Upright Activity and Exercise Intolerance:

Critical Concepts in the Evaluation of Chronic Fatigue

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Objectives

1) Determine the presence or absence of Post-Exertional Malaise (PEM) and utilize the information to develop appropriate physical rehabilitation advice for a patient with chronic fatigue.

2) Assess impairment of function using a combination of readily available standardized questionnaires (HADS, FIQ-R, OHQ/OIQ) and reported HUA (Hours of Upright Activity) as defined in the lecture.

3) Perform bedside orthostatic testing to determine the presence, nature and most appropriate management of orthostatic intolerance.

Case Presentation: 30 year old woman

Childhood:

- Under weight infant. Breastfed.
- Active childhood.

As a teenager:

- Dysmenorrhea/heavy menses
- reflux and constipation
- migraines
- anxiety→ Rx paroxetine
- **"mono"** with normal recovery

During college

- Social anxiety → rx citalopram
- Dx hypothyroid
- Migraines
- **"mono again"**

Left college after first year

Case Presentation: 30 year old woman

Age 20-26:

- Running, half marathon.
- Worked retail

Age 26:

- MVA→ whiplash, low back strain, concussion with sx; no workup

Age 26-28:

- Biking, Yoga, Weights, Pilates

Age 28:

- Weaned off citalopram and PPIs
- Stayed active.
- More GERD→ “restrictive diet
- Anxiety increased
- Moved to UT with boyfriend

Age 29:

- Summer trip to Europe (2017)

Case Presentation: 30 year old woman

Dec 2017:

- Flu-like illness: cough, sinus→ abx. Flared again in 2 weeks. Lasted 6 weeks. Never fully recovered.
- Boyfriend left. Restarted citalopram. Moved in with Mom.

Jan 2018:

- Flu-like illness: chills, fever, later a sinus infection→ abx.
- GERD worse.
- Rx nystatin for "yeast."
- **Crashed.**

Feb 2018:

- "Everything in slow motion"

Mar 2018:

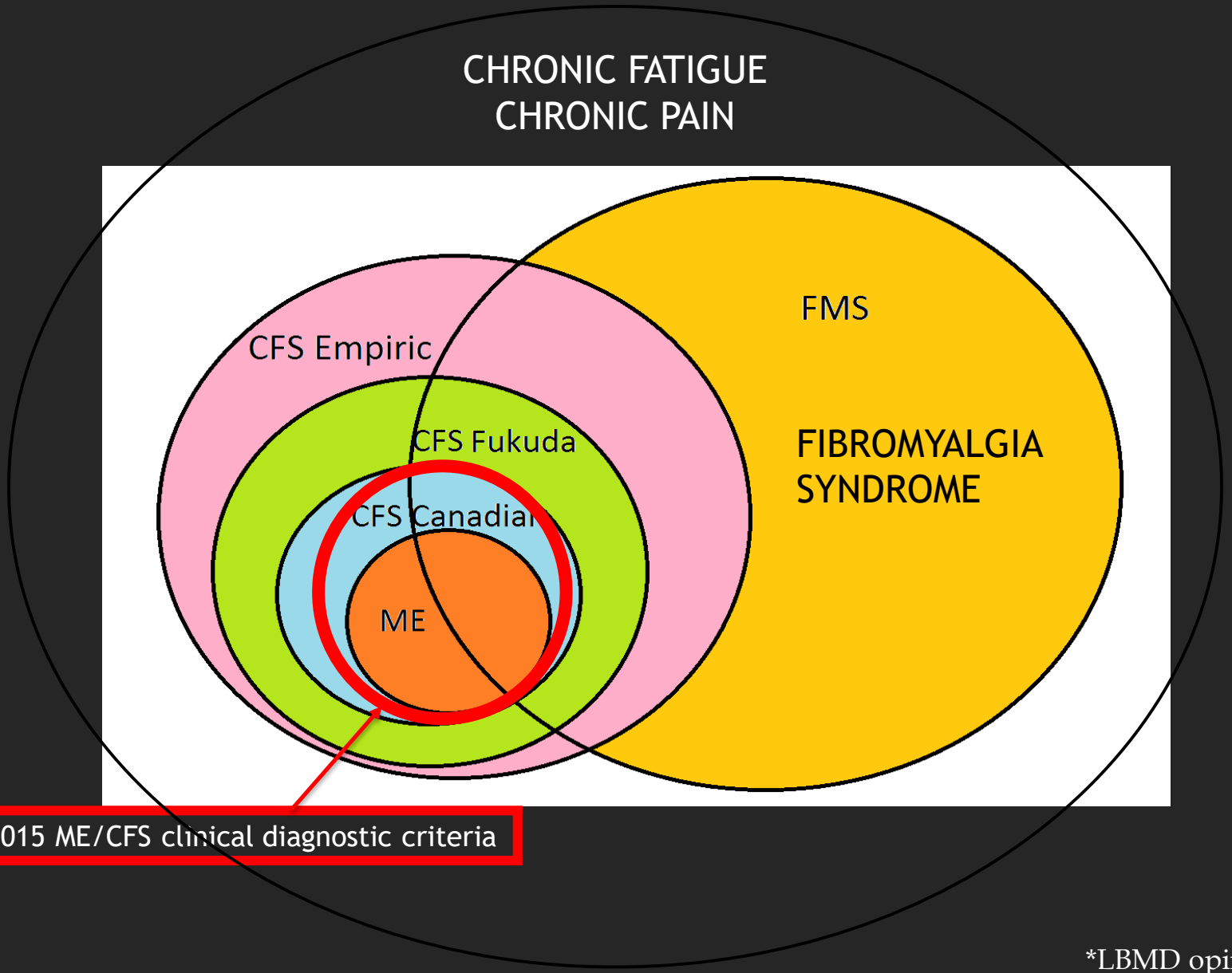
- Medical leave from work.

Providers:

GI, endocrine, OB/gyn, MH APRN, needs PCP.

Case Presentation: 30 year old woman

- Chronic fatigue, “barely able to walk from bed to couch,” persistent after rest. Low energy for activity. After activity she crashes and sx worsen for days/weeks. Weakness of arms/legs. Dizzy and “bumping into walls”
- Widespread pain complaints: burning, achy, morning stiffness, muscle pain, joint (knees), atypical CP (ECG & Echo OK), tension headaches and migraines. Numbness and tingling in hands and feet. Sweating, cold and heat intolerance, sound and light sensitivity.
- Depression, anxiety, suicidal thoughts.



*LBMD opinion ☺

The **Institute of Medicine** (IOM)*
published evidence-based
clinical diagnostic criteria for **ME/CFS**

The 2014 project was published in a report on
Feb 10, 2015

http://nationalacademies.org/HMD/Reports/2015/ME-CFS.aspx
https://www.ncbi.nlm.nih.gov/pubmed/25695122

*The IOM is now **the National Academy of Medicine**

The purpose of the 2015 IOM/NAM Report is to increase clinical diagnosis and improve care.

- The new diagnostic criteria are focused on the **common core symptoms** of ME/CFS (as currently defined) that distinguish it from other disorders.
- Easier for clinicians to recognize and accurately diagnose patients in a timely manner.

ME/CFS Evidence-Based Clinical Diagnostic Criteria 2015:

Myalgic encephalomyelitis/Chronic Fatigue Syndrome

The CORE criteria (required for diagnosis)

1) *Impaired function in association with exhaustion/fatigue/low stamina
2) *PEM: post exertional malaise (illness relapse after physical or cognitive activity)
3) *Unrefreshing sleep (disordered sleep not explained by another disorder)
4) A. *Cognitive impairment and/or
   B. Orthostatic intolerance

*Must be moderate-severe, present >50% of the time

Other common features of illness, not considered "core" or required for diagnosis
---Pain of all types
---Immune impairment (allergy, inflammation, sensitivities)
---Infection symptoms, onset with infection, relapse after an infection

Editors: 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

Diagnose **ME/CFS** definitively after 6 months of supportive care and diagnostic investigations.

- No "exclusionary criteria" are detailed but it is assumed that…
- A **differential diagnosis, appropriate workup and treatment** of symptoms, including referral to specialists, is expected of health care providers.
- All other identifiable illnesses should be diagnosed and treated, including supportive care, observation, reduction of risk factors.
- ME/CFS can be a “working diagnosis” in the meantime.

Editors: 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

Can medical providers Assess Impaired Function and PEM?

- Mental health screen (we use HADS* plus interview)
- Ideally SF-36 (RAND-36) but complex scoring
- Fibromyalgia Impact Questionnaire (FIQ-R)
- **HUA** (Hours of Upright Activity)
- **Good Day/Bad Day** form
- Take a good history about the consequences of physical, cognitive, emotional and upright activity (PEM)
- Orthostatic testing---in clinic: **10 min NASA Lean Test**
- Consider CPET
- Assess cognitive impairment if indicated

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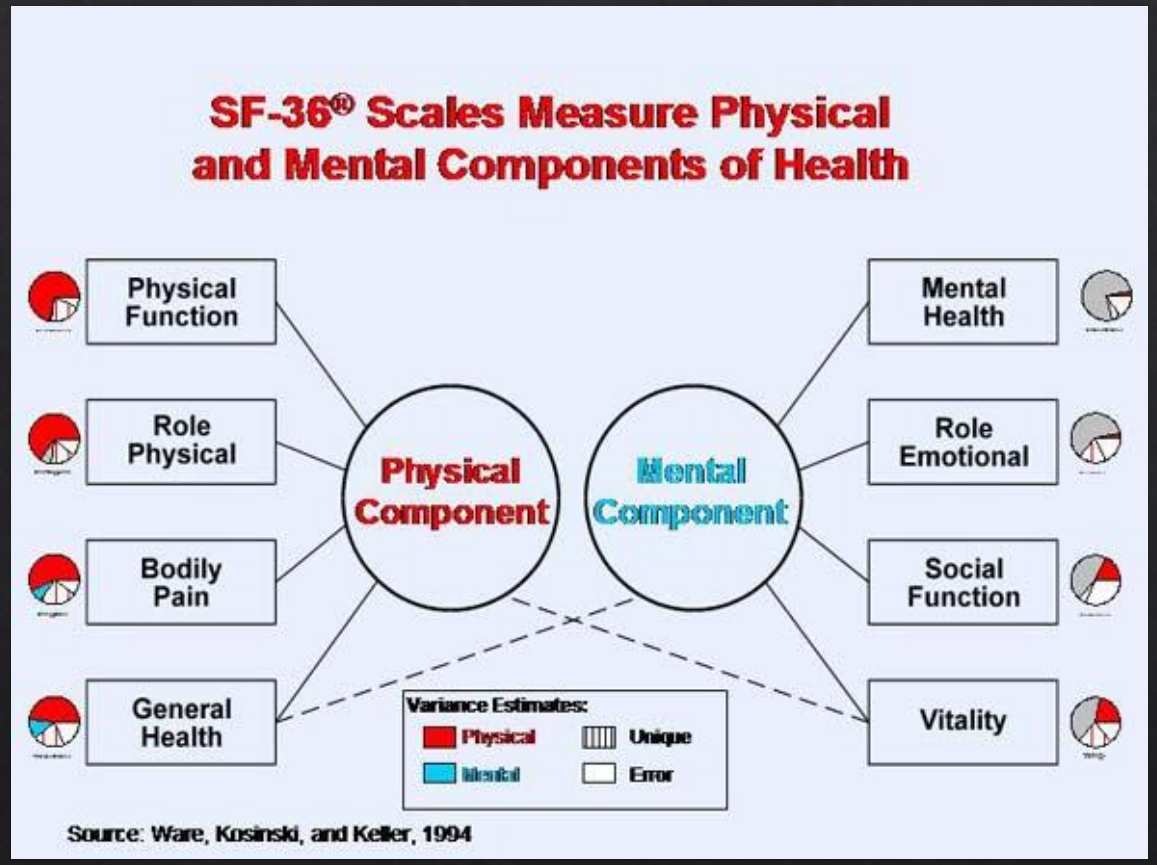
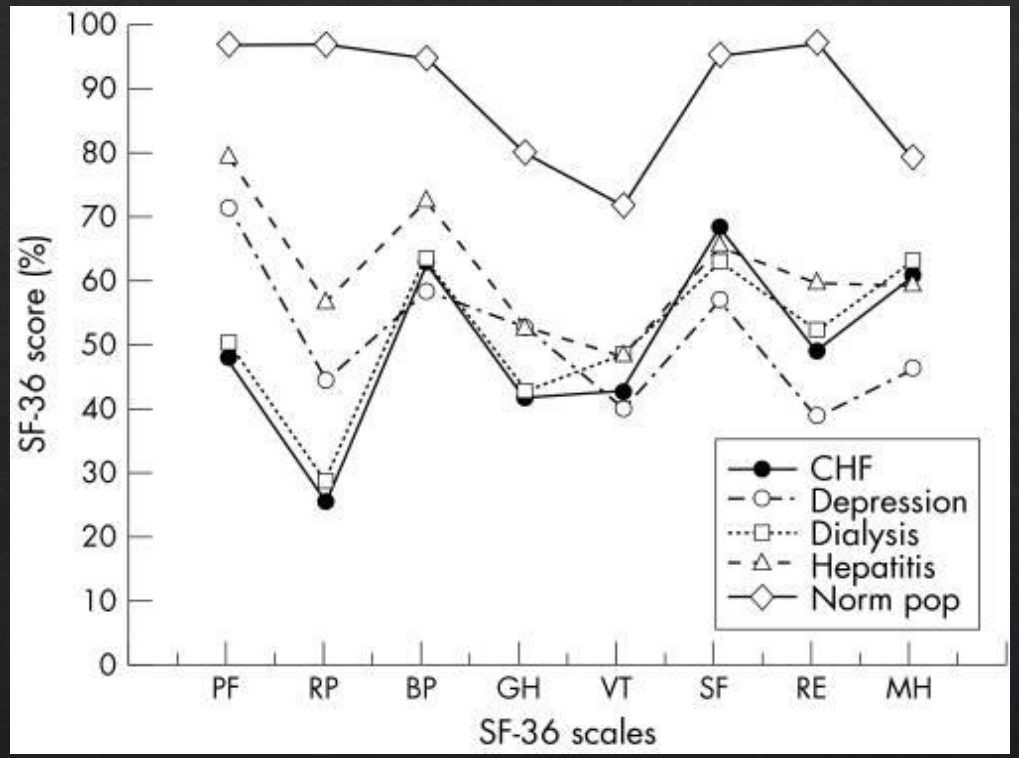
*Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. PMID: 6880820 DOI: 10.1111/j.1600-0447.1983.tb09716.x

Why SF-36? (or RAND-36 free to clinicians)



Ware, J.E Jr. and Sherbourne, C.D. The MOS 36-item short-form health survey (SF-36): conceptual framework and item selection. Med Care. 1992; 30: 473–483

Diagram: http://www.sf-36.org/tools/SF36.shtml



Juenger J. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Heart. 2002 Mar;87(3):235-41

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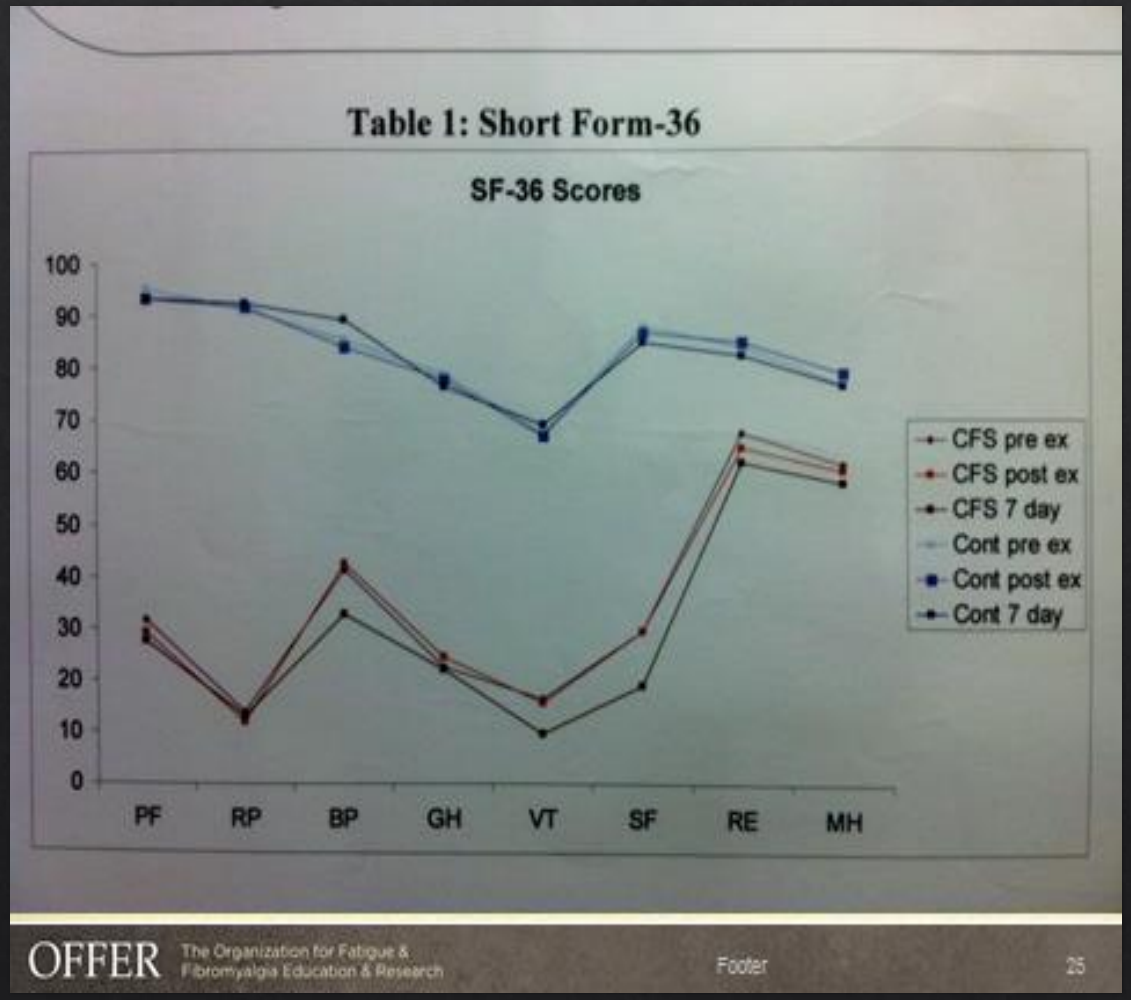
SF-36 Scores in ME/CFS and Our Case



RAND 36 Sub-scale Scores [SF-36]

Physical Function:	0
Role Physical:	0
Bodily Pain:	20
General Health:	25
Vitality/energy/fatigue:	0
Social functioning:	0
Role Emotional:	0
Mental Health:	16

Score Key: 100/100 possible in each sub-scale. A lower score indicates more severe impairment.

Why Fibromyalgia Impact Questionnaire (FIQ-R) ?
Pain Symptoms and the Impact of Pain on Function

http://fiqr.info/FIQR%20FORM.pdf

- Functional domain---9 questions
- Overall domain---2 questions
- Symptom severity---9 questions

There is a version called the Sickness Impact Questionnaire/SIQ

Interpretation of FIQ score

5 min Fibromyalgia Impact Questionnaire

A study of 2228 patients evaluating FM using FIQ suggests the following quartile scores:

- 0 to 42 = mildly affected
- 43 to 59 = moderately affected
- 60 to 74 = severely affected.
- 75 to 100 = extremely affected

The average FIQ-R score in FM studies is 58.2 (± 21.6), with a median value of 58-60.

Bennett RM, et al. Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol. 2009 Jun;36(6):1304-11. Epub 2009 Apr 15.

Our Case FIQ-R Score

FIQ-R (Fibromyalgia Impact Questionnaire-Revised): 86

Score Key (impact of pain on function):

- 0- 42 Mild
- 43- 59 Moderate
- 60- 74 Severe
- 75-100 Extreme

Our Case had no FM Tender Points on physical examination.

My best tool to estimate impaired function: HUA

HUA: Hours of "Upright" Activity:

The #hours spent with feet-on-floor in 24 hours (sitting, standing, walking)

Must ask the question clearly to be sure time spent sitting is considered in the total.

Thanks and credit to David Bell MD

Typical HUA*

HUA in 24 hours

- Normal healthy folks: HUA 14-17
- Chronic illness/FM: HUA 10-12
- ME/CFS HUA 0- 7

*based only on BHC clinical data and my own experience

HUA=Hours of Upright Activity

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Good/Bad Day HUA Questionnaire*

- Average number of GOOD/BAD **days** per MONTH:
- Average hours of UPRIGHT activity (HUA) on a GOOD/BAD day:
  - *sitting, standing, walking --- activities with FEET ON FLOOR*
- Average hours of non-upright activity on a GOOD/BAD day:
  - *lying in bed, reclining, elevating feet, sitting cross legged*

(Hours of upright activity + Hours of non-upright activity = 24 hours)

- Give examples of activities/tasks you CAN do on a good/bad day:
- Give examples of activities/tasks you CAN NOT do on a good/bad day:

*Designed for use at BHC by Lucinda Bateman MD

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Good Day: Our Case Study

Average number of GOOD days per MONTH: “5-10 days”

Average hours of UPRIGHT activity (HUA) on a GOOD day (sitting, standing, walking --- activities with FEET ON FLOOR): “1-2 hours”

Average hours of non-upright activity on a GOOD day (reclining, elevating feet, laying in bed): “23-24 hours”

Give specific examples of activities/tasks you CAN do on a good day: “Drive, go on a short walk, stretch, run an errand with help”

Give specific examples of activities/tasks you CAN NOT do even on a good day: “Clean, make my own meals, go to work”

Bad Day: Case Study

Average number of bad days per MONTH: “20-25 days”

Average hours of UPRIGHT activity (HUA) on a BAD day (sitting, standing, walking --- activities with FEET ON FLOOR): “30 min- maybe”

Average hours of non-upright activity on a BAD day (reclining, elevating feet, laying in bed): “All day”

Give specific examples of activities/tasks you CAN still do on a BAD day: “Sit up, read, watch tv, eat..”

Give specific examples of activities/tasks you CAN NOT do when it's a BAD day: “Walk, have conversations”

What is Post Exertional Malaise (PEM)?

PEM is a prolonged exacerbation of a patient's baseline symptoms after physical/ cognitive/orthostatic exertion or stress. It may be delayed relative to the trigger(s).

Patient Descriptions of PEM

- "crash," "relapse," "collapse"
- mentally tired after the slightest effort
- physically drained or sick after mild activity
- the more demanding, prolonged or repeated the activity, the more severe and prolonged the payback

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Gene Expression Captures a Glimpse of PEM:

the Sensory, Adrenergic, Inflammatory Response after an Exercise Stressor

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The research team used **exercise as a stressor** to study post-exertional gene expression in patients with CFS, CFS/FM and FM-only. Patients exercised on an Airdyne bike at 70% of age-predicted max heart rate for 25 minutes (moderate sustained activity approximating daily needs)

Blood was drawn:

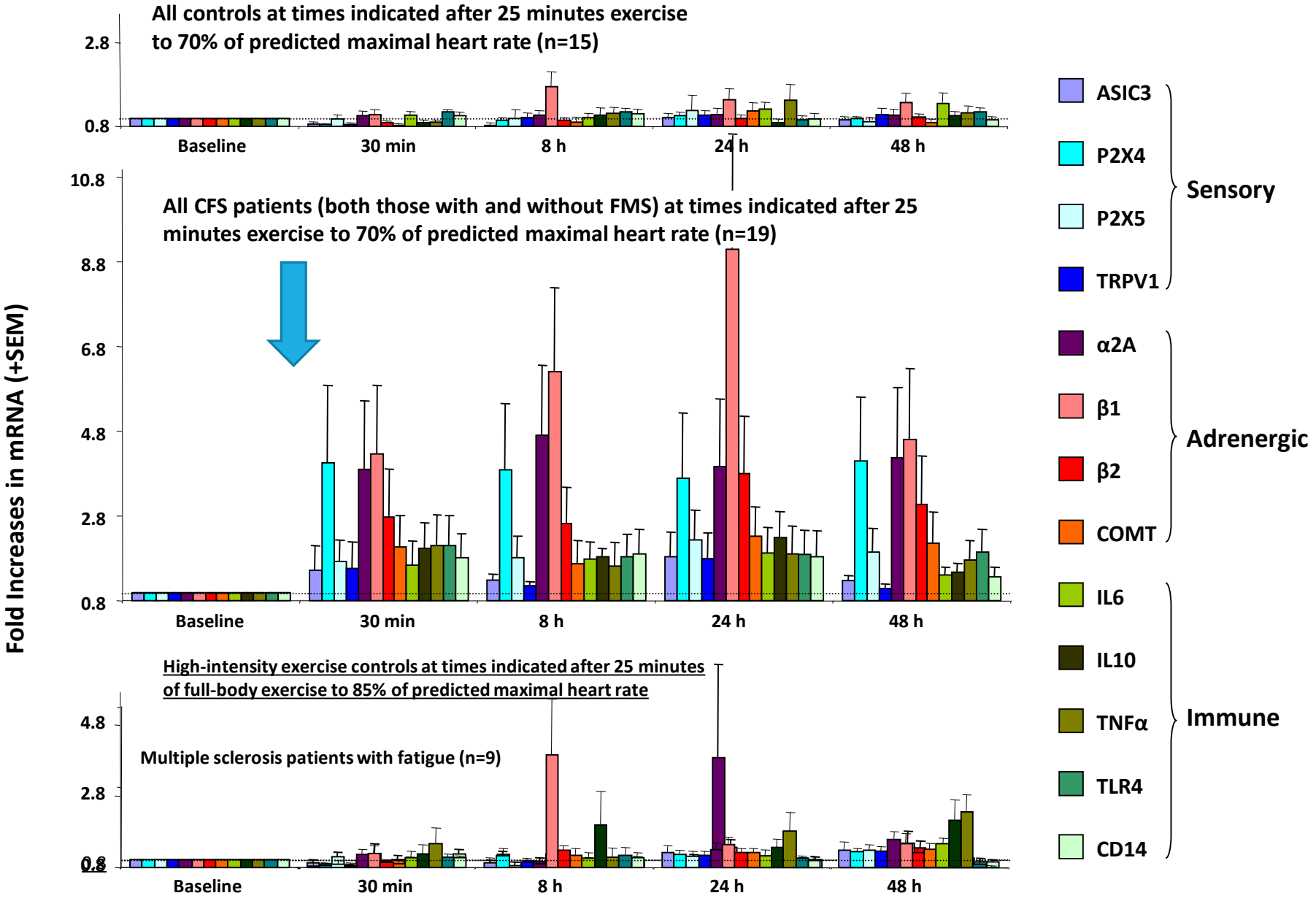
Before exercise

After exercise at 30 min, 8 hours, 24 and 48 hours

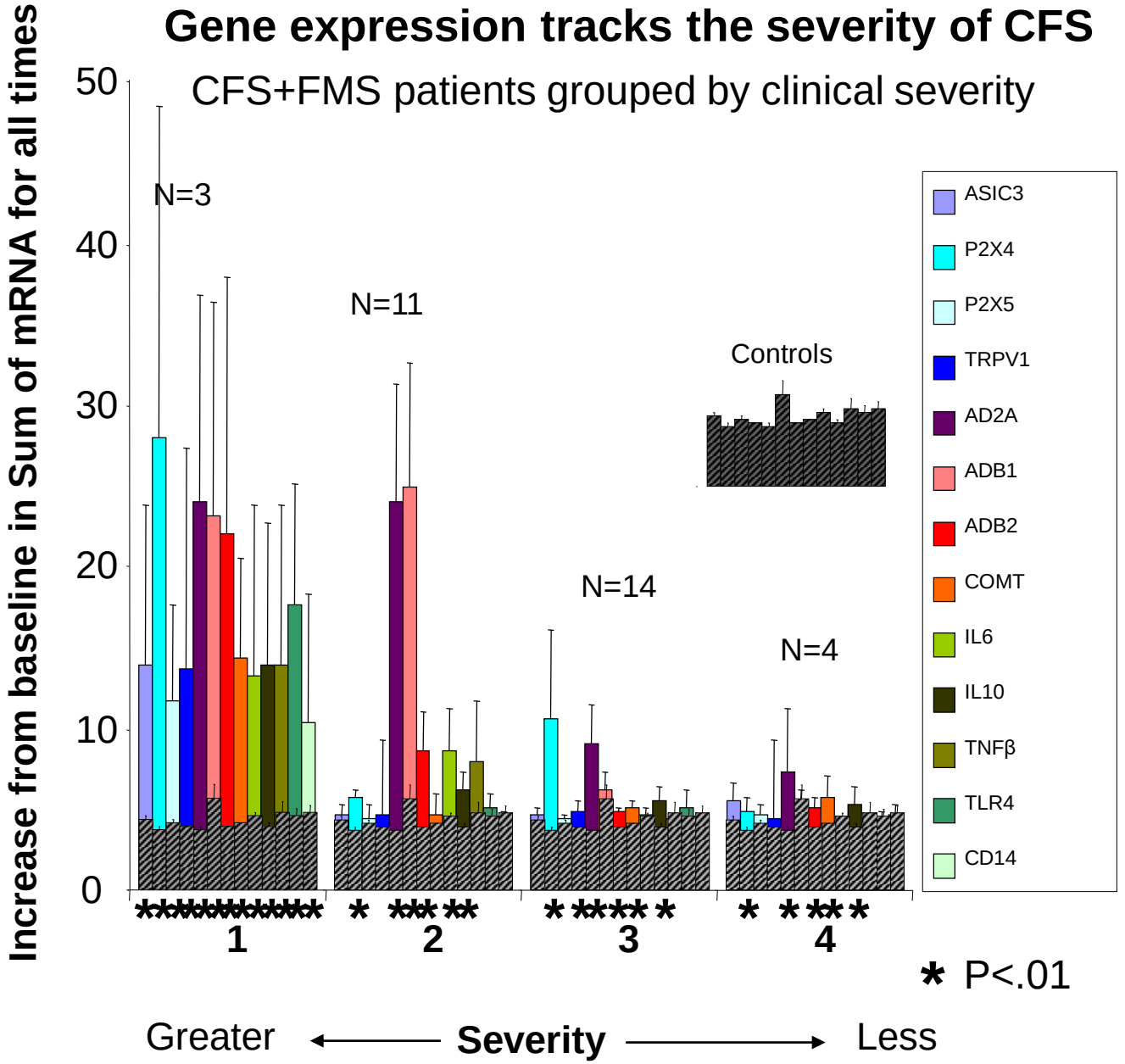
Gene expression changes were analyzed.

Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. Light AR, White AT, Hughen RW, Light KC. **J Pain. 2009** Oct;10(10):1099-112. doi: 10.1016/j.jpain.2009.06.003. Epub 2009 Jul 31. PMID: 19647494

Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. **J Intern Med. 2012** Jan;271(1):64-81. doi: 10.1111/j.1365-2796.2011.02405.x. PubMed PMID: 21615807; PubMed Central PMCID: PMC3175315.



Light A, et al. Journal of Pain. Nov 2009.



Light A, et al. Journal of Pain. Nov 2009.

Survey on PEM

- 150 subjects dx with CFS by Fukuda criteria completed a survey about PEM symptoms: different triggers, onset and duration of PEM.
- 90% experienced PEM after physical and cognitive exertion or emotional distress.
- Onset and duration of PEM varied. 84% experience PEM for 24 hours or more.
- Symptoms of PEM: Fatigue was the most commonly exacerbated symptom but cognitive difficulties, sleep disturbances, headaches, muscle pain, and flu-like feelings were cited by over 30%. At least one inflammatory/ immune-related symptom was reported by 60%. Subjects also cited gastrointestinal, orthostatic, mood-related, neurologic and other symptoms

Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross-sectional survey. PLoS One. 2018 Jun 1;13(6):e0197811. doi: 10.1371/journal.pone.0197811.

Does it help to keep energy expenditure close to available energy? (pacing)

114 ME/CFS subjects were randomly assigned to four interventions in which they were provided 13 biweekly sessions with a trained nurse therapist. We collected baseline, post-treatment, and six- and twelve-month follow-up data. Jason, Benton, et al. divided this entire sample of patients with ME/CFS into two groups:

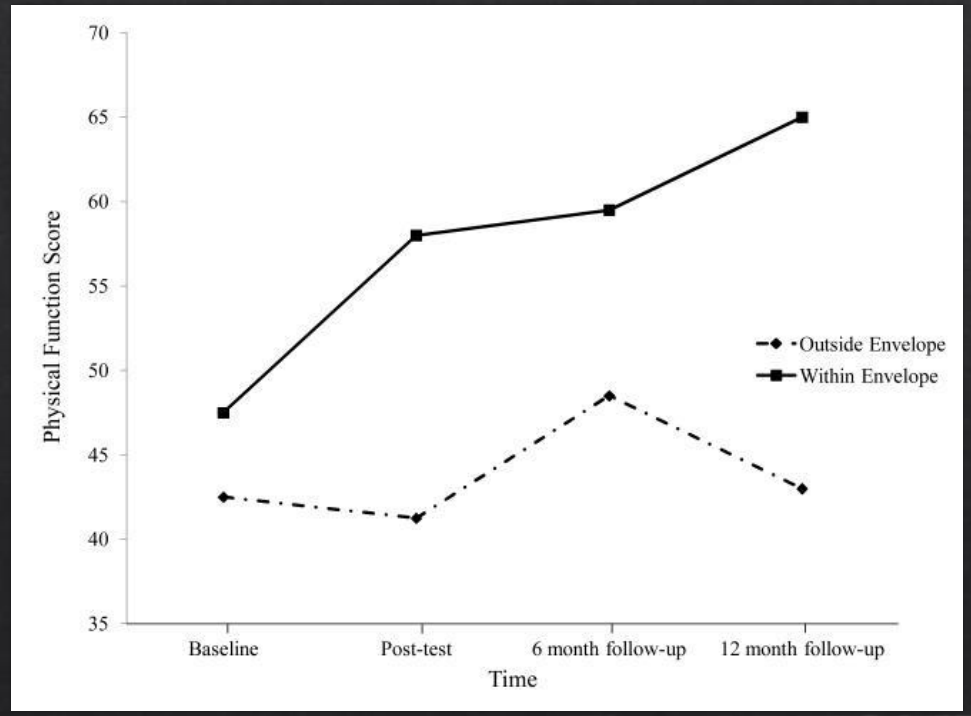
- those who were able to keep expended energy close to available energy
- those who were not successful at this task

Those who were able to stay within their energy envelopes had significant improvements in physical functioning and fatigue severity

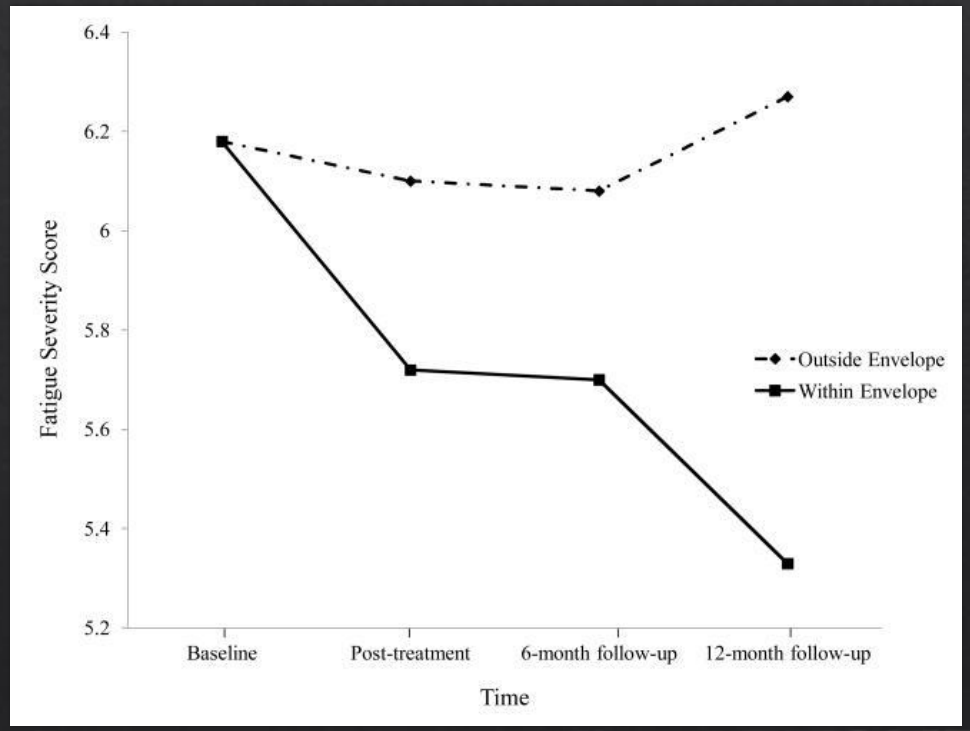
Jason LA, Benton M, Torres-Harding S, Muldowney K. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Education and Counseling. 2009;77:237–241

PACING: Staying "inside energy envelope" versus "outside energy envelope" improves prognosis

Physical Function Scores



Fatigue Severity Scores



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Jason LA, Brown M, Brown A, Evans M, Flores S, Grant-Holler E, Sunnquist M. Energy Conservation/Envelope Theory Interventions to Help Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Fatigue. 2013 Jan 14;1(1-2):27-42.

Clinical significance of PEM

Exceeding cellular energy capacity results in “illness payback” symptoms.

PEM is physiologic and multisystem.

The key to ME/CFS management is to understand these physical and cognitive limitations and learn to preventively “pace” all activity in order to avoid inducing severe or prolonged PEM.

The total of all activity---physical, cognitive, emotional---must not dramatically exceed the patient’s energy capacity to create the opportunity for improvement.

This must be considered in all rehabilitation efforts.

FCE: Functional Capacity Evaluations

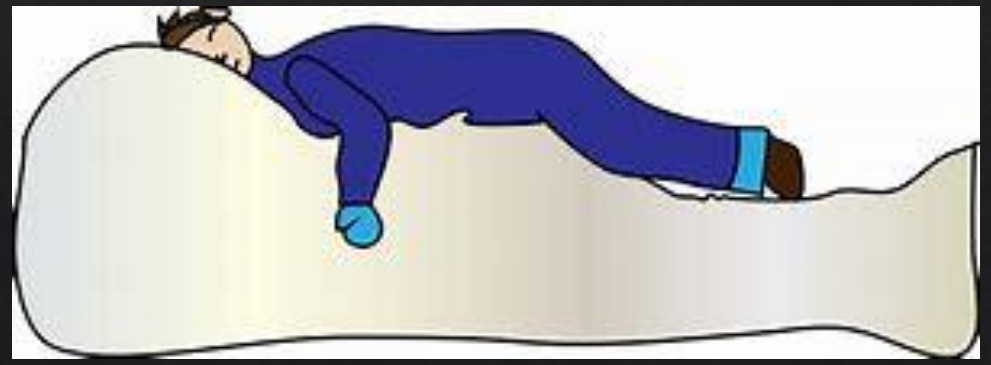
Can be a misleading measure of disability

in patients with ME/CFS

Because they don't evaluate PEM: the consequences of activity

What is Orthostatic Intolerance (OI)?

Orthostatic intolerance is the development of symptoms while **standing upright** that are relieved or partially relieved by **reclining**



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Editors: IOM Report: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. 2015 Feb
Chapter 4, pg 107; Chap 6, pg 185.

Orthostatic Intolerance (OI)

Orthostatic Intolerance/Autonomic Dysfunction/POTS symptoms

1) Cerebral under-perfusion symptoms and signs

- lightheadedness, fainting, impaired cognition, disorientation, headaches, visual changes, unusual neurologic symptoms, exhaustion

2) Peripheral cardiovascular symptoms and signs

- Sympathetic nervous system activation---palpitations, nausea, abdominal and chest discomfort, facial pallor, cold hands and feet, anxiousness, shortness of breath, sweating, tremor…

Worsened by heat, dehydration, prolonged standing, deconditioning and weakness, and feels worse immediately after exercise

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Editors: IOM Report: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. 2015 Feb. **Chapter 4, pg 107; Chap 6, pg 185.**

OI may be caused/worsened by:

- **HEART:** Heart arrhythmias, heart valve failure, myocardial infarction, cardiomyopathies
- **LUNG:** Pulmonary embolus, primary pulmonary hypertension
- **DRUG SIDE EFFECTS**: diuretics, tricyclic antidepressants, blood pressure drugs, drugs for prostate disease (doxazosin, tamsulosin), Yaz birth control (drospirenone/ethinyl estradiol)…
- **CENTRAL NERVOUS SYSTEM**: Brain stem and mid-brain lesions (may underlie ME/CFS), Parkinson's, Multiple Sclerosis, Parkinsons…
- **PERIPHERAL NERVOUS SYSTEM**: diabetic neuropathy, spinal cord injury, craniocervical instability (CCI), small fiber neuropathy…

Symptoms of OI

Acute OI—more obvious

- Fainting, lightheadedness
- Altered vision (blurred, double vision, tunnel vision)
- Anxiety
- Fatigue and weakness
- Headache
- Heart palpitations, heart pounding/racing
- Shortness of breath, hyperventilation
- Tremor

Chronic OI---more subtle

- Nausea or low appetite
- Chest and abdominal complaints
- Neurocognitive deficits, brain fog
- Heat intolerance
- Sleep problems
- Headaches
- Varied dizziness, disequilibrium, vertigo
- Tremor

Causes of chronic OI are numerous: small fiber neuropathy, post-viral autoantibodies to adrenergic and muscarinic receptors, midbrain or brainstem inflammation, hypermobility syndromes…

Why assess and treat OI?

Orthostatic intolerance is:

- Measurable (heart rate, blood pressure, S&S)
- Treatable or at least manageable.

May lead to insight about the underlying disease process(es)

Remember: OI can exist in someone who has low, normal or high blood pressure in the seated position at rest.

Defined Syndromes of Chronic Orthostatic Intolerance/OI

- **Orthostatic hypotension**: a BP reduction of at least 20 mm Hg systolic or 10 mm Hg diastolic within the first 3 min of upright posture
- **Postural Orthostatic Tachycardia Syndrome (PoTS)**: the reproduction of orthostatic symptoms together with a **+30 bpm** increase in HR, from supine to 10 min upright, or an increase in HR of ≥120 . Age 12-19 heart rate increase must be **+40 bpm**
- **Neurally Mediated Hypotension/Syncope (NMH/S)**: synonymous with vasovagal syncope, neurocardiogenic syncope

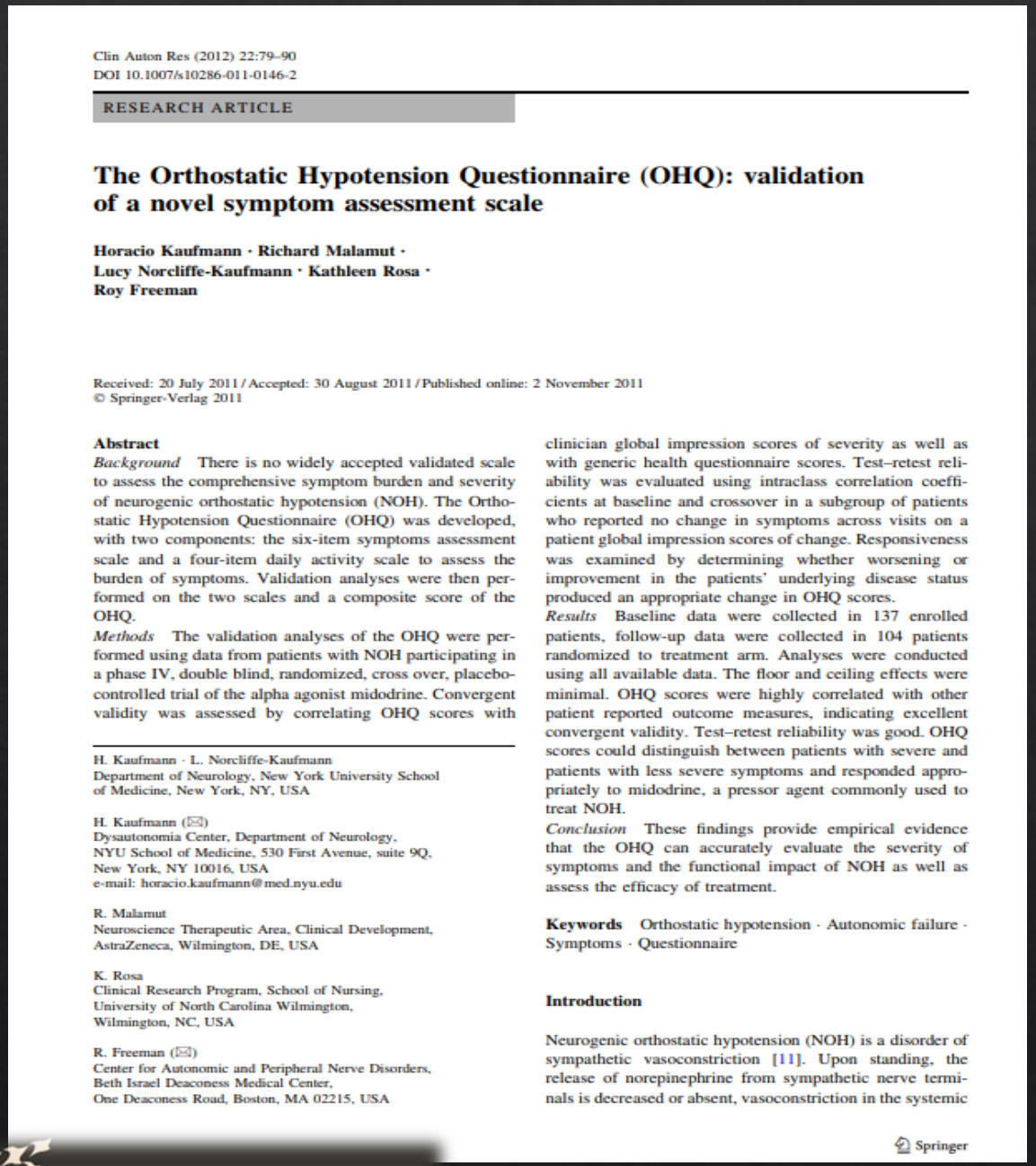
Freeman R et al., Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011 Apr;21(2):69-72.

HR and BP may not tell the whole story

- **150 ME/CFS patient**s and **37 HC** underwent **Tilt Table testing.** **Stroke Volume Index (SVI)** and **Cardiac Index (CI)** were measured by suprasternal aortic Doppler imaging in the supine position, prior to the tilt, and twice during the tilt
- A normal heart rate and blood pressure response was observed during the tilt in both ME/CFS and HC.
- Stroke volumes and cardiac output were related to the severity of the disease in ME/CFS.
- Decreases in **SVI** and **CI** during the tilt were significantly larger in ME/CFS compared to HC
- The decrease in SVI and CI were similar and not significantly different between the mild, moderate, and severe ME groups.

C.(Linda) M.C. van Campen, Frans C. Visser. The Abnormal Cardiac Index and Stroke Volume Index Changes During a Normal Tilt Table Test in ME/CFS Patients Compared to Healthy Volunteers are Not Related to Deconditioning. 7 November, 2018. Journal of Thrombosis and Circulation

“Easy” Clinical Assessment of Chronic Orthostatic Intolerance



Clin Auton Res (2012) 22:79–90
DOI 10.1007/s10286-011-0146-2

RESEARCH ARTICLE

The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale

Horacio Kaufmann · Richard Malamut · Lucy Norcliffe-Kaufmann · Kathleen Rosa · Roy Freeman

Received: 20 July 2011 / Accepted: 30 August 2011 / Published online: 2 November 2011

Abstract
Background There is no widely accepted validated scale to assess the comprehensive symptom burden and severity of neurogenic orthostatic hypotension (NOH). The Orthostatic Hypotension Questionnaire (OHQ) was developed, with two components: the six-item symptoms assessment scale and a four-item daily activity scale to assess the burden of symptoms. Validation analyses were then performed on the two scales and a composite score of the OHQ.
Methods The validation analyses of the OHQ were performed using data from patients with NOH participating in a phase IV, double blind, randomized, cross over, placebo-controlled trial of the alpha agonist midodrine. Convergent validity was assessed by correlating OHQ scores with clinician global impression scores of severity as well as with generic health questionnaire scores. Test–retest reliability was evaluated using intraclass correlation coefficients at baseline and crossover in a subgroup of patients who reported no change in symptoms across visits on a patient global impression scores of change. Responsiveness was examined by determining whether worsening or improvement in the patients' underlying disease status produced an appropriate change in OHQ scores.
Results Baseline data were collected in 137 enrolled patients, follow-up data were collected in 104 patients randomized to treatment arm. Analyses were conducted using all available data. The floor and ceiling effects were minimal. OHQ scores were highly correlated with other patient reported outcome measures, indicating excellent convergent validity. Test–retest reliability was good. OHQ scores could distinguish between patients with severe and patients with less severe symptoms and responded appropriately to midodrine, a pressor agent commonly used to treat NOH.
Conclusion These findings provide empirical evidence that the OHQ can accurately evaluate the severity of symptoms and the functional impact of NOH as well as assess the efficacy of treatment.

Keywords Orthostatic hypotension · Autonomic failure · Symptoms · Questionnaire

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Introduction

Neurogenic orthostatic hypotension (NOH) is a disorder of sympathetic vasoconstriction [11]. Upon standing, the release of norepinephrine from sympathetic nerve terminals is decreased or absent, vasoconstriction in the systemic

- The Orthostatic Hypotension Questionnaire **(OHQ)** was developed with two components: the 6-item symptoms assessment scale and a 4-item daily activity scale to assess the burden of symptoms.
- The OHQ was validated in 137 Neurogenic Orthostatic Hypotension (NOH) subjects in a phase IV, double blind, randomized, cross over, placebo-controlled trial of the alpha agonist midodrine;
- Clinical Validity: The floor and ceiling effects were minimal. OHQ scores were highly correlated with other patient reported outcome measures, indicating excellent convergent validity. Test-retest reliability was good

Kaufmann H, et al. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012 Apr;22(2):79-90. doi: 10.1007/s10286-011-0146-2. Epub 2011 Nov 2.

Hours of Upright Activity (HUA) and OISA/OIDAS (=OIQ)

Hours of Upright Activity (HUA): #hours in 24 hours with feet on the floor.

Upright= sitting with feet on the floor, standing, walking --versus-- Lying down (includes sleeping), reclining or sitting with feet elevated or tucked

Orthostatic Intolerance Symptom Assessment (OISA) Score: 0=None and 10=Severe

- Dizziness, lightheadedness, feeling faint, or feeling like blackout
- Problems with vision (blurring, seeing spots, tunnel vision, etc.)
- Weakness
- Fatigue
- Trouble concentrating
- Head/neck discomfort

Orthostatic Intolerance Daily Activity Scale (OIDAS) 0=No Interference; 10=Complete Interference

- Standing a short time
- Standing a long time
- Walking a short time
- Walking a long time

Kaufmann H, et al. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton Res. 2012 Apr;22(2):79-90. doi: 10.1007/s10286-011-0146-2. Epub 2011 Nov 2.

Jihyun Lee MSPH, BSN, Pelle Wall BS, medical student

- The OIQ and HUA were tested on 25 ME/CFS Female Subjects and 25 matched HC (Age, Gender, Race) via Online form. All subjects reported HUA and completed two questionnaires (OISA, OIDAS). Rating scores were recorded on the REDCap online database.

- HUA was sub-categorized as 1-2 hours, 3-4 hours, 5-7 hours and >8 hours in 24 hours. OIDAS was used to assess interference of daily activity due to OI and the OISA was used to assess OI symptoms.

- Comparisons between ME/CFS and healthy controls (HC) were evaluated

Unpublished. Jiyhun Lee MSPH, BSMN. Data analysis. Presented 3/4/2019 “Thinking the Future: A Workshop for Young/Early Career ME/CFS Investigators.” Protocol designed and implemented by Pelle Wall, medical student at UCSD. Bateman Horne Center.

Hours of Upright Activity (HUA) correlate with OISA (symptom) scores

	Healthy Group (n=25)	ME/CFS Group (n=26)				
	Healthy Control	Mild	Mild-Moderate	Moderate-severe	Severe	P-value
OISA Orthostatic Intolerance Symptom Assessment Mean of 0-10 scores in 6 domains	Mean	HUA:8+	HUA:5-7	HUA:3-4	HUA:1-2	
	N=25	N=7	N=11	N=5	N=2	
Dizziness, lightheadedness, feeling faint, or feeling like you might blackout	**1.16**	**5.57**	**5.09**	**6.4**	**9**	>0.001
Problems with vision (blurring, seeing spots, tunnel vision)	1.04	**2.29**	**3.73**	**5.8**	**5**	>0.001
Weakness	1.12	**6.57**	**4.09**	**7.2**	**9**	>0.001
Fatigue	**1.12**	**7.29**	**6.09**	**8**	**9.5**	>0.001
Trouble concentrating	1.04	**5.29**	**5.9**	**7.6**	**8.5**	>0.001
Head/neck discomfort	1.24	**6.29**	3.72	**5.4**	**7.5**	>0.001

Hours of Upright Activity (HUA) correlate with OIDAS (activity interference) scores

	Healthy Group (n=25)	ME/CFS Group (n=26)				
	Healthy Control	Mild	Mild-Moderate	Moderate-severe	Severe	P-value
OIDAS Mean 0-10 scores Orthostatic Intolerance Daily Activity Scale	mean	HUA: 8+	HUA:5-7	HUA:3-4	HUA:1-2	
	N=25	N=7	N=11	N=5	N=2	
Standing a short time	1	4.1	4.18	4.4	**5**	>0.001
Standing a long time	1.72	**7.85**	**7.91**	**8.6**	**10**	>0.001
Walking a short time	1	4.28	4.36	4.2	4.5	>0.001
Walking a long time	1.36	**8.14**	**8.09**	**9.8**	**9**	>0.001

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Orthostatic intolerance testing

Head Up Tilt Table Testing

The Gold Standard

10 min stand/lean testing

The 10 min NASA Lean Test

10 minute “NASA” Lean test—the standing portion after resting supine measurements.

32 year old woman with fatigue, severe migraines, fibromyalgia, depression, dizziness unresponsive to traditional therapies.

Supine (10-15 min in quiet room):

- Supine BP: **116/60** Pulse: **85** **PULSE PRESSURE: 56**

Standing straight with shoulder blades against the wall and feet 6" from the wall

- Standing 0 minute BP: 104/80 Pulse: 85
- Standing 2 minute BP: 96/70 Pulse: 116
- Standing 4 minute BP: 98/78 Pulse: 120 Arms "almost feel like they are tingling"
- Standing 6 minute BP: 91/73 Pulse: 125 Lightheaded and dizzy (as if she is spinning)
- Standing 8 minute BP: 96/74 Pulse: 122 Increased lightheadedness, nausea
- Standing 10 minute BP: 93/80 Pulse: **120** Increased "electrical buzz"

PULSE PRESSURE: 13

Summary:

-27 mmHg drop in SBP meets criteria for systolic orthostatic hypotension (> 20 mmHg decrease)

+41 bpm increase in Heart Rate meets criteria for POTS (>30 bpm increase for adults)

Postural Orthostatic Tachycardia Syndrome

Our Case: 30 year old woman

OI Questionnaires

OIQ: 76/100

- OHSA 47/100 (symptoms)
- OHDAS 29/100 (activity)

10 min Lean Test

Seated VS: HR 110 BP 116/84

10 min NASA Lean:

- HR 75→118 (+43 bpm= POTS)
- SBP 106--? 100?.
- PP 30→ 16 or less

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Our Case: 10 min NASA Lean test

Supine measurements: Patient has been resting supine for 15 minutes.

- 1 min BP: 102/76 PP: 26 HR (bpm): 75 SpO2: 99%
- 2 min BP: 106/76 PP: 30 HR (bpm): 75 SpO2: 99%

Standing measurements: Standing straight, shoulder blades against the wall, feet 6" from the wall

- 2 min BP: 102/? PP: ? HR (bpm): 110
- 4 min BP: ? PP: ? HR (bpm): 108 Mild mottling of feet and toes cool to touch. "Legs hurt, mild tingling of feet."
- 6 min BP: 110/94 PP: 16 HR (bpm): 103 Diastolic blood pressure dropped out.
- 8 min BP: 100/92 PP: 8 HR (bpm): 119 Quiet BP, moderate purple hue of toes.
- 10 min BP: ? PP: 0 HR (bpm): 118 SpO2: 99%

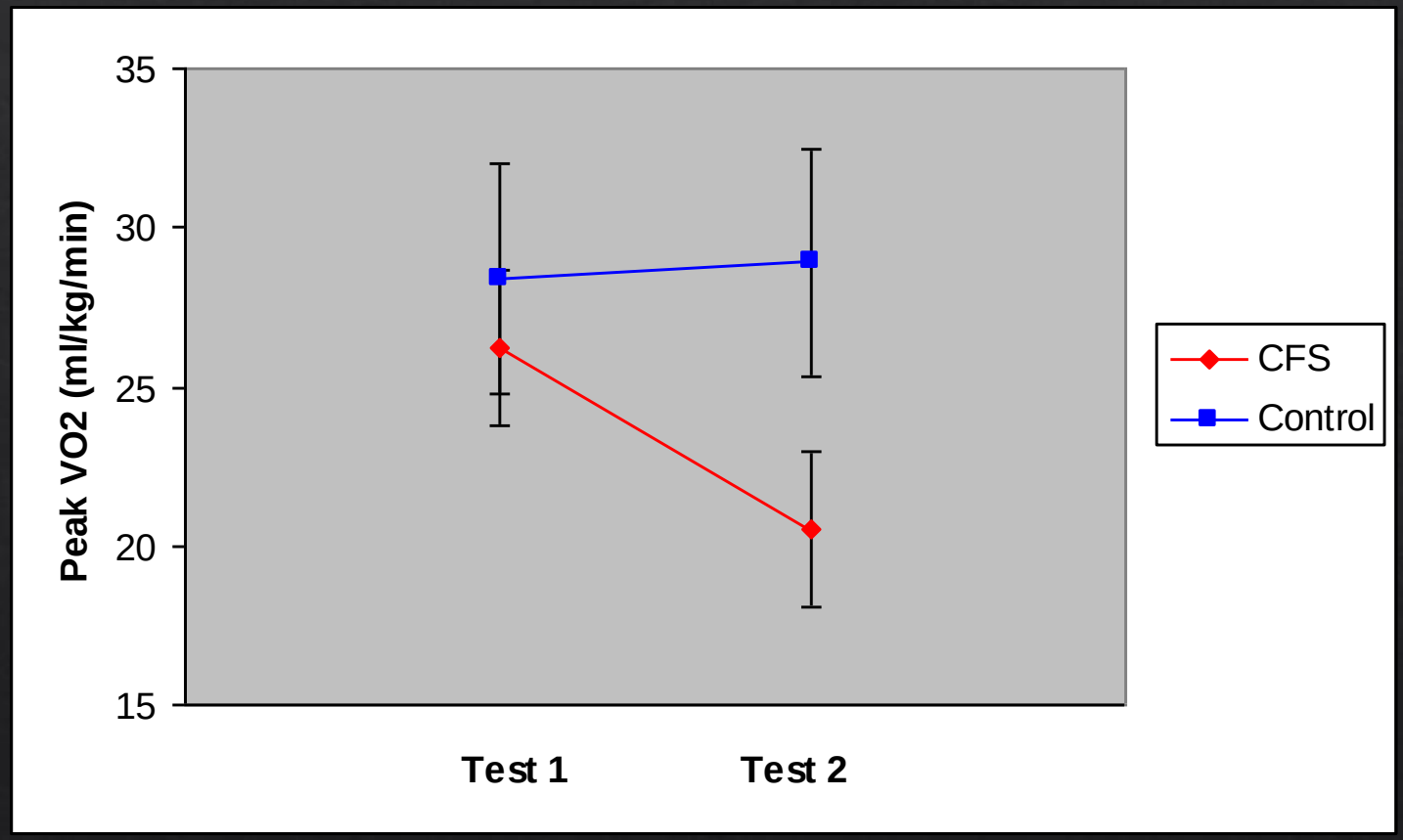
SUMMARY: HR 75→118 (+43 bpm). SBP 106→ 100?. PP 30→ 16 or less

Cardiopulmonary Exercise Testing (CPET)

Most patients with ME/CFS are unable to replicate the test parameters when tested 2 days in a row.

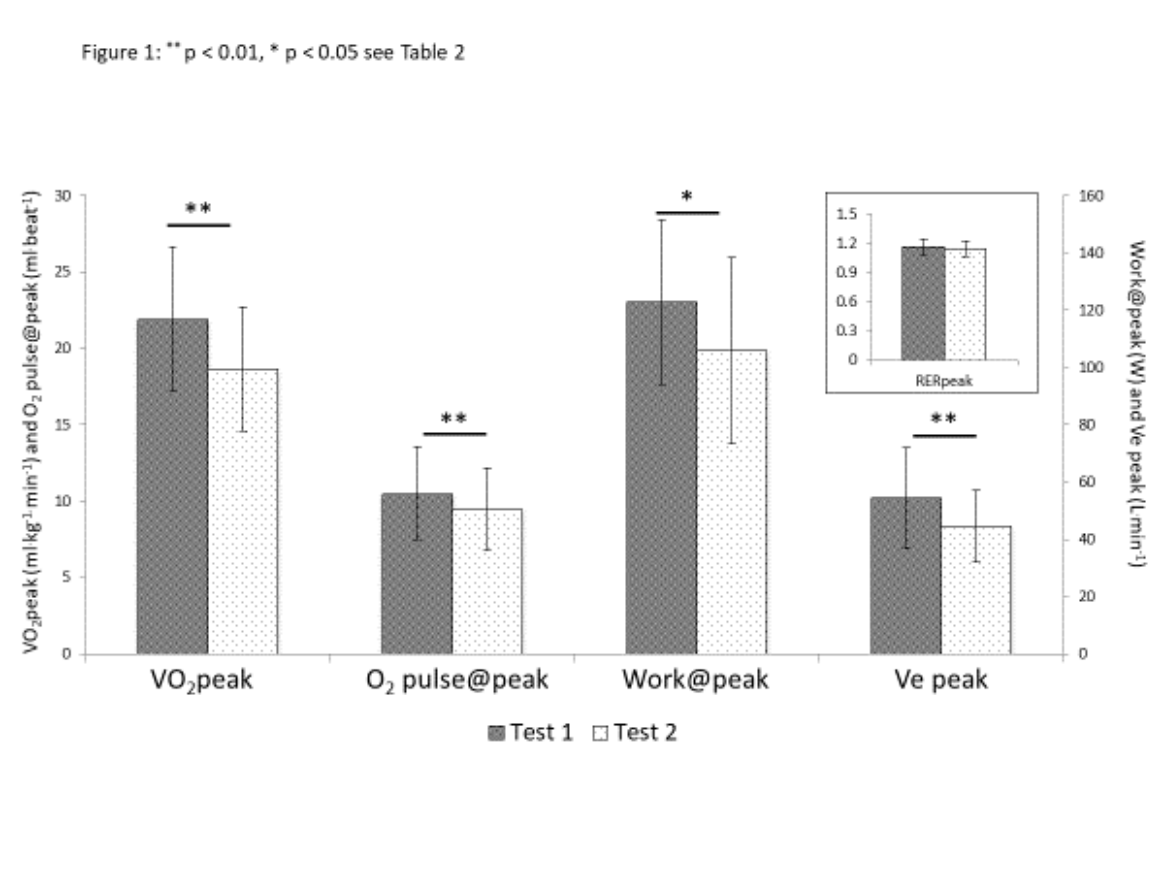
This can be helpful for documenting disability, but can exacerbate ME/CFS…

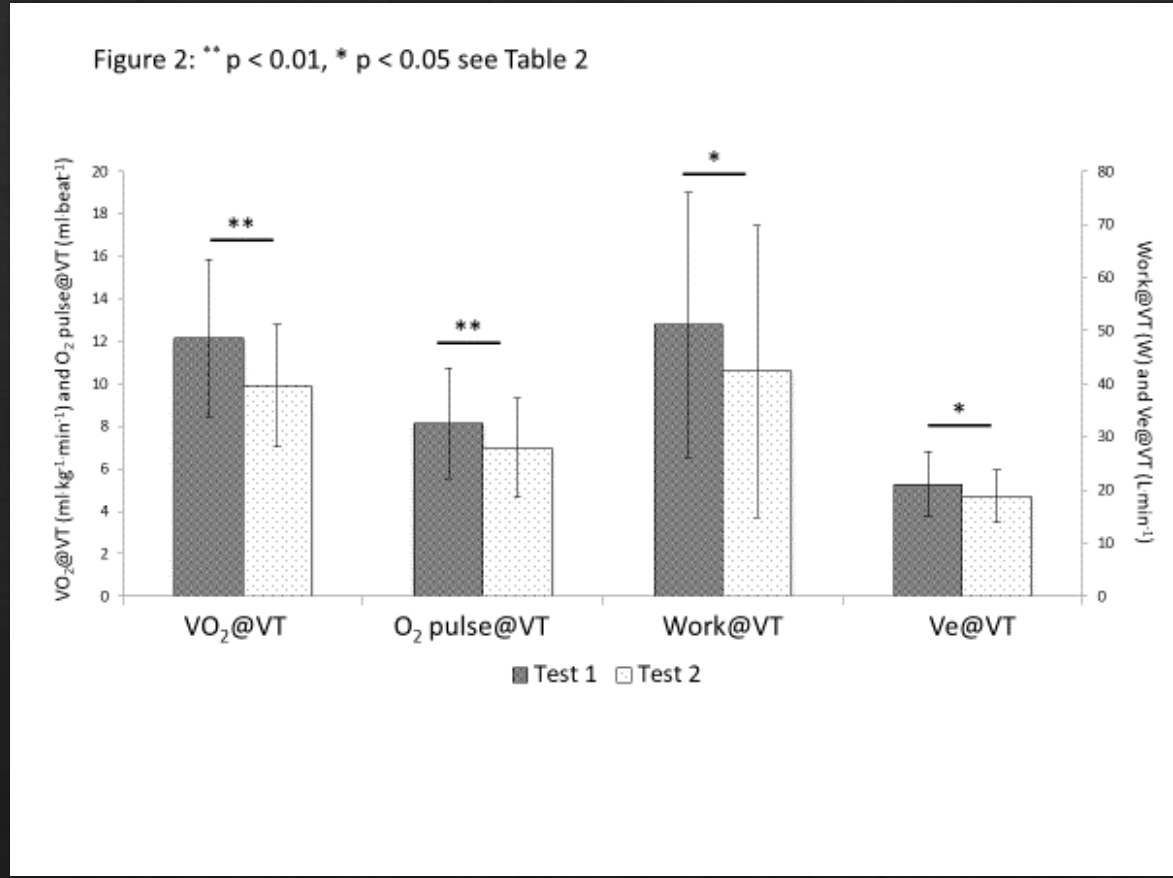
Peak Oxygen Consumption (VO2) in ME/CFS compared to **Healthy Controls** tested twice in 24 hours



Using serial cardiopulmonary exercise tests to support a diagnosis of Chronic Fatigue Syndrome. VanNess, JM, et al. Med. Sci. Sports. Exerc. 38(5), 2006.

This decrement of exercise capacity has been replicated
Test 1 = dark grey bars Test 2= light grey bars





Keller B, et al. Inability of ME/CFS patients to reproduce VO2 peak indicates functional impairment. Journal of Translational Medicine 2014, 12:104.

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Cognitive impairment

Neurocognitive manifestations (IOM Report Chap 4, pp 96-107)

- Impairments in cognitive function are frequently reported
- Cognitive impairment can be measured. The strongest evidence demonstrates *slowed information processing.* There are some data to support *deficits in working memory* and *reduced attention*.
- Neuroinflammation has been documented*

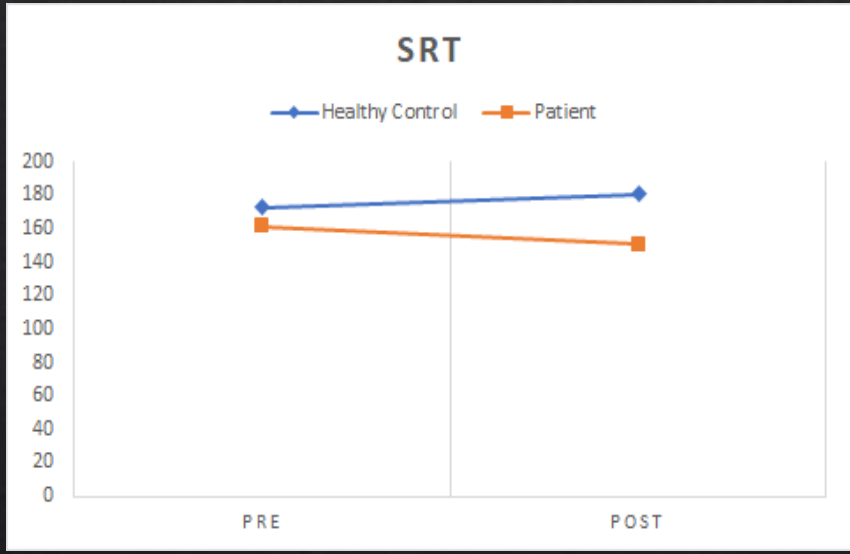
*J. Nucl Med. 2014 Jun;55(6):945-50. doi: 10.2967/jnumed.113.131045. Epub 2014 Mar 24. **Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET Study. Nakatomi Y et al.**.

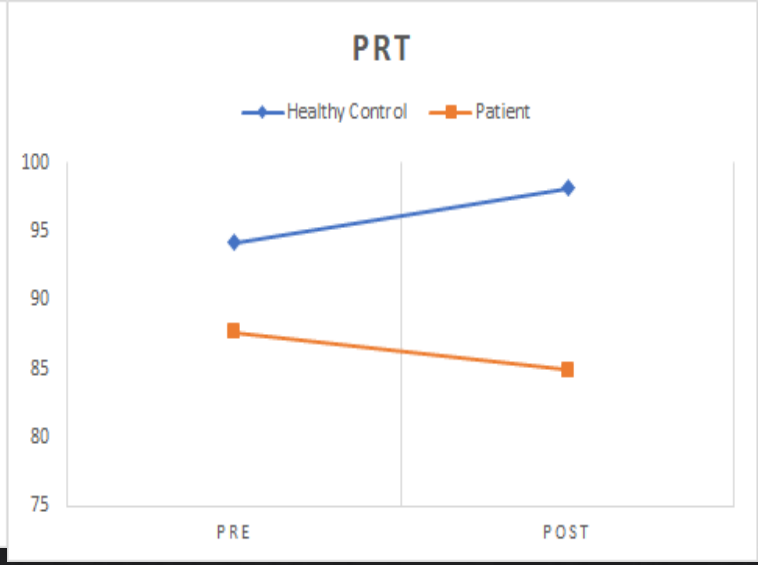
Observation is objective

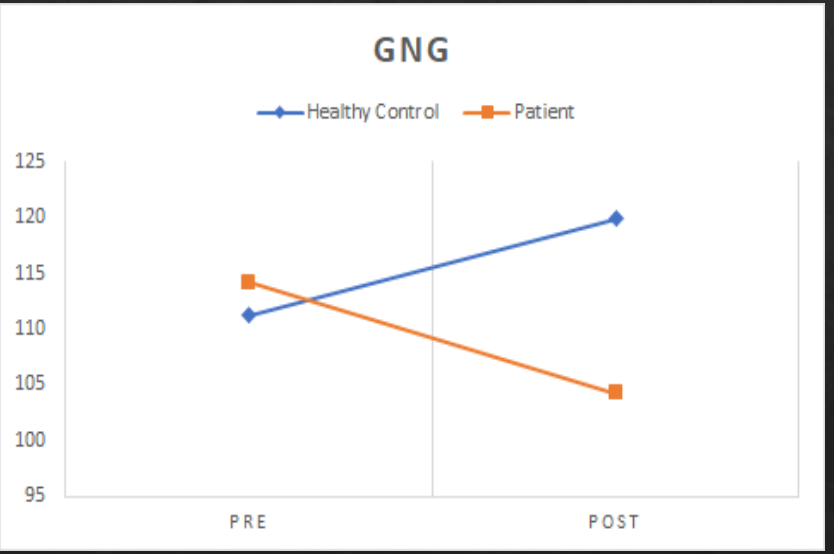
Signs of cognitive impairment:

- Difficulty remembering instructions from previous visit
- Completely forgot to do something suggested in the previous visit
- Delayed verbal responses, worsening as fatigue progresses
- Easily confused by long complex explanations or instructions
- Looks to companion for help answering questions or remembering details
- Trouble remembering medications and pill strength
- Dull eyes
- Brings notes to visit to remember items of discussion
- Attempts to take notes during visit but may have trouble

Cognitive efficiency worsens after orthostatic stress (Pre- Post)







Unpublished. Jiyhun Lee MSPH, BSMN. Data analysis. Presented 3/4/2019 "Thinking the Future: A Workshop for Young/Early Career ME/CFS Investigators." Protocol designed and implemented by Pelle Wall, medical student at UCSD.

Clinical significance (cognition):

- Cognitive slowing, cognitive fatigability and cognitive PEM may be the most limiting aspects of ME/CFS illness, and a primary reason people with ME/CFS are unable to sustain employment or succeed in school.

Objectives

1) Determine the presence or absence of Post-Exertional Malaise (PEM) and utilize the information to develop appropriate physical rehabilitation advice for a patient with chronic fatigue.

2) Assess impairment of function using a combination of readily available standardized questionnaires (HADS, FIQ-R, OHQ/OIQ) and reported HUA (Hours of Upright Activity) as defined in the lecture.

3) Perform bedside orthostatic testing to determine the presence, nature and most appropriate management of orthostatic intolerance.

Supplemental Slides

Cognitive Testing (DANA Brain Vital app)

SRT PRT GNG

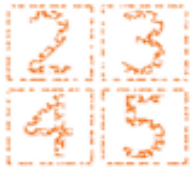
DANA Brain Vital

This is a test of response speed, so respond as fast as possible.

Tap this symbol quickly when it appears.

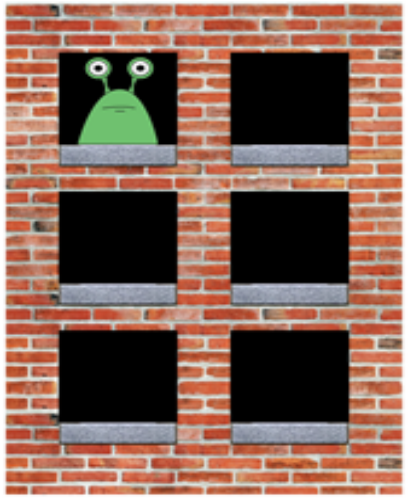
Tap the symbol above to start

One of these numbers will appear. Tap the appropriate button as quickly as possible.



Tap a button below to start.

2 OR 3 | 4 OR 5



BLAST

*DANA Brain Vital Set : SRT , PRT, GNG

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Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least **moderate severity** that occurred **at least half of the time** during the past 6 months.

	ME/CFS	Healthy Controls
Problems remembering	80%	7%
Difficulty expressing thoughts	73%	2%
Difficulty paying attention	69%	7%
Slowness of thought	66%	2%
Absentmindedness	68%	5%
Difficulty understanding	55%	2%

IOM report 2015

Potential contributors to "brain fog" and cognitive slowing

- **Medications** for sleep, pain, anxiety, migraine
- **Chronic sleep disturbances**
- Secondary **mental health** conditions---depression, anxiety
- **Orthostatic intolerance** and other causes of reduced cerebral blood flow and perfusion. *"Perfusion" is the circulation or delivery of blood to every cell, bringing oxygen, glucose, nutrients, everything needed for cell function…*
- Cognitive fatigue and fatigability
- **Low cellular energy production**. Capacity for "function" is reduced.
- PEM—the consequences of exceeding cellular energy capacity
- Neuroinflammation

Neural Consequences of PEM in ME/CFS.

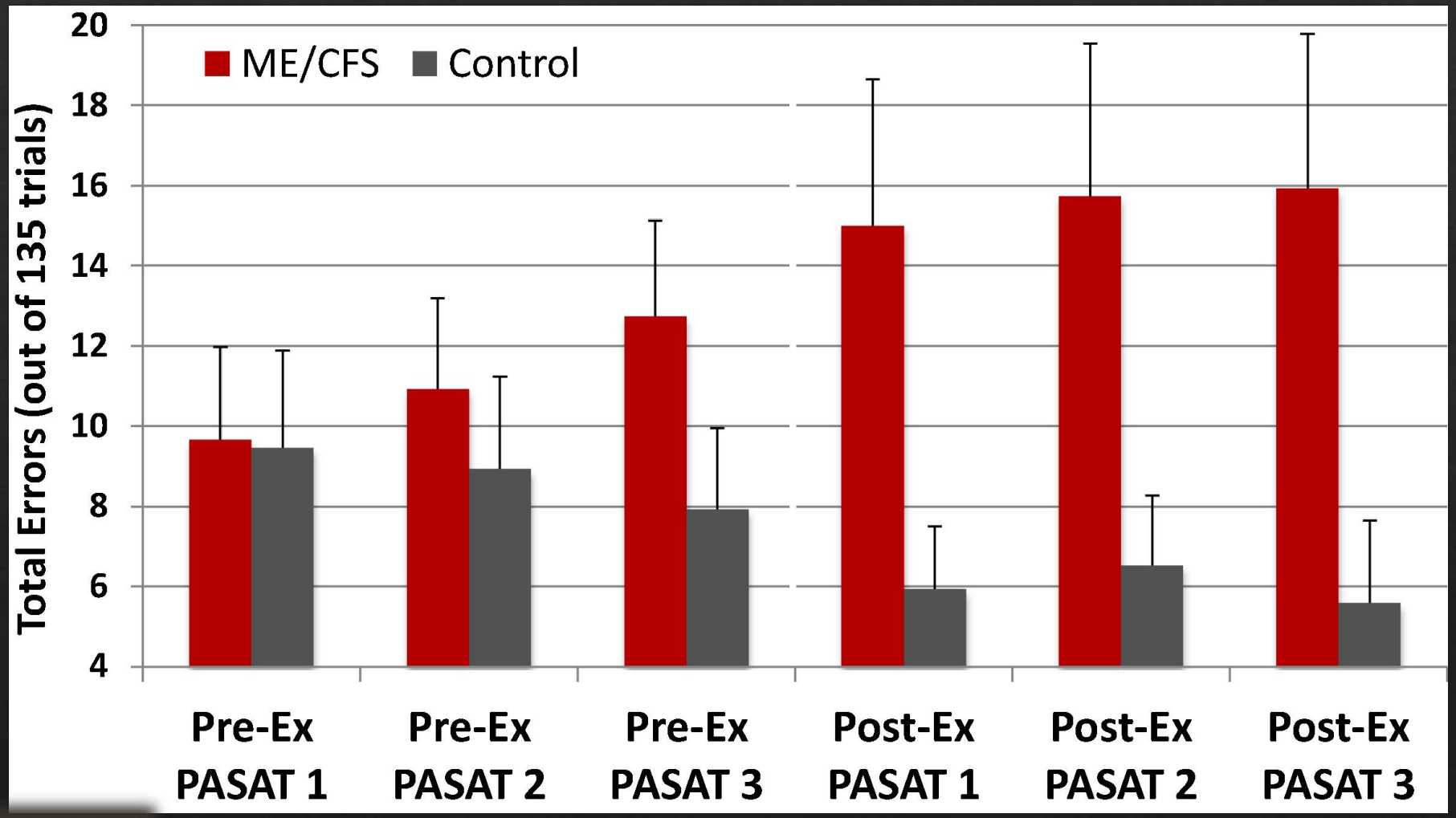
15 female ME/CFS and 15 female HC. 30 min sub max exercise (70% peak HR) cycle ergometer. fMRI during a fatiguing cognitive task. PASAT: paced auditory serial addition task

Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in ME/CFS patients.

Neural Consequences of Post-Exertion Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Brain Behav Immun. 2017 Feb 16. Cook DB1, Light AR2, Light KC2, Broderick G3, Shields MR4, Dougherty RJ4, Meyer JD4, VanRiper S4, Stegner AJ4, Ellingson LD5, Vernon SD6.

Total errors on PASAT testing

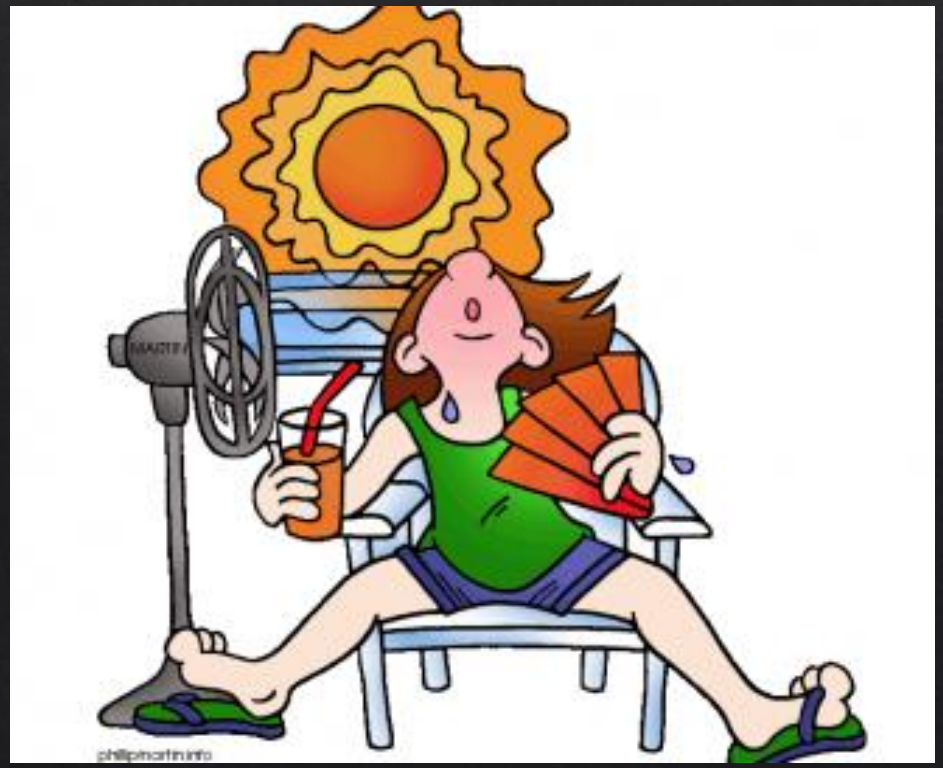
Total errors represent both incorrect responses and missed responses (i.e. errors of omission).
There was a significant Group by Time Interaction (F = 8.4, *p* = 0.007).



Interventions for OI:

Recognize and avoid the common triggers

- Heat, getting overheated
- Dehydration
- Prolonged standing in place
- Prolonged sitting with feet on floor
- Prolonged bedrest (confuses the ANS)
- Muscle atrophy and weakness
  - Abdomen/core, upper and lower legs
- Medications that cause/worsen OI



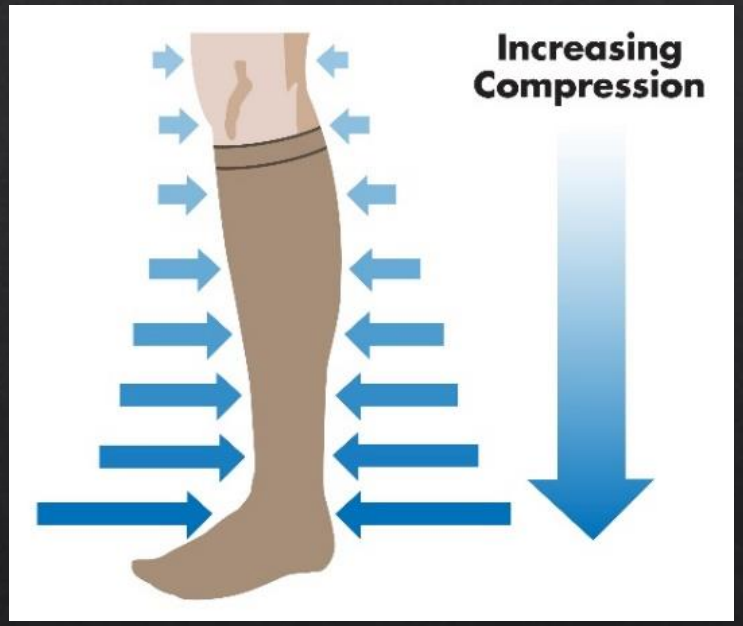
Interventions for OI:

External compression or internal constriction of blood vessels

- Compression socks, pants, sleeves, abdominal binder
- Midodrine, a peripheral alpha-1 receptor agonist (stimulates the receptor) FDA approved for orthostatic hypotension

Increase volume in the vasculature (blood vessels)

- Consume extra **water/fluids** to expand blood volume
- Increased **salt intake** helps retain water in the circulation and tissues
- **fludrocortisone** 0.1 mg once or twice daily FDA approved for orthostatic hypotension
- **Rapid water ingestion** (16 oz) helps reduce OI within 20 minutes (chugging)
- **IV normal saline.** Can be very helpful as "rescue" and support, especially when ill, dehydrated, or having medical procedures such as colonoscopy



Interventions for OI:

Control the rapid heart rate response if indicated and helpful.

- **Low dose beta blockers:** Propranolol 10 mg bid to tid (off label use--FDA approved for supraventricular tachycardia, migraine, tremor)

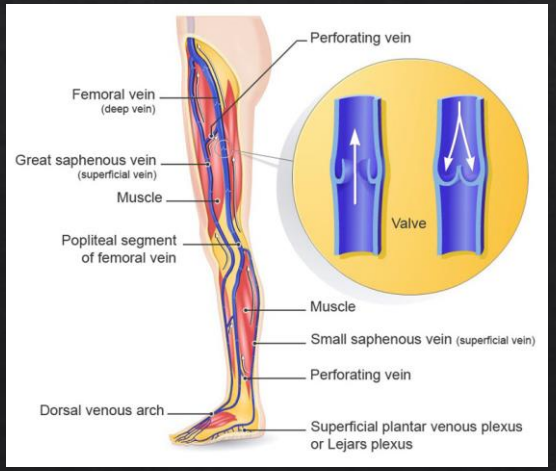
Augment parasympathetic nervous system

- **Pyridostigmine** (off label use—FDA approved for myasthenia gravis, but recommended in the literature for POTS) Raises acetylcholine, the neurotransmitter at the neuromuscular junction and much of the parasympathetic nervous system.

Strengthen and use the muscular "pumps"

for better venous return.

Muscular pumps = leg and abdominal muscles



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Raj SR1, Black BK, Biaggioni I, Harris PA, Robertson D. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. Circulation. 2005 May 31;111(21):2734-40. Epub 2005 May 23.

Orthostatic Intolerance/OI
Suggested ICD-10 coding?

- **Orthostatic Hypotension (OH)** ICD-10 I95.1
- **Conditions with no ICD-10 codes:**
  - Postural Orthostatic Tachycardia Syndrome (PoTS)
  - Neurally Mediated Hypotension (NMH)
  - Neurogenic Orthostatic Hypotension/Syncope (NOH)
- **Misc. dysautonomias:**
  - Other disorders of the autonomic nervous system G90.8
  - Disorder of the autonomic nervous system G90.9