



An Illustrative Case Series: Psychiatric Conditions in Long Covid

Karanbir Padda¹, MD, Daniel Shalev¹, MD, Kiran T. Thakur², MD, Andrew Edelstein¹, MD, Yochai Re'em¹, MD

Weill Cornell Medicine

¹Department of Psychiatry, NewYork-Presbyterian/Weill Cornell Medical Center, New York, NY

²Department of Neurology, NewYork-Presbyterian/Columbia Irving Medical Center, New York, NY

NewYork-Presbyterian

Background

- Long Covid, or Post-Acute Sequelae of COVID-19 (PASC), is a heterogeneous post-Covid syndrome that affects multiple organ systems (Table 1 & 2).
- Neuropsychiatric studies have identified depression and anxiety in >30% of COVID-19 survivors, and post-traumatic stress disorder (PTSD) in up to 43%.¹
- The high rates of post-exertional malaise and autonomic dysfunction in PASC have led to parallels being drawn between PASC and Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)² and dysautonomias such as Postural-Orthostatic Tachycardia Syndrome (POTS)³ (Table 1).
- Guided by sample cases, we leverage our clinical experience with PASC, as well as existing data from ME/CFS and POTS literatures to develop an approach to evaluation and management of psychiatric disorders in this population, focusing on anxiety and depressive disorders.

Illustrative Cases

- A 31 year old athletic woman with no prior psychiatric or medical history began experiencing fever and shortness of breath in March 2020 followed by loss of appetite, nausea, abdominal pain, and diarrhea. At time of diagnostic testing in May 2020, she remained symptomatic, with SARS-CoV-2 rPCR negative. Antibody testing obtained in December 2020 was positive. Since her acute illness, she has been experiencing panic attacks in crowded areas, and continues to intermittently awaken from sleep gasping for air. She experiences palpitations and tachycardia at rest, with ECG changes showing PVCs, PACs, and trigeminy. Her cardiologist started her on metoprolol succinate. With every episode of tachycardia, palpitations, or dyspnea, she experiences a compulsion to check her pulse oximeter. She is hopeless and frustrated by her inability to exercise without experiencing worsening in symptoms the following day. She experiences intrusive vivid imagery of the ambulance and hospital, often accompanied by a sensation of choking and chest pain. Her family notices her to be more irritable and easily startled. Safe physical therapy protocols were pursued, and she remained prone to recurrence of GI disturbance, fatigue, and palpitations on the days following strenuous sessions. Fluoxetine resulted in intolerable worsening of her palpitations, while clonazepam 0.25 mg TID significantly improved her anxiety.
- A 54 year old man with a history of one depressive episode in his 20s and no significant medical history began experiencing chest tightness and fatigue in June 2020. At time of diagnostic testing in July 2020, SARS-CoV-2 rPCR was positive; antibody testing was positive when obtained in November 2020. As he recovered from acute illness at home, he continued experiencing profound fatigue, along with what he described as a “buzzing sensation” in his abdomen and legs. He also described lightheadedness and racing heart on standing from a lying position, with his heart rate going from 90s to 130s while walking across the room. He continues to experience these symptoms, with fatigue exacerbated by both physical and cognitive exertion. He was diagnosed with ME/CFS in February of 2021 based on the Institute of Medicine (IOM) 2015 criteria. His psychiatric symptoms developed about two months after his first day of COVID-19 symptoms, and include low mood, hopelessness, and irritability, all of which are exacerbated following periods of intense physical or mental exertion.

Depressive/Anxiety Disorders	Long Covid	ME/CFS	Dysautonomias
Fatigue Sleep disturbance Cognitive dysfunction Poor appetite Musculoskeletal complaints Pain Shortness of breath Palpitations GI disturbance Headache	Fatigue Post-exertional malaise Cognitive dysfunction Peripheral neuropathy Myalgias Shortness of breath Palpitations GI disturbance Headache Dizziness Chest tightness Anoma/Dysgeusia	Fatigue Post-exertional malaise Cognitive dysfunction Orthostatic intolerance Musculoskeletal pains Shortness of breath Irregular heartbeat GI disturbance Headache Chills, night sweats Allergies and sensitivities Sore throat Tender lymph nodes	Fatigue Sleep disturbance Difficulty concentrating Lightheadedness Shortness of breath Chest pain Palpitations Headache GI disturbance Nausea Tremulousness

Table 1. Differential Comparison of Symptoms; Psychiatric diagnoses, ME/CFS, dysautonomias, and Long Covid are not mutually exclusive

Recommended Workup	Long Covid	ME/CFS	POTS
Vital signs Complete blood count Complete metabolic panel Urinalysis CRP ESR TSH/free T4 Vitamin D Vitamin B12	- Symptoms that start within 3 months of suspected or confirmed SARS-CoV2 infection - ≥2 months duration - Impairs functioning	- New onset fatigue not alleviated by rest, post-exertional malaise, unrefreshing sleep, plus cognitive impairment or orthostatic intolerance - ≥6 months duration - Impairs functioning	- Orthostatic intolerance defined by a rise in HR > 30 bpm or HR >120 bpm occurring within 10 min of head-uptilt or standing, without orthostatic hypotension - ≥6 months duration

Table 2. Recommended Workup & Diagnostic Criteria of Differential Diagnoses

Psychotropic Medications	Long Covid Symptoms & Conditions														
	Constitutional			Gastrointestinal				Cardiac			Neuropsychiatric			Genitourinary	
	Fatigue	Hair Sweating	Decreased appetite	Nausea	GI upset	Constipation	Diarrhea	Palpitations	Arrhythmia	Headache	Anxiety	Insomnia	Dizziness	Tremor	Sexual
Selective Serotonin Reuptake Inhibitors															
Citalopram	x								x						
Escitalopram	x								x						
Fluvoxamine						x									x
Fluoxetine	x						x			x	x	x	x	x	x
Paroxetine	x						x			x	x	x	x	x	x
Sertraline	x						x			x					x
Serotonin Norepinephrine Reuptake Inhibitors															
Desvenlafaxine	x						x								
Duloxetine	x						x					x	x		
Venlafaxine	x	x					x			x		x	x		
Tricyclic antidepressants: Tertiary amine (5-HT>NE): Amitriptyline, Clomipramine, Doxepin, Imipramine. Secondary amine (NE>5-HT): Desipramine, Maprotiline, Nefopam.															
Amitriptyline	x						x		x	x				x	
Atypical Antidepressants															
Bupropion	x		x									x	x	x	
Mirtazapine	x														
Second Generation Antipsychotics															
Aripiprazole	x						x				x	x	x	x	
Brexipiprazole															
Cariprazine	x						x				x				
Lurasidone	x						x								
Olanzapine	x						x								
Paliperidone	x								x						
Quetiapine	x									x					
Risperidone	x														
Ziprasidone	x						x								
Mood Stabilizers															
Carbamazepine	x						x							x	
Divalproex	x	x					x							x	
Lamotrigine	x						x								
Lithium	x	x					x							x	
Oxcarbazepine	x						x								
Anxiolytics: Benzodiazepines, Buspirone, Gabapentin															
Benzodiazepines	x														
Psychostimulants: Armodafinil, Lisdexamphetamine, Mixed amphetamine salts, Modafinil															
Armodafinil															
Lisdexamphetamine							x								
Mixed amphetamine salts							x								
Modafinil															

Table 3. Selected Common Psychotropic Side Effects & Overlap With Long Covid Symptoms

Discussion

Initial evaluation, differential diagnosis, medical workup

- Our cases demonstrate the complexity of presentation, extent of medical comorbidity, and burden of somatic symptoms in Long Covid (Table 1).
- Differential may include a comorbid diagnosis of psychiatric conditions, ME/CFS, and dysautonomia. A comprehensive medical workup is necessary (Table 2).

Psychiatric evaluation

- PASC overlap with somatic symptoms of depressive and anxiety disorders but can exist in the absence of psychiatric comorbidity (Table 1).
- MDD symptoms improve over the course of the day and with exercise, and characterized by early insomnia; ME/CFS symptoms worsen over the course of the day and with exercise, and is characterized by multiple nighttime awakenings.
- Anxiety disorder somatic symptoms are triggered by non-physiologic triggers and shortness of breath (SOB) is characterized by tachypnea; POTS symptoms are triggered by physiologic triggers (e.g. exertion) and SOB is characterized by hyperpnea.

Treatment approach

- Psychotropics should be started at low doses, titrated slowly in order to avoid triggering drug sensitivities, and selected in the context of a patient's PASC symptoms (Table 3).
- Antidepressants**
 - SSRI improve depression in PASC⁴ and ME/CFS⁵, have antiplatelet properties, and may improve dysautonomia.
 - Bupropion improves depression in ME/CFS⁵ and is useful in those who have failed to show response to alternative antidepressant treatment.
 - SNRI has more limited evidence in ME/CFS⁵, may be helpful for neuropathic pain and headache, but may worsen dysautonomia.
 - Low dose TCA improve depression in ME/CFS⁵ and is useful for comorbid pain and headache, but carry risks of worsening fatigue, dysautonomia, and cardiotoxicity.
- Anxiolytics**
 - Short-term benzodiazepines (BZD) may be useful for anxiety and insomnia but could worsen fatigue, brain fog, and potentiate PASC if used long-term.⁶
 - Gabapentin, pregabalin, and buspirone may be useful alternatives for anxiety.
- Antipsychotics & Mood Stabilizers**
 - Aripiprazole 0.5-2 mg/day has been shown to improve ME/CFS symptoms and is efficient in lowering cytokines known to be elevated in PASC.⁷
 - Thorazine, with its immunomodulatory effects via sigma-1-receptor, may be useful
 - Lithium, lamotrigine, carbamazepine, and most D2 receptor antagonists have anti-inflammatory and/or antiviral effects.
- Psychostimulants**
 - Methylphenidate improves fatigue and brain fog, dextroamphetamine improves fatigue, and modafinil improves cognition in ME/CFS.⁸

Conclusion

- Consider SSRI, SNRI, and low dose TCA for treatment of depression and anxiety in PASC.
- Bupropion, low dose aripiprazole, and methylphenidate may be useful for augmentation of antidepressant treatment.
- Evidence is currently limited and low-quality. Thus, further research is required to guide psychiatric treatment in PASC.

References:

- Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 – A systematic review. *Brain Behav Immun.* 2021;97:328-348. doi:10.1016/j.bbi.2021.07.018
- Sukocheva OA, Maksoud R, Beeraka NM, et al. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. *J Adv Res.* Published online November 26, 2021. doi:10.1016/j.jare.2021.11.013
- Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med.* 2021;21(1):e63-e67. doi:10.7861/clinmed.2020-0896
- Mazza MG, Zanardi R, Palladini M, Rovere-Querini P, Benedetti F. Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. *Eur Neuropsychopharmacol.* 2022;54:1-6. doi:10.1016/j.euroneuro.2021.09.009
- Pae CU, Marks DM, Patkar AA, Masand PS, Luyten P, Serretti A. Pharmacological treatment of chronic fatigue syndrome: focusing on the role of antidepressants. *Expert Opin Pharmacother.* 2009;10(10):1561-1570. doi:10.1517/14656560902988510
- LaCorte S. How chronic administration of benzodiazepines leads to unexplained chronic illnesses: A hypothesis. *Med Hypotheses.* 2018;118:59-67. doi:10.1016/j.mehy.2018.06.019
- Crosby LD, Kalandidhi S, Bonilla A, Subramanian A, Ballon JS, Bonilla H. Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole. *J Transl Med.* 2021;19:50. doi:10.1186/s12967-021-02721-9
- Kim DY, Lee JS, Park SY, Kim SJ, Son CG. Systematic review of randomized controlled trials for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *J Transl Med.* 2020;18(1):7. doi:10.1186/s12967-019-02196-9

