Anxiety & PTSD in PASC

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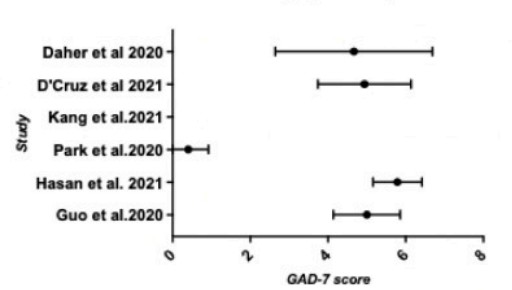
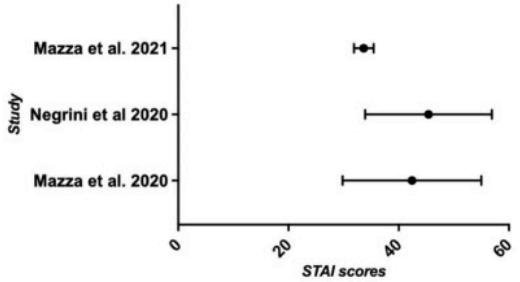
Rates of Anxiety after Acute COVID-19 Infection

- 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

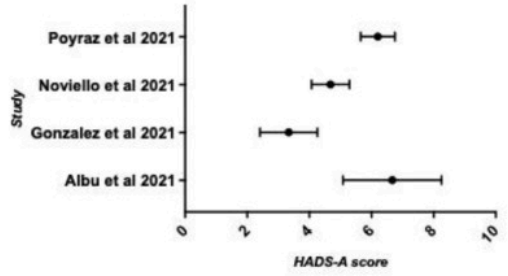
Plot A: Generalized Anxiety (GAD-7)



Plot B: State Trait Anxiety scale – state subscale (STAI-S)



PloT C: Hospital Anxiety and Depression score – Anxiety (HADS-A)



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Bourmistrova, Nicole Wallbridge, et al. “Long-Term Effects of COVID-19 on Mental Health: A Systematic Review.” *Journal of Affective Disorders*, vol. 299, 2022, pp. 118–125., https://doi.org/10.1016/j.jad.2021.11.031.

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

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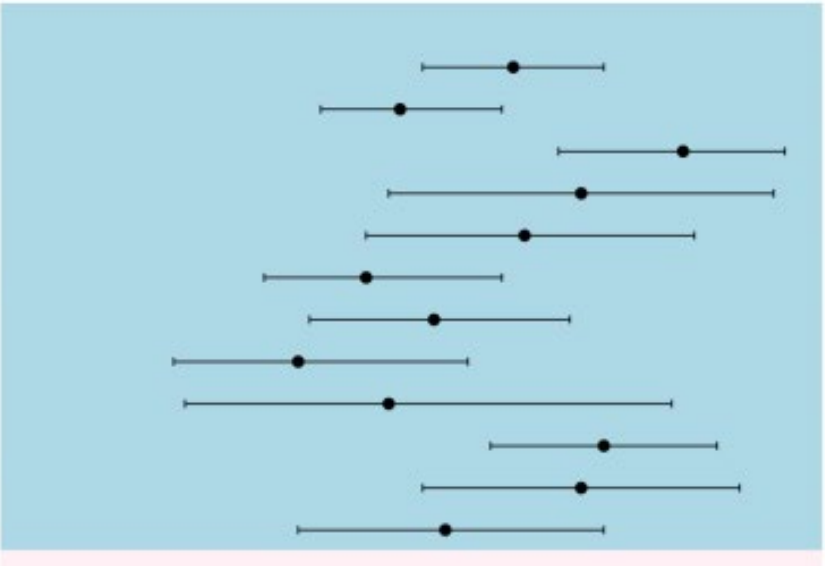
Prevalence of PASC after COVID-19 Infection

- 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

Outcome	Pooled Prevalence 95% CI
PASC	
Pooled PASC	0.43 [0.35; 0.51]
Hospitalized and Non-Hospitalized Mix	0.33 [0.26; 0.42]
Hospitalized	0.58 [0.47; 0.67]
Asia	0.49 [0.32; 0.66]
Europe	0.44 [0.30; 0.59]
USA	0.30 [0.21; 0.42]
30 days	0.36 [0.25; 0.48]
60 days	0.24 [0.13; 0.39]
90 days	0.32 [0.14; 0.57]
120 days	0.51 [0.41; 0.61]
Female	0.49 [0.35; 0.63]
Male	0.37 [0.24; 0.51]



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Chen, Chen, et al. "Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review." 2021, https://doi.org/10.1101/2021.11.15.21266377.

Systematic Review of Symptoms in those Diagnosed with Long-Covid

Symptoms, sequelae and difficulties conducting usual activities	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*)	Long-term (>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*)
Anxiety or depression	22% [19%, 25%] (2 studies)(30,56) ■ *low certainty*	23% [21%, 25%] (1 study)(12) ■
Anxiety and depression	No studies	2% [0%, 5%] (1 study)(18) ■
Postpartum depression	No studies	17% [8%, 27%] (1 study)(58) ■
Post-traumatic stress disorder	23% [14%, 35%] (5 studies)(5,30,37,53,59) ■ *low certainty*	18% [7%, 41%] (4 studies)(38,55,58,60) ■ *very low certainty*
Depression or post-traumatic stress disorder	No studies	22% [12%, 32%] (1 study)(58) ■ *very low certainty*
Obsessive compulsive	No studies	26% [18%, 34%] (1 study)(55) ■ *low certainty*
Feelings of distress due to symptoms (only a little/quite a lot/a great deal)	35% [19%, 52%] (1 study)(4) ■	42% [32%, 52%] (1 study)(4) ■
Overall mental health (poor/fair) Mental health - poor	17% [12%, 22%] (1 study)(31) ■ No studies	No studies 33% [27%, 37%] (1 study)(13) ■
Psychiatric morbidities	17% [7%, 27%] (1 study)(37) ■	No studies
Other mental health symptoms		
Low mood	No studies	40% [31%, 48%] (1 study)(14) ■
Panic attack	13% [11%, 16%] (1 study)(56) ■	No studies
Always/often emotional	14% [9%, 19%] (1 study)(31) ■	No studies
Thoughts of self-harm	2% [0%, 5%] (1 study)(30) ■	No studies
Anorexia	2% [0%, 4%] (1 study)(8) ■	No studies
Mental Health		
At least one mental health symptom (depression/anxiety/PTSD/obsessive compulsive)	No studies	36% [30%, 42%] (1 study)(55) ■
At least one current major psychiatric disorder (DSM-5 criteria for diagnosis)	No studies	24% [19%, 30%] (1 study)(55) ■
Anxiety	19% [10%, 32%] (4 studies)(5,8,33,37) ■ *low certainty*	32% [22%, 43%] (4 studies)(11,14,54,55) ■ *very low certainty*
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) ■ *low certainty*	17% [13%, 23%] (3 studies)(11,55,58) ■ *low certainty*
Major depressive disorder (DSM-5 criteria for diagnosis)	No studies	9% [5%, 13%] (1 study)(55) ■

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Domingo, Francesca Reyes, et al. "Prevalence of Long-Term Effects in Individuals Diagnosed with Covid-19: An Updated Living Systematic Review." 2021, https://doi.org/10.1101/2021.06.03.21258317.

Common Symptoms in a PASC Cohort

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

Symptoms	All (N=100)
Post Exertional Malaise	57%
Fatigue	54%
Daytime sleepiness	46%
Brain fog	35%
Unrefreshing Sleep	33%
Insomnia	28%
Anxiety and/or Depression	23%
Headache	17%
Lightheadedness	16%
Shortness of Breath	14%
Change in smell	12%
Change in taste	12%
Change in sweat	12%
Chest pain	11%

15 most common symptoms in PASC Cohort

Symptoms	All (N=100)	Female (N=63)	Male (N=37)
Fatigue	84%	85.7%	81.1%
Brain Fog	83%	81.0%	86.5%
Post Exertional Malaise	83%	84.1%	81.1%
Daytime sleepiness	79%	81.0%	75.7%
Unrefreshing Sleep	76%	79.4%	70.3%
Insomnia	68%	73.0%	59.5%
Headache	65%	66.7%	62.2%
Anxiety and/or Depression	65%	60.3%	73.0%
Lightheadedness	53%	54.0%	51.4%
Shortness of Breath	47%	52.4%	37.8%
Nasal Congestion	44%	49.2%	35.1%
Cough	42%	49.2%	29.7%
Change in Smell	40%	46.0%	29.7%
Change in Taste	40%	47.6%	27.0%

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Proal, Amy D., and Michael B. VanElzakker. "Long Covid or Post-Acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms." *Frontiers in Microbiology*, vol. 12, 2021, https://doi.org/10.3389/fmicb.2021.698169.

POTS/OI & hEDS Rates Higher in those with PASC…

	Control	POTS	*P* value
Cognitive	19 ± 3	37 ± 4	0.04
Cardiac	16 ± 3	25 ± 3	< 0.001
Gastro	14 ± 2	17 ± 3	0.32
Respiratory	22 ± 3	33 ± 5	0.06
Humiliation	17 ± 3	23 ± 3	0.16
Dissociation	18 ± 3	27 ± 2	0.03
ASP full (/420)	107 ± 15	158 ± 17	0.02

- 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%

Total Sample n = 137	JHS Status						
	JHS present *n* = 29		JHS absent *n* = 108				
	n	%	*n*	%	*RR*	95% CI	*P*
Anxiety Disorders							
Panic/Agoraphobia	12	41.4	2	1.9	22.3	(4.6 to 108.7)	0.0001***
Social Phobia	7	24.1	4	3.7	6.5	(1.7 to 24.2)	0.001*
Simple Phobia	8	27.6	9	8.3	3.3	(1.1 to 9.6)	0.02*
GAD	7	24.1	9	8.3	2.9	(0.97 to 8.62)	0.14 ns
Other Disorders							
Depression/Dysthymia	7	24.1	7	6.48	3.7	(1.2 to 11.7)	0.15 ns

JHS, Joint Hypermobility Syndrome according to Beighton criteria assessed at baseline.
GAD, Generalized Anxiety Disorder
Statistical significance: * p<0.05, ** p<0.001, *** p<0.0001, ns: non significant.

Table 3. Incident cases and relative risk after 15 years of follow-up according to JHS status (Bulbena et al., 2011).

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Anderson, Jake W., et al. "Cognitive Function, Health-Related Quality of Life, and Symptoms of Depression and Anxiety Sensitivity Are Impaired in Patients with the Postural Orthostatic Tachycardia Syndrome (POTS)." *Frontiers in Physiology*, vol. 5, 2014, https://doi.org/10.3389/fphys.2014.00230.

Bulbena-Cabré, Antonio, et al. "Joint Hypermobility Links with Anxiety: History and Present." *International Musculoskeletal Medicine*, vol. 33, no. 4, 2011, pp. 132–136., https://doi.org/10.1179/175361511x13153160075017.

Bulbena, Antoni, et al. "Joint Hypermobility, Anxiety and Psychosomatics: Two and a Half Decades of Progress toward a New Phenotype." *Clinical Challenges in the Biopsychosocial Interface*, 2015, pp. 143–157., https://doi.org/10.1159/000369113.

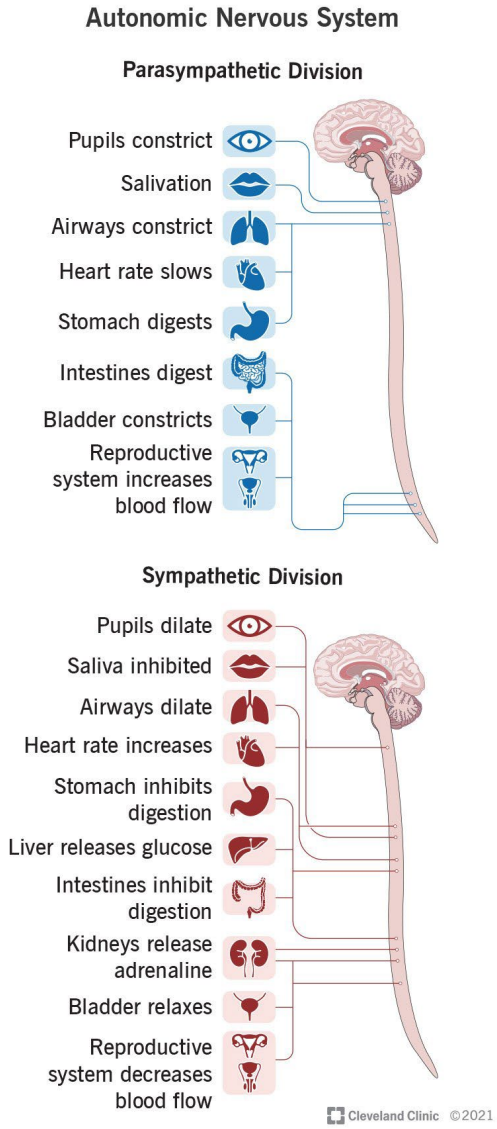
Bulbena, Antonio, and Guillem Pailhez. *Somatic Conditions Intrinsic to Anxiety Disorders*. INTECH Open Access Publisher, 2011.

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)

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

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

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

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 → can increase sympathetic tone by activating adrenergic receptors and having an allosteric effect on muscarinic GPCR's
  - Autoantibody activation of adrenergic and cholinergic receptors → 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

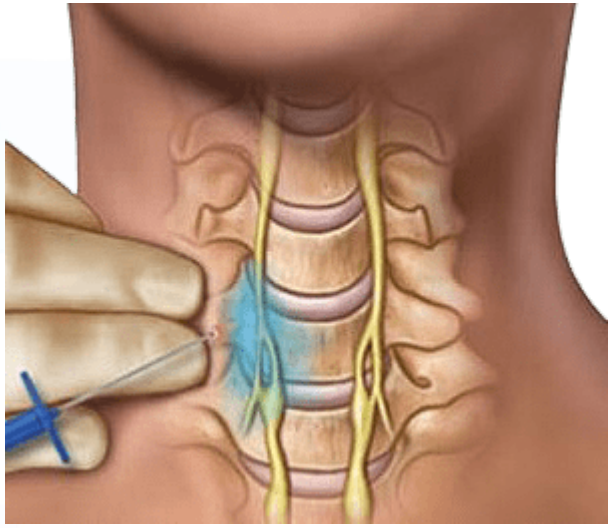
Bisaccia, Giandomenico, et al. "Post-Acute Sequelae of Covid-19 and Cardiovascular Autonomic Dysfunction: What Do We Know?" *Journal of Cardiovascular Development and Disease*, vol. 8, no. 11, 2021, p. 156., https://doi.org/10.3390/jcdd8110156.

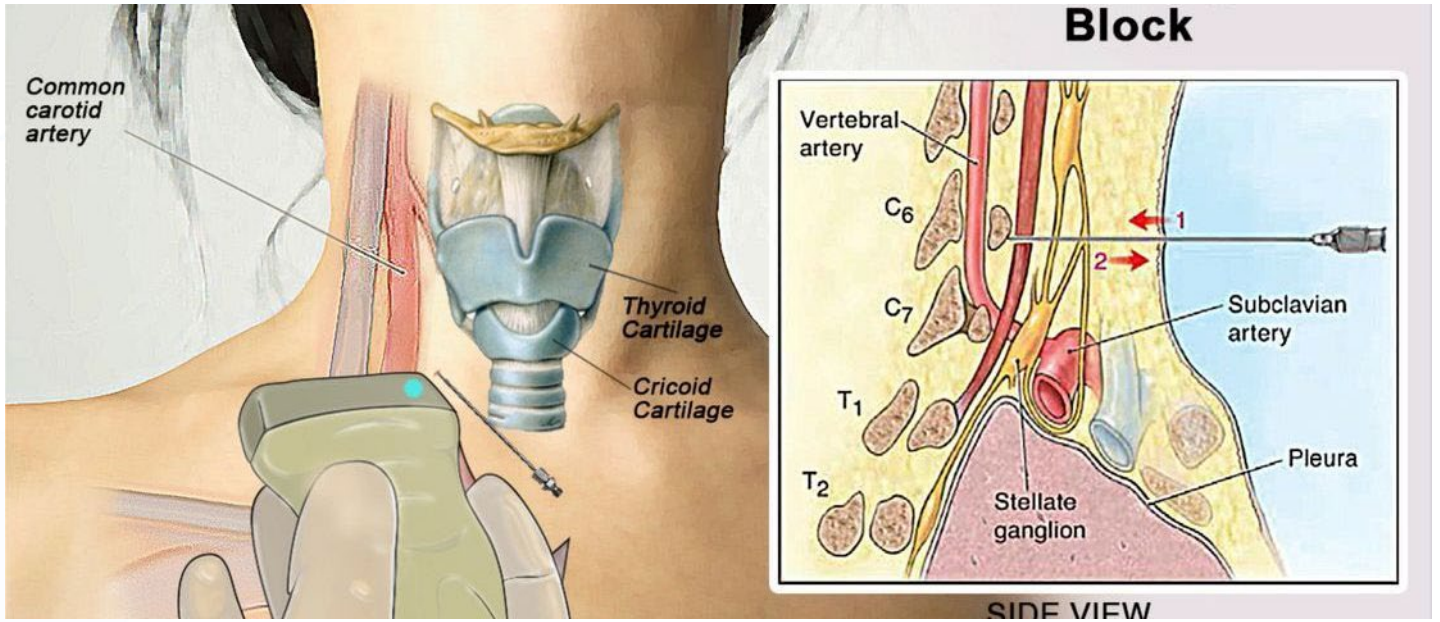
Do methods for reducing sympathetic nervous system signaling and transmission reduce symptoms of “anxiety” and “PTSD” in those with PASC?

YES!

Stellate Ganglion Injections?

- Cervical sympathetic chain (including the superior, middle, and inferior cervical ganglions 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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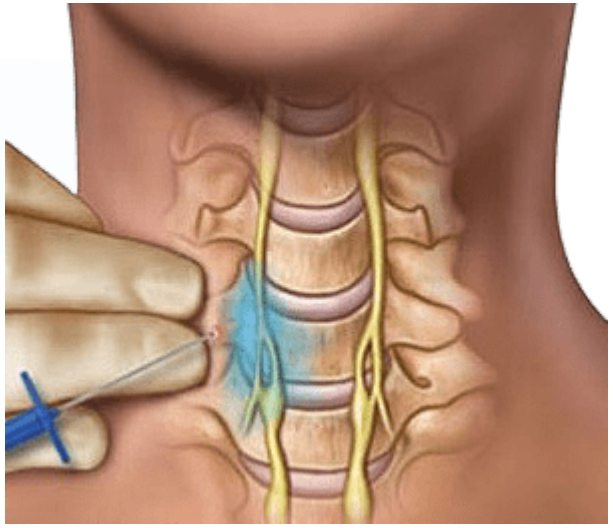
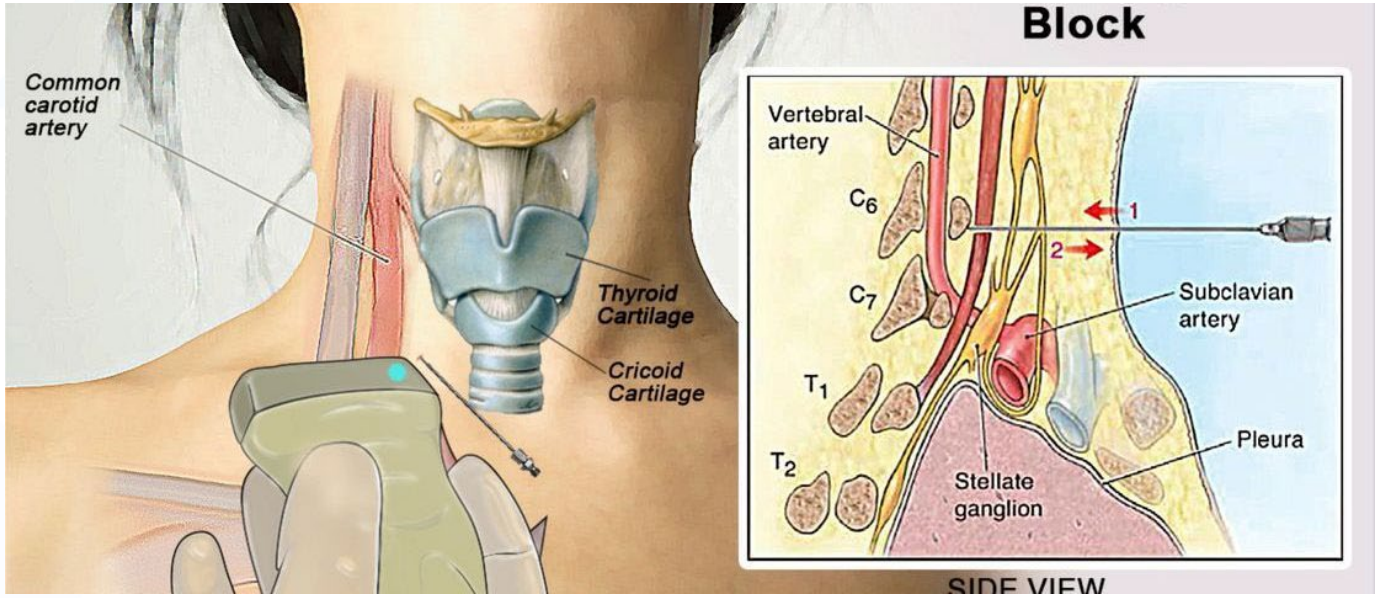
Liu, Luke D., and Deborah L. Duricka. “Stellate Ganglion Block Reduces Symptoms of Long COVID: A Case Series.” *Journal of Neuroimmunology*, vol. 362, 2022, p. 577784., https://doi.org/10.1016/j.jneuroim.2021.577784.

Porzionato, Andrea, et al. “Sympathetic Activation: A Potential Link between Comorbidities and Covid-19.” *The FEBS Journal*, vol. 287, no. 17, 2020, pp. 3681–3688., https://doi.org/10.1111/febs.15481.

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





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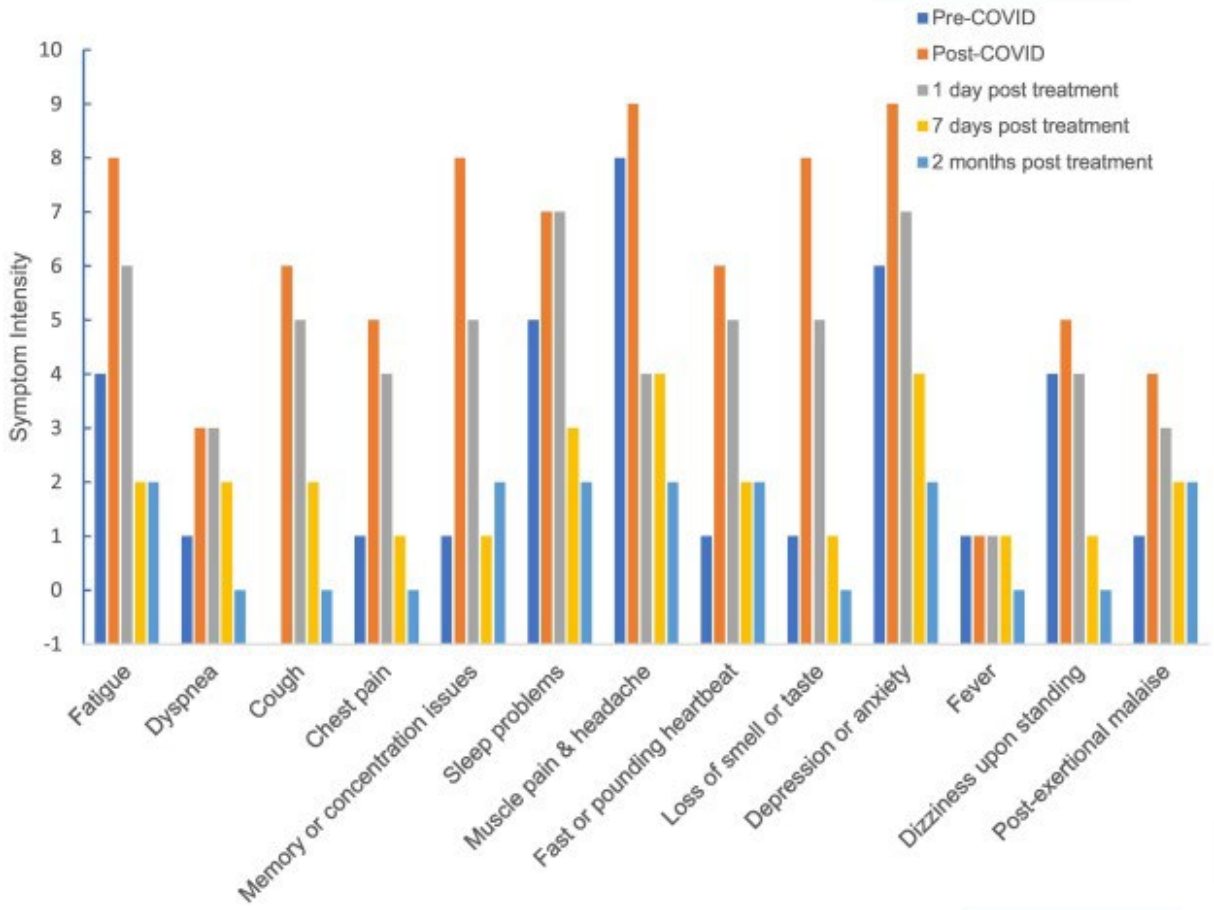
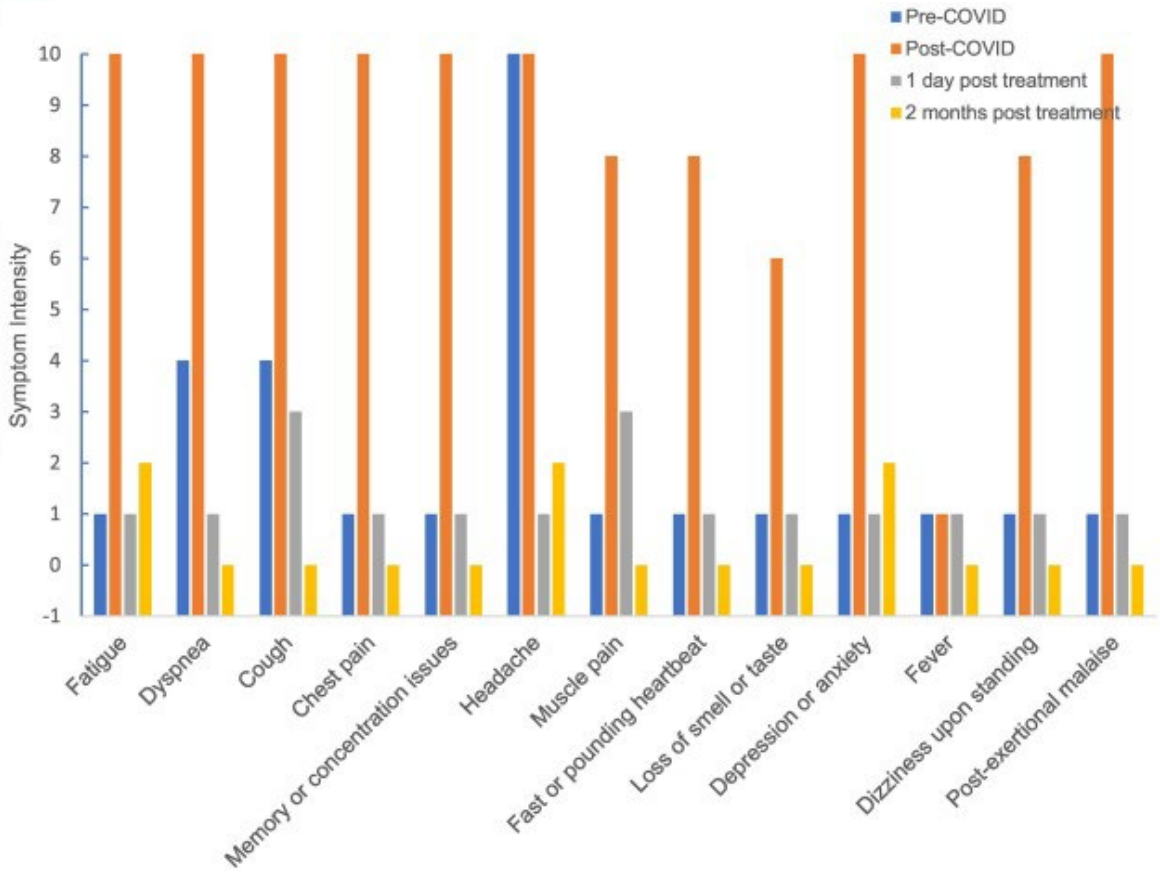
Stellate Ganglion Injections?

Patient #1



Patient #2



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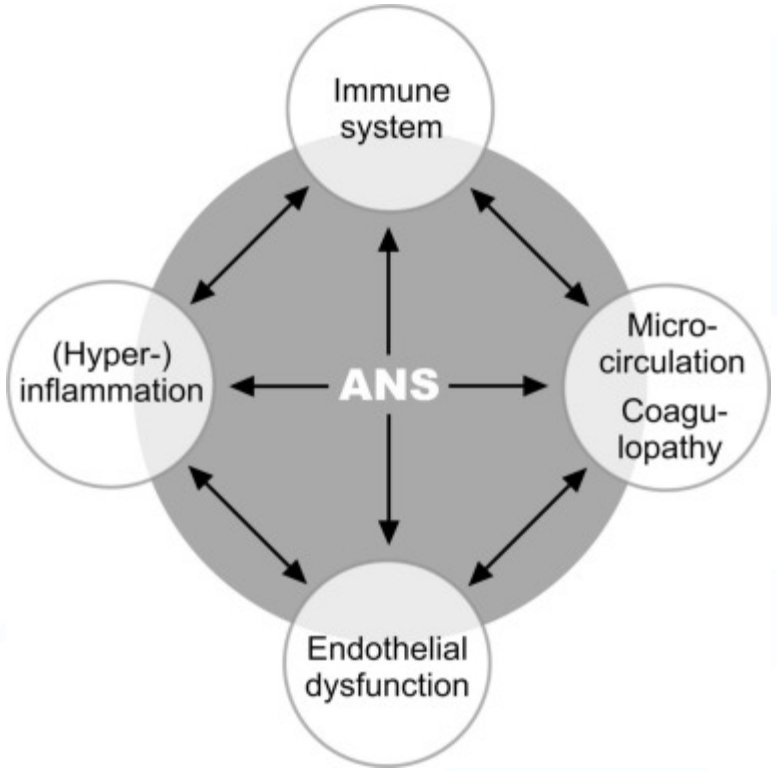
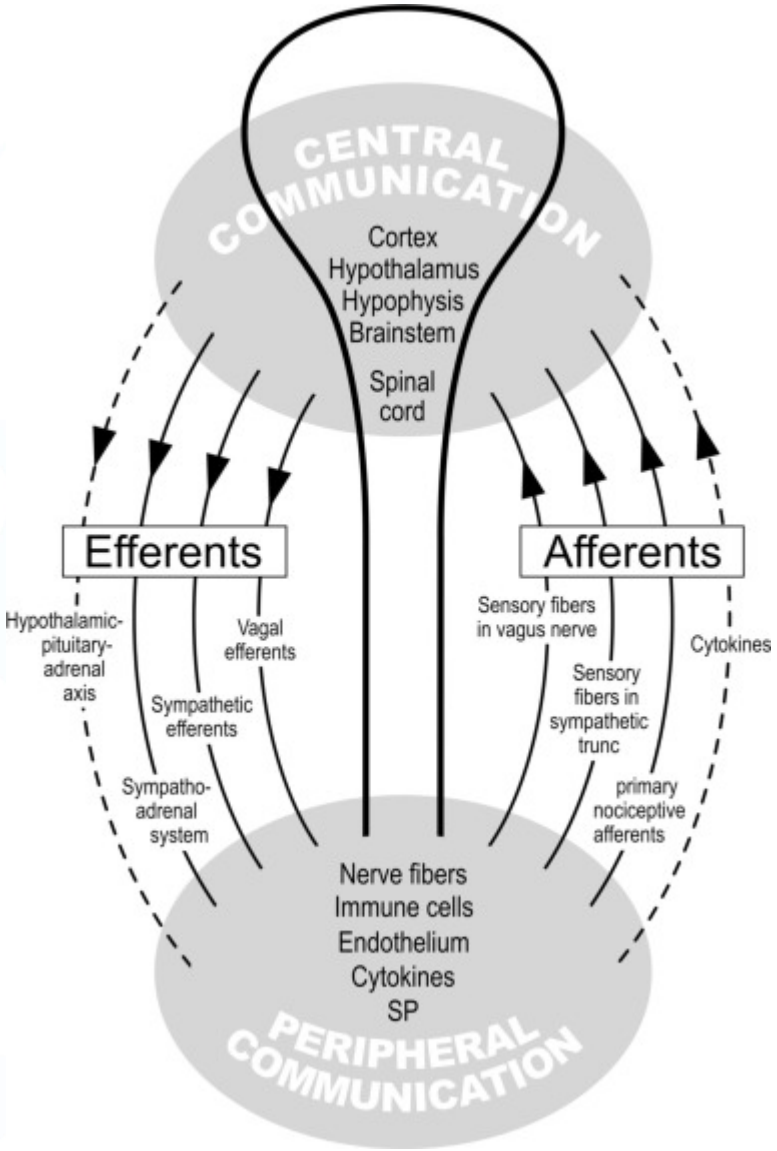
Stellate Ganglion Injections?



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



Autonomic nervous system and immune system central and peripheral communication

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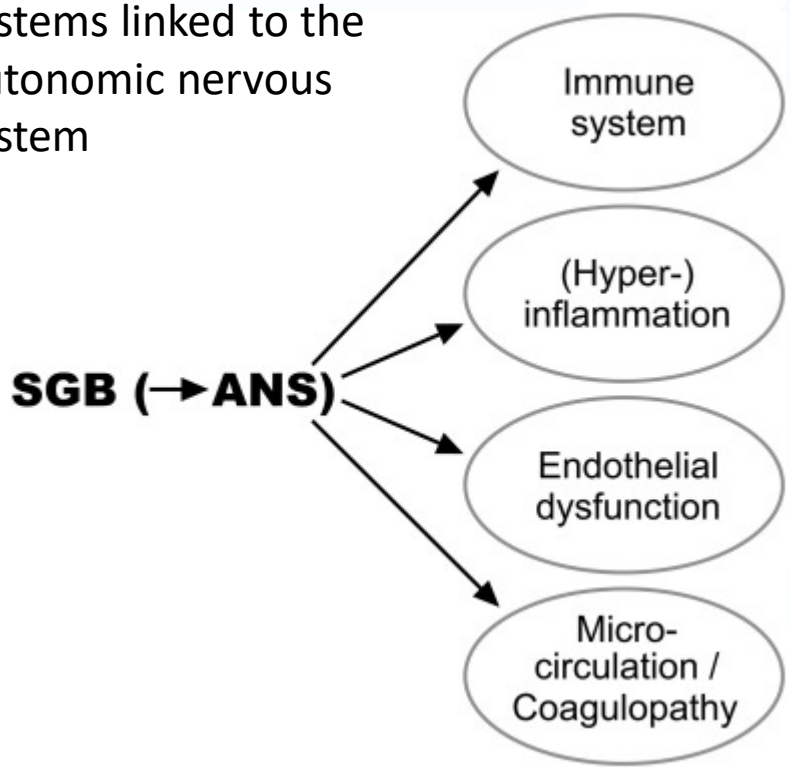
Fischer, Lorenz, et al. "Regulation of Acute Reflectory Hyperinflammation in Viral and Other Diseases by Means of Stellate Ganglion Block. A Conceptual View with a Focus on Covid-19." *Autonomic Neuroscience*, vol. 237, 2022, p. 102903., https://doi.org/10.1016/j.autneu.2021.102903.

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

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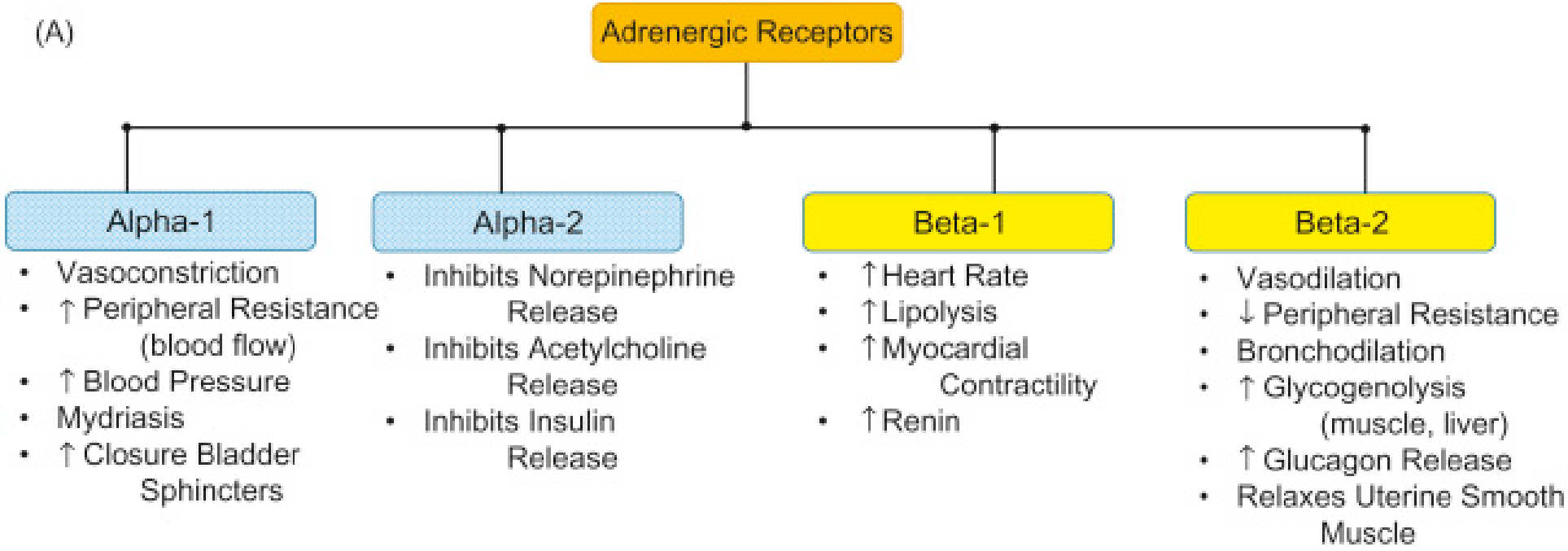
Treatments: Beta Blockers

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

(A)



- Ivabradine (Corlanor) has no direct effect on the sympathetic nervous system

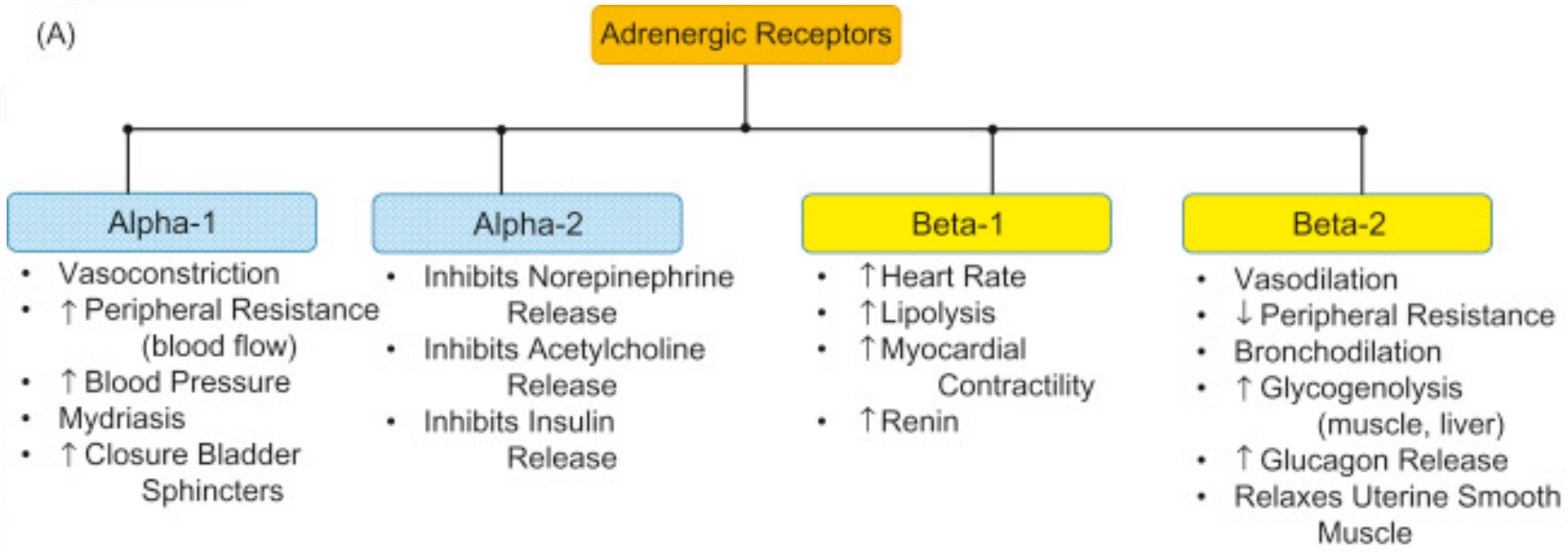
(B)

Alpha-1	Alpha-2	Beta-1	Beta-2
NE > E	E > NE	E = NE	E >> NE
NE = Norepinephrine; E = Epinephrine			

Treatments: Alpha Blockers

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

(A)



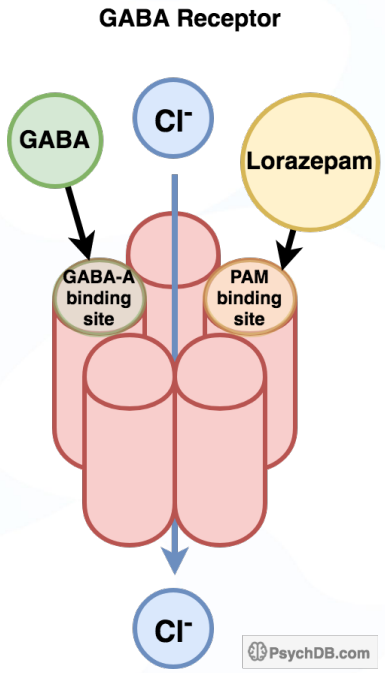
(B)

Alpha-1	Alpha-2	Beta-1	Beta-2
NE > E	E > NE	E = NE	E >> NE
NE = Norepinephrine; E = Epinephrine			

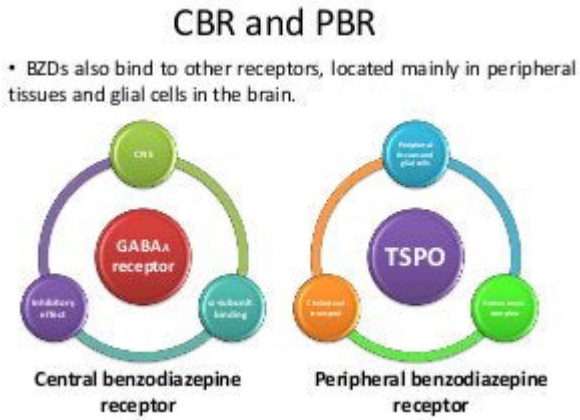
Treatments: Benzodiazepines

Bind to $GABA_A$ 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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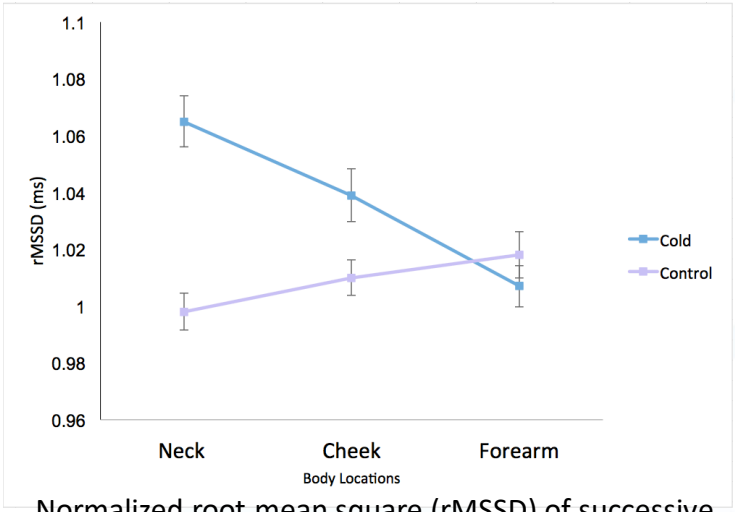
Galiegue, Sylvaine, et al. "The Peripheral Benzodiazepine Receptor: A Promising Therapeutic Drug Target." *Current Medicinal Chemistry*, vol. 10, no. 16, 2003, pp. 1563–1572., https://doi.org/10.2174/0929867033457223.

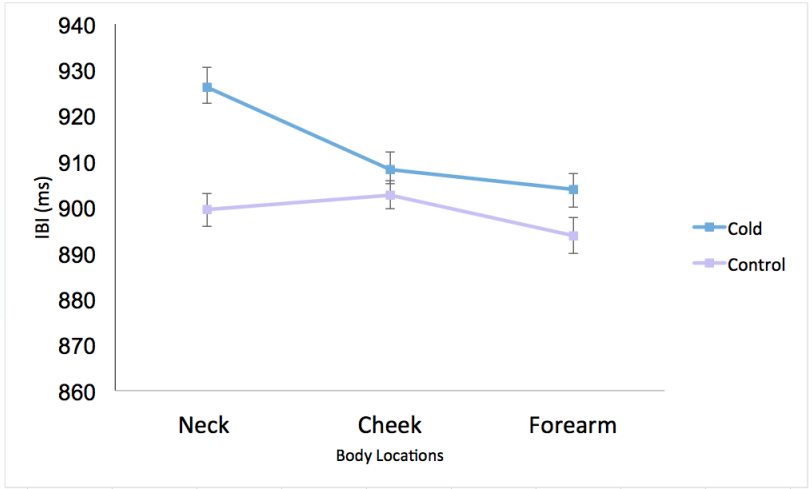
Treatments: Vagal Maneuvers

- 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



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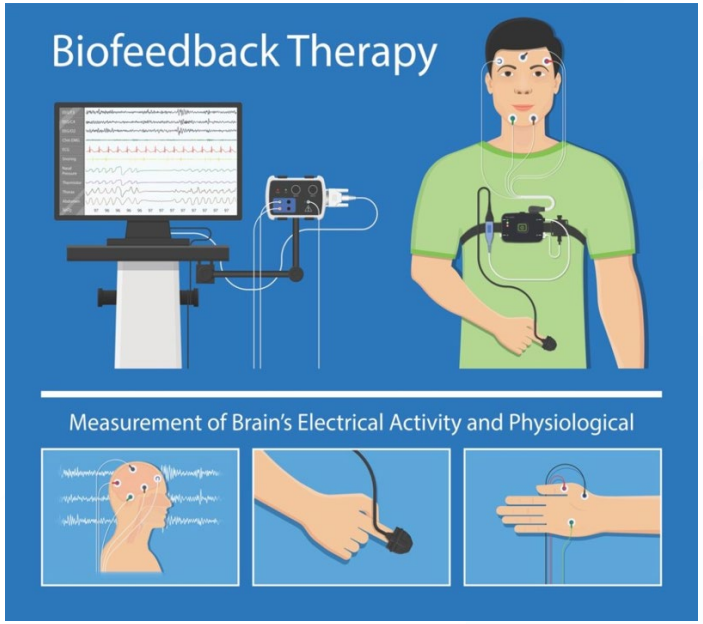
Jungmann, Manuela, et al. “Effects of Cold Stimulation on Cardiac-Vagal Activation in Healthy Participants: Randomized Controlled Trial.” *JMIR Formative Research*, vol. 2, no. 2, 2018, https://doi.org/10.2196/10257.

Treatments: Conscious Control Over Autonomic Responses

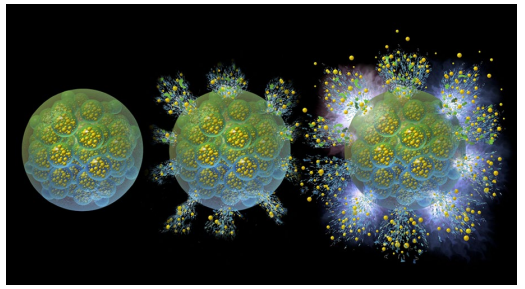
DNRS Dynamic Neural Retraining System™



The Gupta Program
for health & happiness

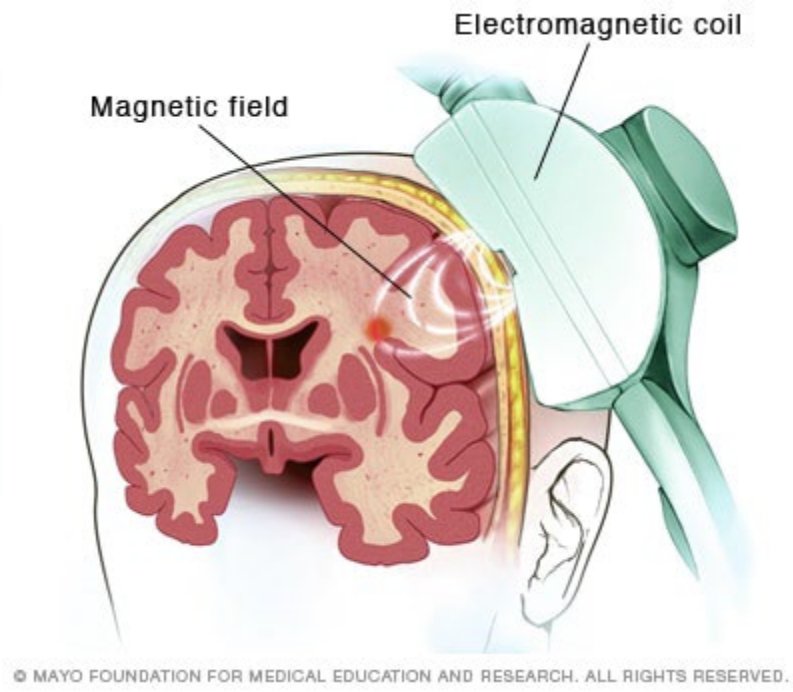
Treatments: Treat Co-morbidities

- 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



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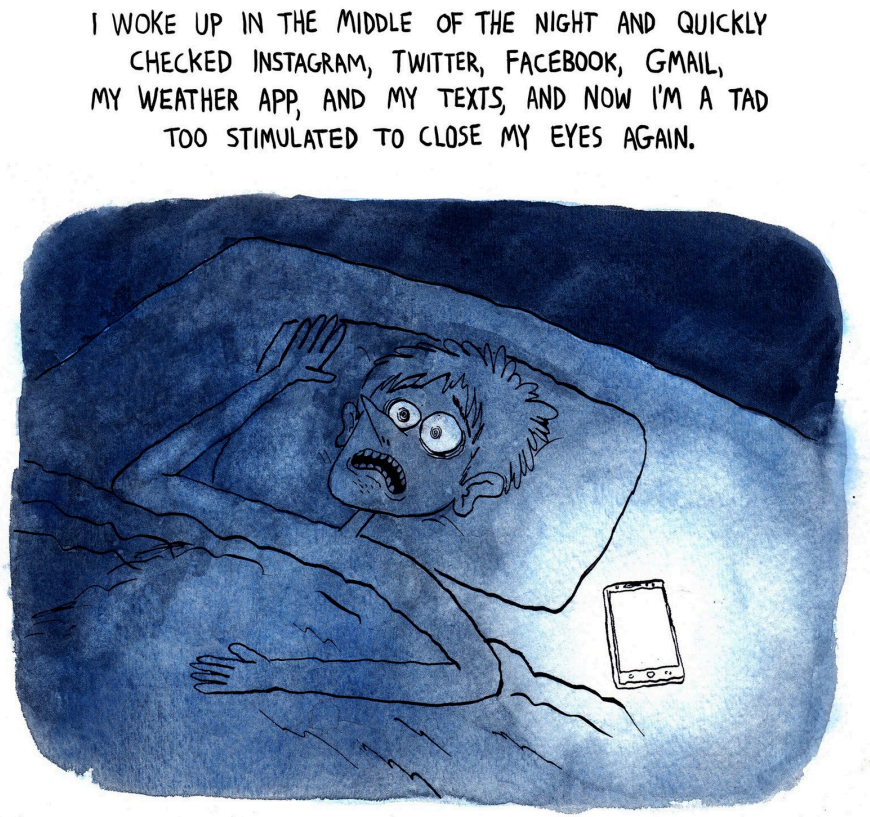
Becker, Richard C. "Autonomic Dysfunction in SARS-COV-2 Infection Acute and Long-Term Implications COVID-19 Editor's Page Series." *Journal of Thrombosis and Thrombolysis*, vol. 52, no. 3, 2021, pp. 692–707., https://doi.org/10.1007/s11239-021-02549-6.

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?