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Sleep disturbances Long COVID and ME/CFS

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Outline of today's discussion (objectives)

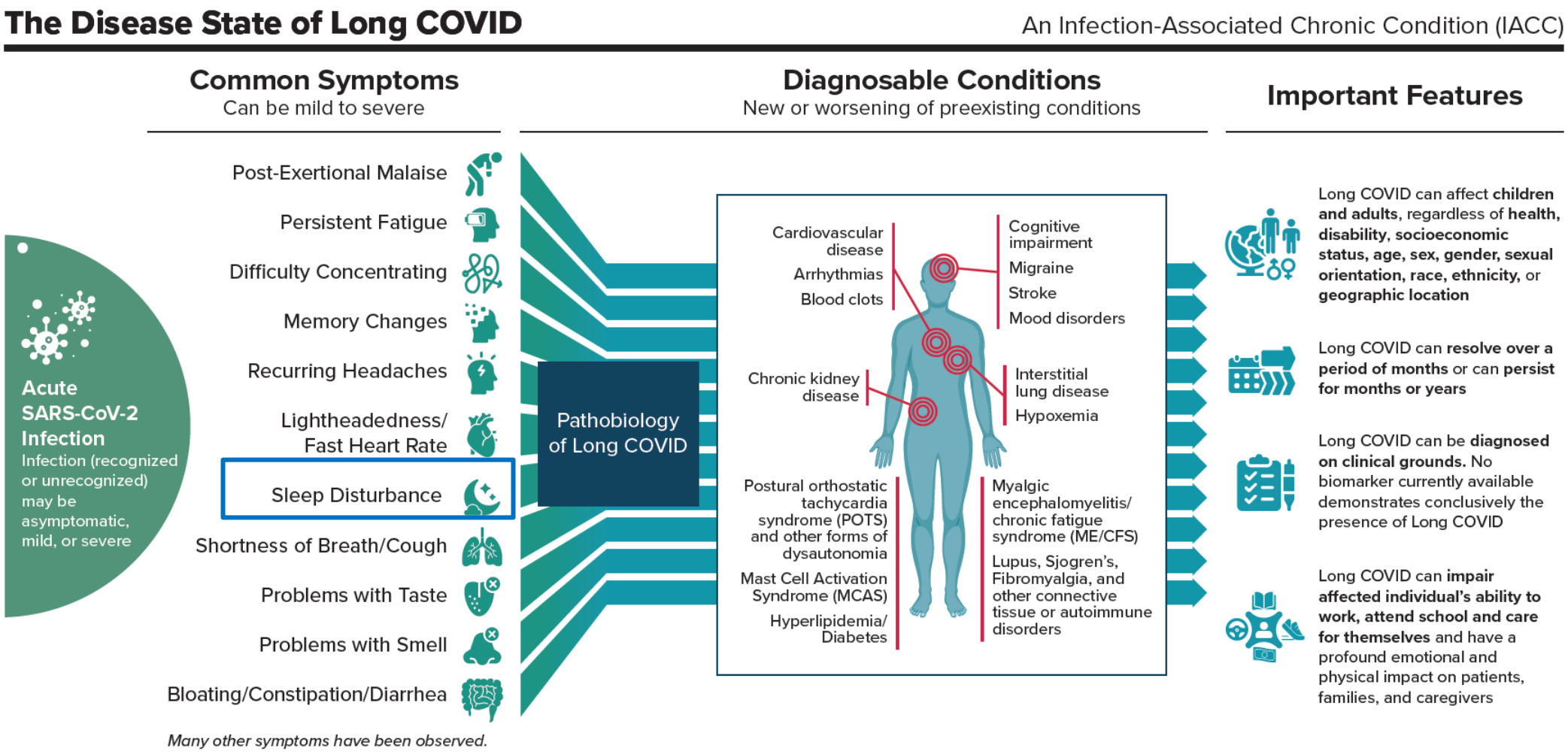
- Are sleep disturbances (unrefreshing sleep) present in LC, ME/CFS and related conditions?
- What are causes of sleep disturbances in LC, ME/CFS and related conditions?
- How are sleep disturbances evaluated?
- Does treating sleep disturbances change prognosis?
- What are reasonable treatment and supportive care approaches?

1. Are sleep disturbances (unrefreshing sleep) present in LC, ME/CFS and related conditions?

Yes…

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2024 NASEM LC Definition: Figure & Features



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NASEM publications and in L Chu et al;, JGIM, March 2025

Sleep disturbances have a high prevalence in patients with PCC (Post COVID Conditions), occurring in upwards of 70% of patients and rank third behind fatigue and dyspnea in meta-analyses of PCC (n=280)

- Significant comorbidities of insomnia at the initial visit were symptoms of anxiety, depression, and PTSD
- Chronic insomnia correlated with worse ability to resume usual activities and worse overall QOL.

Kadl A, et al. **Prevalence and associations of insomnia after COVID-19 infection**. J Clin Sleep Med. 2025 Feb 1;21(2):383-391. doi: 10.5664/jcsm.11420. PMID: 39436395; PMCID: PMC11789262
https://jcsm.aasm.org/doi/10.5664/jcsm.11420

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RECOVER clinical trials: RECOVER-SLEEP

enrolling 1000+ participants

- **Hypersomnia:** sleeping longer than usual or feeling very sleepy or tired during the day, even after getting a full night's sleep *(modafinil or solriamfetol)*
- **Complex sleep disturbances:** poor sleep quality of problems falling asleep or staying asleep *(melatonin + light therapy)*

All patients enrolled will first be screened for obstructive sleep apnea.

https://en.wikipedia.org/wiki/Solriamfetol

https://trials.recovercovid.org/sleep

Unrefreshing sleep in ME/CFS & FM

- Sleep disturbances are common
  - Included in all CFS, ME/CFS, ME and FM case definitions or criteria
  - So… present in >90% of all diagnosed
- Sleep abnormal in
  - Quality (light, restless, interrupted, heavy)
  - Duration/timing (delayed, prolonged, irregular)

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Polysomnography 300 Dutch ME/CFS patients:

(those with primary sleep disorders excluded)

Four types of sleep presentation (1 PSG):

- Sleep time ↑ REM ↑ *[catch up sleep?]*
- REM ↓ *[drugged sleep?]*
- #arousals/hour ↑ *[light disrupted sleep?]*
- Sleep ↓ REM ↓ *[insomnia?]*

Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. BMJ Open. 2013;3(6):e002999

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SLEEP

MUST include
frequency (50%+)
and
severity (mod+)
to separate
from healthy controls

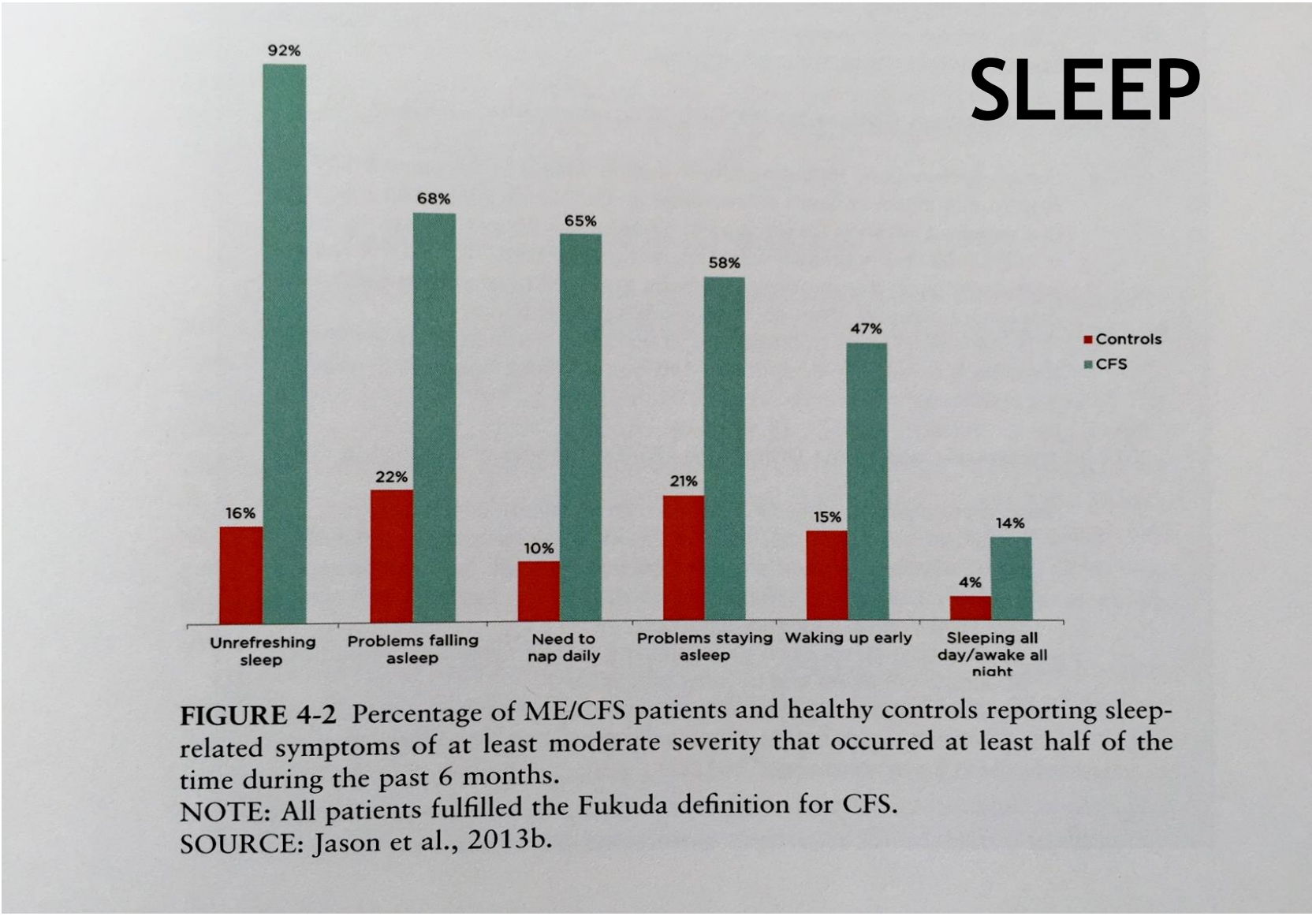


FIGURE 4-2 Percentage of ME/CFS patients and healthy controls reporting sleep-related symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.
NOTE: All patients fulfilled the Fukuda definition for CFS.
SOURCE: Jason et al., 2013b.

Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine. **Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness**. Washington (DC): National Academies Press (US); 2015 Feb 10. PMID: 25695122.

Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. Jason LA, et al. Fatigue: Biomedicine, Health and Behavior 2(1) 2013.

2. What are some causes of sleep disturbances in LC, ME/CFS and related conditions?

Treatable comorbid conditions may contribute to fatigue and sleep disturbances

- Primary sleep disorders
  - Obstructive sleep apnea, airway resistance
  - Central sleep apnea
  - Movement disorders (RLS, myoclonus)
- Pain disorders
- Mental health conditions
- Urinary frequency disorders
- Medications
- Snoring spouse. Active pets. Etc…

There may be unique disruptors of normal sleep in LC, ME/CFS and related disorders

- Central sensitivity/sensory amplification
- Autonomic nervous system dysregulation
- HPA-axis dysregulation

Central Sensitivity/sensory amplification

- The clinical and pathophysiological features of long COVID, fibromyalgia and ME/CFS …provide a…unifying framework of **central sensitivity syndromes**.
- “Expert opinion: Once long COVID is redefined to exclude patients with well-defined organ disease, it fits best as a model of central sensitization…”

Goldenberg DL. **The pivotal role of central sensitization in long COVID, fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome**. Expert Rev Neurother. 2025 Aug;25(8):973-989. doi: 10.1080/14737175.2025.2516097. Epub 2025 Jun 13. PMID: 40512228.

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Autonomic Nervous System (ANS) dysregulation

- **Sympathetic** >> *parasympathetic*
  - Fight and flight >> Rest and digest

- ANS dysregulation well documented in ME/CFS*
  - "ME/CFS patients exhibit a substantial autonomic symptom burden that correlates with greater illness severity. Individualized care strategies targeting dysautonomia assessment and intervention may offer meaningful improvements in symptom management and quality of life for those with ME/CFS and similar chronic conditions."
- ANS dysregulation in LC…. (next slide)

*Issa A, Lin JS, Chen Y, et al. MCAM Study Group. **Autonomic Dysfunction in ME/CFS: Findings from the Multi-Site Clinical Assessment of ME/CFS (MCAM) Study in the USA**. J Clin Med. 2025 Sep 5;14(17):6269. doi: 10.3390/jcm14176269. PMID: 40944028; PMCID: PMC12428951.

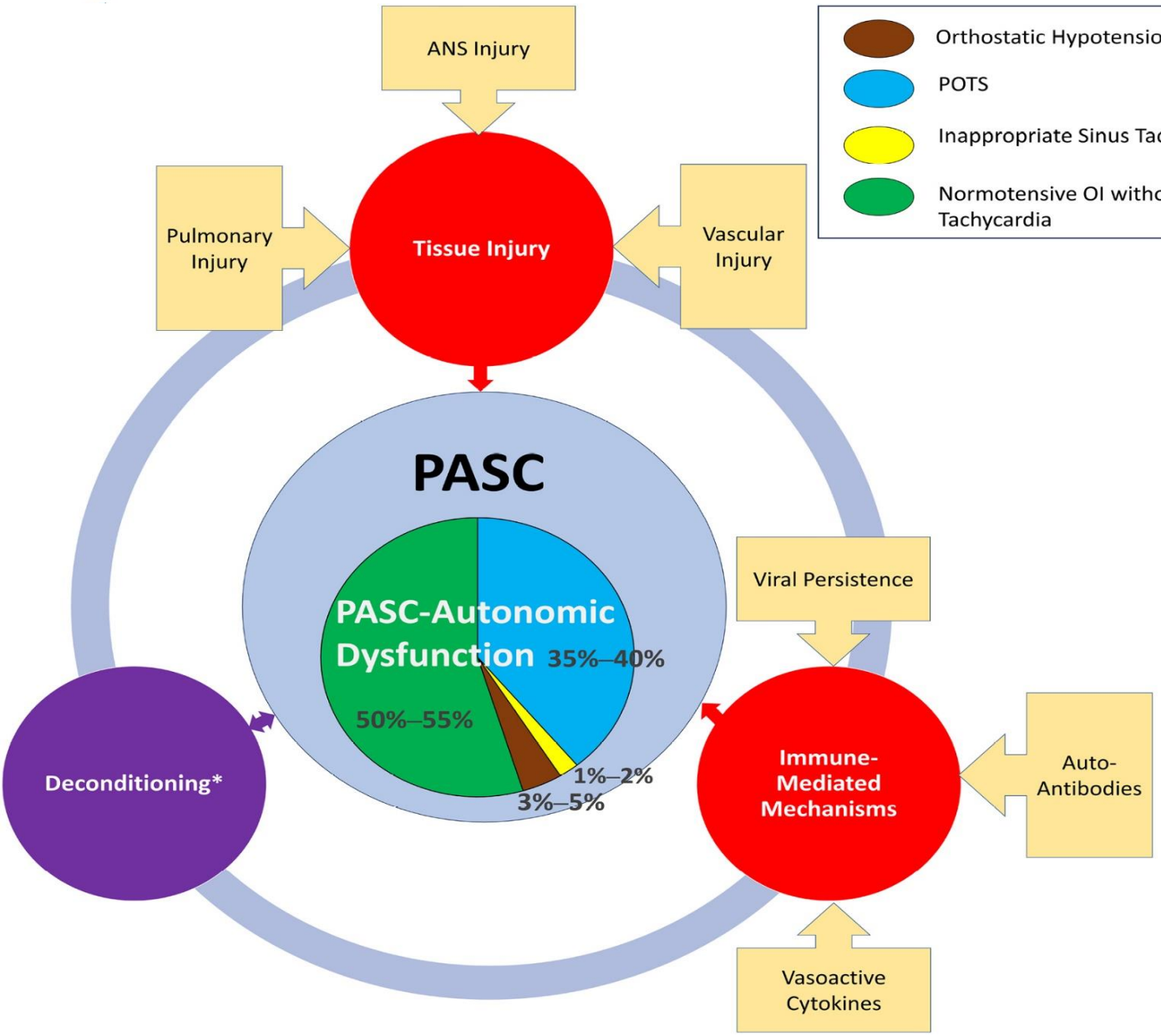
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Cardiac Arrhythmias and Autonomic Dysfunction Associated With COVID-19: A Scientific Statement From the **American Heart Association**.

Autonomic Dysfunction (AD) associated with COVID-19 section

- POTS (Postural Orthostatic Tachycardia Syndrome) occurs in **25% to 35%** of patients with PASC.
- OH (Orthostatic Hypotension) occurs in **3% to 5%** of patients with PASC.
- Orthostatic intolerance without POT/OH occurs in **50-55%**

Gopinathannair R, Olshansky B, Chung MK, et al. AHA Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Council on Hypertension. **Cardiac Arrhythmias and Autonomic Dysfunction Associated With COVID-19: A Scientific Statement From the American Heart Association. Circulation. 2024 Nov** 19;150(21):e449-e465. doi: 10.1161/CIR.0000000000001290. PMID: 39397661



"As part of a complete history and physical, orthostatic vital signs in the form of a **10-minute stand test** should be completed and are sufficient to delineate AD.

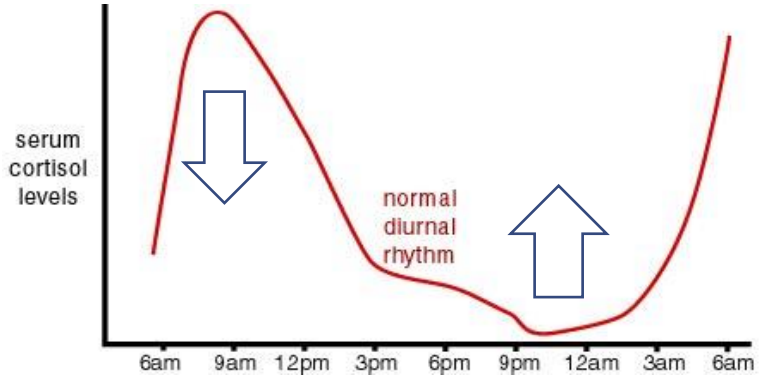
Because PASC-associated autonomic disorders may represent a new clinical entity, conventional treatment for AD may be ineffective; however, given the lack of treatment data for PASC-AD, the most prudent strategy is to **manage this condition according to existing autonomic disorder guidelines"**

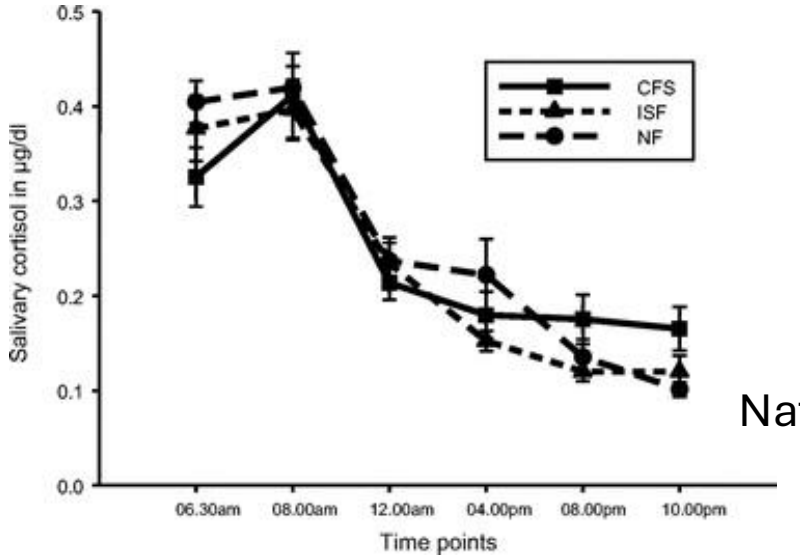
Requested permission for use from AHA

Gopinathannair R, Olshansky B, Chung MK, et al. AHA Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Council on Hypertension. **Cardiac Arrhythmias and Autonomic Dysfunction Associated With COVID-19: A Scientific Statement From the American Heart Association. Circulation. 2024 Nov** 19;150(21):e449-e465. doi: 10.1161/CIR.0000000000001290. PMID: 39397661

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HPA-axis dysregulation





Nater et al.

- Attenuated AM cortisol level (still under debate in Long COVID)
- Loss of normal circadian rhythm affecting cortisol levels?
- Total cortisol levels are lower than average (low normal in ME/CFS)

Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. Nater UM, et al. Psychosom Med 2008;70:298-305. (CDC)

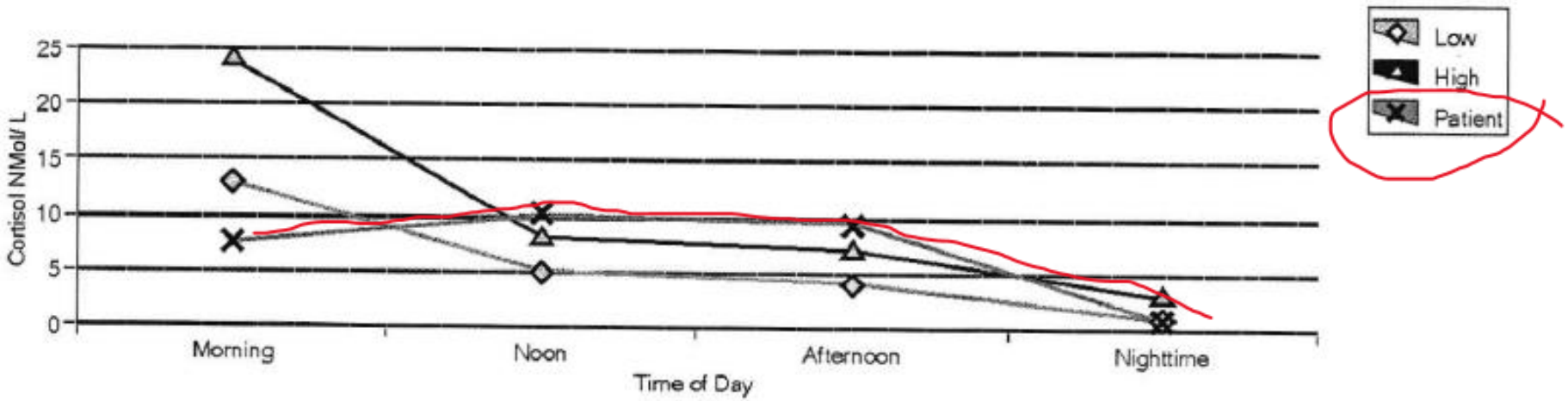
Salivary cortisol response to awakening in chronic fatigue syndrome. Roberts AD, et al. Br J Psychiatry 2004;184:136-41.

Distinguishing features of Long COVID identified through immune profiling. Klein J, ... Iwasaki A. Nature. 2023 Sep 25. doi: 10.1038/s41586-023-06651-y. PMID: 37748514.

Alaedini, Armin et al. **Is Low Cortisol a Marker of Long COVID?** The American Journal of Medicine, Volume 137, Issue 7, 564 – 565 (July 2024)

Functional Adrenal Stress Profile - 201

Parameter	Result	Reference Range	Units
Cortisol - Morning (6 - 8 AM)	**7.6***	13.0 - 24.0	nM/L
Cortisol - Noon (12 - 1 PM)	**10.4***	5.0 - 8.0	nM/L
Cortisol - Afternoon (4 - 5 PM)	**9.4***	4.0 - 7.0	nM/L
Cortisol - Nighttime (10 PM - 12 AM)	**0.9***	1.0 - 3.0	nM/L
Cortisol Sum	28.3	23.0 - 42.0	nM/L
DHEA-S Average	3.19	2.0 - 10.0	ng/mL
Cortisol/DHEA-S Ratio	**8.87***	5.0 - 6.0	Ratio



33 year old male with ME/CFS of 2 year duration. LB clinic record

3. How are sleep disturbances evaluated?

Observing/Monitoring sleep

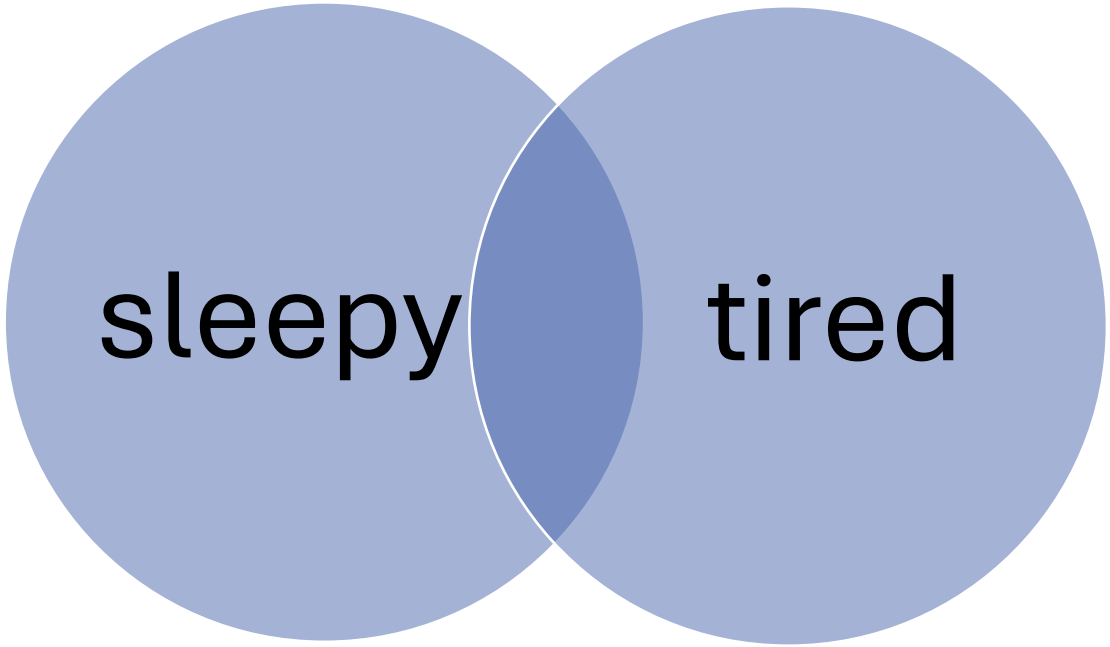
- Polysomnography- Gold standard but "sleep lab artifact" can be high
- Home sleep study--- strengths and weaknesses
- Pulsoximetry overnight---only records episodes of hypoxemia
- **Patients can also monitor their own sleep— useful if not obsessive or anxiety producing**

Polysomnography (PSG)

- PSG reveals Primary Sleep Disorders that may respond to treatment
- PSG is otherwise non-diagnostic in ME/CFS and FM
  - Increased alpha (dozing, light sleep)
  - Decreased delta (slow wave, deep sleep)
  - Fragmentation
  - Delayed onset

Sleep Structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. Arthritis Research & Therapy 10(3):R56. Togo 2008
Are patients with chronic fatigue syndrome just "tired" or also "sleepy"? Neu et al 2009. Journal of Sleep Research 17(4):427-431
Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis. A review. Jackson et al 2012. Journal of Clinical Sleep Medicine. 8(6):719-728

Somnolence may not be equivalent to fatigue/tiredness



Somnolence may be more treatable

- Sleep deprivation (all causes)
- Medications
- Illness (neurologic, endocrine, inflammation)

ESS (Epworth Sleepiness Scale) helps identify sleepiness vs fatigue

4. Does treating sleep disturbances change prognosis?

- Few treatment trials have assessed the benefit of drugs for sleep disturbances in ME/CFS or LC, nor how drugs may alter daytime symptoms or function. More studies in FM.
- The RECOVER-SLEEP trial outcomes are pending.

- **My expert clinical opinion:** treating sleep (skillfully) helps improve quality of life and gives patients some control over their challenging multisystem illness

https://www.rheumatologyadvisor.com/features/managing-fibromyalgia-and-sleep-disorders/

Choy EH. **The role of sleep in pain and fibromyalgia**. Nat Rev Rheumatol. 2015 Sep;11(9):513-20. doi: 10.1038/nrrheum.2015.56. PMID: 25907704.

5. What are reasonable treatment and supportive care approaches?

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Sleep disruptions are varied

0123 Can’t go to sleep
0123 Restless sleep
0123 Wake up too early
0123 Can’t go back to sleep
0123 Need too much sleep
0123 Need to take naps
0123 Unrefreshing sleep
0123 Restless legs
0123 Leg cramps
0123 Myoclonic jerks (involuntary jerking of limbs)
0123 Snoring
0123 Stop breathing during sleep



0= none 1= infrequent 2= moderate in severity or frequency 3= severe or frequent

Sleep problems:

0 1 2 3 Can't go to sleep
0 1 2 3 Restless sleep
0 1 2 3 Wake up too early
0 1 2 3 Can't go back to sleep
0 1 2 3 Need too much sleep
0 1 2 3 Need to take naps
0 1 2 3 Unrefreshing sleep
0 1 2 3 Restless legs
0 1 2 3 Leg cramps
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0 1 2 3 Snoring
0 1 2 3 Stop breathing during sleep

Sleep problems:

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Sleep problems:

0 1 **2** 3	Can't go to sleep
0 1 **2** **3**	Restless sleep
0 1 2 3	Wake up too early
0 1 **2** 3	Can't go back to sleep
0 **1** 2 3	Need too much sleep
0 **1** 2 3	Need to take naps
0 1 2 **3**	Unrefreshing sleep
0 1 2 **3**	Restless legs
0 1 **2** 3	Leg cramps
0 1 **2** 3	Myoclonic jerks (involuntary jerking)
0 **1** 2 3	Snoring
0 1 2 3	Stop breathing during sleep

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General Recommendations:

- Improve sleep hygiene (routine timing, environment).
- Identify the impact of stimulating medication on sleep



- Daytime activity. Get physically tired---but not exhausted, "wound up" or relapsing (PEM).
- Be wary of long or late naps.
- Minimize sedating drugs during the day.
- Aim at the CAUSES of sleep disruption.
- Simplify use of medications and use them skillfully
  - Sleep onset (wind down, establish cycles, short acting drugs, earlier dosing of longer acting sedating medications)
  - Light sleep and frequent awakening (reduce interruptions, low dose longer acting meds)
  - Early morning awakening (med rebound or withdrawal? Too much sleep? Depression? Establish cycles…)

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Meds based on causes of sleep disruption to consider:



- **Primary sleep disorders** (obstructive or central sleep apnea)
- **Restless legs syndrome** www.rls.org
  - 1st line: FDA approved gabapentin enacarbil (Horizont), plus *off-label gabapentin, pregabalin*
  - 2nd line: FDA approved dopaminergic agents (pramipexole, ropinirole)
  - Other meds used off-label: *clonazepam, opioids (tramadol, methadone)*
- **Chronic pain** (many pain drivers---muscle, joint, nerve, widespread pain amplification, etc)
  - FDA approved for pain: antidepressants (amitriptyline, duloxetine), pregabalin, SL cyclobenzaprine (Tonmya for FM). Topiramate for migraine. *Off-label gabapentin*
  - Muscle relaxants FDA approved for spasticity or muscle spasm: (cyclobenzaprine, tizanidine)
- **Mental health** disorders---examples of FDA approved meds for anxiety, PTSD, depression, bipolar disorder
  - Hydroxyzine, benzodiazepines (clonazepam, diazepam, lorazepam, alprazolam), mirtazapine, trazodone, amitriptyline/doxepin, atypical antipsychotics (low dose quetiapine, olanzapine)

FDA approved meds for “insomnia”



- Benzodiazepine receptor agonists: zolpidem, zaleplon, eszopiclone *(tolerance, rebound)*
- Benzodiazepines, ex: triazolam, temazepam, etc *(tolerance, rebound)*
- Orexin receptor antagonists: suvorexant (Belsomra), lemborexant (Dayvigo), daridorexant (Quviviq) *(expensive and variable insurance coverage)*
- TCA: doxepin (Silenor, 3 and 6 mg) *(…doxepin comes in a solution 10 mg/ml)*
- Melatonin receptor agonist (sleep onset insomnia): ramelteon

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REVIEW of Rx for chronic insomnia in adults (2017)

Clinical practice recommendations based on drugs reviewed (all WEAK data support)

We suggest that clinicians USE:

suvorexant for **sleep maintenance** insomnia (versus no treatment) in adults (WEAK)

doxepin as a treatment for **sleep maintenance** insomnia (versus no treatment) in adults. (WEAK)

zaleplon as a treatment for **sleep onset** insomnia (versus no treatment) in adults. (WEAK)

triazolam as a treatment for **sleep onset** insomnia (versus no treatment) in adults. (WEAK)

ramelteon as a treatment for **sleep onset** insomnia (versus no treatment) in adults. (WEAK)

eszopiclone as a treatment for **sleep onset and sleep maintenance** insomnia (versus no treatment) in adults. (WEAK)

zolpidem as a treatment for **sleep onset and sleep maintenance** insomnia (versus no treatment) in adults. (WEAK)

temazepam as a treatment for **sleep onset and sleep maintenance** insomnia (versus no treatment) in adults. (WEAK)

We suggest that clinicians NOT USE:

trazodone, tiagabine, diphenhydramine, melatonin, tryptophan, valerian as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults. (WEAK)

Journal of Clinical Sleep Medicine. Volume 13, Issue 02. **Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline**. Michael J. Sateia, MD, et al. Online: February 15, 2017. https://jcsm.aasm.org/doi/10.5664/jcsm.6470

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Natural sleep (drug free) is best,
but chronically disrupted or inadequate sleep
may be insidiously harmful as well.

There is no perfect medication for sleep.
Almost all have some adverse effects.

Learn about the medications and use them skillfully.