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Impact of Baseline Anxiety on Well-being in People with Post-COVID-19 Condition: A Secondary Analysis

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Original Research

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Abstract

Background. Post-COVID-19 condition (PCC) is associated with a host of psychopathological conditions including prominent anxiety symptoms. However, it is not known what effect anxious symptoms have on measures of well-being in individuals living with PCC. This study aims to evaluate anxiety's association with measures of well-being in people with PCC.

Methods. This is a post hoc analysis utilizing data from a placebo-controlled, randomized, double-blind clinical trial assessing the effect of vortioxetine on cognitive impairment in individuals with PCC (NCT05047952). Baseline data with respect to anxiety and well-being were collected using the Generalized Anxiety Disorder Scale, 7-Item (GAD-7), and the World Health Organization (WHO) Well-Being Index, 5-Item (WHO-5), respectively. A generalized linear model (GLM) analysis on baseline GAD-7 and WHO-5 scores was conducted with age, sex, employment status, education level, previous major depressive disorder (MDD) diagnosis, and confirmed COVID-19 cases as covariates.

Results. Data was analyzed in a sample of 144 participants ($N = 144$). After controlling for the aforementioned covariates, the results found that GAD-7 and WHO-5 scores had a significant negative correlation ($\beta = -0.053$, $p = <0.001$), signifying that increased anxiety had adverse effects on the overall well-being of individuals with PCC.

Conclusion. Herein, we observed a clinically meaningful level of anxiety in individuals with PCC. We also identified a robust correlation between anxiety in PCC and measures of general well-being. Our results require replication, providing the impetus for recommending screening and targeting anxious symptoms as a tactic to improve general well-being and outcomes in individuals with PCC.

Introduction

COVID-19 is an acute infectious disease that results in mild-to-moderate respiratory symptoms; however, more recently, researchers have shed light on the fact that COVID-19 extends beyond the initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, manifesting as long-term effects known as post-COVID-19 condition (PCC).[1] The World Health Organization (WHO) defines PCC syndrome as a collection of debilitating symptoms in individuals who were formerly diagnosed with COVID-19, commencing within 3 months of infection and persisting for approximately 2 months.[2] Global cumulative COVID-19 cases exceed 750 million with 10–20% of these individuals estimated to be "long haulers".[3,4] The debilitating effects of PCC are far-reaching, extending beyond respiratory disturbances to impact multiple organ systems, and are associated with a significant functional impairment.[5] The most notable burden is observed in the nervous, respiratory, musculoskeletal, and immune systems, with symptoms including cognitive impairment (i.e., "*brain fog*," memory lapses, attention issues), fatigue, neuropsychiatric syndromes (i.e., depression, anxiety), dyspnea, and chronic pain.[6]

Comorbid neuropsychiatric syndromes are well documented in individuals with PCC, with a recent 6-month follow-up study revealing that approximately 23% of individuals with PCC reported increased symptoms of depression and anxiety.[7] The aforementioned mental health-related difficulties, including anxiety and depression, are distinct from the cognitive impairments associated with PCC and uniquely impact an individual's quality of life.[8] The prevalence and severity of these neuropsychiatric symptoms vary significantly, influenced by several risk factors. Keys among these are the severity of the initial SARS-CoV-2 infection and whether hospitalization or intensive care unit (ICU) intervention was necessary.[9–11] A recent meta-analysis highlighted that patient cohorts with >20% ICU admissions for acute SARS-CoV-2 infection showed

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markedly higher rates of anxiety and depression.[9] Other contributing factors include gender, post-COVID-19 functional impairment, general fatigue, existing comorbidities, and a prior history of mental health issues.[11–13] Interestingly, reduced motivation has also been identified as an important correlate with neuropsychiatric symptom severity, suggesting a complex interplay between mental health and diminished well-being in PCC.[11,14,15]

Well-being is a comprehensive domain that encompasses both the physical and neuropsychiatric outcomes associated with PCC. The aftermath of the COVID-19 pandemic has been correlated with a marked decrease in overall well-being, attributable to many factors that increase the risk of anxiety and depression including COVID-19 infection, financial stress, and social isolation[16,17] Furthermore, a recent survey conducted in Switzerland revealed that individuals suffering from PCC experience a significant decline in well-being, as measured by the WHO Well-Being Index, 5-Item (WHO-5).[18] Analogous to neuropsychiatric disorders, the deterioration in well-being among individuals with PCC is linked to various risk factors, including age, physical comorbidities, and duration of COVID-19 symptoms.[19]

Although a direct correlation between anxiety and well-being in PCC remains to be established, anxiety disorders have well-characterized negative effects on well-being outside the context of PCC.[20,21] The primary objective of this study is to evaluate the association between anxiety and measures of well-being in individuals with PCC. The findings of this research will ascertain whether anxiety serves as a predictor of diminished well-being in PCC and determine whether the WHO-5 can be a screening tool for anxiety in PCC.

Methods

Study design

This investigation is a post hoc analysis utilizing data from a recently published randomized, placebo-controlled, double-blind clinical trial (NCT05047952), which evaluated the efficacy of vortioxetine for treating cognitive deficits in individuals with PCC.[22] The study protocol was approved by Advarra, a local research ethics board that operates in compliance with Health Canada Regulations (IRB#00000971), and it was conducted in accordance with Good Clinical Practice principles and the Declaration of Helsinki. The manuscript reporting the primary outcomes of this trial is reported elsewhere.[21]

Recruitment and study population

Participants were recruited in Canada between November 2021 and January 2023 through media promotions (i.e., Facebook, Instagram, Twitter, print ads) and by referral from an individual's primary healthcare provider. All participants went through an initial virtual pre-screening where their eligibility to participate was assessed according to inclusion and exclusion criteria (Table S1 in the Supplementary Material). All eligible participants were required to be aged ≥18 years, be a current resident of Canada, meet the WHO definition of PCC, and have a documented history of SARS-CoV-2 infection. Acceptable proof of infection included a positive SARS-CoV-2 test (ie, polymerase chain reaction (PCR), antigen, or serology) or signed confirmation of clinical diagnosis by a healthcare provider. Eligible participants who provided written informed consent were enrolled in the study.

Randomization and masking

Eligible participants were randomly assigned in a 1:1 ratio to receive either vortioxetine (5–20 mg/day) or a placebo. The randomization process was carried out by staff members who were blinded to treatment assignments. All additional study personnel were blinded to treatment assignments, with an exception for two unblinded individuals who were responsible for dispensing the treatments. The two unblinded individuals did not interact with study participants. Further information on the clinical trial methodology is available in NCT05047952.

Outcome measures

Outcome measurements were collected at baseline (week 0) and at weeks 2, 4, and 8. The post hoc analysis herein analyzed baseline measures only. Baseline anxiety was measured by the Generalized Anxiety Disorder Scale, 7-Item (GAD-7). On the GAD-7, participants rank the degree to which generalized anxiety symptoms cause functional and/or social difficulties. A score of 0 on the GAD-7 suggests an individual has no anxiety, while the maximum score of 32 suggests an individual is suffering from severe anxiety. Baseline well-being was measured by the WHO-5. Higher scores on the WHO-5 denote higher well-being in the past 2 weeks, while any score < 13 denotes poor well-being.

Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 28.0.1.1. A generalized linear model (GLM) analysis, with a Poisson probability distribution, was conducted to examine the relationship between baseline well-being (total WHO-5 scores) and anxiety (total GAD-7 scores). Participants' age, sex, education level, and employment status, as well as the absence/presence of a previous major depressive disorder (MDD) diagnosis and confirmed COVID-19 case, were treated as covariates. Significance was determined at $p < 0.001$.

Results

Participant demographics

Baseline data was collected from a total of 147 individuals ($N = 147$), of whom 74 were randomized to the placebo group ($n = 74$) and 73 to the vortioxetine group ($n = 73$). Baseline demographics and clinical information, including age, sex, education level, employment status, previous MDD diagnosis, and confirmed COVID-19 diagnosis, were collected from all participants and incorporated into the GLM analysis as covariates. Notably, there was no significant difference in any of the baseline participant demographic and clinical characteristics between the vortioxetine and placebo groups (Table 1).

Impact of anxiety on general well-being

The GLM analysis examined the impact of GAD-7 scores on WHO-5 scores. Results from this analysis indicated that after controlling for the aforementioned covariates only baseline GAD-7 scores were significantly negatively correlated with baseline WHO-5 scores ($\beta = -0.016$, $p < 0.001$) (Table 2).

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Table 1. Baseline Characteristics of the Intent-to-Treat (ITT) 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)	
Associate's 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-19 diagnosis, n (%)	59 (79.7)	57 (78.1)	0.807[b]
MDD diagnosis, n (%)	25 (33.78)	22 (30.14)	0.595[b]
FSS (total score), mean (SD)	51.84 (10.20)	49.78 (10.96)	0.083[a]

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

Table 2. Generalized Linear Model of the Relationship Between GAD-7 and WHO-5 in People with Post-COVID-19 Condition

				95% confidence interval			
DV	Parameter	β	Standard error	Lower	Upper	Wald's chi-square value	P-Value
WHO-5	Age	−0.003	0.0022	−0.007	0.002	1.436	0.231[a]
	Sex	−0.014	0.0623	−0.136	0.109	0.048	0.827[a]
	Education level	0.021	0.0222	−0.023	0.064	0.858	0.354[a]
	Suspected confirmed COVID-19 case	−0.072	0.0649	−0.200	0.055	1.245	0.264[a]
	GAD-7	−0.053	0.0060	−0.065	−0.041	79.018	< 0.001[a]
	Employment status	−0.014	0.0119	−0.037	0.009	1.415	0.234[a]
	MDD diagnosis	0.138	0.0570	0.026	0.250	5.870	0.015[a]

[a]T-test.
*p < 0.001.
Abbreviations: DV, dependent variable; GAD-7, Generalized Anxiety Disorder Scale, 7-Item; MDD, major depressive disorder; WHO-5, World Health Organization Well-Being Index, 5-Item.

Discussion

Key findings

In this post hoc analysis, we explored the effect of baseline anxiety on well-being in adults with PCC, as measured by GAD-7 and WHO-5 scores for anxiety and well-being, respectively. Herein, our GLM analysis identified a significant negative correlation between anxiety levels and well-being, suggesting that increased anxiety has detrimental effects on the general well-being in people with PCC. To our knowledge, this is the first study to report a correlation between anxiety symptoms and validated measures of well-being in individuals living with PCC. This finding is consistent with the broader understanding of anxiety's negative impact on well-being. For instance, a recent Canadian study reported that individuals with mood or anxiety disorders had significantly lower levels of life satisfaction (LS) and self-rated mental health (SRMH).[23] Additionally, another study linked anxiety and depression with reduced sleep quality and physical activity, both key determinants of well-being.[24]

The findings from this analysis further emphasize the importance of mental health management in enhancing the overall

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well-being of patients with PCC. The positive effects of physical activity on mental health and well-being have been well established in the literature. Recent studies have evaluated these anxiolytic effects in PCC, demonstrating that physical rehabilitation can significantly improve anxiety symptoms and bolster improvements in quality of life in individuals with PCC.[25–27] Additionally, the existing literature has also shown that psychological interventions can effectively improve anxiety related to PCC and address associated mental health concerns.[28] The results of our study support these findings as we identified a strong correlation between anxiety and well-being in PCC. Enhancing well-being is not only vital for an individual's health but may also help improve work productivity and reduce functional impairments, which are prevalent challenges faced by people with PCC.[29]

Strengths, limitations, and future directions

A strength of our analysis is the use of validated measures of anxiety and well-being. The WHO-5 has undergone rigorous evaluation as a screening instrument for mood disorders, particularly depression. In 2015, a comprehensive systematic review highlighted the WHO-5's exceptional sensitivity in screening for depression in research participants.[30] Subsequent analyses have further corroborated this by identifying its validity in assessing depression in various disorders, including diabetes, human immunodeficiency virus (HIV), and acne vulgaris.[31–33]

There are methodological and conceptual aspects to consider that affect inferences and interpretations of our results. First, anxiety is one of many factors that can impact well-being. Notably, cognitive function has been recognized as a direct correlate of well-being.[34] Cognitive impairment is recognized as the primary symptom of PCC, and therefore, it may also be involved in the lower well-being of people with PCC.[7] This putative correlation warrants further exploration in future research endeavors. Also, it is important to highlight that this study is a post hoc analysis, and as such, the relationships between anxiety and well-being were not predefined as primary or secondary outcomes in the original study design.

Conclusion

In this study, we demonstrated that patients with PCC experience a significant increase in generalized anxiety symptoms. Furthermore, a robust negative correlation was identified between the levels of anxiety and overall well-being in individuals with PCC. These observations align with broader understandings of mental health and well-being but uniquely highlight this connection in the context of PCC for the first time. These results suggest that incorporating anxiety screening and anxiety-related therapeutic interventions could enhance the well-being of PCC patients. However, these conclusions are preliminary, as they are based on secondary analysis. Further research is needed to confirm these findings before they can be considered definitive.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000099.

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