Anxiety & PTSD in PASC

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Rates of Anxiety after Acute COVID-19 Infection

- Systematic review involving 15 studies assessing anxiety after mild to moderate COVID-19 infection
- These studies included 3431 patients (17.52%) of whom had “at least mildly severe anxiety symptoms”
- Anxiety prevalence in severe COVID-19 cases was 19.03% of 309 patients that were experiencing at least mild anxiety symptoms
- Sensitivity analysis showed a decrease in anxiety prevalence from 20.68% to 11.11% between 1-3 month follow up and more than three-month follow-up
- There was inconsistency in anxiety prevalence based upon the tools used to assess symptoms
- Interestingly, self-reported anxiety prevalence was significantly higher compared to “clinical diagnosis”
- Overall, these prevalences are thought to be consistent with the general population
Rates of PTSD after Acute COVID-19 Infection

- Thirteen studies measured PTSD in non-severe COVID-19 cases
- Seven of these studies measured DSM-5 derived PCL-5 (post-traumatic stress disorder checklist) questionnaires, one study used the TSQ (trauma screening questionnaire), and two studies used the DTS (Davidson Trauma Scale), and three studies used the IES-R (impact of event scale – revised)
- The overall prevalence of PTSD was 17.68% in 3405 patients
- The overall prevalence of PTSD in severe COVID-19 infection was 19% from a pool of 200 patients
- PTSD prevalence in cohorts of patients followed for longer than three months was at 18.99% compared to 12.19% at 1-3 months post-infection follow-up
- Overall, however, these prevalences are thought to be consistent with the general population
Prevalence of PASC after COVID-19 Infection

- Global meta-analysis over 29 studies found a 43% rate of PASC with a rate of 57% among those hospitalized during the acute phase of the infection.

- Slightly higher rates of PASC in Asia compared with Europe and North America.

- Rates of PASC began to increase 90 days and then further, 120 days after infection after an initial decline 30 and 60 days after infection.
### Systematic Review of Symptoms in those Diagnosed with Long-Covid

<table>
<thead>
<tr>
<th>Symptoms, sequelae and difficulties conducting usual activities</th>
<th>Short-term (4-12 weeks after COVID-19 diagnosis) (prevalence* in %, [95% CI], number of studies, risk of bias across studies [low, moderate or high]), GRADE assessment where applicable</th>
<th>Long-term (&gt;12 weeks after COVID-19 diagnosis) (prevalence* in %, [95% CI], number of studies, risk of bias across studies [low, moderate or high]), GRADE assessment where applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety or depression</td>
<td>22% [19%, 25%] (2 studies) {30,50}</td>
<td>23% [21%, 25%] (1 study) {12}</td>
</tr>
<tr>
<td>Anxiety and depression</td>
<td>2% [0%, 5%] (1 study) {18}</td>
<td>1% [8%, 27%] (1 study) {58}</td>
</tr>
<tr>
<td>Postpartum depression</td>
<td>No studies</td>
<td></td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>23% [14%, 35%] (5 studies) {30,37,53,59}</td>
<td>18% [7%, 41%] (4 studies) {38,55,58,60}</td>
</tr>
<tr>
<td>Depression or post-traumatic stress disorder</td>
<td>No studies</td>
<td>22% [12%, 32%] (1 study) {58}</td>
</tr>
<tr>
<td>Obsessive compulsive</td>
<td>No studies</td>
<td>26% [18%, 34%] (1 study) {55}</td>
</tr>
<tr>
<td>Feelings of distress due to symptoms (only a little/quite a lot/a great deal)</td>
<td>35% [19%, 52%] (1 study) {4}</td>
<td>42% [32%, 52%] (1 study) {4}</td>
</tr>
<tr>
<td>Other mental health symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low mood</td>
<td>No studies</td>
<td>40% [31%, 48%] (1 study) {14}</td>
</tr>
<tr>
<td>Panic attack</td>
<td>13% [11%, 16%] (1 study) {56}</td>
<td>No studies</td>
</tr>
<tr>
<td>Always/often emotional</td>
<td>14% [9%, 19%] (1 study) {31}</td>
<td>No studies</td>
</tr>
<tr>
<td>Thoughts of self-harm</td>
<td>2% [0%, 5%] (1 study) {10}</td>
<td>No studies</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2% [0%, 4%] (1 study) {8}</td>
<td>No studies</td>
</tr>
</tbody>
</table>

**Mental Health**

- At least one mental health symptom (depression/anxiety/OCD/obsessive compulsive)
- At least one current major psychiatric disorder (DSM-5 criteria for diagnosis)

- Anxiety | 19% [10%, 32%] (4 studies) {5,8,33,37} | 32% [22%, 43%] (4 studies) {11,4,5,55} |
- Major anxiety disorder (DSM-5 criteria for diagnosis) | No studies | 9% [5%, 13%] (1 study) {55} |
- Depression | 23% [14%, 34%] (5 studies) {5,6,33,37,53} | 17% [5%, 30%] (1 study) {55} |
- Major depressive disorder (DSM-5 criteria for diagnosis) | No studies | 9% [5%, 13%] (1 study) {55} |

### Common Symptoms in a PASC Cohort

#### 15 most common symptoms with highest severity (4s & 5s)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>All (N=100)</th>
<th>Female (N=63)</th>
<th>Male (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Exertional Malaise</td>
<td>57%</td>
<td>85.7%</td>
<td>81.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>54%</td>
<td>81.0%</td>
<td>86.5%</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td>46%</td>
<td>81.0%</td>
<td>75.7%</td>
</tr>
<tr>
<td>Brain fog</td>
<td>35%</td>
<td>86.5%</td>
<td>81.1%</td>
</tr>
<tr>
<td>Unrefreshing Sleep</td>
<td>33%</td>
<td>79.4%</td>
<td>70.3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>28%</td>
<td>73.0%</td>
<td>59.5%</td>
</tr>
<tr>
<td>Anxiety and/or Depression</td>
<td>23%</td>
<td>60.3%</td>
<td>73.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
<td>54.0%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>16%</td>
<td>52.4%</td>
<td>37.8%</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>14%</td>
<td>49.2%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Change in smell</td>
<td>12%</td>
<td>49.2%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Change in taste</td>
<td>12%</td>
<td>49.2%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Change in sweat</td>
<td>12%</td>
<td>49.2%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>11%</td>
<td>47.6%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

Many case-control studies have been reviewed and found to confirm an association between joint hypermobility (hyperlaxity) and anxiety disorders in both directions.

Those with joint hypermobility syndrome have an absolute risk for panic disorder of 44.1% versus 2.8% in non-hypermobile subjects, which corresponds to a relative risk of 22.3%.
Could Anxiety and/or PTSD be Driven by Underlying Dysautonomia?

Patient reported symptoms in our clinic:

- Internal tremor sensations
- Waking up in the middle of the night with heart rates in the 180-220 bpm range
- Anxiety/panic attacks without clear provocation
- Excessive sweating
- Blurry vision
- Nightmares (not involving patient’s experiences of COVID infection, the pandemic itself, or due to their current symptoms or disability related to PASC)
- Chest tightness, palpitations
- Insomnia

Majority of these patients had no prior psych history before COVID-19 infection
DSM-5 Criteria for Anxiety

A. Excessive anxiety and worry occurring more days than not for at least six months, about a number of events or activities
B. The individual finds it difficult to control the worry
C. The anxiety and worry are associated with three (or more) of the following six symptoms:
   • Restlessness or feeling keyed up or on edge
   • Being easily fatigued
   • Difficulty concentrating or mind going blank
   • Irritability
   • Muscle tension
   • Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. Symptoms cause significant distress or impairment in social, occupational, or other functioning
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism)
DSM-5 Criteria for PTSD

A. Traumatic Event Exposure:
   • Directly experiencing or witnessing, learning about the event in a close acquaintance, or experiencing repeated or extreme exposure to traumatic event details

B. Presence of one (or more) intrusion symptoms associated with the traumatic event(s):
   • Recurrent distressing memories, dreams, dissociative events/flashbacks where individual relives the events, psychological distress in response to event-related cues, physiological reactions to event-related cues

C. Avoidance of stimuli associated with the traumatic event(s)
   • Avoidance of distressing memories, thoughts, feelings, external reminders (people, places, conversations, activities, objects, situations)

D. Negative alterations in cognitions and mood
   • Inability to remember aspects of the event, exaggerated negative beliefs about oneself, others, or the world, distorted sense of the cause and consequences of the event that lead to self-blame, persistent negative emotions, diminished interest or participation in activities, feelings of detachment, and inability to experience positive emotions

E. Marked alterations in arousal and reactivity
   • Irritable behavior, angry outbursts (with verbal or physical aggression), reckless or self-destructive behavior, hypervigilance, exaggerated startle response, difficulty with concentration, sleep disturbances,

F. Symptoms for more than one month

G. Distress or impairment in social, occupational, or other functioning

H. Symptoms not related to drugs or other medical conditions
How Might COVID-19 Cause Dysautonomia?

Proposed Mechanisms:

• Hypovolemia – may trigger hyperadrenergic POTS/OI, leading to cerebral hypoperfusion and impairment of central autonomic networks

• Brainstem Dysfunction – direct viral invasion, neuroinflammation, vascular activation, brainstem compression
  • Many autonomic centers housed in the brainstem

• Autoimmunity –
  • Autoantibodies to G-protein coupled receptors have been observed \(\rightarrow\) can increase sympathetic tone by activating adrenergic receptors and having an allosteric effect on muscarinic GPCR’s
  • Autoantibody activation of adrenergic and cholinergic receptors \(\rightarrow\) inappropriate peripheral vasodilation
  • Anti-phospholipid antibodies noted in patients who developed both APS and MCAS following COVID-19 infection
  • Other elevated autoantibodies described including ANA’s, anti-thyroid AB’s, anti-cardiac protein Ab’s, Sjogren’s Ab’s

• Postganglionic Sympathetic Neuron Damage – direct viral invasion or related immune attack with collateral damage

• Excessive Mast Cell Activation – inappropriate release of histamine and other cytokines in response to physical activity or orthostatic stress can lead to orthostatic tachycardia, flushing, headaches, GI symptoms
  • Case reports show improvement in dysautonomia after treatment for MCAS in PASC
Do methods for reducing sympathetic nervous system signaling and transmission reduce symptoms of “anxiety” and “PTSD” in those with PASC? YES!
Stellate Ganglion Injections?

• Cervical sympathetic chain (including the superior, middle, and inferior cervical ganglia and first thoracic ganglion) provides sympathetic innervation to the head, neck, upper limbs, and upper thoracic region (including the heart, lungs, lacrimal, salivary, thyroid, and pineal glands)

• The “stellate ganglion” is a fusion of the inferior cervical and first thoracic ganglia present in 80% of individuals

• Injection of local anesthetic into the sympathetic chain, known as a stellate ganglion block, can improve blood flow and deactivate or reset sympathetic tone

• Can cause “Horner’s syndrome (ipsilateral ptosis, meiosis, anhidrosis, facial flushing

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**Stellate Ganglion Injections?**

- Originally described in the 1930’s for treatment of reflex sympathetic dystrophy (now complex regional pain syndrome)

- Also used effectively to treat Raynaud’s and hyperhidrosis in the upper limbs as well as in PTSD and hot flashes associated with chemotherapy and menopause

- The pro-inflammatory cytokine/chemokine profile recognized in those with PASC have been associated with and even implicated in excessive sympathetic nervous system activity

- Stellate ganglion injections were provided in two PASC patients to see if down-regulation of sympathetic overdrive could improve their symptoms
Stellate Ganglion Injections?

Patient #1

Patient #2

Stellate Ganglion Injections?

Overview of affected systems following a viral infection like COVID-19

Autonomic nervous system and immune system central and peripheral communication
Stellate Ganglion Injections?

Stellate ganglion block (SGB) is thought to simultaneously regulate systems linked to the autonomic nervous system.

- A sympathetically maintained interdependent positive feedback loop involving the neuroimmune system can eventually reorganize itself (autoregulation) after changes of state (such as by a stellate ganglion block).

- Previous clinical data suggest that repeated, temporary SGB with the local anesthetic procaine is capable of regulating sympathetic-triggered neurogenic inflammatory processes.

- It is because of the lack of direct measurements of the ANS in pain, immune, and inflammatory processes that proponents of SGB suspect have limited consideration of this modality thus far.
Treatments: Beta Blockers

- Propranolol (short and long-acting)
- Atenolol
- Metoprolol

- Ivabradine (Corlanor) has no direct effect on the sympathetic nervous system
Treatments: Alpha Blockers

- Clonidine (alpha 2a agonist → reduces peripheral sympathetic outflow)
- Guanfacine (selective alpha 2a agonist)
- Prazosin (alpha-1 blocker)
Treatments: Benzodiazepines

Bind to GABA<sub>A</sub> receptors, potentiating GABA neurotransmission, increasing chloride influx into neurons and increasing the neuronal excitability threshold

- Diazepam (scheduled or prn)
- Clonazepam (scheduled)
- Lorazepam (prn)

- Importantly, there are many peripheral nervous system as well as glial cell benzodiazepine receptors
- These peripheral benzodiazepine receptors are present in particularly high concentrations on immune cells, platelets, erythrocytes, and cells within the gastrointestinal tract
- Some peripheral benzodiazepine receptors have also been implicated in regulation of mitochondrial function

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Treatments: Vagal Maneuvers

- Cranial nerves responsible for cardiac-vagal stimulation and that participate in trigeminal-brainstem-vagal pathways are located in the facial area, head, and neck regions.

- Using cold to active these nerves has been referred to as the “diving reflex,” which involves a pattern of respiratory, cardiac, and vascular responses thought to help control oxygen conservation and survival when diving.

Normalized root mean square (rMSSD) of successive differences of body locations for cold stimulus – statistical measure of heart rate variability

Mean interbeat intervals (IBI’s) of all body locations for cold stimulus – statistical measure of heart rate responses
Treatments: Conscious Control Over Autonomic Responses
Treatments: Treat Co-morbidities

• Uncontrolled orthostatic intolerance can drive very significant exacerbations of sympathetic overdrive

• Mast cell activation exacerbations often significantly worsen sympathetic overdrive

• Neurological sensory sensitivities to light, sound, conversation, multiple sensory inputs can exacerbate
  • Consider aripiprazole, dextromethorphan

• Sympathetic overdrive is usually worse during PEM, try to avoid PEM or wait it out during PEM → not much you can do to emerge from PEM other than to not make it worse
Treatments: Transcranial Magnetic Stimulation?

- Targeting the dorsal left prefrontal cortex, pregenual, and mid-anterior cingulate cortex with 10 Hz 3000-4000 pulses can contribute to parasympathetic tone via the vagus nerve and has shown improvements in diaphragmatic function.
A Word on SLEEP…

Sympathetic overdrive is often the most common cause of sleep disturbances in those with PASC and ME/CFS, with pain being the second most common cause

• Cannot fall asleep
• Nightmares
• Wake up frequently (sometimes as often as every hour)
• Wake up too early and cannot fall back asleep
• Mind racing
• Circadian rhythm disrupted, awake at night and sleeping in the day
A Word on Stimulants...

• Stimulant therapies (bupropion, modafinil, dextroamphetamine-amphetamine, methylphenidate, lisdexamphetamine) are often used to help improve brain fog, attention, and other cognitive complains in PASC.

• Remember that stimulants can significantly alter or worsen sympathetic overdrive or hypervigilance.

• Generally best practice to implement these therapies only after making some clinical improvements in symptoms of sympathetic overdrive first.
Questions?