ORIGINAL RESEARCH

Examining the Long-Term Sequelae of SARS-CoV2 Infection in Patients Seen in an Outpatient Psychiatric Department

Muhammad Farooqi[1], Anum Khan[1], Asaf Jacobs[1], Vanessa D'Souza[1], Faith Consiglio[1], Carol L Karmen[1], Rhea Dornbush[1], Gull Shamir Hasnat[2], Stephen J Ferrando[1]

[1]Department of Psychiatry, Westchester Medical Center Health System-New York Medical College, New York, NY, USA; [2]Psychiatry, CMH, Lahore Medical College, Lahore, Pakistan

Correspondence: Stephen J Ferrando, Department of Psychiatry, Westchester Medical Center Health System, New York Medical College, 100 Woods Road, Suite N324-A, Valhalla, New York, NY, 10595, USA, Tel +914-493-1905, Fax +914-493-1015, Email Stephen.ferrando@wmchealth.org

Background: The acute phase of Coronavirus disease-19 (COVID-19) is well known. However, there is now an increasing number of patients suffering from the post-acute sequelae of COVID-19 (PASC Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis), including neuropsychiatric symptoms. The purpose of this report is to describe the sociodemographic, diagnostic and treatment characteristics of patients evaluated in an outpatient psychiatric setting for PASC.

Methods: A retrospective review of 30 individuals with documented COVID-19 illness treated at a university hospital-based Post-COVID-19 Recovery Program were referred to an outpatient psychiatric department for consultation and treatment from December 2020 to July 2021. All individuals complained of neuropsychiatric symptoms including anxiety, depression, fatigue and cognitive problems. Data on sociodemographic characteristics, psychiatric diagnosis, prominent psychological themes and treatment prescribed were described and, where applicable, analyzed with SPSS software.

Results: The study population consisted of patients between 25 and 82 years old, with a predominance of women between 46 and 60 years. Approximately half of the patient population had a primary diagnosis of major depressive disorder, often combined with prominent anxiety. Over two-thirds of the patient population reported a combination of depression, fatigue and cognitive complaints, predominantly memory and slowed processing speed. Prominent stressors and psychological themes included social and occupational decline, isolation, lack of empathy and understanding from family, friends and employers, and apprehension about future ability to return to their baseline level of function. Treatments recommended included individual and group psychotherapy, medication and cognitive rehabilitation. Modafinil and antidepressants, often in combination, were the most commonly used medications, intended to target the pervasive fatigue, depressive, and anxiety these individuals were facing.

Conclusion: Clinical experience from this patient population underscored the significant medical, emotional, neurocognitive and functional sequelae of PASC. Management of these individuals requires a collaborative approach with the availability of psychotherapeutic interventions, pharmacologic treatment, neurocognitive assessment and remediation to address these symptoms.

Keywords: COVID-19, long-term sequelae, anxiety, depression, fatigue, modafinil

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has swept across the globe, killing over a million people in the United States alone.[1] Research supports the hypothesis that individuals with psychiatric disorders are more likely to contract COVID-19 infection.[1] Simultaneously, COVID-19 infection itself is associated with new-onset psychiatric disorders, including anxiety, depression, psychosis and post-traumatic stress disorder.[1,19] Several factors are implicated in association of COVID-19 infection with psychiatric disorders, including homelessness, group living situations, economic challenges, social isolation, diminished

personal self-care and adherence to COVID-19 preventive guidelines.[2] This correlation can also be partially attributed to the comorbidity of psychiatric disorders with medical conditions like cardiovascular disease, asthma and other lung conditions and diabetes.

While the acute physical symptoms of COVID-19 have been appropriately highlighted, there is an increasing number of patients who are suffering from the colloquially termed "Long COVID" or "post-acute sequelae of COVID-19 (PASC).[3] The World Health Organization's (WHO's) case definition is as follows:

> Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning.[3]

An increasing body of evidence suggests that the long-term neuropsychiatric sequelae (cognitive dysfunction, depression, anxiety, fatigue) are common and cause persistent distress and functional decline.[1]

A recent cohort study of over 13,000 adults suggested that SARS-CoV-2 positivity was strongly associated with self-reported memory and concentration problems, even after 8 months of follow-up.[3] Groff et al, in their systematic review of 57 studies, found that some of the most prevalent PASC symptoms were neurological and psychological in nature. The most common of these were difficulty concentrating (median IQR 23.8%), generalized anxiety disorder (median IQR, 29.6%), general functional impairments (median IQR 44%) and fatigue or muscle weakness (median IQR 37%).[5] Some biological mechanisms possibly responsible for these neuropsychiatric symptoms include cytokine-driven inflammatory responses, entrance of the virus into the CNS via angiotensin converting enzyme 2 receptors, breakdown of the blood brain barrier, and blood clotting abnormalities.[6] In addition to these viral-based mechanisms, factors such as age, comorbid medical conditions, the psychological and socioeconomic trauma of COVID-19 illness may also contribute to these longer-term neuropsychiatric symptoms.

The pathogenesis of the illness has been widely studied; however, there is a gap in existing medical literature about the phenomenology, confounding variables and treatment strategies of the neuropsychiatric sequelae of COVID-19. Despite the prevalence of long-term symptoms following COVID-19 infection, there is little information on the assessment and treatment of the psychiatric component of PASC. The present study, which is one of the first to focus on the assessment and treatment of this patient population in a clinical setting, aims to address this dearth of information by describing the psychiatric evaluation and treatment of 30 patients who were referred from a university hospital-based post-COVID Recovery Program.

Aims and Objectives

- To identify socio-demographic characteristics of a sample of patients referred for psychiatric consultation for PASC.
- To identify co-morbid medical problems in the patient population.
- To describe the neuro-psychiatric symptom clusters and psychiatric diagnoses in this population including; Presenting Complaints, Diagnosis and Past Psychiatric History.
- To identify the co-occurring stressors that impact the neuropsychiatric presentation.
- To determine whether a previously diagnosed psychiatric condition impacted diagnosis and symptom severity.
- To describe treatments recommended to this clinical population in order to identify potentially effective treatments.

Methods
Study Design
A retrospective review of the medical records of patients who had COVID-19 illness and received a psychiatric consultation in the outpatient setting was performed. Data collection involved obtaining the following information:

1. Demographic Characteristics: age, ethnicity, domicile status, relationship status.
2. Psychiatric Diagnosis: eg, major depression, substance use disorder, comorbid personality disorder.
3. Medical Comorbidities: eg, hypertension, diabetes, asthma, obesity.

4. Medication treatments: eg, antidepressants, antipsychotics (including long-acting injectable medications), mood stabilizers.
5. COVID-19 illness history and long-term symptoms of COVID including fatigue, memory impairment, cognitive slowing and worsening of depression and anxiety.
6. Neuropsychiatric measures, including: Physical Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 (GAD-7), Columbia Suicide Severity Rating Scale (C-SSRS) and Fatigue Severity Scale (FSS) and Montreal Cognitive Assessment (MOCA).

Research Subject Population

Thirty adult patients referred and assessed for psychiatric complications of COVID-19 to the outpatient department of an academic Behavioral Health Center between December 1, 2020 and July 26, 2021 were included in this review. All adult individuals referred within the time period for psychiatric assessment were included. The study was approved by the Institutional Review Board of New York Medical College (IRB #14648) and Clinical Research Institute of Westchester Medical Center. The protocol was granted exempt status by the institutional review board and, therefore, consent was not required. As a retrospective medical record review, patient data were extracted from the medical record and entered into a de-identified encrypted database. All data were analyzed and reported without specific patient identifiers. Privacy and confidentiality were maintained in accordance with the principles of the Declaration of Helsinki on the ethical principles for medical research involving human subjects.

Diagnostic impressions were documented based on the psychiatric clinical interview and self-assessment tools were included to assess severity of symptoms including depression, anxiety, fatigue and suicidal ideation. All individuals had been evaluated in the Post-COVID-19 Recovery Center in the Department of Medicine and were given a diagnosis of the Post-COVID syndrome prior to evaluation in the psychiatric outpatient department. Patients generally presented with multisystem complaints (ie, pulmonary, cardiologic) and saw medical subspecialists prior to psychiatric assessment. For this review, the research team worked collaboratively to review the psychiatric evaluations and determine sociodemographic and medical characteristics, psychiatric diagnoses and treatments recommended.

Measurements

The self-report scales utilized to assess symptom severity as part of the psychiatric evaluation were the Patient Health Questionnaire-9 (PHQ-9),[8] the Generalized Anxiety Disorder Questionnaire (GAD-7),[9] the Fatigue Severity Scale (FSS)[10] and the Columbia Suicide Severity Rating Scale (C-SSRS).[11] For data synthesis and standardization, a PHQ-9 score ≥10 was considered consistent with clinically significant depression symptoms. The breakdown of the PHQ-9 scale included: 0–4 no depression, 5–9 minimal depression, 10–14 moderate depression, and >15 severe depression. GAD-7 score equal or >5 was consistent with anxiety. The breakdown of GAD-7 scale included: 0–4 no or low risk, 5–9 low anxiety, 10–14 moderate anxiety, >15 severe anxiety. For the FSS, a score more than 36 was consistent with a finding of fatigue, with higher scores warranting intervention. The degree of insomnia was rated based on the PHQ-9 individual scoring (0- no insomnia, 1 = sleep difficulties some of the days, 2 = more than half of the days and 3 = nearly every day). Two participants did not have detailed PHQ-9 documented and their subjective assessment was used to categorize them; since both had not reported difficulties with sleep, 0 score was given to both of them. A subset of patients were screened cognitively utilizing the Montreal Cognitive Assessment (MOCA), with score less than 26 indicating potential cognitive problems.11

Data Analysis

The demographic features, symptoms and illness characteristics of the study group were identified along with delineation of the COVID-19 risk status based on CDC high-risk categories for COVID-19.[7] Quantification and categorization of comorbid conditions was also performed. Some individuals reported headaches, shortness of breath and cardiovascular complaints of PASC; these symptoms and associated diagnoses were not included as comorbid conditions.

Data were analyzed using IBM SPSS statistics for windows, version 26; descriptive statistics, including frequencies, means and standard deviations were used to characterize the sample in terms of demographic information, psychiatric diagnoses/symptoms, utilizing *t*-tests and regression analyses.

A subgroup analysis was performed after dividing the cohort into groups 1) individuals with past psychiatric history prior to COVID-19 and 2) those who had new onset of neuropsychiatric symptoms after COVID-19 in order to see if the two groups differed in demographic background, neuropsychiatric symptoms or treatment interventions recommended. Regression analyses were conducted comparing the severity of COVID with anxiety and depression scores to assess whether individuals with moderate or severe illness were more likely to develop more severe neuropsychiatric symptoms compared to those with milder illness.

As a secondary analysis, the number of individuals who had a predominant presentation of fatigue, cognitive changes and mood disturbance in comparison to individuals who experienced anxiety and mood shifts precipitated by stressful events was analyzed.

The data that support the findings in this study are available from the corresponding authors upon reasonable request.

Results
Sociodemographic Characteristics
The study population comprised an age range between 25 and 82 years with a median age of 51 years. Demographic data revealed a predominance of Caucasian, middle-aged women, between 46 and 60 years (Table 1).

The majority of individuals in this study experienced significant difficulty maintaining job responsibilities. Among the 26 (86%) of the participants who were employed prior to the pandemic, three-fourths experienced a significant interruption in their professional lives due to circumstances directly related to COVID-19 infection or its sequelae. The

Table 1 Demographics Including Age, Gender, Race, Employment Status and Relationship Status

	Total Number		No Past History		Past History		p-value
N	30		13		17		
Age (Avg, SD)	51.34	12.61	45.69	12.24	55.94	10.94	0.030
Gender							0.875
Gender Male (N,%)	04	13.%	01	8%	03	18%	
Gender Female (N,%)	26	87%	12	92%	14	82%	
Race							
Caucasian (N, %)	16	53%	6	46%	10	59%	
Black	04	13%	03	23%	01	6%	
Hispanic	04	13%	03	23%	01	6%	
Asian	01	3%	00	0%	01	6%	
Other	05	20%	01	7%	04	23%	
Employment Status							0.626
Current	07	23%	02	15%	05	29%	
Significant Interruption	18	60%	9	69%	09	53%	
Not employed/retired before pandemic	05	17%	02	15%	03	18%	
Relationship Status							0.816
Not Specified	07	23%	03	23%	04	24%	
In a Relationship	17	57%	7	54%	10	59%	
Not in a Relationship	06	20%	03	23%	03	18%	

remaining one-fourth of the employed patients who remained in active employment after the COVID-19 illness also reported cognitive difficulties and occupational performance issues, but these problems did not produce a prolonged interruption from work.

Among the individuals who experienced significant interruption, one-third had not been able to return to work on the most recent psychiatric assessment, as they were negotiating the terms of their return to work or were considering whether to stop work and file for disability. The remainder returned to work after a prolonged medical leave, filed for disability or were considering retirement. A smaller fraction changed their job or returned to work after significant adjustments to job designations.

It was also noteworthy that 7 out of the 30 individuals were active health-care professionals before the pandemic, while 1 was a recently retired nurse and 1 other individual worked for a scientific lab researching vaccines. This raised the question of post-traumatic stress in health-care workers exacerbating the neuropsychiatric sequelae.

Medical Characteristics

Out of 30 participants, 30% (N = 9) were diagnosed with the COVID-19 infection during February–March of 2020 which marked the introduction and widespread proliferation of the virus in North America. Simultaneously, 30% (N = 9) of the individuals were diagnosed with COVID-19 in January–February, 2021, coinciding with the colloquial "second wave" of the pandemic. The remainder were diagnosed with the infection ranging from January 2020 through March 2021. The average period of months that elapsed from the timing of consult to timing of COVID diagnosis was 7.23 months (SD ± 4.89 months). Pertaining to risk stratification, more than half of the individuals were designated as "high risk" in terms of COVID-19 risk stratification. Approximately three-fifths of the patients (63%) had a mild medical illness from COVID-19 itself with most of them reporting flu-like symptoms, gastrointestinal upset, gustatory or olfactory dysfunction. One-third of the patients had moderate illness constituting pulmonary symptoms, short-term hospitalization, or significant symptoms while at home. One of our study participants had a significant illness requiring intubation for hypoxia and prolonged hospitalization. The most common comorbid medical conditions noted in the study group were obesity, diabetes, hypertension and asthma (Table 2).

Psychiatric Characteristics

Most of the individuals in our study group sought consultation and treatment for memory impairment, fatigue, issues with cognitive processing, depression, and anxiety. The majority of these individuals (24, or 80%) reported that their psychiatric symptoms started simultaneously with the onset of the COVID-19 illness, while 6 (20%) reported that their symptoms started a few months after the initial diagnosis of COVID-19 illness.

Based on diagnostic outcomes (Table 3), approximately two-thirds (68%) of the patient population had a combination of depression and/or anxiety in addition to reported complaints of fatigue and cognitive problems, ie, memory impairments and slowed processing speed. Out of these, 14 (47%) met the criteria for a primary depressive disorder, followed by 17% (n = 5) who met the criteria for a primary anxiety disorder and 7% (n = 2) who met the clinical criteria for both a depressive disorder and an anxiety disorder. Another 17% (n = 5) met the primary diagnosis of adjustment disorder.

Table 2 Analysis of Past Psychiatric History and Medical Comorbidities

	Total Number		No Past History		Past History		p-value
N*	30		13		17		
Medical Co-morbidities (Avg., SD)	1.13	0.96	1	0.96	1.24	0.96	0.521
Risk Stratification							0.794
Low	13	43%	6	46%	7	41%	
High	17	57%	7	54%	10	59%	

Note: *Total number of individuals (N).

Table 3 Psychiatric Self-Report Measures Including GAD-7, PHQ-9, FSS, C-SSRS, and Psychiatric Diagnosis Categorized Based on Previous Past Psychiatric History

	Total Number		No Past Psychiatric History		Past Psychiatric History		p-value
N*	30		13		17		
GAD-7(Avg., SD)**	8.70	4.97	8.69	4.16	8.71	5.51	0.994
PHQ-9*(Avg., SD)**	10.13	6.99	11.38	6.46	9.18	7.23	0.409
FSS**(Avg., SD)**	44.43	14.72	38.77	14.73	48.76	13.16	0.069
Insomnia (Avg., SD)	1.81	1.19	2.25	1.09	1.47	1.15	0.095
C-SSRS***							0.064
C-SSRS Negative (N,%)	26	87%	13	100%	13	76%	
C-SSRS Positive (N,%)	04	13%	00	0%	04	24%	
Substance Use							0.214
Substance Use None (N,%)	28	93%	13	100%	15	88%	
Substance Use present (N,%)	02	7%	00	0%	02	12%	
Psychiatric Diagnosis							0.126
No psychiatric diagnosis	04	13%	03	23%	01	6%	
Anxiety Disorder	05	17%	01	8%	04	24%	
Depressive Disorder	14	47%	06	46%	008	47%	
Depressive Disorder, Anxiety Disorder	02	7%	00	0%	02	12%	
Adjustment Disorder	05	17%	3	60%	02	20%	

Notes: *Total number of individuals (N). **Generalized anxiety disorder scale 7; the score of greater than 5 was considered positive for anxiety. ***Patient health questionnaire-9; the score equal or greater than 10 was positive for depression. ****Fatigue severity score; the score of 36 or greater was considered positive for fatigue. *****Columbia suicide rating scale – previous history of suicide attempts or severe ideation was considered positive.

Four (15%) of the patients had no primary psychiatric diagnosis and presented exclusively for fatigue and cognitive complaints.

Based on the self-report scales, approximately half of the study population reported significant depression and three-fourths of the cohort had clinically significant anxiety (mild n = 12, moderate n = 7 and severe n = 4). The FSS scale revealed 70% (N = 21) individuals reporting significant interference in activities of daily living (ADLs) because of fatigue. Insomnia was also noted in slightly less than three-fourths of individuals. None of the individuals reported current suicidal ideation on the C-SSRS; however, 13% (N = 4) in the group reporting past psychiatric history had remote history of suicide attempt or ideation (N = 2 for suicide attempt, N = 2 for suicidal thoughts). Substance abuse was reported in just 2 (7%) of the patients, with one individual reporting an increase in use secondary to COVID-19 illness and the pandemic.

A small number of patients had dyadic symptoms with cognitive difficulties and fatigue. None of the individuals who complained of isolated cognitive difficulties with fatigue had a prior psychiatric history. A more inclusive analysis with an addition of mood disturbances revealed that 33% patients experienced these neurological symptoms with or without mood disturbance.

The regression analysis predicting PHQ-9 and GAD-7 scores by the severity of acute COVID-19 illness showed no association between the severity of the medical illness and the severity of depression or anxiety symptoms (depression: (R-square 0.018, P-value 0.479; anxiety R-square 0.02, P = 0.377 respectively). Comparison of patients 1) with a past

psychiatric history (n = 17) with 2) no psychiatric history (n = 13) on the basis of age, gender, race and employment status revealed those with prior psychiatric history were older (Mean age = 55.94 SD = 10.94 versus Mean age = 45.69, SD = 12.24, P = 0.03). There was no difference between the two groups on any other variable (Table 1).

Sixteen patients were screened cognitively utilizing the MOCA, with no systematic differences between those who were or were not screened. Of these, 10 (63%) had scores <26. Seven of those 10 individuals (70%) had cognitive complaints and 3 individuals did not. Of the 12 individuals who presented to the consultation with cognitive complaints, 7 individuals (58%) had MOCA scores <26. Finally, among those with impairment, psychiatric diagnosis reflected the overall sample, with 5 individuals having a diagnosis of depression, 1 individual with a diagnosis of anxiety and 2 individuals with adjustment disorder with mixed anxiety and depression, while 2 had no psychiatric diagnosis but complaints of fatigue. Correlation of total MOCA score and PHQ-9 was not statistically significant (R-square 0.02, P-value 0.938).

The semi-structured nature of the review also allowed for assessment of the nature of stressors faced by patients seen in psychiatric consultation. Death of a loved one, lack of access to healthcare, financial loss, vocational issues, reduced capacity for attention, diminished stamina, internalization of negative self-appraisal, isolation, post-traumatic symptoms, increases in substance use, increases in dietary intake and lack of physical activity causing weight gain were among the self-reported stressors.[20]

Treatment Characteristics

Among the treatments recommended, modafinil was the most commonly prescribed medication, with or without concomitant antidepressant use, to target pervasive fatigue (Table 4). A smaller fraction of individuals were recommended antidepressant

Table 4 Treatments Recommended and Response to Treatment

	Total Number	
N*	30	
Total Treatment Offered		
Antidepressant	04	13%
Antidepressant and sleep medication	01	3%
Antidepressant, short-term benzodiazepines	01	3%
Modafinil	10	33%
Modafinil, antidepressant	02	7%
Modafinil, antidepressant and short-term benzodiazepines	02	7%
None	05	17%
Sleep medication	01	3%
Therapy	04	13%
Continuation of previous treatment	05	17%
Response to Treatment		
Not Available	20	67%
Minimal improvement	2	7%
Moderate improvement	2	7%
Substantial improvement	6	20%

Note: *Total number of individuals (N).

treatment alone for anxiety or depressive symptoms. Out of the individuals offered antidepressant treatment, 80% (N = 8) individuals were offered selective serotonin reuptake inhibitors (SSRI) while the remaining one-fifth (N = 2) were treated with serotonin norepinephrine reuptake inhibitor (SNRI) or norepinephrine-dopamine reuptake inhibitor (NDRI). Some patients who were in psychiatric treatment prior to the consultation were continued on the same medication after considering their current symptoms. The remainder were recommended to have psychotherapeutic interventions, cognitive remediation or sleep medication. Five participants did not require any further treatment intervention.

Discussion

This study examined the long-term neuropsychiatric sequelae of COVID-19 patients evaluated in an outpatient psychiatric clinic setting, revealing several important findings regarding the demographics, psychiatric symptoms, psychosocial characteristics, and treatments recommended.

Analysis revealed that on average, these individuals had been diagnosed with COVID more than 6 months prior to psychiatric consultation and reported new-onset symptoms, which is consistent with the diagnosis of the PASC. In light of the timing of diagnosis and COVID surges, we infer that most individuals assessed suffered from the Alpha variant of SARS-CoV2 and some with the Delta variant. It is noteworthy that patients were facing multiple psychosocial stressors, including personal, occupational and financial losses contributing to their psychiatric presentation.

In this patient group, depression, often with comorbid anxiety, was the most commonly observed disorder for which patients sought treatment. However, fatigue and cognitive problems were also prominent aspects of their presentation. These findings are consistent with prior non-clinical literature on PASC.[2–4] An important finding from the study of these patients was that those with past psychiatric history were not more likely to report new symptoms of anxiety, depression, or insomnia following COVID-19 illness, than those with no past psychiatric history (Tables 1–3). This supported the recommendation that new symptoms of anxiety, depression, or insomnia should not be attributed to a pre-existing psychiatric diagnosis, and may be part of COVID-19 sequelae. However, it was also possible that some underlying psychiatric pathologies remained undiagnosed prior to infection with COVID-19, which due to enhanced stress may have unmasked anxiety or depressive symptoms. Statistical analysis revealed age to be the only significant difference between groups of patients with and without past psychiatric diagnoses. It was possible that older age provided more time for patients to have a psychiatric condition diagnosed. Based on our clinical experience with this cohort, where depression, anxiety, fatigue and cognitive complaints were prominent, the manifestation of depression after COVID-19 may best lend itself to a dimensional diagnostic approach because there may be multiple "depression" symptom presentations.[13] Characterizing potential Post-COVID-19 depression subtypes and differentiating from other forms of depression is a fruitful area of potential research.

Fatigue and cognitive complaints were also commonplace in this patient group, and were most often comorbid with depression and anxiety symptoms. Interestingly, in those screened for cognitive problems by the MOCA, nearly two-thirds scored below the cut-off score of 26, suggesting the need for further neuropsychological investigation.[12]

Another important finding in this cohort of mildly to moderately ill COVID-19 patients was that the severity of acute medical illness from COVID-19 did not appear correlated with probability of experiencing neuropsychiatric sequelae. In addition, patients with increased comorbid conditions did not present with increased neuropsychiatric of COVID-19. This stressed the importance of screening all patients with COVID-19 for neuropsychiatric symptoms regardless of medical disease severity.

In this patient population, different treatment modalities were considered to target the neuropsychiatric symptoms associated with the PASC based on the patient's medical history, as well as weighing the risks and benefits associated with each treatment offered. The study provides a glimpse into treatment options for long-term sequelae of COVID-19, especially depression, fatigue and cognitive complaints.

In this group, antidepressants and modafinil were the most commonly prescribed medications, often in combination, to address depression, fatigue and cognitive complaints. The use of Modafinil was off-label for fatigue; however, this agent has been shown to improve mood, sleepiness, cognition and fatigue associated with other medical conditions.[14] Bivard et al demonstrated in a randomized cross-over trial how modafinil alleviated post-stroke fatigue and improved quality of life.[15] In addition, the use of modafinil has been shown to be effective and well tolerated in treating fatigue in other viral syndromes including human immunodeficiency virus/acquired immune deficiency syndrome and hepatitis C.[16,17] Among

those treated, there was a subjective positive response from the use of Modafinil, as patients reported that their symptoms of fatigue improved and they were able to return to their level of function prior to the COVID-19 infection. This supports the consideration by Wainwright (2021) regarding the use of modafinil as a safe and effective intervention targeting fatigue associated with the long-term sequelae of COVID-19 and warrants further clinical observation.[18] While patients in this clinic were prescribed modafinil for fatigue, other psychostimulant or wakefulness agents may be considered for these symptoms if modafinil is not available.

Based on the stressors and psychosocial themes presented by these patients, the use of non-pharmacologic approaches, including individual and group psychotherapies addressing issues of loss, diminished social and occupational function and coping with illness were recommended. Such interventions were often delivered via telehealth. Psychotherapeutic interventions specific to pandemic stressors need to be developed and tested.

Limitations to the present study affect its generalizability and emphasize the need for further research with broader, more diverse clinical populations. This patient group comprised a relatively small sample and all patients were referred from the same post-COVID care program, which might have biased referral patterns. Further, the patients were predominantly caucasian and female, which does not reflect the broader demographics of the pandemic[17]. This difference could be explained by barriers in access to care, local population demographics, societal stigmas around seeking care, and gender differences in symptom and referral patterns. While depression, anxiety, insomnia, and cognitive complaints were encountered as a part of this study, other psychiatric disorders such as schizophrenia or bipolar disorder were not. Furthermore, formal neuropsychological testing was not available in this group of patients, so that actual neurocognitive performance could not be determined. Finally, the lack of long-term follow-up by study participants posed a limitation on reporting treatment outcomes.

Conclusion

Despite limitations to the present study, the significant impact of neuropsychiatric, psychosocial and occupational sequelae of COVID-19 illness on patients referred for psychiatric evaluation and treatment emphasizes the importance of research involving new and effective treatment options. Further, screening for neuropsychiatric sequelae and the development of referral options for patients presenting to primary care physicians and specialists for symptoms of PASC is highly recommended.

Disclosure

Authors have no financial/non-financial conflicts of interest in this work.

References

1. Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. *World Psychiatry*. 2021;20(1):124–130. doi:10.1002/wps.20806
2. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. *JAMA*. 2020;323(24):2466–2467. doi:10.1001/jama.2020.8598
3. World Health Organization. A clinical case definition of post-COVID-19 condition by a Delphi consensus; 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1. Accessed April 1, 2022.
4. Søraas A, Bø R, Kalleberg KT, Støer NC, Ellingjord-Dale M, Landrø NI. Self-reported memory problems 8 months after COVID-19 infection. *JAMA Netw Open*. 2021;4(7):e2118717. doi:10.1001/jamanetworkopen.2021.18717
5. Groff D, Sun A, Ssentongo AE, et al. short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open*. 2021;4(10):e2128568. doi:10.1001/jamanetworkopen.2021.28568
6. Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. *Cell*. 2020;183(1):16–27.e1. doi:10.1016/j.cell.2020.08.028
7. Kompaniyets L, Pennington AF, Goodman AB, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020–March 2021. *Prev Chronic Dis*. 2021;18:E66. doi:10.5888/pcd18.210123
8. Costantini L, Pascuarella C, Ordone A, et al. Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): a systematic review. *J Affect Disord*. 2021;279:473–483. doi:10.1016/j.jad.2020.09.131
9. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–1097. doi:10.1001/archinte.166.10.1092
10. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022
11. 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. doi:10.1176/appi.ajp.2011.10111704

12. Davis DH, Creavin ST, Yip JL, Noel-Storr AH, Brayne C, Cullum S. Montreal cognitive assessment for the diagnosis of alzheimer's disease and other dementias. *Cochrane Database Syst Rev.* 2015;2015(10):CD010775. doi:10.1002/14651858.CD010775.pub2

13. Ng QX, Lim DY, Chee KT. Reimagining the spectrum of affective disorders. *Bipolar Disord.* 2020;22:638–639. doi:10.1111/bdi.12960

14. Kumar R. Approved and investigational uses of modafinil: an evidence-based review. *Drugs.* 2008;68(13):1803–1839. doi:10.2165/00003495-200868130-00003

15. Bivard A, Lillicrap T, Krishnamurthy V, et al. MIDAS (Modafinil in Debilitating Fatigue After Stroke): a randomized, double-blind, placebo-controlled, cross-over trial. *Stroke.* 2017;48(5):1293–1298. doi:10.1161/STROKEAHA.116.016293

16. Rabkin JG, McElhiney MC, Rabkin R, McGrath PJ. Modafinil treatment for fatigue in HIV/AIDS: a randomized placebo-controlled study. *J Clin Psychiatry.* 2010;71(6):707–715. doi:10.4088/JCP.09m05171bro

17. Rabkin JG, McElhiney MC, Rabkin R. Modafinil and armodafinil treatment for fatigue for HIV-positive patients with and without chronic hepatitis C. *Int J STD AIDS.* 2011;22(2):95–101. doi:10.1258/ijsa.2010.010326

18. Wainwright L. Lessons from psychiatry for treating post-acute Covid-19 fatigue. *Australas Psychiatry.* 2021;29(5):560–561. doi:10.1177/10398562211003598

19. Costanza A, Amerio A, Aguglia A, et al. "The Interpersonal Theory Of Suicide" to "The Interpersonal Trust": an unexpected and effective resource to mitigate economic crisis-related suicide risk in times of Covid-19? *Acta Biomed.* 2021;92(S6):e2021417. doi:10.23750/abm.v92iS6.12249

20. Costanza A, Macheret L, Folliet A, et al. COVID-19 related fears of patients admitted to a psychiatric emergency department during and post-lockdown in Switzerland: preliminary findings to look ahead for tailored preventive mental health strategies. *Medicina.* 2021;57(12):1360. doi:10.3390/medicina57121360