Post-COVID Neurological Symptoms:

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Objectives

- Identify signs and symptoms of long COVID which occur after the acute phase of SARS-CoV-2 infection.
- Identify potential multidisciplinary teams for patient care.
- Describe common challenges to post-acute COVID-19 care.

As reports of long-term COVID-19 symptoms emerged, the need for scientific research about **long COVID** has intensified.

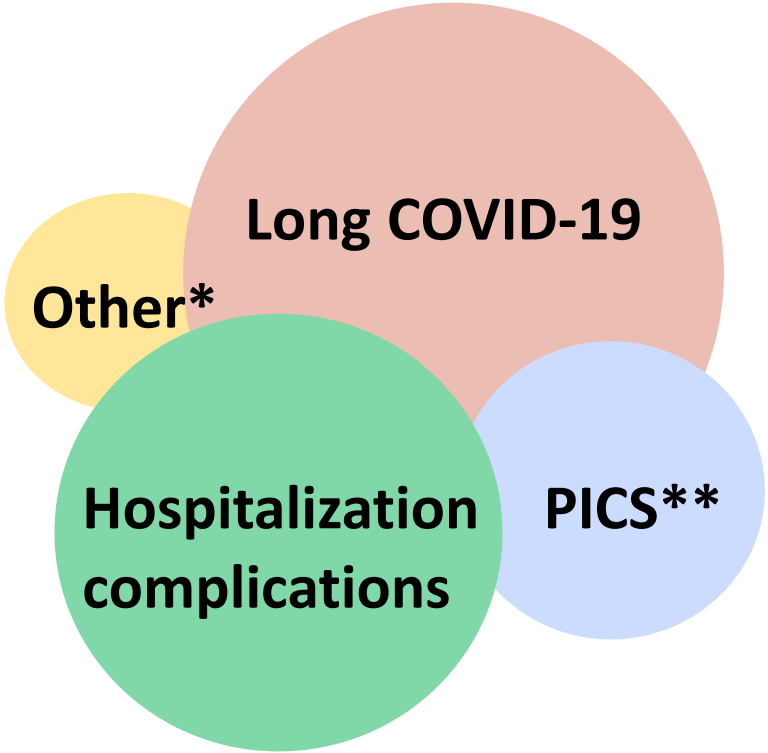
Definition:

Long COVID often presents as reported **persistent severe fatigue, headaches, and brain fog (mild subjective cognitive impairment) >4 weeks** after acute illness and may be **independent of acute illness severity.**

Greenhalgh et al., BMJ. 2020

we define post-acute covid-19 as extending beyond three weeks from the onset of first symptoms and chronic covid-19 as extending beyond 12 weeks. Since many people were not tested, and false negative tests are common, we suggest that a positive test for covid-19 is not a prerequisite for diagnosis.

Long COVID may overlap with other complications of acute COVID-19 illness making it **hard to define**.



*Multisystem inflammatory disorder, Guillain-Barre, among others
**Post-Intensive Care Syndrome

Post-acute covid-19 (“long covid”) seems to be a multisystem disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective.

What are the symptoms?

Post-acute covid-19 symptoms vary widely. Even so-called mild covid-19 may be associated with long term symptoms, most commonly cough, low grade fever, and fatigue, all of which may relapse and remit. Other reported symptoms include shortness of breath, chest pain, headaches, neurocognitive difficulties, muscle pains and weakness, gastrointestinal upset, rashes, metabolic disruption (such as poor control of diabetes), thromboembolic conditions, and depression and other mental health conditions. Skin rashes can take many forms including vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (so called covid- toe).

Pathogenesis:

It is not known why some people's recovery is prolonged. **Persistent viraemia** due to weak or absent antibody response, **relapse or reinfection**,**inflammatory and other immune reactions**, **stress deconditioning**, and **mental factors** such as post-traumatic may all contribute. Long term respiratory, musculoskeletal, and neuropsychiatric sequelae have been described for other coronaviruses (SARS and MERS) and these have pathophysiological parallels with post-acute covid

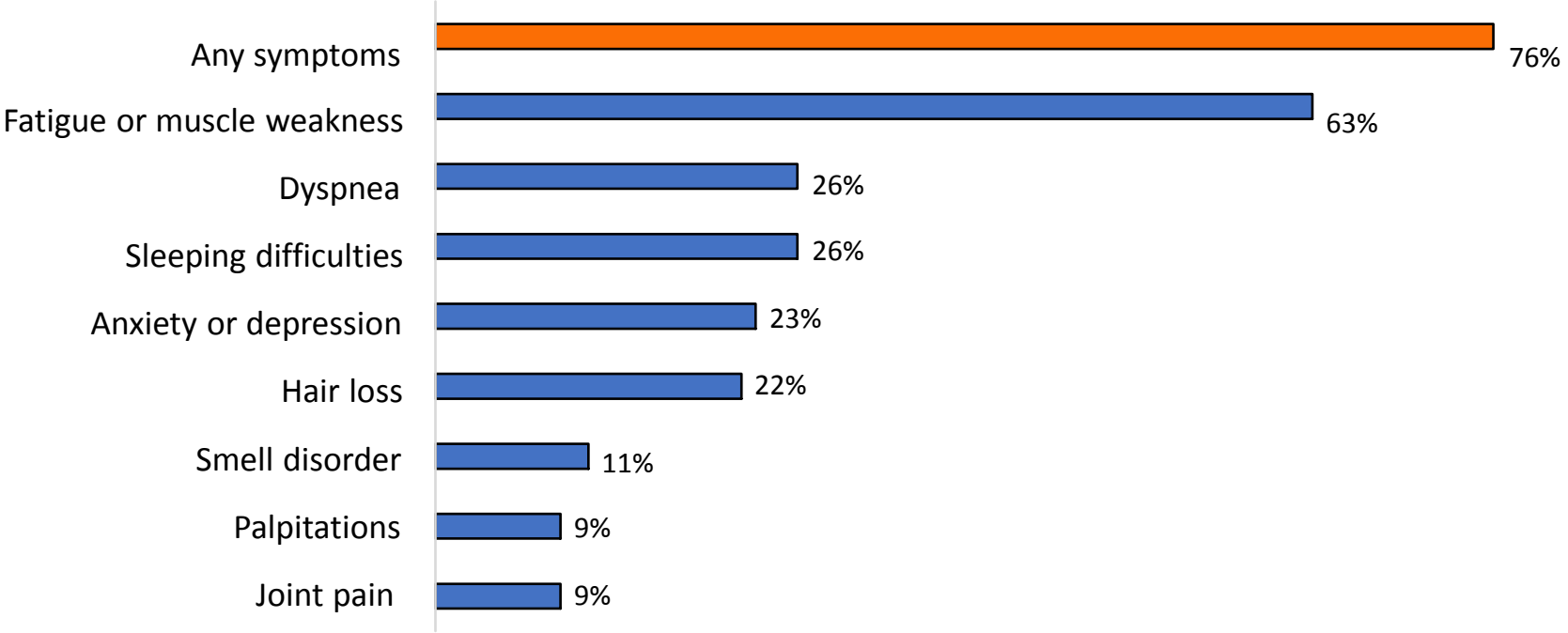
Pathogenesis:

In view of the greater mortality among the aged, it is worth noting the presence of low-grade chronic inflammation and allready down-regulated ACE-2 levels in older individuals and those with chronic diseases such as hypertension, previous stroke, metabolic syndrome, diabetes, obesity. Such individuals are likely to suffer with a higher probability of disruption of the rennin-angiotensin-aldosterone system as well as endothelial dysfunction in the setting of COVID-19 and with even greater disruption of the blood-brain barrier as well as hyper inflammation . Thus, the particular pathobiology associated with COVID-19 infection and inflammation predicts that acute and longer-term neurological manifestations are to be expected, especially in older individuals.

In 2020 alone, the number of papers reporting longer-term Post COVID Neurological effects is increasing rapidly . The neuropsychological impact of COVID-19 has been associated with varying degrees of depression, sleep impairment and anxiety, among seventy medical workers Post COVID-19 . Another study on 714 COVID-19 patients in China has revealed that nearly 97% of the patients were displaying symptoms of severe post-traumatic stress disorder (PTSD) . Lastly, a large study from Belgium and Netherland involving 112 hospitalized and 2001 non-hospitalized COVID-19 positive patients have noted that even among a large number of asymptomatic or very mildly symptomatic patients, prolonged symptoms such as muscle pain, dizziness, headaches, fatigue, and anosmia continued to experience for months, highlighting the need for on-going vigilance for PCNS by neurologists.

Three quarters of patients hospitalized with COVID-19 had **at least one ongoing symptom** 6 months after their acute illness.

Symptoms among 1,733 patients after hospitalization for COVID-19, China



Huang et al., Lancet. 2021

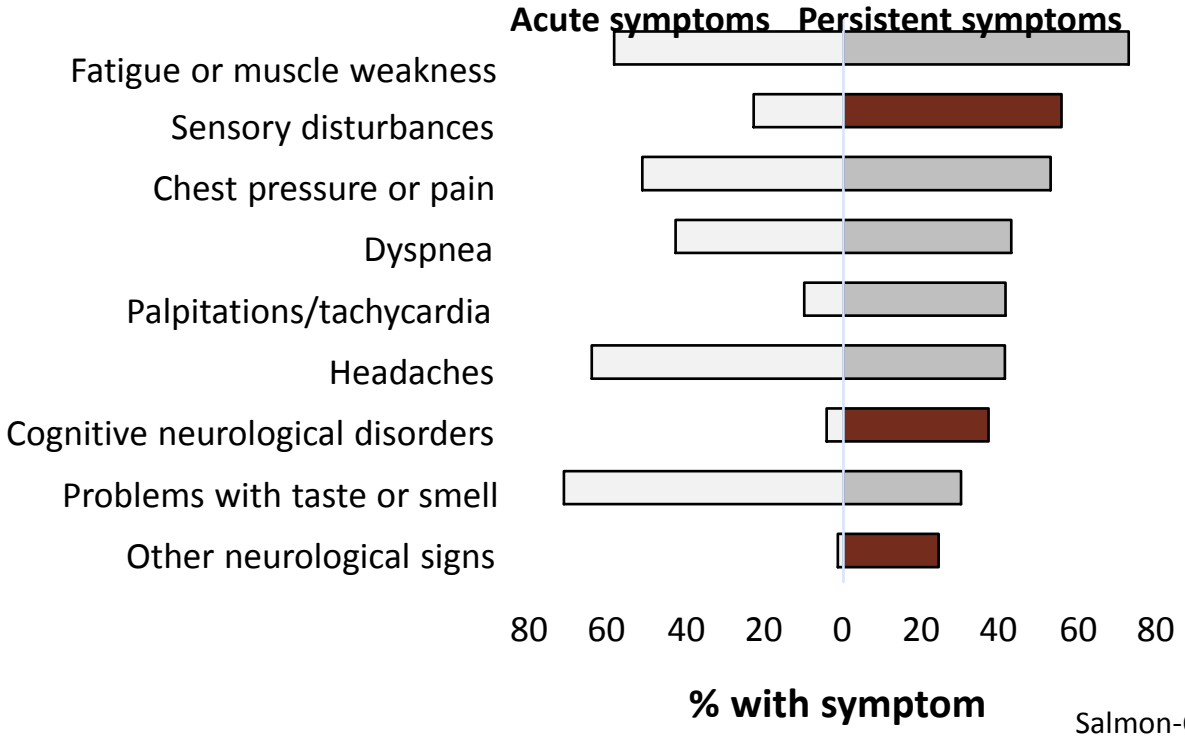
Prolonged symptoms are common among patients with mild COVID-19 disease **not requiring hospitalization**.

- Survey of patients in a post-COVID 19 clinic in France[1] and telephone surveys in the Faroe islands[2] and Switzerland[3]
  - 35-54% of patients with mild acute COVID-19 had **persistent symptoms after 2-4 months**
  - 50-76% of patients **reported new symptoms** not present in their acute COVID-19 illness **or symptoms that resolved and reappeared**[1]
  - 9% reported prolonged symptoms as **severe**[2]

1. Salmon-Ceron et al., J Infect. 2020
2. Petersen et al., Clin Infect Dis. 2020
3. Nehme et al., Ann Intern Med. 2020

More than one quarter of patients **developed new neurological symptoms** after their acute COVID-19 illness.

COVID-19 symptoms among 70 non-hospitalized patients, France

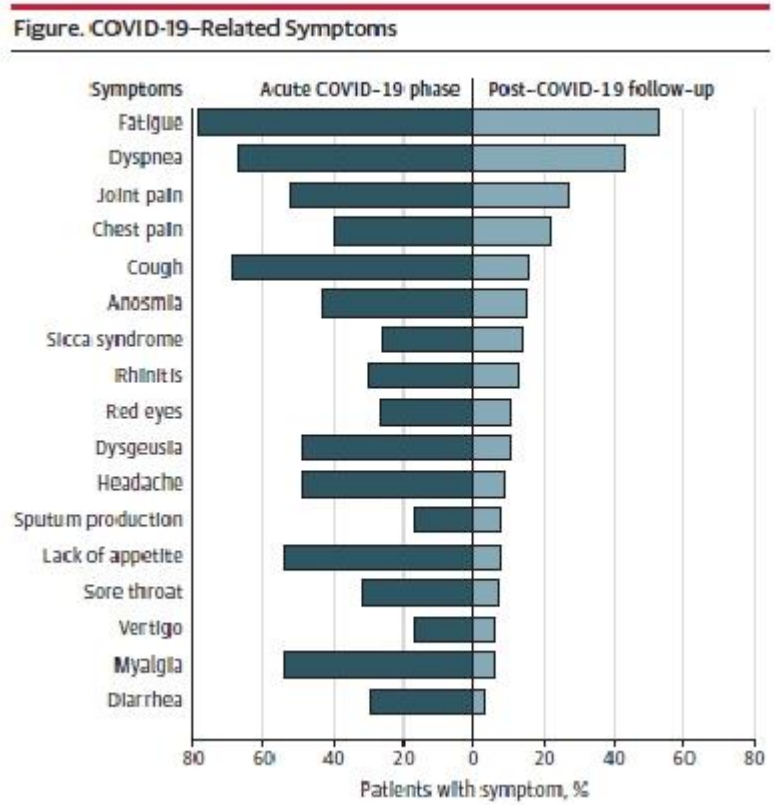


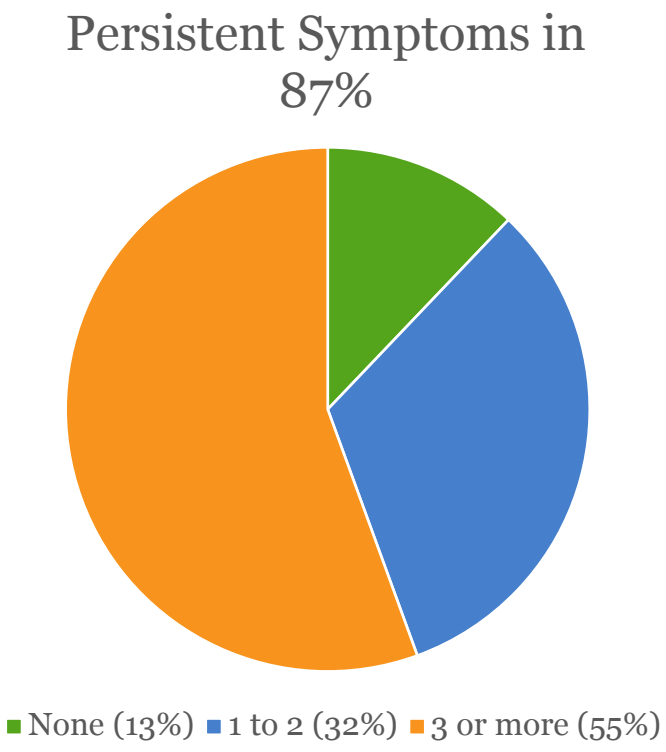
Salmon-Ceron et al., J Infect. 2020

Key points

- New or persistent symptoms (lasting >4-6 months) may occur among patients with COVID-19 **regardless of acute episode severity.**
- In addition to respiratory symptoms, **patients may present with fatigue, sleeping difficulties, depression, anxiety, and neurological dysfunction**.
- Baseline and serial **comprehensive reviews of systems and physical exams** may better document possible long COVID manifestations and improve management.
- There is still **a lot we do not understand,** and **empathy toward patients** experiencing long COVID is fundamental.

Post-COVID-19 symptoms are common and diverse, with respiratory symptoms a frequent feature:





Carfi A et al, JAMA 2020

Observations for our next iteration:

- Imaging most helpful in those with abnormal PFTs or previously extensive abnormalities
- Partnership with PT has been essential, but what is the ideal rehab structure for this population?
- Social work heavily utilized and very effective
- Neurocognitive sequelae have been common
- “Subjective/objective mismatch” is common, optimal diagnostic pathway uncertain
- Most people slowly improving – therefore supportive interventions may be more high value than serial diagnostics

Example Post-COVID Patient

- 42-year-old woman, no medical history, had COVID in April. Was sick for 2 weeks with fever, myalgias, headache and anosmia. Not hospitalized.

- Was feeling better but then noted in June she was having trouble with short-term memory and focus. Works at a non-profit, continuing to work but has cut hours and struggles.

- Also notes physical fatigue that worsens with exercise. Gets tingling sensation throughout her body but worst in hands. Also with heart rate elevations, palpitations, and shortness of breath.

Neurological Symptoms--Brain Fog

- Most common neurological symptom
- Issues with short-term memory, concentration and word-finding/speech difficulty
- No clear correlation with severity of COVID infection, age or comorbidities
- Symptoms often fluctuate, “good and bad days”
  - Fluctuations often correlate with other symptoms like fatigue and dysautonomia
- Impact on life varies: some able to still work, others on disability
- Sleep: many patients with poor sleep
- Mood: many patients experiencing depression, anxiety and/or PTSD

Neurological Symptoms--Headaches, Paresthesias and Dysautonomia

- Headaches
  - Often describes as constant pressure that can fluctuate in severity
  - May have migraine symptoms or not
  - Many don’t have a history of headaches

- Paresthesias
  - Tingling, numbness and/or burning sensation
  - May be focal, diffuse, alternating in locations
  - Sometimes more in distal extremities (stocking-glove distribution)

- Dysautonomia
  - Fluctuating blood pressure and heart rate
  - Lightheadedness, palpitations, GI disturbances

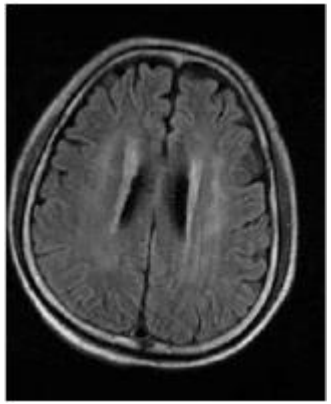
Most patients have multiple chief complaints. Rare to have someone coming in for only one issue

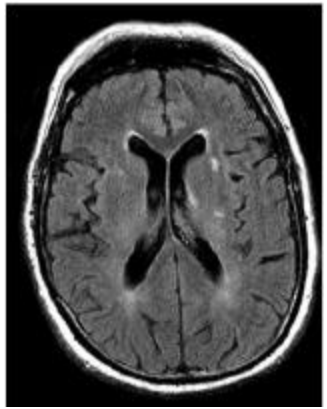
Approach to workup: typical findings

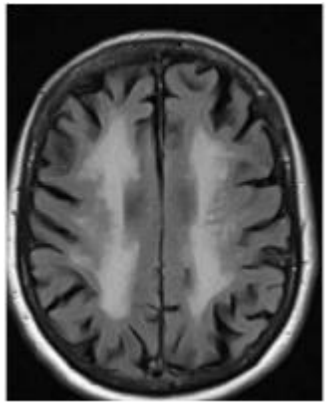
- Initially, broad workup undertaken
- Bloodwork for contributing, reversible causes
- Neuroimaging- no widespread signs of damage from infection or inflammation
- Neuropsychological testing- variable
- EEG if concern for seizures- seizures do not appear to be a common complication
- EMG for paresthesias- negative for neuropathy in vast majority
- Rare instances, lumbar puncture- no major inflammatory/infectious changes

Neuroimaging: typical findings

- Not seeing large inflammatory/infectious appearing lesions
- Not seeing many strokes, including lacunar strokes
- White matter changes (i.e., microvascular ischemic changes)
  - Very common imaging finding regardless of COVID
  - Occurs with age, vascular risk factors, migraines
  - Unless severe, often not considered clinically relevant
  - Caution in attributing to COVID without comparison imaging, or, if more severe than expected for age







Cognitive test: typical findings

- Younger patients: results more often within normal limits
  - May be some decrease from presumed prior level of function
  - May show more issues with attention
- Older adults: deficits in varying domains
  - No clear pattern, or ”post-COVID cognitive profile”
  - COVID unmasking underlying cognitive impairment versus causing
- Reports often comment on mood (depression, anxiety, PTSD), sleep and fatigue as potential contributing factors
- **Brain Fog ≠ Dementia** for most people
  - Does not mean cognitive changes are not present and interfering with life

What else may be occurring?
Our evolving understanding

What may be occurring?

- Damage to central nervous system (CNS)?
  - Lack of evidence to support/refute
  - Unlikely widespread CNS infection. Role of vasculature?

- Peripheral nervous system may be affected
  - Much more vulnerable to systemic insults than central nervous system
  - Presence of small fiber neuropathy?
  - Small fiber neuropathy leading to dysautonomia?

- Other, possibilities:
  - Postural orthostatic tachycardia syndrome (POTS)
    - Hyperadrenergic POTS relating to excessive catecholamines?
  - Myalgic encephalomyelitis/chronic fatigue syndrome (MECFS) like process?

- Small fiber neuropathy
  - Paresthesias
  - Dysautonomia/autonomic neuropathy
  - Chronic pain syndromes
  - Fatigue?

- POTS
  - Dysautonomia (orthostasis and tachycardia)
  - Headaches
  - Fatigue/ generalized weakness
  - Paresthesias
  - Brain fog

- MECFS
  - Overwhelming fatigue, not improved by rest
  - Post-exertional malaise
  - Associated with orthostatic intolerance, pain, poor sleep and brain fog

Current Approach to Workup and Management

History

- Symptoms and their correlation
  - If multiple symptoms, do they fit with a larger diagnosis?
- Severity of COVID
  - Associated complications, cytokine storm, hypoxia
- Age and medical comorbidities of patient
- Impact of symptoms on ability to work and/or activities of daily living
- FOCAL neurological deficits or symptoms
- Sleep
- Mood

Workup--often aimed to look for contributing factors

- Bloodwork
  - TSH, Vitamin B12 and Vitamin D
  - HIV, RPR, thiamine, folate (if severe cognitive deterioration)
  - Hemoglobin A1c if neuropathy

- Imaging- MRI Brain (or CT Head)

ConsiderImaging:	CanConsiderHoldingImaging:
•Moderate-SevereCOVID •Over50yearsofage •Medicalcomorbidities/riskfactors •ImpactonjoboriADLs •Focalneurologicaldeficitsorsymptoms	•NothospitalizedwithCOVID •Lessthan50yearsofage •Otherwisehealthy •Correlationwithothersymptoms,has“good days”

- Neuropsychological Testing
  - Can be helpful in highlighting if/what deficits present as well as potential contributing factors

Workup

- EEG: if episodes of altered consciousness, seizure-like activity
- Lumbar puncture: only in cases of severe cognitive deterioration or other concerning neurological deficits.
- EMG: for neuropathy. Normal in small fiber neuropathy
- Skin biopsy for small fiber neuropathy- confirms diagnosis. Doesn’t change management
- Autonomic function/tilt table testing- if concern for POTS

Likely okay to do a small, focused workup. Extensive testing has not been helpful in vast majority of patients.

Treatment: mostly symptomatic and supportive

- Brain fog:
  - No specific treatment
  - Address any abnormalities in bloodwork
  - Address contributing factors
  - If attention is major issue: Atomoxetine, dextroamphetamine/amphetamine, methylphenidate, modafinil

- Dysautonomia:
  - Hydration, increase salt intake, compression stockings
  - Meditation, breathwork
  - POTS: consider adding in midodrine or fludrocortisone
  - Hyperadrenergic POTS: beta-blocker

- Small fiber neuropathy:
  - Address any abnormalities in bloodwork
  - Symptomatic treatment of paresthesias: gabapentin, pregabalin, tricyclics, duloxetine
  - Dysautonomia as above

- Fatigue:
  - Treat associated symptoms as above
  - Pacing of exercise: low-impact, short duration exercise with gradual increase.

Other critical factors

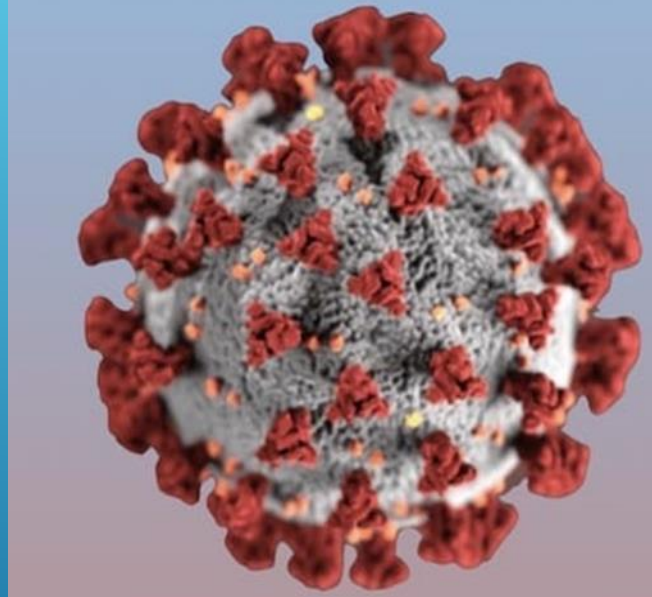
- Sleep:
  - Sleep hygiene
  - Assess for possible sleep apnea
  - Sleep aids: melatonin, mirtazapine, gabapentin or amitriptyline (if paresthesias or headaches also present)

- Mental Health:
  - May be “the result of”, not the primary cause of symptoms.
  - Depression, anxiety and PTSD can affect cognition
  - Something we can act on
  - Anti-depressants like duloxetine or venlafaxine may be beneficial in also treating paresthesias and/or headaches

Conclusion

- Many neurological symptoms present in post-COVID patients
- Many symptoms may correlate, important to get broad history
- So far, diagnostic workup is not providing much information
  - Likely okay to do less testing, unless red-flag symptoms present
  - Important to not over-interpret things like imaging
- Treatment is supportive and symptomatic
  - We don’t have medications to “cure” neurological damage
- Multi-disciplinary approach with post-COVID experience is critical
- We don’t know what is causing symptoms, but that does not mean this is not real.
- Reassurance. Patients can/do get better.

THANK YOU



Coronavirus
SARS-CoV-2
COVID-19