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Case Report

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Methylphenidate for the Treatment of Post-COVID Cognitive Dysfunction (Brain Fog)

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Abstract

A substantial number of patients develop cognitive dysfunction after contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), significantly contributing to long-coronavirus disease (COVID) morbidity. Despite the urgent and overwhelming clinical need, there are currently no proven interventions to treat post-COVID cognitive dysfunction (PCCD). Psychostimulants like methylphenidate may enhance both noradrenergic and dopaminergic pathways in mesolimbic and pre-frontal areas, thus improving memory and cognition. We present a case series of six patients who were treated at the Johns Hopkins Post-Acute COVID-19 Team (PACT) clinic for PCCD with methylphenidate 5 - 20 mg in the context of routine clinical care and followed for 4 to 8 weeks. Baseline and post-treatment outcomes included subjective cognitive dysfunction and objective performance on a battery devised to measure cognitive dysfunction in long-COVID patients. Three out of the six patients reported subjective improvement with methylphenidate, one patient described it as "notable" and another as "marked" improvement in memory and concentration. We also found significant pre-treatment subjective complaints of cognitive dysfunction; however, formal cognitive assessment scores were not severely impaired. A statistically significant difference in pre and post scores, favoring intervention, was found for the following cognitive assessments: Hopkins verbal learning test (HVLT) immediate recall, HVLT delayed recall and category-cued verbal fluency. The current series demonstrates promising neurocognitive effects of methylphenidate for long-COVID cognitive impairment, particularly in recall and verbal fluency domains.

Keywords: Long-COVID; Cognitive dysfunction; Brain fog

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Introduction

Although most individuals recover from acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a significant minority develop persistent symptoms known as long-coronavirus disease (COVID) or post-acute sequelae of SARS-CoV-2 (PASC). Up to 35% of these individuals develop unexplained cognitive symptoms that are frequently referred post-COVID cognitive dysfunction (PCCD) [1]. Although there is no standardized definition of PCCD, it is generally described as a condition in which patients with a history of SARS-CoV-2 infection, usually 3 months from the onset, exhibit subsequent cognitive impairment in various cognitive domains, and cannot be explained by an alternative diagnosis [1]. By contrast, "brain fog" is a colloquial term that may encompass anxiety, mood alterations, forgetfulness, trouble focusing, and a general sense of mental sluggishness [2]. PCCD incorporates symptoms in multiple cognitive domains such as concentration issues, word-finding difficulties, memory impairment, disorientation and executive functions [3]. PCCD is correlated with psychological distress and decreased psychomotor performance and continued disability [4]. An analysis of retrospective cohort studies including nearly 1.3 million patients showed that up to 2 years after COVID-19 infection, risk of PCCD continued to be elevated [5].

Despite the urgent and overwhelming clinical need, there are currently no proven interventions to treat PCCD. Neurobiological data can help in hypothesizing treatments for PCCD. Methylphenidate is a piperidine-derived central nervous system stimulant and is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. It works as a central norepinephrine and dopamine reuptake inhibitor.

A recent systematic review reports that methylphenidate can improve attention and memory in ADHD [6]. Additionally, our group previously used methylphenidate to successfully treat apathy in dementia, which has several phenomenological similarities with PCCD [7], such as diminished motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress [8]. Therefore, we hypothesized that methylphenidate could be an effective intervention for PCCD. This approach is based on the understanding that motivated behaviors rely not only on the dopaminergic mesolimbic brain reward system but also on newly evolved prefrontal cortical circuits [9] which may be dysregulated in long-COVID and methylphenidate may enhance both noradrenergic

and dopaminergic signals to strengthen cognitive function. Methylphenidate has been found to be safe and well-tolerated in multiple previous studies [10, 11]. We present a case series of six patients presenting for treatment of cognitive deficits associated with COVID-19 treated with methylphenidate in the context of routine clinical care.

Case Report

We followed six patients treated at Johns Hopkins Post-Acute COVID-19 Team (PACT). All of these patients reported functionally limiting post-COVID cognitive impairment, with subjective complaints of impaired memory, concentration, fatigue, confusion and listed "brain fog" as one of the main reasons for not being able to return to work post-COVID-19 illness. Mean duration of the post-COVID symptoms was 2.1 years. They were treated with methylphenidate 5 - 20 mg and followed for 4 to 8 weeks. This treatment was in the context of routine clinical care and thus did not require any ethics board approval. We used cognitive assessment procedures based on previously developed measures of cognitive dysfunction in the long-COVID patients [12], to monitor clinical progress, which included the following components.

Hopkins verbal learning test-revised (HVLT-R)

The HVLT-R is a test of new auditory-verbal learning, memory, and recognition discrimination. A list of 12 words is read aloud over three consecutive exposure trials, each of which is followed immediately by the testing of free recall. Following a 20-min delay, a delayed free recall trial is administered followed by a test of yes/no recognition memory for target words versus foils. Scores reflect the correct numbers of words recalled over immediate recall trials (range = 0 - 36), delayed recall (range = 0 - 12), and in response to recognition testing (range = -12 to 12). Administration time is approximately 10 min [13].

Oral trail making test parts A and B (oral TMT)

The oral TMT is a brief, motor-free test of mental processing speed (part A) and executive functioning requiring sequential set shifting (part B). Part A involves asking the participant to count from 1 to 25 aloud as quickly as possible. Part B requires participants to count aloud while switching between numbers (1-13) and letters (A-L) as quickly as possible. Performances are based on the time in seconds required to complete each part. Administration time is 5 min [14].

Letter-cued verbal fluency

Letter-cued verbal fluency assesses speeded word retrieval in response to phonetic cues. The participant is asked to name as many words as possible beginning with a certain letter of the alphabet. The score reflects the total number of unique responses beginning with the given letter across two 1-min trials. Cues are letters S, and P. Perseverations (repeated words) and intrusions (words that break the task rules, such as starting with a different letter) are also recorded. Administration time is 4 min [15].

Category-cued verbal fluency

Category-cued verbal fluency assesses rapid access to semantic information. The participant is asked to name as many items of a given semantic category as possible. The score reflects the total number of unique category-congruent responses given across two 1-min trials. Cues for English are animals and supermarket items. Cues for Spanish trials are animals. Perseverations (repeated words) and intrusions (words that break the task rules, such as stating a proper noun) are also recorded. Administration time is 3 min [15].

Narrative results are presented in Table 1. Methylphenidate was well-tolerated, and four of six patients did not report any adverse effects. The remaining two patients complained of gastric upset and increased fatigue, with one discontinuing methylphenidate due to the adverse effects. Another patient was advised to stop all psychiatric medications by her pharmacist after being started on clopidogrel for concerns of drug-drug interactions. One patient decided to go back to his old regimen of modafinil after trying methylphenidate for 4 weeks without any cognitive improvement. Three out of the six patients reported subjective improvement with methylphenidate, one patient described it as "notable" and another as "marked" improvement in memory and concentration.

Patient demographics and cognitive scores at baseline and follow-up are summarized in Table 2. We found significant subjective complaints of cognitive dysfunction during this case series: qualitatively defined as complaints of having "word finding difficulties, slow processing speed, difficulty paying attention and concentrating, and difficulty reading and retaining read information and general increased feelings of physical and mental fatigue". The main complaint was the patient's report of reduced energy levels. Four out of the six patients reported feeling that their cognition worsens in the evening, some referring to this as feeling "spent", experiencing mental "crashes" or having a "heaviness on (their) brain that slows (them) down". We prescribed immediate-release generic formulation of methylphenidate and patients were instructed to take it in the morning. Despite these subjective complaints, formal cognitive assessment scores were not severely impaired. We found a statistically significant difference in pre and post scores for HVLT immediate recall (mean difference: 3.3, 95% confidence interval (CI): 1.02 - 5.64, P = 0.006), HVLT delayed recall (mean difference: 1.0, 95% CI: 0.75 - 1.93, P = 0.019) and category-cued verbal fluency (mean difference: 3.3, 95% CI: 0.89 - 7.56, P = 0.05). The scores from cognitive assessment and results of the statistical analyses are summarized in Table 3.

Discussion

PCCD continues to be one of the most prevalent and challeng-

Table 1. Qualitative Visit Notes on Pre-/Post-Psychostimulant Drug

Subject	Pre-drug	Post-drug
1	Patient described problems with word finding and slow speed of processing. Symptoms better in the morning and get worse in the afternoon as the day goes on. patient is an attorney and writes all day for work. Also has some troubles conversing and preparing for any kind of legal argument. Patient also described troubles with short-term memory and repeating themself. Had to keep lists in personal life, but not so much in his work life. Finds that brain fog comes and goes particularly alongside their physical condition. For example, if they are physically fatigued.	Patient continued to complain of problems with concentration and sustained attention as well as fatigue. Patient did not respond well to Ritalin and went back on modafinil (200 mg). Medication stopped; patient returned to new "normal" baseline.
2	Patient reported dyspnea on exertion, easy fatigability, and difficulties with memory and concentration. Finds that when having a conversation thy often forget what their partner said. Patient's partner had noticed this and is the reason they came to the COVID clinic. Subjective memory complaints which impair the patient occupationally, but remarkably patient was quite normal on formal neuropsychologic testing.	Patient had been taking Ritalin currently 5 mg with breakfast and lunch did not notice any benefit nor any side effects at this time. At the beginning patient reported having headaches for a few days but they went away. Patient reported that they do not notice that Ritalin has significantly affected cognition for the better, nor any adverse events. Patient did not notice any benefit nor any significant adverse events from low-dose Ritalin and the dose increase the dose to 10 mg twice daily. Patient developed slight stuttering and poor appetite after the dose increase. However, he did not notice any improvement in his brain fog or concentration and methylphenidate was stopped.
3	Severe case of COVID-19, had collapsed lung and pneumonia. Patient reported problems with memory, concentration and also possible language. Unable to read or write for a several months following COVID-19 infection. Difficulty writing. Cannot keep track of the day or what they are doing. Sometimes they lose track of whole days or sections of the day. Easily overstimulated and when overstimulated has a hard time concentrating. Sometimes has to pull over and take a rest while driving to calm their mind down. Has to use their GPS or they will get lost even in their own neighborhood. Describes trouble with sustained attention.	Started patient on methylphenidate (Ritalin) 5 mg in the morning with breakfast and as instructed to increase after 2 weeks to 5 mg with breakfast and lunch (10 mg total). They had a lot of adverse effects and stopped the medicine after approximately 10 days. These adverse effects included nausea, some vomiting, and disturbed sleep. They really tried quite hard to stick with the medicine hopefully go away but they did not. Once stopped the medication, the side effect dissipated in a couple of days and they are back to their normal self. They describe some dissociative symptoms and also problems with retrieving information and concentration.
4	Had mild case of COVID-19 in December 2021. Around March 2022 patient noted that they were not thinking as clearly as they should. Patient describes it "like a heaviness on their brain that slows them down". Patient described struggling under any "mental or physical exertion". For example, they feel that the "stress of today's visit will exhaust them". Post-COVID complaints of problems with concentration, and some modest deficits on testing (recall and lexical fluency). Patient has had to stop working due to cognitive changes. Patient found they were making mistakes, taking longer to get the same amount of work done, and had to finish up the day at home because they had to double-check everything, they had done at work that day.	Patient reported improved cognitive energy and focus. Patient had a greater ability to complete tasks, used to leave everything pretty much half-done but now not as much. However, patient reported notable ups and downs, the downs he refers to as "crashes". Some of them seemed related to medication wearing off, i.e., getting cognitively fatigued at around 3 p.m. This was not a consistent symptom. Patient reported no adverse effects: Ritalin hasn't affected sleep or appetite, or increased omnipresent anxiety.
5	Patient reported marked fatigue and dyspnea on exertion, accompanied by "cognitive fatigue" particularly later in the day. Patient says they were so fatigued and short of breath on several doctor's visits that they couldn't get up, and the doctors said they would need to be hospitalized if they couldn't, but they did. Patient had had 1st booster vaccine at the time of infection. Since time of infection, patient feels a little better but still has "mental fatigue". By the end of the day, they feel "mentally empty", like they can't think, and are really "spent". Sleep is somewhat interrupted and patient is taking Atarax for sleep. Post-COVID concentration deficit. Like many people with these syndromes, patient scores well on these standard cognitive tests but has marked complaints of cognitive fatigue particularly late in the day.	Patient initially reported notable benefit from methylphenidate. It helped with fatigue and concentration and to get work done. However, patient had had a very busy 6-week period which led to the resurgence of fatigue and insomnia; methylphenidate was increased to 10 mg per day. Patient reported difficulty sleeping but thought that insomnia was due to stress. Reported some dyspnea and used an inhaler. Patient continued to report fatigue and dose was further increased to 10 mg twice a day. He reported a distinct improvement in cognitive deficits but only a mild amelioration of fatigue.
6	COVID long-hauler with concentration and working memory problems. Like most persons with these syndromes patient doesn't have any gross deficits on neuropsychological screening but they are affecting his daily life. He was on Modafinil, which was switched to methylphenidate.	Patient experienced many side effects at first: blurry vision one hour after dose, headaches, cognitively more confused and foggier. However, despite these side effects, patient did report that they had improved energy and less fatigue. most of the side effects went away except minimal headaches. Definitely reported more energy. More confident with tasks. Once again able to do mindfulness exercises/meditation which helps patient concentrate. Patient still had difficulties with language and reading and was seeing a speech therapist. Had no problem with IADLs but fatigue frustrated his ability to complete tasks.

Table 2. Demographic Characteristics, Baseline, Follow-Up Scores and Adverse Effects Reported by the Patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	32	36	56	56	40	38
Sex	Male	Male	Female	Male	Female	Male
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Weight (pounds)	194	291	203	201	157	160
Duration of long-COVID symptom	1.9 years	2.4 years	2 years	2.2 years	2.7 years	1.9 years
Comorbidities	None	H/O concussion	None	None	None	None
Methylphenidate dose	5 mg	20 mg	5 mg	10 mg	20 mg	10 mg
Follow-up interval	4 weeks	4 weeks	3 weeks	4 weeks	8 weeks	4 weeks
Treatment duration	10 days	16 days	10 days	10 months	3 months	1 year
HVLT immediate recall - baseline	29	32	25	26	34	26
HVLT immediate recall - follow-up	33	35	32	25	36	31
HVLT delayed recall - baseline	9	12	11	8	12	10
HVLT delayed recall - follow-up	12	12	12	9	12	11
HVLT delayed recognition - baseline	11	24	23	19	24	24
HVLT delayed recognition - follow-up	5	4	4	10	12	10
Oral trail A - baseline	21.79	8.1	18.47	9.8	6.34	7.48
Oral trail A - follow-up	13.17	8.6	15.39	9.42	6.35	6.67
Oral trail B - baseline	48	24.87	43.11	32.9	38.82	32.61
Oral trail B - follow-up	55.2	27.93	35.58	26	27.3	34.8
Letter-cued verbal fluency - baseline	17	51	24	26	40	25
Letter-cued verbal fluency - follow-up	21	44	30	24	37	31
Category-cued fluency - baseline	44	61	40	49	67	41
Category-cued fluency - follow-up	40	64	41	55	78	44
Adverse effects reported	Fatigue	None	Disturbed sleep, GI upset	None	None	None

HVLT: Hopkins verbal learning test; GI: gastrointestinal.

ing manifestations of long-COVID syndrome. A recent analysis has shown that a year after SARS-CoV-2 infection, PCCD persists in a third of patients with long-COVID [1]. PCCD is associated with other long-COVID symptoms and is independently associated with persistent debility [16]. The underlying physiological mechanisms contributing to PCCD are unknown. Physiological responses specific to SARS-CoV-2 may contribute to long-term brain pathology, particularly immune-mediated neuroinflammation and neuronal loss in hippocampus [17]. Neuroinflammation, even without viral invasion of the central nervous system, may also trigger decreased hippocampal neurogenesis affect cognition [18]. A recent study exploring cognitive dysfunction in PCCD through eye movement abnormalities suggests impairments in frontal subcortical circuits PCCD patients who report subjective cognitive complaints [19].

This case series suggests that methylphenidate may be helpful in improving free or spontaneous recall. A previous study found that spontaneous recall is the most severely impacted cognitive domain in PCCD [20]. In our case series,

Table 3. Cognitive Assessment Scores at Baseline and Follow-Up Analysis Results

	HVLT immediate recall	HVLT delayed recall	HVLT delayed recognition	Oral trail A	Oral trail B	Letter-cued verbal fluency	Category-cued verbal fluency
Difference in mean (SD)	3.33 (1.02 - 5.64)	1 (0.75 - 1.93)	1.16 (-7.38 - 5.04)	2.06 (-0.84 - 4.9)	2.25 (-3.98 - 8.48)	3.3 (0.89 -7.56)	3.3 (0.89 - 7.56)
z	-2.18	-2.19	-1.12	1.69	0.85	-0.34	-1.53
Hedge's g	0.91	0.71	-0.21	-0.40	-0.23	-0.64	0.25
P-value	0.006	0.019	0.35	0.93	0.79	0.36	0.05

HVLT: Hopkins verbal learning test.

methylphenidate was well-tolerated; however, two patients reported increased complaints of fatigue, although on clinical assessment they seemed to be functioning better. The association between depressed mood and cognitive complaints following COVID-19 also continues to be explored. In a study of 137 patients a year after COVID-19 recovery, depression was found to be the strongest predictor of PCCD [21]. In this study, patients with long-COVID did not have severe cognitive deficits on formal testing despite subjective complaints of brain fog. However, it should be noted that this study used self-rated depression scale (SDS) to screen depression, which includes somatic symptoms that can be caused by other long-COVID comorbid conditions. We noticed a similar trend in our case series, where patients mentioned feeling "dispirited" or "mentally empty". It has been hypothesized that viral infection and type I interferon-driven inflammation reduces peripheral serotonin, in turn impeding the activity of the vagus nerve and thereby impairing hippocampal responses and memory [22]. However, to date, there is no conclusive evidence that serotonergic enhancers such as selective serotonin reuptake inhibitors improve PCCD.

Currently, there are no proven treatments for PCCD. There are several ongoing clinical trials to test the safety and efficacy of potential drugs for the treatment of PCCD, including donepezil (IRCT2021081605 2203N1), famotidine (IRCT20090117001556N138), vortioxetine (NCT05047952), temelimab (NCT05497089) and atorvastatin (NCT04904536). In addition, nirmatrelvir/ritonavir, is also currently undergoing clinical trials, with cognitive function as a primary (NCT05595369) and secondary (NCT05668091, NCT05576662) outcome measure. There is also preliminary evidence that luteolin, a natural flavonoid, may alleviate cognitive impairment by inhibiting mast cell and microglial activation [23]. A case series reported that a combination of guanfacine and N-acetylcysteine improved cognitive symptoms in eight of the 12 long-COVID patients; however, four patients discontinued the regimen due to the adverse effects of hypotension and/or dizziness related to guanfacine [24]. A previous case report also reported improvement in post-COVID inattention and fatigue symptoms with methylphenidate, along with lisdexamfetamine and bupropion in a 61-year-old patient [25]. These observations suggest some of the symptoms of PCCD may present as an ADHD-like syndrome, despite the evidently different etiology of symptoms.

There are several case reports of non-pharmacological interventions as well. A case series of 23 PCCD reported that repetitive transcranial magnetic stimulation (rTMS) may have beneficial effects on neuropsychiatric symptoms, including depressive symptoms, chronic fatigue, and cognitive impairment [26]. Another case report of two patients reported that neuromodulation with non-invasive brain stimulation using microcurrent (NIBS) was effective in improving visual and cognitive deficits in two confirmed SARS-CoV-2 patients [27].

This case series has several limitations. The dose of methylphenidate was low (5 to 20 mg per day). This limitation is important in the light of recent guidelines recommending dose optimization for methylphenidate for treatment of inattentive symptoms in adult ADHD [28]. Therefore, use of higher doses may have resulted in additional benefits such as reduction in fatigue. Furthermore, we used the immediate-release dose of methylphenidate, which may have been insufficient for symptom control throughout the day. In addition, due to the very small sample size, the statistical inferences derived in our analysis may not be valid.

The current report suggests potential beneficial neurocognitive effects of methylphenidate for long-COVID cognitive impairment. Future placebo-controlled trials are warranted to rigorously evaluate the role of methylphenidate in PCCD but given methylphenidate's relatively favorable safety profile, it can be considered as a potential therapy for this often-disabling condition at a time when there are no approved interventions.

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Conflict of Interest

None to declare.

Informed Consent

All patients provided informed consent.

Author Contributions

Phoebe Clark, Paul Rosenberg, and Mansoor Malik: analysis of data and writing the manuscript. Esther S. Oh, Ann Parker, Tracy Vannorsdall, Alba Azola, Elizabeth Nickles, and Panagis Galiatsatos: review of manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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