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Impact of depressive symptoms on motivation in persons with post-COVID-19 condition

Juliana West[1], Angela T.H. Kwan[1,2], Kayla M. Teopiz[1], Ziji Guo[1], Gia Han Le[1,3], Sebastian Badulescu[1,3], Taeho Greg Rhee[6,7], Sabrina Wong[1,4], Bing Cao[8], Roger Ho[9,10], Joshua D. Rosenblat[3,4,5], Rodrigo B. Mansur[1,3], Lee Phan[1], Mehala Subramaniapillai[1] and Roger S. McIntyre[5]

[1]Brain and Cognition Discovery Foundation, Toronto, ON, Canada; [2]Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; [3]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [4]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada; [5]Department of Psychiatry, University of Toronto, Toronto, ON, Canada; [6]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; [7]Department of Public Health Sciences, Farmington, CT, USA; [8]Key Laboratory of Cognition and Personality, Faculty of Psychology, Ministry of Education, Southwest University, Chongqing, P. R. China; [9]Department of Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore and [10]Institute for Health Innovation and Technology (iHealthtech), National University of Singapore, Singapore, Singapore

Original Research

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Corresponding author:
Roger S. McIntyre;
Email: roger.mcintyre@bcdf.org

Abstract

Objective. The World Health Organization (WHO) has defined Post-COVID-19 Condition (PCC) as the onset of symptoms within three months after resolution of an acute SARS-CoV-2 infection, wherein symptoms persist for at least two months and cannot be explained by another medical/psychiatric condition. Persons living with PCC report debilitating symptoms including, but not limited to, depressive symptoms and motivational deficits. The aim of this post-hoc analysis was to evaluate the association between depressive symptoms and motivation in adults with PCC.

Methods. We conducted a post-hoc analysis of an 8-week, double-blind, randomized, placebo-controlled trial evaluating adults (18 years or older) in Canada with WHO-defined PCC and cognitive symptoms. This post-hoc analysis is comprised of baseline data that evaluates the association between depressive symptom severity measured by the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16) and motivational systems measured by the Behavioral Inhibition System/Behavioral Activation System Questionnaire (BIS/BAS).

Results. There was a statistically significant association between depressive symptoms and BIS (**β** = -0.041 95% CI [-0.066, -0.016], p<0.05), BAS reward responsiveness (**β** = 0.043 95% CI [0.012, 0.074], p<0.05), sex (**β** = -0.137 95% CI [-0.266, -0.008], p<0.05), and confirmed COVID-19 infection (**β** = 0.196 95% CI [0.061, 0.332], p<0.05).

Conclusions. Depressive symptoms were associated with motivational deficits in persons living with PCC. Optimizing treatment for depressive symptoms may potentially improve aspects of motivational impairment amongst persons with PCC. All patients presenting with MDD and a history of COVID-19 infection should be assessed for the presence of PCC.

Introduction

According to the World Health Organization (WHO), over 750 million cases of coronavirus disease 2019 (COVID-19) infection have been reported as of November 2024.[1] 10–20% of persons who have recovered from acute COVID-19 infection report persistent symptoms.[2] The WHO has defined post-COVID-19 condition (PCC; also referred to as Long COVID) as new or continued symptoms, such as fatigue or shortness of breath, that occur three months following a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, persist for at least two months and cannot be explained by an alternative diagnosis.[3] Persons with PCC have reported a worsening of mental health symptoms including, but not limited to, depression and motivation.[2,4]

It is estimated that 17%–48% of persons with PCC experience depressive symptoms.[4] Extant literature suggests that inflammation in the brain and altered brain glucose metabolism are associated with depression in persons with PCC.[5] Some evidence suggests that distress (e.g., inflammation/immune response) in the prefrontal cortex as a result of a SARS-CoV-2 infection may contribute to the underlying pathoetiology of PCC symptoms, including, but not limited to, depressive and cognitive symptoms (e.g., "brain fog").[5,6] However, the mechanisms that may subserve PCC and depression are not fully characterized.

It is reported that individuals with PCC experience reduced quality of life as well as impaired functioning in daily activities.[7,8] Moreover, people that experienced a more severe SARS-CoV-2 infection were prone to developing PCC-related depression.[5] In addition, cognitive impairment

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including deficits in motivation are a common feature of PCC.[7] It is further reported that persons with PCC may experience lower motivation and energy.[9] For example, replicated evidence indicates that working memory, motivation and executive functioning are impaired in persons living with PCC.[2]

There are a number of studies which indicate that depressive symptoms and motivational deficits are associated with PCC, and thus contribute to a reduced quality of life and increased functional impairment such as brain fog and fatigue.[2,4,5,6,8,10] Therefore, a better characterization of PCC symptomatology is needed to inform treatment options for affected individuals. Herein, we conducted a post-hoc analysis to assess the relationship between depressive symptoms and motivational systems in persons with PCC.

Materials and methods

Study design and participants

This is a post-hoc analysis of an 8-week randomized, double-blind, flexible-dosed, placebo-controlled trial that evaluated the effect of vortioxetine on cognitive symptoms in adults living with PCC.[11] Study recruitment occurred in Canada between November 2021 to January 2023. Participant recruitment utilized media advertisements (e.g., Twitter, Instagram, Facebook, print) and referrals from medical professionals. A local research ethics board (REB) approved the trial design of the primary study. The trial adhered to the Guidelines of Good Clinical Practice and the Declaration of Helsinki.[12,13] All data and protocols are from the primary study (ClinicalTrials.gov number: NCT05047952).[11] Procedures involving human subjects were approved by Advarra (Pro00055939).

Randomization and masking

Trial personnel conducted preliminary screening assessments of individuals interested in the study. Individuals who met inclusion criteria, including 1.) aged 18 or older, 2.) reside in Canada, 3.) had a history of confirmed SARS-CoV-2 infection, underwent further eligibility assessment.

Eligible participants who provided informed written consent were randomized in a 1:1 ratio to receive either vortioxetine (5-20 mg/day) or a placebo during an 8-week period. Detailed information regarding the randomization process can be found in the primary paper.[11] Study personnel (e.g., investigators, research coordinators) and participants were blinded to treatment allocation. Two additional study personnel that were not blinded and did not have any interaction with study participants were responsible for the inventory of the investigational product. The randomization code remained blinded for all participants in the study.

Procedures

Participants were 18 years or older, resided in Canada, and had a history of COVID-19 infection that was confirmed through a clinical diagnosis by a healthcare provider or positive SARS-CoV-2 polymerase chain reaction (PCR), rapid antigen, or serology test. Clinical diagnoses from a healthcare provider required a signed confirmation from the healthcare provider of a presumptive case or a formal diagnosis from the study physician. Additionally, participants must have experienced PCC symptoms for three months since their acute SARS-CoV-2 infection in order to meet WHO-defined PCC. Persons were excluded from the study if they met any of the exclusion criteria (Supplementary Materials S1.) Written consent was also received at the baseline or initial visit.

Assessments occurred at baseline and follow up evaluations at weeks 2, 4 and 8. If a participant withdrew from the study, a follow-up visit was completed at the earliest possible time following withdrawal.

Outcome measures

Depressive symptoms were measured using the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-16). The QIDS-SR-16 was administered at baseline and at weeks 2, 4 and 8. The QIDS-SR-16 is a 16-item self reported scale which assesses the severity of depressive symptoms; a higher score (up to 27) represents a greater severity of depressive symptoms.[14]

Motivational systems (e.g., behavioural inhibition and activation) were measured in adults with PCC using the 24-item Behaviour Inhibition System/Behavioural Activation System Questionnaire (BIS/BAS). The BIS/BAS is validated to measure aversion to threat and reward-seeking behaviour.[15] Items on the BIS/BAS are based on a 4-point Likert scale. A lower score on BIS indicates low aversion to threat and greater likelihood to pursue goals despite negative consequences. The BAS component has three subcategories: reward responsiveness, fun-seeking, and drive. Lower scores on BAS indicate low positive response to rewards, low drive to reach goals, and low desire to seek new rewards.[16]

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics software, version 28.0.1.1 (15), with a two-sided statistical significance level (α) set at 0.05. Descriptive statistics for categorical variables were presented as frequencies (%), and descriptive statistics for normally-distributed continuous variables were presented as means [standard deviation (SD)].

A generalized linear model (GLM) with a Poisson probability distribution was used to explore the association between depressive symptoms and behavioral activation/inhibition at baseline. Covariates included in the GLM were age, sex, education level, COVID-19 diagnosis confirmed by positive test for SARS-CoV-2 infection, employment status, and history of past MDD diagnosis. A p-value less than 0.05 was considered significant.

Results

Participant characteristics

Of the 147 participants enrolled in the primary trial, 145 (98.6%) had available baseline measures of QIDS-SR-16 and BIS/BAS for the post-hoc analysis herein. Sociodemographic and clinical characteristics of the intent-to-treat population (n = 147) are described in Table 1.

Association between depressive symptoms and motivation in persons with PCC

A GLM analysis was conducted to evaluate the association between depressive symptom severity and motivational systems (i.e., motivation to follow goals, fun-seeking behaviours, reward responsiveness, and motivation to avoid adverse outcomes) with age, sex, education level, confirmed COVID-19 diagnosis by positive test for SARS-CoV-2

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Table 1. Baseline Characteristics of the Intent-to-Treat Population (N = 147)

Characteristic	Placebo (n = 74)	Vortioxetine (n = 73)	p-value*
Age (Years), Mean (SD)	44.89 (12.14)	43.84 (12.35)	0.602[a]
Sex (Female), n (%)	55 (74.32)	56 (76.71)	0.736[b]
Education, n (%)			0.390[b]
< High School	0 (0)	1 (1.37)	
High School Graduate	4 (5.41)	8 (10.96)	
College/University Degree	10 (13.51)	7 (9.59)	
Associates Degree	15 (20.27)	13 (17.81)	
Bachelor's Degree	27 (36.49)	34 (46.58)	
Graduate Degree	15 (20.27)	9 (12.33)	
Professional Degree	3 (4.05)	1 (1.37)	
Employment, n (%)			0.483[b]
Paid Employment/ Self-Employed	39 (52.70)	48 (65.75)	
Voluntary Employment	5 (6.76)	4 (5.48)	
Sheltered/Welfare Employment	1 (1.35)	0 (0)	
Unemployed	6 (8.10)	5 (6.85)	
Student	4 (5.41)	6 (8.22)	
Retired	3 (4.05)	1 (1.37)	
Other	16 (21.62)	9 (12.33)	
Confirmed COVID Diagnosis, n (%)	59 (79.7)	57 (78.1)	0.807[b]
MDD Diagnosis, n (%)	25 (33.78)	22 (30.14)	0.595[b]
BAS Drive, Mean (SD)	9.50 (2.21)	9.90 (2.59)	0.313
BAS fun-seeking, Mean (SD)	9.31 (2.30)	9.24 (2.72)	0.858
BAS Reward Responsiveness, Mean (SD)	8.65 (2.19)	8.76 (2.45)	0.765
BIS, Mean (SD)	15.08 (2.22)	14.49 (2.56)	0.136

[a]T-test
[b]Chi-square test
*Two-sided p values

infection, employment status and history of prior MDD diagnosis as covariates (Table 2).

After adjusting for covariates (i.e., age, sex, education level, COVID-19 diagnosis confirmed by positive test for SARS-CoV-2, employment status, and history of prior MDD diagnosis), a positive statistically significant association was detected between depressive symptoms, as measured by the QIDS-SR-16, and reward responsiveness (β = 0.043, 95% CI [0.012, 0.074], $p < 0.05$) (Table 2). Furthermore, there was also a negative statistically significant relationship between BIS and depressive symptoms (β = -0.041, [95% CI -0.066, -0.016], $p < 0.05$) (Table 2).

Additionally, our results indicate that there was a negative statistically significant association between depressive symptoms and sex (β =-0.137, 95% CI [-0.266, -0.008], $p < 0.05$). There was also a positive statistically significant association between depressive symptoms and confirmed COVID-19 diagnosis (β = 0.196, 95% CI [0.061, 0.332], $p < 0.05$) (Table 2). There was no significant association between QIDS-SR and BAS Drive or fun-seeking.

Discussion

Herein, we observed a significant association between depressive symptom severity and measures of motivation in persons with PCC. Specifically, we observed a negative association between behavioural inhibition and depressive symptoms in adults with PCC. Additionally, we observed a positive association between reward responsiveness and depressive symptoms in adults with PCC. The association between depressive symptom severity and measures of motivation may in part be attributed to the overlapping presentation of motivational deficits reported in MDD.[17] Notwithstanding, it is also well documented that motivational deficits are a common, persistent and debilitating feature of PCC.[4,6] It is also separately observed that persons living with PCC present to the health care system with clinical concerns that arise from aspects of motivational deficits, such as fatigue or tiredness, the are associated with functional impairment.[18,19,20]

Our post-hoc analysis introduced conceptual and clinical aspects that warrant additional attention. First, the correlation between motivational deficits and depressive symptomatology suggests that the neurobiology subserving both of these phenomena are overlapping.[21] It is also hypothesized that common motivational deficits in PCC involve aspects of hedonic tone and/or cognitive impairment.[22] However, in our analysis herein, we did not observe an association between motivational drive or fun-seeking behaviour, as measured by the BAS Drive and BAS fun-seeking subscales, and depressive symptoms in persons with PCC. Our observation does not accord with other lines of research that suggest the reward responsiveness score, another BAS subscale, is highly associated with depression. One possible explanation for the foregoing observation is that reward responsiveness may represent an aspect of motivation that is uniquely correlated with depression, but distinct from other categories on the BAS component (i.e., drive, fun-seeking behaviour).[23] It could be hypothesized that there are additional factors that mediate or moderate the relationship between depressive symptoms and select aspects of motivation, which warrants further investigation.

Clinical practitioners who are treating patients with PCC and/or a history of COVID-19 infection who are presenting with motivational deficits, should assess for the possibility of comorbid depression. In persons living with MDD, optimising treatment for MDD is expected to not only improve symptoms of depression but also symptoms of motivational impairment.[24] Although no drugs are approved by the United States Food and Drug Administration (FDA) for the treatment of PCC, our results suggest that treatments that target depression (e.g., vortioxetine, psychostimulants, modafinil) may potentially benefit persons living with PCC who are experiencing clinically significant depressive symptoms.

Optimising treatment outcomes in MDD is warranted; strategies to target and improve motivational deficits, (e.g., behavioural lifestyle), should be evaluated empirically in persons living with PCC and clinically relevant depressive symptoms.[25] Future research should also investigate the mechanisms underlying motivational deficits and depressive symptomatology in persons with PCC to inform prevention and treatment strategies.

There are a number of methodological limitations that affect inferences and interpretations of our results that should be considered. Firstly, our analysis herein is a post-hoc analysis of a clinical trial that did not pre-specify motivational deficits or depressive symptom severity as primary outcome measures.[26]

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Table 2. A GLM Model of the Association Between QIDS-SR and Motivation to Follow Goals, Fun-Seeking Behaviours, Reward Responsiveness, and Motivation to Avoid Adverse Outcomes Adjusting for Covariates

Parameter	Beta coefficient	Standard error	95% confidence interval		Hypothesis test Wald Chi-squared	p-value
			Lower	upper		
(intercept)	2.830	.2380	2.364	3.296	141.385	.000
Age	.002	.0022	−.002	.007	1.230	.267
Sex	−.137	.0656	−.266	−.008	4.356	.037
Education	−.037	.0218	−.080	.006	2.839	.092
Confirmed COVID–19 Diagnosis	.196	.0692	.061	.332	8.063	.005
Employment Status	.017	.0110	−.004	.039	2.438	.118
MDD diagnosis	−.014	.0579	−.127	.099	.058	.810
BAS Drive	−.017	.0144	−.045	.011	1.398	.237
BAS fun-seeking	−.010	.0130	−.035	.016	.553	.457
BAS reward responsiveness	.043	.0157	.012	.074	7.475	.006
BIS	−.041	.0128	−.066	−.016	10.324	.001
(scale)	1[a]					

Dependent Variable: Depressive symptoms
Model: (Intercept), age, sex, education, history of confirmed COVID-19 infection, employment status, history of past MDD diagnosis, BAS Drive Sub-scale, BAS Fun-seeking Sub-scale, BAS Reward Responsiveness Sub-scale, BIS Sub-scale.
MDD = major depressive disorder
BAS = Behavioural activation system
BIS = behavioural inhibition system
[a]Fixed at the displayed value.

Additionally, there are potential confounding factors that we were unable to adjust for in our analysis (e.g., medical comorbidities).

Conclusion

A significant association between motivational deficits and depressive symptoms was observed in a sample of adults with PCC. All patients presenting with MDD and a history of COVID-19 infection should be assessed for PCC.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000440.

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Juliana West, Angela T.H. Kwan, Ziji Guo, Gia Han Le, Sebastian Badulescu, Sabrina Wong, Bing Cao, Roger Ho, Joshua D. Rosenblat, Rodrigo B. Manusr, Lee Phan, Mehala Subramaniapillai have nothing to disclose.

Statement of ethical considerations. The primary clinical trial presented in had its study design by a local research ethics board, Advarra (Pro00055939). Adverra follows Health Canada Regukations, 21, CFR parts 56 and 312.3 and 45 CFR 46. The primary clinical trial complied with Health Canada regulations and FDA 21 CFR parts 50 and 56, Good Clinical Practice, the Declaration of Helsinki, DHHS 45 CFR part 46. Written informed consent was given prior to participation(page 6).

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