen-Burgos HF, Galvez-Florez JF, Moreno-Lopez S, et al. Factors associated with mental health outcomes after COVID-19: a 24-month follow-up longitudinal study. *Gen Hosp Psychiatry*. 2023;84:241–249.
7. Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun*. 2022;101:93–135.
8. Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry*. 2022;9(10):815–827.
9. Taquet M, Geddes JR, Husain M, et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416–427.
10. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. 2022;9(2):137–150.
11. McIntyre RS, Phan L, Kwan ATH, et al. Vortioxetine for the treatment of post-COVID-19 condition: a randomized controlled trial. *Brain*. 2024;147(3):849–857.
12. McIntyre R, Harrison J, Loft H, et al. The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. *Int J Neuropsychopharmacol*. 2016;19(10):pyw055.
13. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557–1567.
14. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018;38(5):513–519.
15. Lam RW, Lamy F-X, Danchenko N, et al. Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. *Neuropsychiatr Dis Treat*. 2018;14:2861–2877.

16. Quilty LC, Robinson JJ, Rolland JP, et al. The structure of the Montgomery–Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res*. 2013;22(3):175–184.
17. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
18. Cano JF, Gomez Restrepo C, Rondón M. Validación en Colombia del instrumento para evaluación de la depresión Montgomery-Åsberg Depression Rating Scale (MADRS). *Rev Colomb Psiquiatr*. 2016;45(3):146–155.
19. Ganesh R, Ghosh AK, Nyman MA, et al. PROMIS scales for assessment of persistent post-COVID symptoms: a cross sectional study. *J Prim Care Community Health*. 2021;12:21501327211030413.
20. Yang M, Keller S, Lin J-MS. Psychometric properties of the PROMIS® Fatigue Short Form 7a among adults with myalgic encephalomyelitis/chronic fatigue syndrome. *Qual Life Res*. 2019;28(12):3375–3384.
21. Posner K, Brown GK, Stanley B, et al. The Columbia–Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12): 1266–1277.
22. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573–577.
23. Talmon M, Rossi S, Pastore A, et al. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. *Br J Pharmacol*. 2018;175(1):113–124.
24. McIntyre RS, Cha DS, Soczynska JK, et al. Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. *Depress Anxiety*. 2013;30(6):515–527.
25. Beck AT, Bredemeier K. A unified model of depression: integrating clinical, cognitive, biological, and evolutionary perspectives. *Clin Psychol Sci*. 2016;4: 596–619.
26. Liu J, Chen Y, Xie X, et al. The percentage of cognitive impairment in patients with major depressive disorder over the course of the depression: a longitudinal study. *J Affect Disord*. 2023;329:511–518.
27. Mazza MG, Zanardi R, Palladini M, et al. Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. *Eur Neuropsychopharmacol*. 2022; 54:1–6.
28. Prado CE, Watt S, Crowe SF. A meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples. *Neuropsychol Rev*. 2018;28(1):32–72.
29. Boulenger J-P, Loft H, Olsen CK. Efficacy and safety of vortioxetine (Lu AA21004), 15 and 20 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder. *Int Clin Psychopharmacol*. 2014;29(3):138–149.
30. Henigsberg N, Mahableshwarkar AR, Jacobsen P, et al. A randomized, double-blind, placebo-controlled 8-week trial of the efficacy and tolerability of multiple doses of Lu AA21004 in adults with major depressive disorder. *J Clin Psychiatry*. 2012;73(7):953–959.
31. Alvarez E, Perez V, Dragheim M, et al. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in patients with major depressive disorder. *Int J Neuropsychopharmacol*. 2012;15(5):589–600.
32. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012;27(4):215–223.
33. Alboni S, Benatti C, Colliva C, et al. Vortioxetine prevents lipopolysaccharide-induced memory impairment without inhibiting the initial inflammatory cascade. *Front Pharmacol*. 2020;11:603979.
34. Li Y, Abdourahman A, Tamm JA, et al. Reversal of age-associated cognitive deficits is accompanied by increased plasticity-related gene expression after chronic antidepressant administration in middle-aged mice. *Pharmacol Biochem Behav*. 2015;135:70–82.
35. Guilloux J-P, Mendez-David I, Pehrson A, et al. Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and neurogenesis outcomes in mice. *Neuropharmacology*. 2013;73: 147–159.
36. Bétry C, Etiévant A, Pehrson A, et al. Effect of the multimodal acting antidepressant vortioxetine on rat hippocampal plasticity and recognition memory. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;58:38–46.
37. Tedeschini E, Levkovitz Y, Iovieno N, et al. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry*. 2011;72(12):1660–1668.
38. Dale E, Zhang H, Leiser SC, et al. Vortioxetine disinhibits pyramidal cell function and enhances synaptic plasticity in the rat hippocampus. *J Psychopharmacol*. 2014;28(10):891–902.
39. Jensen JB, du Jardin KG, Song D, et al. Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: evidence for direct 5-HT receptor modulation. *Eur Neuropsychopharmacol*. 2014;24(1):148–159.
40. du Jardin KG, Jensen JB, Sanchez C, et al. Vortioxetine dose-dependently reverses 5-HT depletion-induced deficits in spatial working and object recognition memory: a potential role for 5-HT1A receptor agonism and 5-HT3 receptor antagonism. *Eur Neuropsychopharmacol*. 2014;24(1):160–171.
41. Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*. 2013;246:199–229.
42. Hodes GE, Kana V, Menard C, et al. Neuroimmune mechanisms of depression. *Nat Neurosci*. 2015;18(10):1386–1393.
43. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol*. 2016;16(1):22–34.
44. Del Valle DM, Kim-Schulze S, Huang HH, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26(10): 1636–1643.
45. Iwamura APD, Tavares da Silva MR, Hümmelgen AL, et al. Immunity and inflammatory biomarkers in COVID-19: a systematic review. *Rev Med Virol*. 2021; 31(4):e2199.
46. Ponti G, Maccaferri M, Ruini C, et al. Biomarkers associated with COVID-19 disease progression. *Crit Rev Clin Lab Sci*. 2020;57(6):389–399.
47. Anaya J-M, Herrán M, Beltrán S, et al. Is post-COVID syndrome an autoimmune disease? *Expert Rev Clin Immunol*. 2022;18(7):653–666.
48. Lai Y-J, Liu SH, Manachevakul S, et al. Biomarkers in long COVID-19: a systematic review. *Front Med*. 2023;10:1085988.
49. Renaud-Charest O, Lui LMW, Eskander S, et al. Onset and frequency of depression in post-COVID-19 syndrome: a systematic review. *J Psychiatr Res*. 2021;144:129–137.
50. Mazza MG, Palladini M, De Lorenzo R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun*. 2021;94:138–147.
51. Hazumi M, Usuda K, Okazaki E, et al. Differences in the course of depression and anxiety after COVID-19 infection between recovered patients with and without a psychiatric history: a cross-sectional study. *Int J Environ Res Public Health*. 2022; 19(18):11316.
52. Di Nicola M, Pepe M, De Mori L, et al. Physical and cognitive correlates, inflammatory levels, and treatment response in post-COVID-19 first-onset vs. recurrent depressive episodes. *Eur Arch Psychiatry Clin Neurosci*. 2024;274(3):583–593.
53. Villarreal-Zegarra D, Paredes-Angeles R, Mayo-Puchoc N, et al. An explanatory model of depressive symptoms from anxiety, post-traumatic stress, somatic symptoms, and symptom perception: the potential role of inflammatory markers in hospitalized COVID-19 patients. *BMC Psychiatry*. 2022;22(1):638.
54. Badinlou F, Lundgren T, Jansson-Fröjmark M. Mental health outcomes following COVID-19 infection: impacts of post-COVID impairments and fatigue on depression, anxiety, and insomnia - a web survey in Sweden. *BMC Psychiatry*. 2022;22(1):743.
55. Straus DS, Glass CK. Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. *Trends Immunol*. 2007;28(12):551–558.
56. Youssef J, Badr M. Role of peroxisome proliferator-activated receptors in inflammation control. *BioMed Res Int*. 2004;2004(3):156–166.
57. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association Publishing; 2022.
58. McMorris T, Barwood M, Hale BJ, et al. Cognitive fatigue effects on physical performance: a systematic review and meta-analysis. *Physiol Behav*. 2018;188: 103–107.
59. Van Cutsem J, Marcora S, De Pauw K, et al. The effects of mental fatigue on physical performance: a systematic review. *Sports Med*. 2017;47(8):1569–1588.
60. Badulescu S, Le GH, Wong S, et al. Impact of vortioxetine on psychosocial functioning moderated by symptoms of fatigue in post-COVID-19 condition: a secondary analysis. *Neurol Sci*. 2024;45(4):1335–1342.
61. Zhang X, Qi S, Lin Z, et al. Pre-operative administration of butorphanol mitigates emergence agitation in patients undergoing functional endoscopic sinus surgery: a randomized controlled clinical trial. *Front Psychiatry*. 2022;13:1090149.
62. Lenze EJ, Stevens A, Waring JD, et al. Augmenting computerized cognitive training with vortioxetine for age-related cognitive decline: a randomized controlled trial. *Am J Psychiatry*. 2020;177(6):548–555.
63. Smith J, Browning M, Conen S, et al. Vortioxetine reduces BOLD signal during performance of the N-back working memory task: a randomised neuroimaging trial in remitted depressed patients and healthy controls. *Mol Psychiatry*. 2018;23(5): 1127–1133.
64. Tan SN, Tan C. Vortioxetine improves cognition in mild cognitive impairment. *Int Clin Psychopharmacol*. 2021;36(6):279–287.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Vortioxetine for Cognitive Impairment in Major Depressive Disorder during Post-COVID Syndrome: Real-World Evidence

Authors: Hernan F. Guillen-Burgos, MD; Juan F. Galvez-Florez, MD; Sergio Moreno-López, PhD; Juan-Manuel Anaya, MD, PhD; Angela T.H. Kwan, MSc; Roger S. McIntyre, MD, FRCPC

DOI Number: 10.4088/JCP.24m15387

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

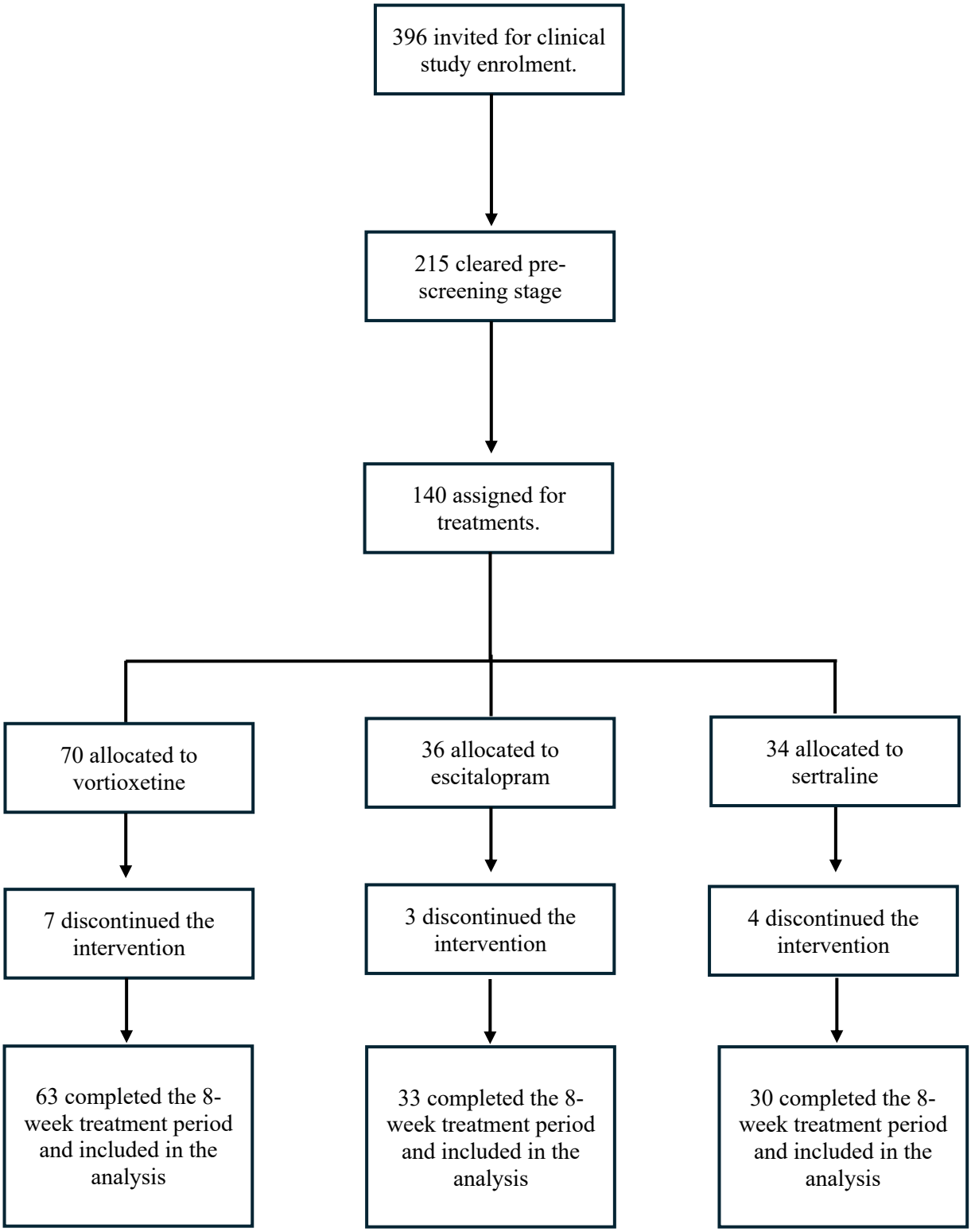
1. ***Figure 1*** STROBE Flow Diagram of the Participants Enrolment, Assigned and Follow-up in the Real-World-Evidence Study of Vortioxetine vs SSRIs for PCS with MDD
2. ***Figure 2*** LS Mean Score of PROMIS 7a in Individuals With PCS and MDD Treated With Vortioxetine vs Escitalopram vs Sertraline
3. ***Figure 3*** Response rate (MADRS reduced ≥50 symptoms) and remission (MADRS ≤10) in individuals with PCS and MDD treated with vortioxetine vs escitalopram vs sertraline

DISCLAIMER

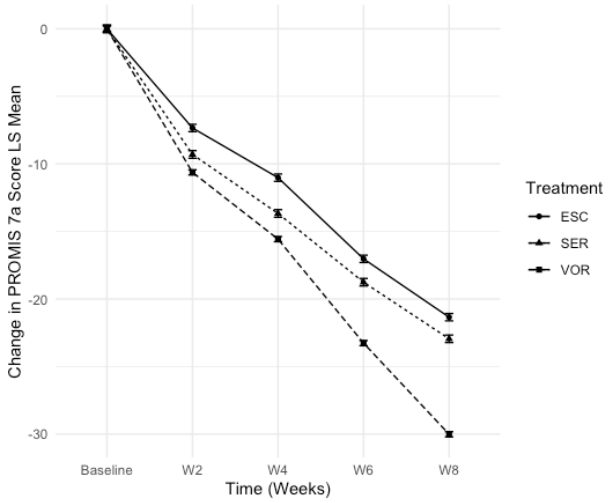
This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material.

Supplementary Material Figure 1. STROBE flow diagram of the participants enrolment, assigned and follow-up in the real-world-evidence study of vortioxetine vs SSRIs for PCS with MDD.

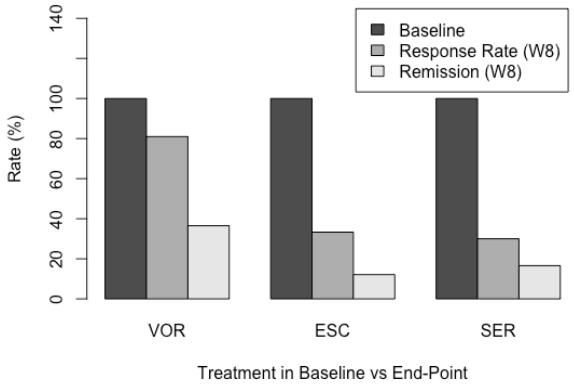


Supplementary Material Figure 2. LS mean score of PROMIS 7a in individuals with PCS and MDD treated with vortioxetine vs escitalopram vs sertraline.



VOR = Vortioxetine, ESC = Escitalopram, SER = Sertraline. Fatigue is a common symptom occurring in MDD and PCS. Our results showed that fatigue measured by PROMIS 7a decreased during the 8-week treatment with significant statistical differences at endpoint in vortioxetine arm than SSRIs groups.

Supplementary Material Figure 3. Response rate (MADRS reduced ≥50 symptoms) and remission (MADRS ≤ 10) in individuals with PCS and MDD treated with vortioxetine vs escitalopram vs sertraline.



VOR = Vortioxetine, ESC = Escitalopram, SER = Sertraline. In the baseline participants have a MADRS ≥ 26. After 8-weeks of treatment, the rate of response in vortioxetine arm was 81%, remission rate 36.5%. For escitalopram, the response rate was 33.3% and remission rate 12.1%, and for sertraline the response rate was 30% and remission rate 16.6%.