Dysautonomia International Conference

July 27 – 28, 2019

Philadelphia, PA

Notes taken by Kim & David Allen

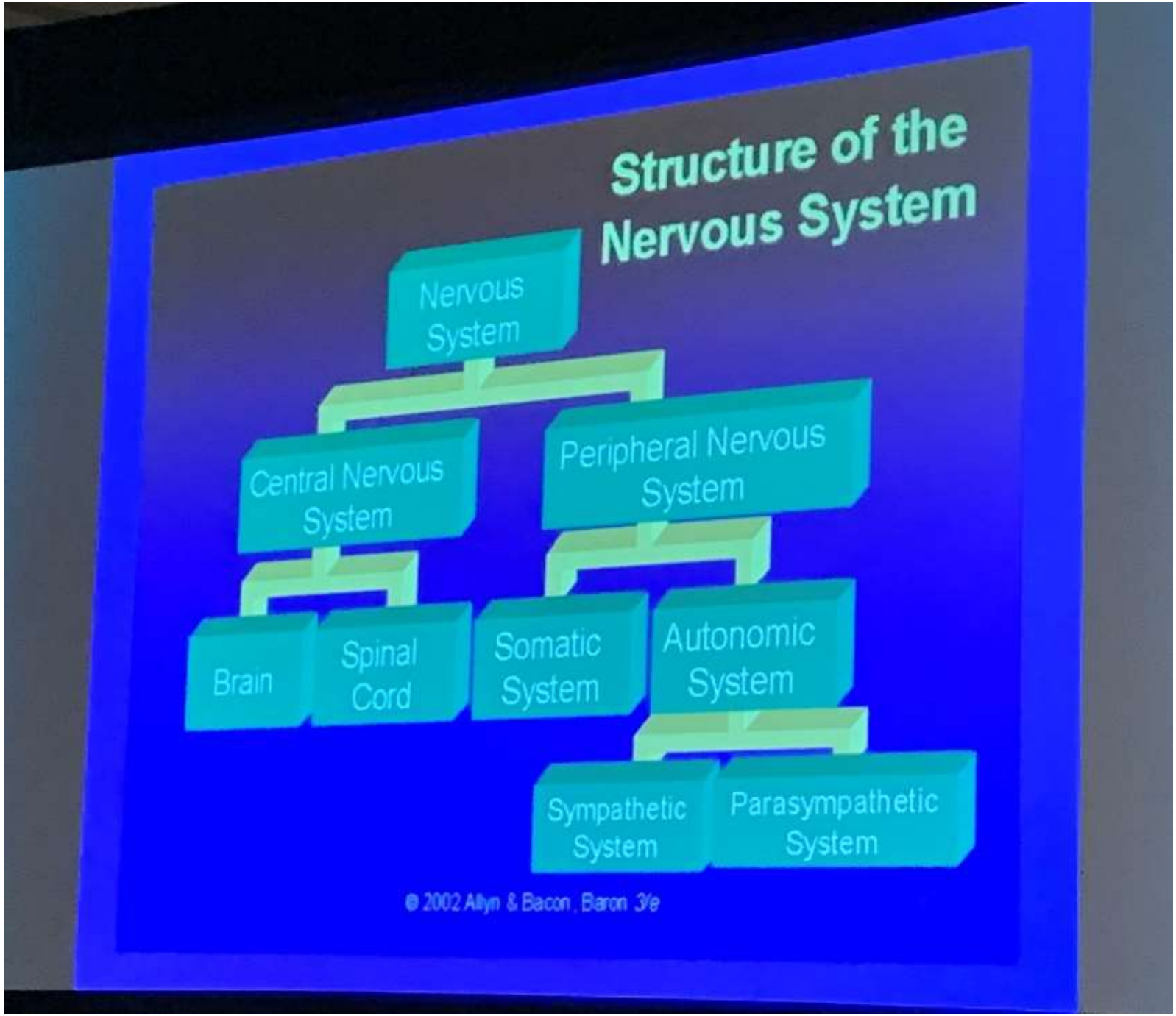
Disclaimer: These notes may not be 100% accurate (we did our best). Slides are photos I took from during the presentations.

Table of Contents

Overview of Autonomic Disorders – Dr. Blair Grubb

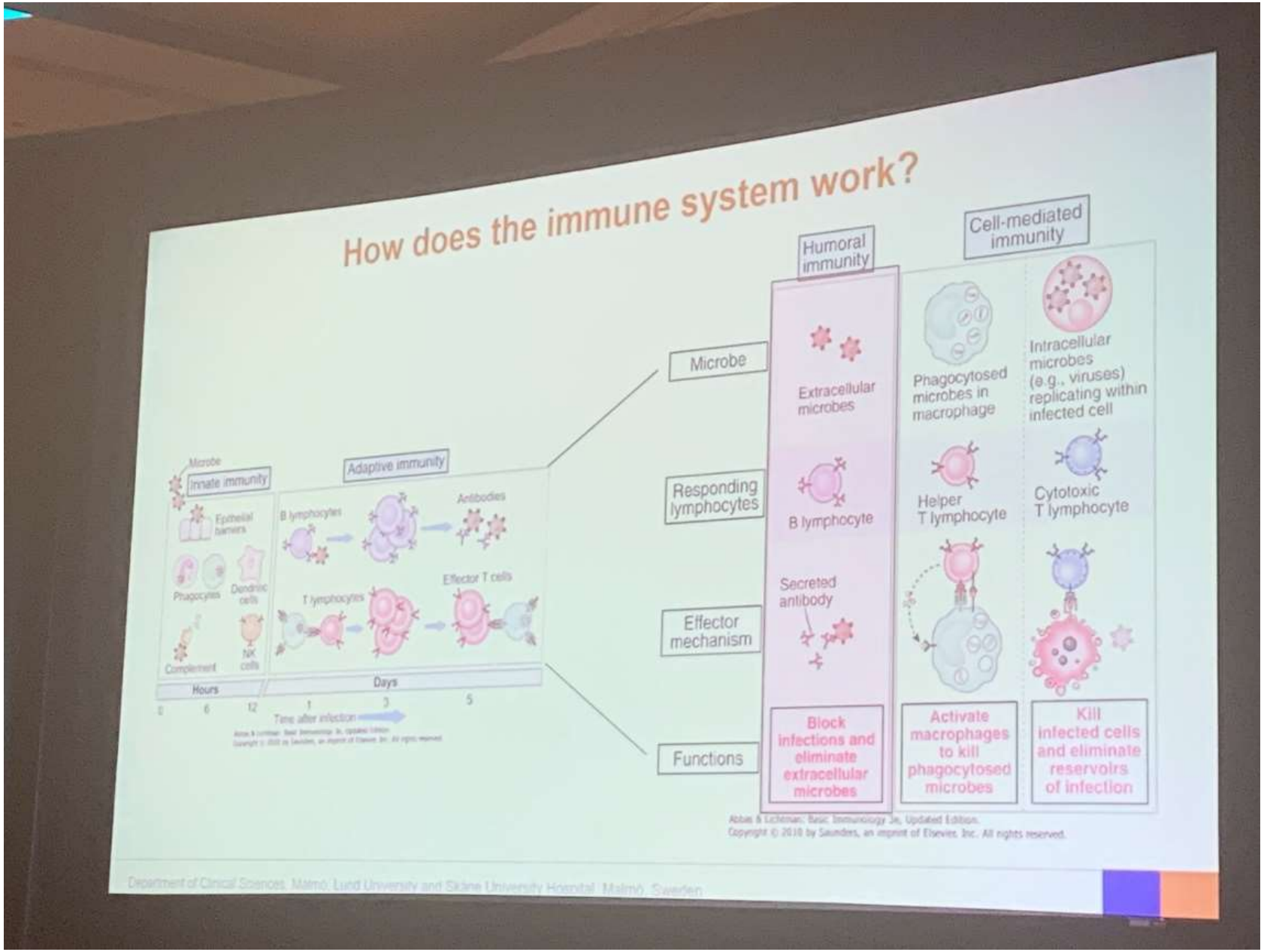
- Somatic nervous system is a 1:1 mapping of brain cell to peripheral cell
- Autonomic nervous system is a nonlinear system of 1 to many, unlike the central nervous system (which is why you can identify exactly where a stroke has occurred in the brain)
- Autonomic ganglion is like a "junction box"
- This nonlinear system allows a small amount of brain tissue to cause a lot to go wrong
- Hypothalamus measures everything and send out directions
- Autonomic nervous system is composed of the parasympathetic and sympathetic nervous system. It's currently the model that is being used; however, there are things that don't fit into this. Since we don't have a new model that accounts for those things that don't fit so we are still using this one.
- Theory: Could pure autonomic failure be a form of Parkinson's??

(Note: He had a lot more slides with a lot of good information but didn't have time to go through them.)


Structure of the Nervous System
Nervous System
Central Nervous System
Peripheral Nervous System
Brain
Spinal Cord
Somatic System
Autonomic System
Sympathetic System
Parasympathetic System
© 2002 Allyn & Bacon, Baron 3/e

The New Horizons of Autoimmune POTS – Dr. Artur Fedorowski (cardiologist)

- An autoimmune disease is caused by autoantibodies or Tcells that attack molecules, cells, or tissues of the organs that produce them
- OPRC1 – controls pain; perhaps this receptor doesn't work in POTS? Can this cause fibromyalgia?
- Doctors "ignore" patients because they feel like a failure because they can't help
- EDS may make someone more vulnerable to autoimmune diseases


How does the immune system work?
Humoral immunity
Cell-mediated immunity
Microbe
Responding lymphocytes
Effector mechanism
Functions
Extracellular microbes
Phagocytosed microbes in macrophage
Intracellular microbes (e.g., viruses) replicating within infected cell
B lymphocyte
Helper T lymphocyte
Cytotoxic T lymphocyte
Secreted antibody
Block infections and eliminate extracellular microbes
Activate macrophages to kill phagocytosed microbes
Kill infected cells and eliminate reservoirs of infection
Innate immunity
Adaptive immunity
Epithelial barriers
Phagocytes
Dendritic cells
Complement
NK cells
B lymphocytes
Antibodies
T lymphocytes
Effector T cells
Hours
Days
0
6
12
1
3
5
Time after infection
Abbas & Lichtman: Basic Immunology 3e, Updated Edition.
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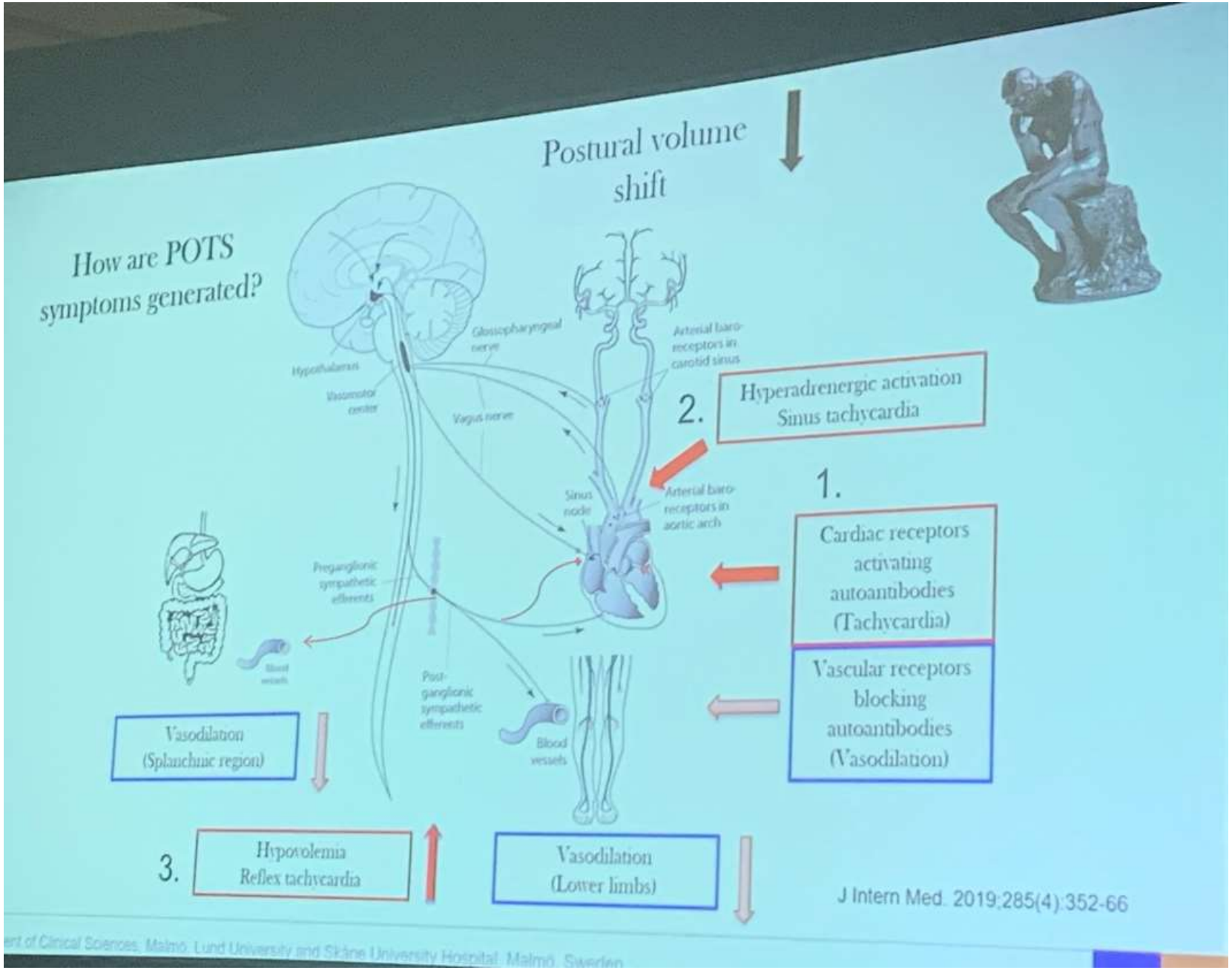
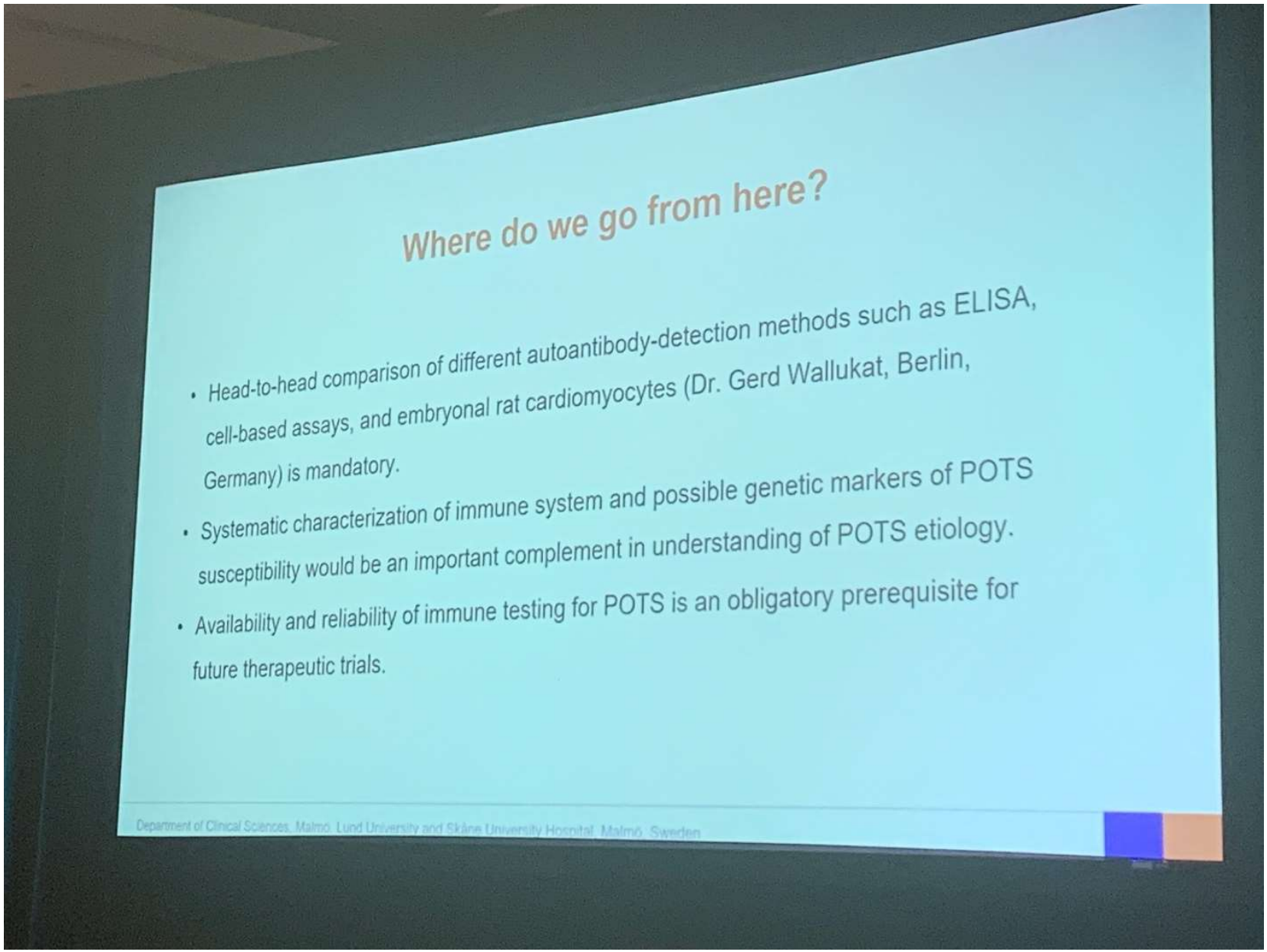
Department of Clinical Sciences, Malmö, Lund University and Skåne University Hospital, Malmö, Sweden


How are POTS symptoms generated?
Postural volume shift
Hypothalamus
Vasomotor center
Glossopharyngeal nerve
Vagus nerve
Arterial baro-receptors in carotid sinus
Sinus node
Arterial baro-receptors in aortic arch
Preganglionic sympathetic efferents
Post-ganglionic sympathetic efferents
Blood vessels
Blood vessels
2. Hyperadrenergic activation Sinus tachycardia
1.
Cardiac receptors activating autoantibodies (Tachycardia)
Vascular receptors blocking autoantibodies (Vasodilation)
Vasodilation (Splanchnic region)
3. Hypovolemia Reflex tachycardia
Vasodilation (Lower limbs)
J Intern Med. 2019;285(4):352-66


Death Star & X-Wing Rebel Spacecrafts
Immunoglobulin G
Epinephrine


Where do we go from here?
• Head-to-head comparison of different autoantibody-detection methods such as ELISA, cell-based assays, and embryonal rat cardiomyocytes (Dr. Gerd Wallukat, Berlin, Germany) is mandatory.
• Systematic characterization of immune system and possible genetic markers of POTS susceptibility would be an important complement in understanding of POTS etiology.
• Availability and reliability of immune testing for POTS is an obligatory prerequisite for future therapeutic trials.
Department of Clinical Sciences, Malmo, Lund University and Skåne University Hospital, Malmö, Sweden

Autoantibodies detected in POTS exceeding the expected prevalence in the general population

The category of autoimmune target	Specific autoimmune targets
G-protein coupled receptors	1. Adrenergic receptors: a) Alpha-1 b) Beta-1 c) Beta-2 1. Muscarinic M1 and M2 receptors 2. Angiotensin II Type 1 receptor
Ganglionic Acetylcholine-receptor (g-AChR)	1. g-AChR alpha3 subunit 2. g-AChR beta4 subunit
Sjögren autoantibodies	1. Novel Sjögren Syndrome panel (carbonic anhydrase-6; parotid secretory protein; salivary protein-1) 2. Traditional Sjögren Syndrome -A antibodies (SS-A)
Antinuclear antibodies (ANAs)	Positive ANAs in general
Antiphospholipid antibodies	
Anti-NMDA (*N*-methyl-D-aspartate)-type glutamate receptor	
Thyroid gland	1. Thyroid stimulating hormone receptor antibodies 2. Thyroglobulin antibodies 3. Thyroid peroxidase antibodies
Cardiac lipid raft-associated proteins and other cardiac proteins	

J Intern Med. 2019;285(4):352-66

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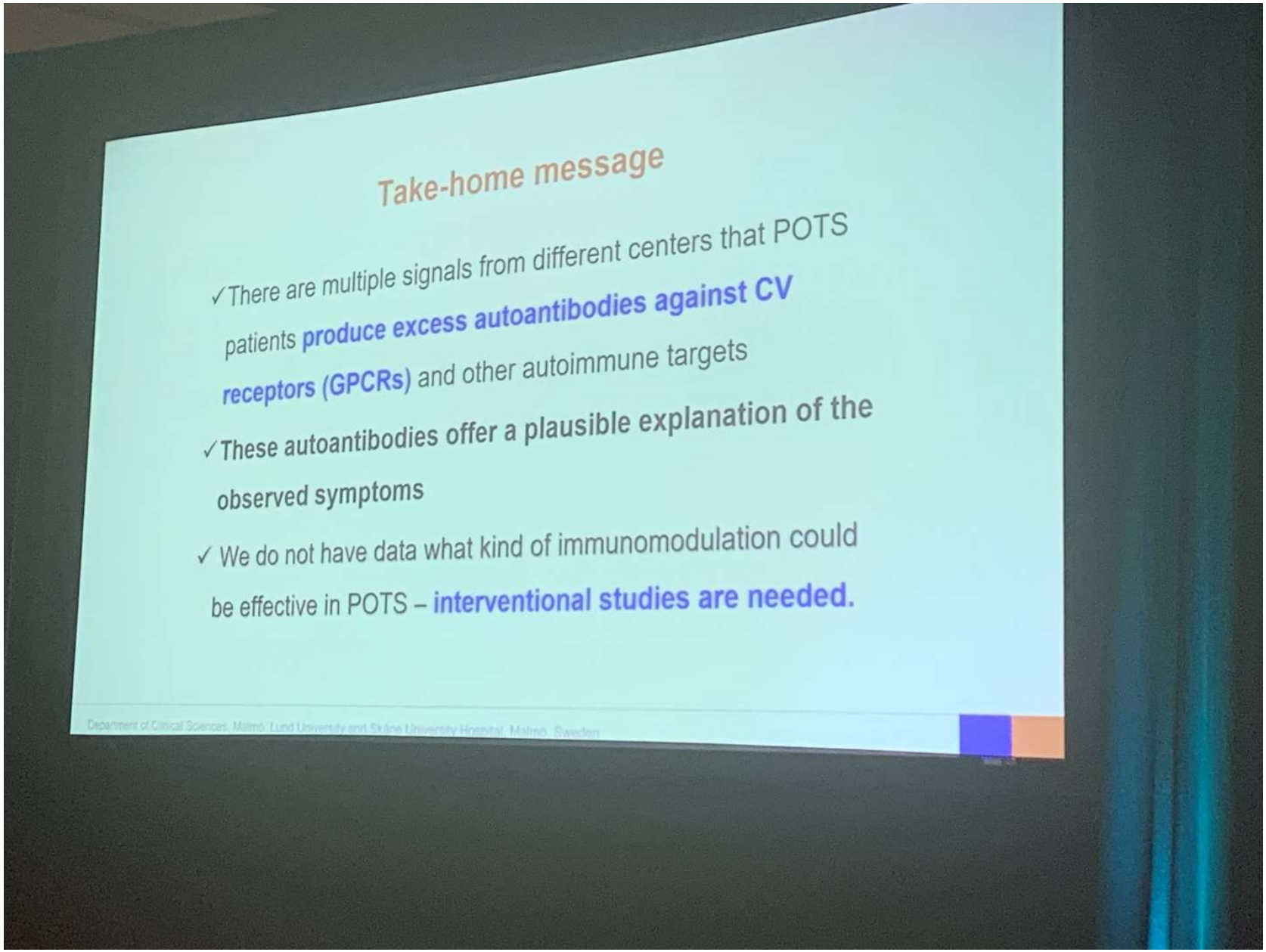
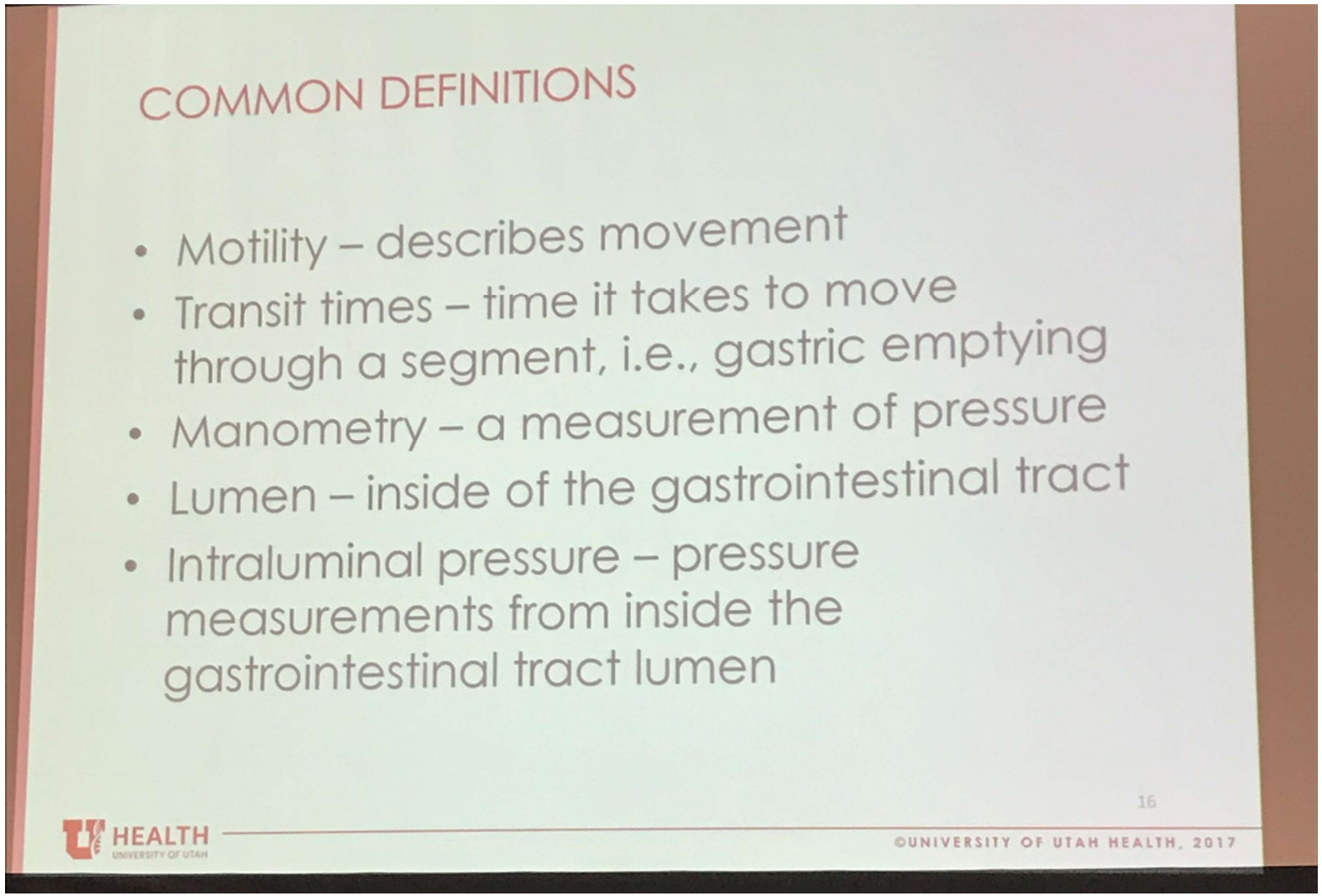

Take-home message
✓There are multiple signals from different centers that POTS patients produce excess autoantibodies against CV receptors (GPCRs) and other autoimmune targets
✓These autoantibodies offer a plausible explanation of the observed symptoms
✓ We do not have data what kind of immunomodulation could be effective in POTS – interventional studies are needed.
Department of Clinical Sciences, Malmö, Lund University and Skåne University Hospital, Malmö, Sweden

Gastrointestinal Disorders in Dysautonomia: From Dysmotility to Immunology – Dr. Laura Pace

- Parasympathetic innervates motility; sympathetic slows
- Functional disorders such as IBS, dyspepsia is just groupings based on symptoms
- Rome Foundation – classification of disorders; up to Rome IV, organized by disorders of gut-brain interactions
- Minor esophageal disorders include ineffective motility (common in dysautonomia)
- Major esophageal disorders include Achalasia (esophagus doesn't tighten or will tighten all at once). Loss of neuronal cells and increase in mast cells is seen in these patients.
- Antroduodenal-Jejunal Manometry is considered he "gold standard" in testing motility but not readily available. Testing will help determine if it's a nerve or muscle issue.
- Smart Pill reveals issues in patients who may have a normal gastrointestinal emptying scan
- She sees a lot of patients whose initial symptom was abdominal pain
- MALS surgical outcome is 30-70%
- Hypothesis: Vascular MALS is a subset of neurogenic MALS
- Surgical decompression if caught early can fix nMALS; immunological treatment in addition if caught later


COMMON DEFINITIONS
• Motility – describes movement
• Transit times – time it takes to move through a segment, i.e., gastric emptying
• Manometry – a measurement of pressure
• Lumen – inside of the gastrointestinal tract
• Intraluminal pressure – pressure measurements from inside the gastrointestinal tract lumen
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HEALTH
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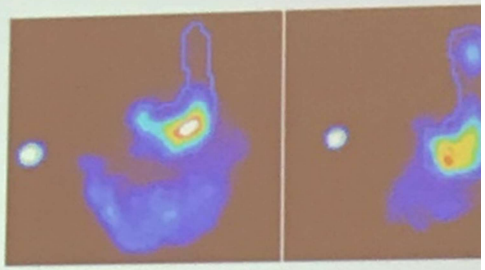
GASTROINTESTINAL MOTILITY TESTING

Transit time studies
- NM gastric emptying studies
- Other scintigraphy testing
- Sitz marker study



Manometry based studies
- Esophageal
- Antroduodenal-jejunal
- Colonic
- Anorectal

SmartPill wireless motility capsule

Note: Text in Red is widely available; Gray is Not

ESOPHAGEAL MOTILITY DISORDERS

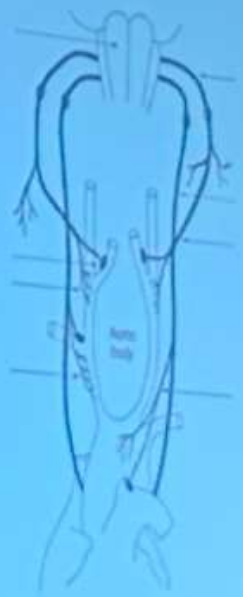
- Neuroimmune mediated disorders?
  - Dysautonomia
  - Autoimmune (antibody mediated)
  - Immune infiltrative (eosinophilic, lymphocytic, mast cell)
  - Inflammatory (inflammatory cytokines/chemokines)
  - Neurogenerative (loss of ICC, nNOS cells, etc.)

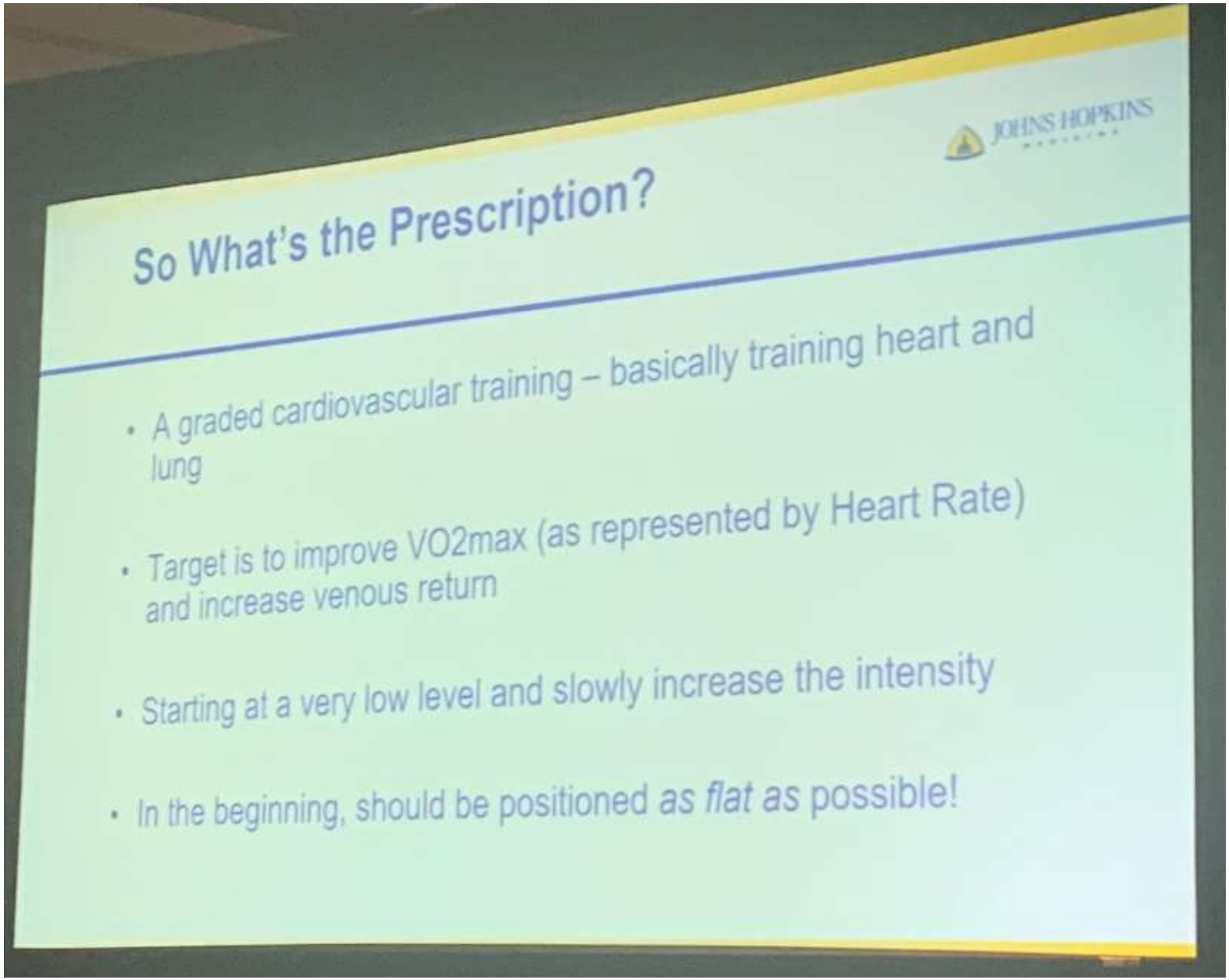
Exercise Rehabilitation in Dysautonomia – Dr. Tae Chung

- POTS patients tend to not faint because the baroreceptor Reflex ("pressure gauge") is intact
- Skeletal muscles in lower limbs act as a pump
- Normal cardiac output is 4-8L; during exercise, this increases to 20-25L
- 3 types of exercises: endurance, cardiovascular, resistance
- Every 3 – 4 months you should challenge yourselves and gradually increase
- Target heartrate is most practical measure to determine target exercise range; if that isn't accurate because of beta blockers, you can use the Borg scale (Perceived Exertion Scale); POTS patients should target 13-18 on that scale
- Perhaps start with core strengthening before starting cardiovascular or endurance exercise

Why Do POTS pts Not Always Faint Then?

- Baroreceptor Reflex ("pressure gauge") is intact
- Reduced fluid return -> strong sympathetic response to try to "fix" the pump
- Suggesting intact CNS




So What's the Prescription?
JOHNS HOPKINS
• A graded cardiovascular training – basically training heart and lung
• Target is to improve VO2max (as represented by Heart Rate) and increase venous return
• Starting at a very low level and slowly increase the intensity
• In the beginning, should be positioned as *flat* as possible!

POTS 101 – Dr. Satish Raj

- 40-50% POTS patients meet Chronic Fatigue Syndrome criteria
- POTS is not a fainting disorder, it is a FEELING faint disorder
- Peak age of onset is 14
- Emphasis on expercies – 4x/week, 30-60 min
- Beta blockers are effective at low doses only
- SNRIs tend to make POTS symptoms worse

POTS: Treatment Approaches

- Exercise
- Increase Blood Volume
  - Oral Water
  - Increase Salt (diet vs. tablets)
  - Fludrocortisone
  - Octreotide
  - IV Saline
  - Acute DDAVP-H_2O
- Hemodynamic Agents
  - Midodrine
  - Propranolol
  - Pyridostigmine
  - Ivabradine (emerging)
- Behavioral Therapies

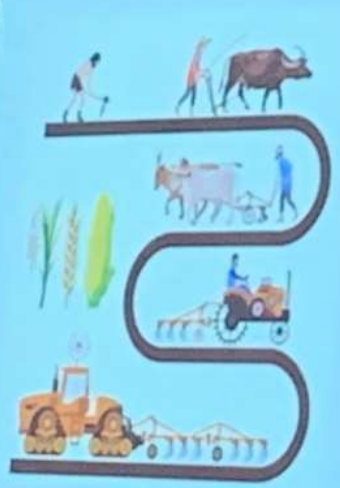
POTS - Pathophysiologies

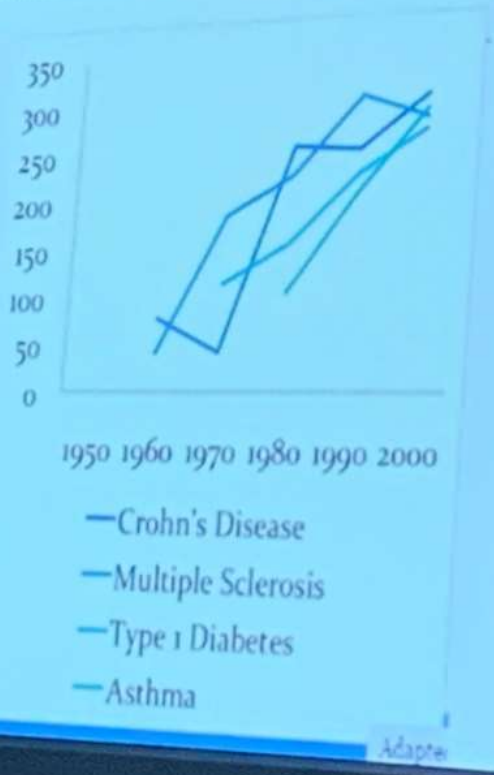
- Mast Cell Activation
- Partial Autonomic Neuropathy
- Leg Blood Flow Abnormalities
- Hypovolemia
- Hyperadrenergic
  - Increased Release
  - Decreased Clearance
- Antibodies are Evil…

Managing Refractory Mast Cell Activation Syndrome in Dysautonomia – Dr. Anne Maitland

- Mast cells talk to nerves all the time
- Mast cells are not blood born, they are tissues
- Mast cells start in bone marrow and get called into action
- 100 trillion microbes on our body's surface area
- "We do not know what a normal tryptase level is. I REPEAT: We do not know what a normal tryptase level is."
- You should get a baseline tryptase and then when you are having a reaction, get a level measured. You may have trouble getting ER docs to run this. Her trick: You can often get them to order a metabolic panel and then Dr. Maitland will call and ask the lab to add a tryptase test to it
- If your tryptase > 6, see if you have a duplicate tryptase gene (Gene by Gene cheek swab)
- Mayo Clinic is about to come out with a spot urine test
- Mast cells are worse at night
- Dr. Maitland likes the Tricyclic Antidepressant Doxepin at night
- Question was asked about Xolair and whether there was benefit to dosing at about 300; Dr. Maitland said Yes but it may be difficult to get insurance to cover it

The human race has come to dominate its environment so completely that any analysis of the increase or appearance of a disease has to take changes in our lifestyle into account….diet, water quality, and personal behavior over the last 150 years have played a dominant role in the specificity of these diseases, as well as in prevalence and severity… it is clear that the consequences of hygiene, indoor entertainment, and changes in diet or physical activity have never been predicted. Thomas A. E. Platts-Mills, The allergy epidemics: 1870-2010; J Allergy Clin Immunol 2015;136:3-13.





MODERN TIMES:

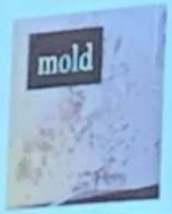
1 OUT OF 2 AMERICANS HAVE A CHRONIC DISORDER.

20th century inventions were hugely influenced by major developments in technology and resources, enabling the inventions of key items and devices which changed the way we live today.

Americans, on average, spend approximately 90 percent of their time indoors,[1] where the concentrations of some pollutants are often 2 to 5 times higher than typical outdoor concentrations.

Environmental Protection Agency, 2019 https://www.epa.gov/report-environment/indoor-air-quality

1908 Assembly Line Production



1950s Disposable single use bottles

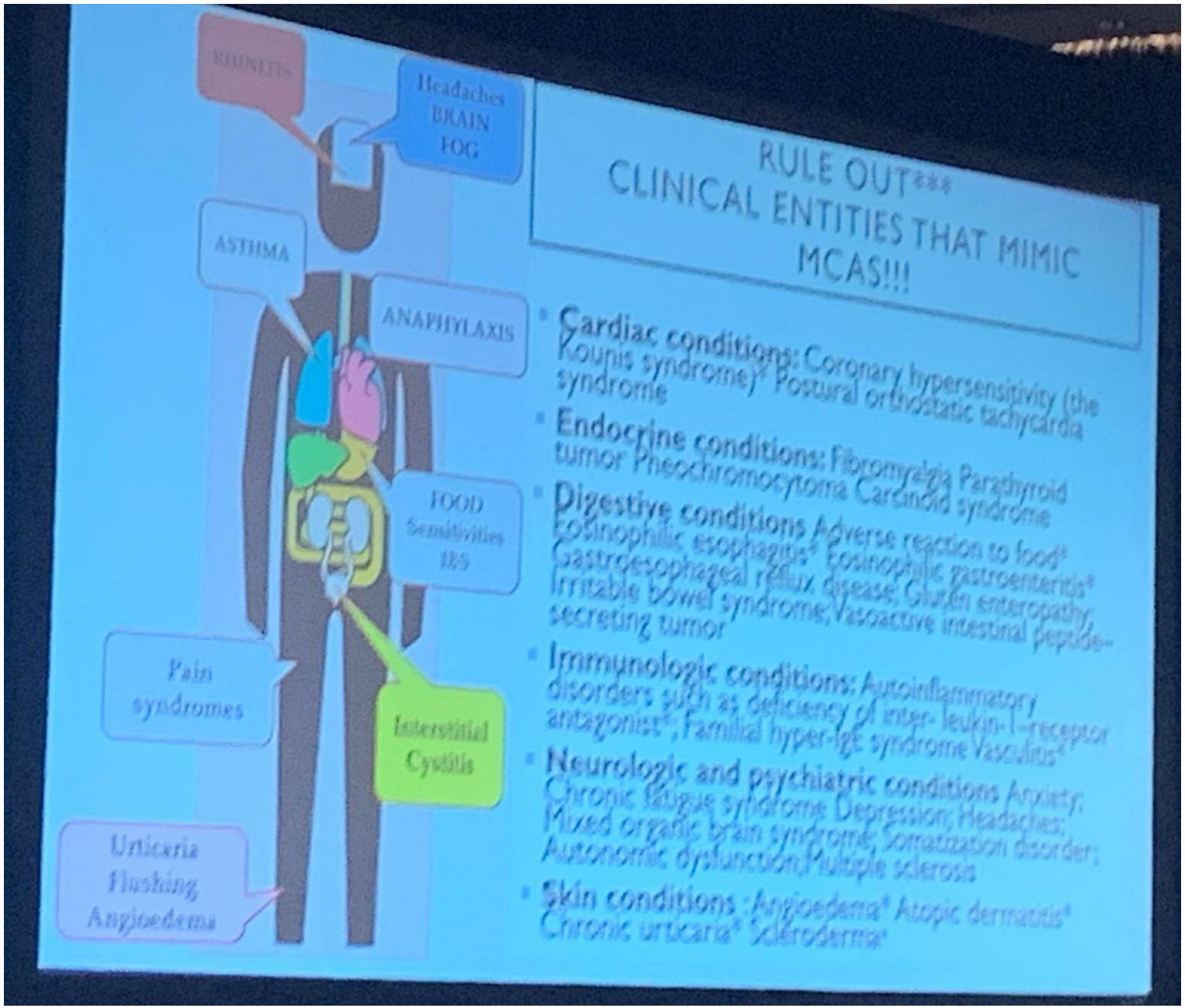
INDOOR AIR POLLUTION

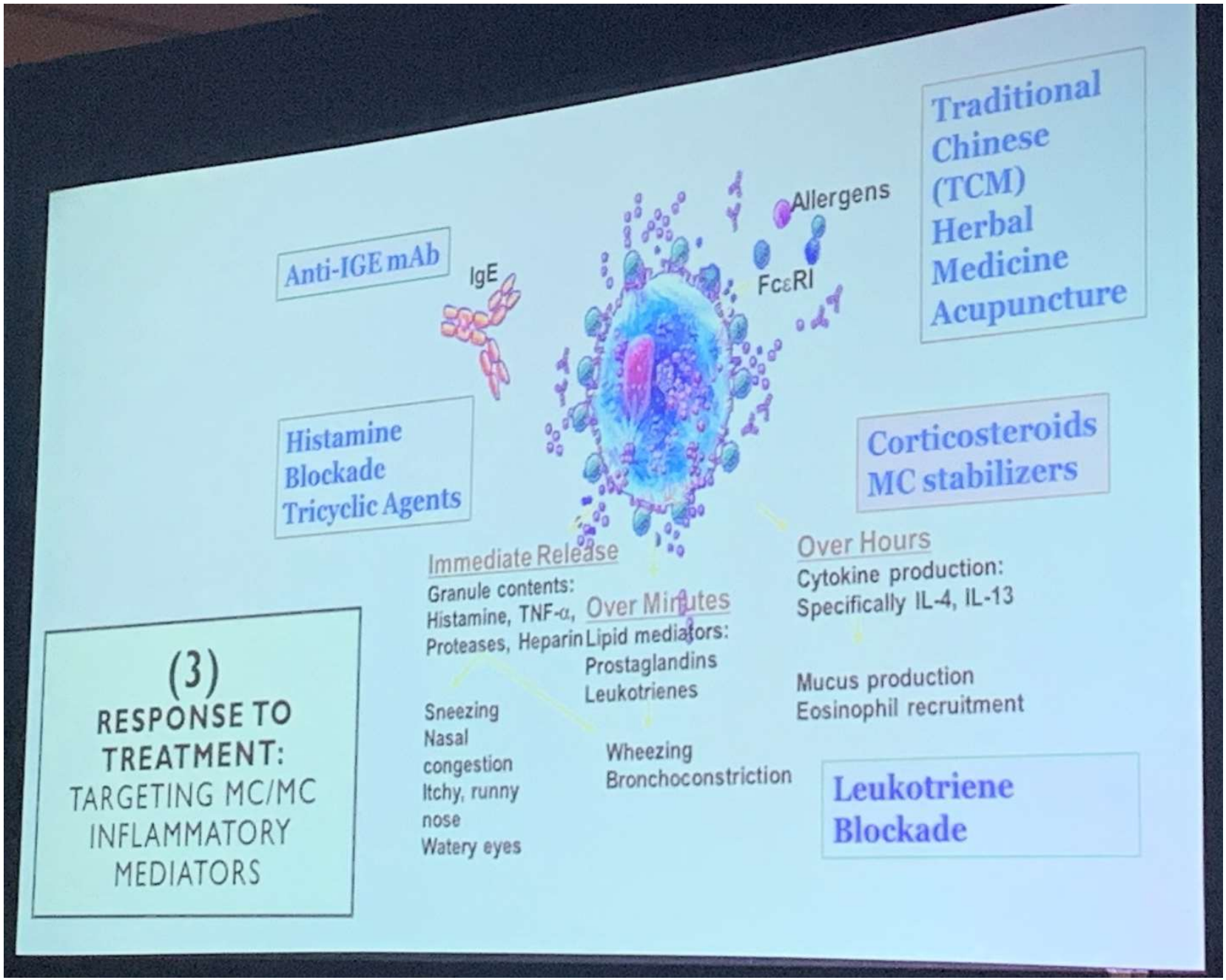
Dust Mites

Volatile Organic Compounds

1960s Engineered Hardwood = formaldehyde

Modern Living
Road to Hypersensitivity


RHINITIS
Headaches
BRAIN
FOG
ASTHMA
ANAPHYLAXIS
FOOD
Sensitivities
IBS
Pain
syndromes
Interstitial
Cystitis
Urticaria
Flushing
Angioedema
RULE OUT***
CLINICAL ENTITIES THAT MIMIC
MCAS!!!
Cardiac conditions: Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome
Endocrine conditions: Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome
Digestive conditions Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor
Immunologic conditions: Autoinflammatory disorders such as deficiency of inter- leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*
Neurologic and psychiatric conditions Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction Multiple sclerosis
Skin conditions :Angioedema* Atopic dermatitis* Chronic urticaria* Scleroderma*


Traditional Chinese (TCM) Herbal Medicine Acupuncture
Anti-IGE mAb
IgE
Allergens
FcεRI
Histamine Blockade Tricyclic Agents
Corticosteroids MC stabilizers
Immediate Release
Granule contents:
Histamine, TNF-α,
Proteases, Heparin
Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes
Over Hours
Cytokine production:
Specifically IL-4, IL-13
Mucus production
Eosinophil recruitment
Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes
Wheezing
Bronchoconstriction
Leukotriene Blockade
(3)
RESPONSE TO TREATMENT:
TARGETING MC/MC INFLAMMATORY MEDIATORS

Autonomic Testing & Small Fiber Neuropathies – Kamal Chemali

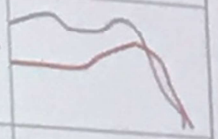
- EMG shows only large fibers
- Autonomic testing includes Valsva, Themoregulatory sweat test, CardoVegal test (response to deep breathing)
- Vitamin B12 deficient needs MMA; Homocysteine to confirm
- Alcohol isn't good for POTS patients

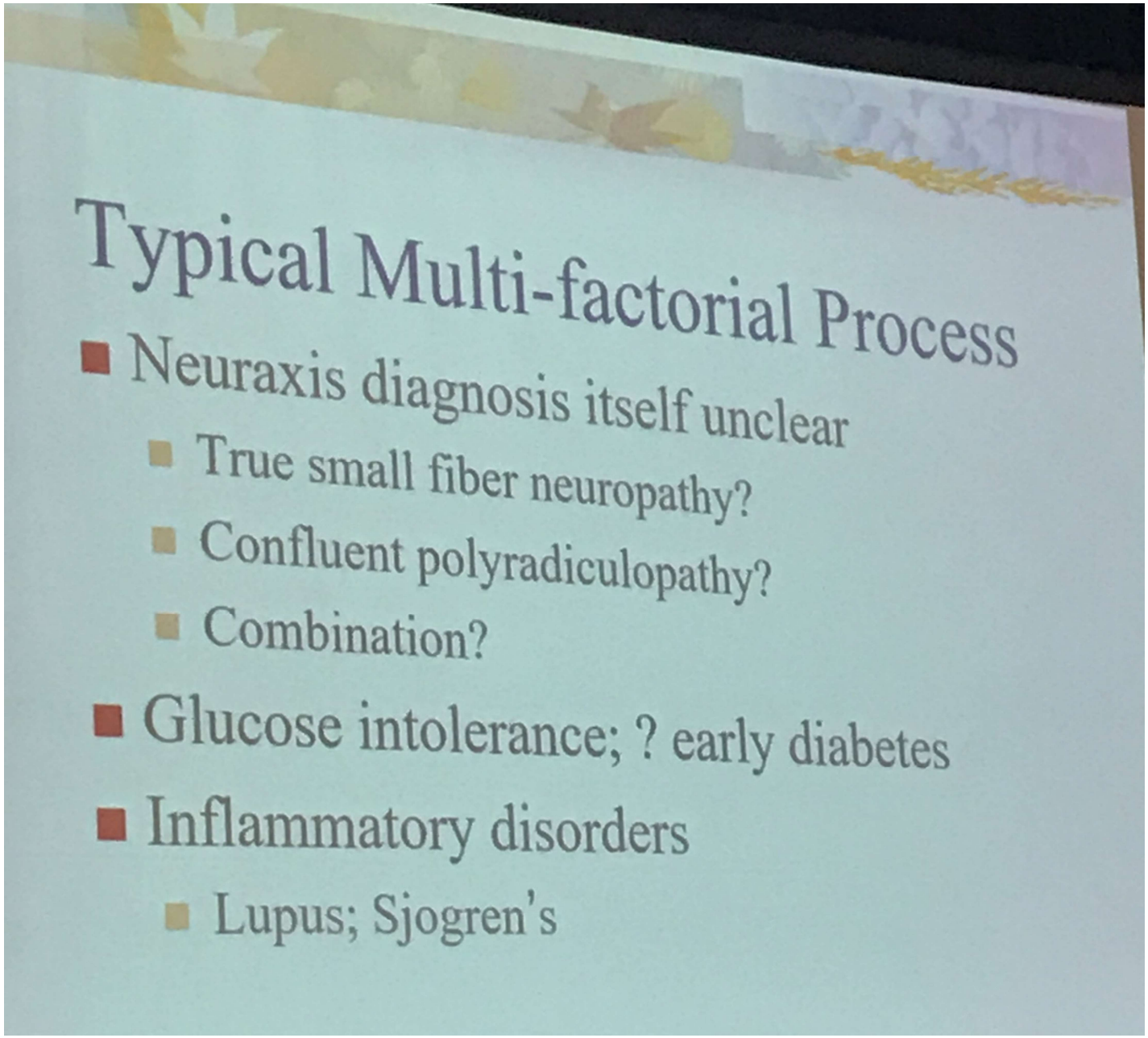
Hereditary causes

- Strong family history in SFN
- HSAN types I to V
- HSAN III is Familial Dysautonomia
  - Absent fungiform papillae
  - Pain insensitivity
  - Absent tearing
  - No flare on histamine flare test
  - Autosomal recessive in Ashkenazi Jews mutation of IKBKAP on chromosome 9.
- Familial "burning feet syndrome"
- Fabry's disease
- Porphyrias

SENTARA®

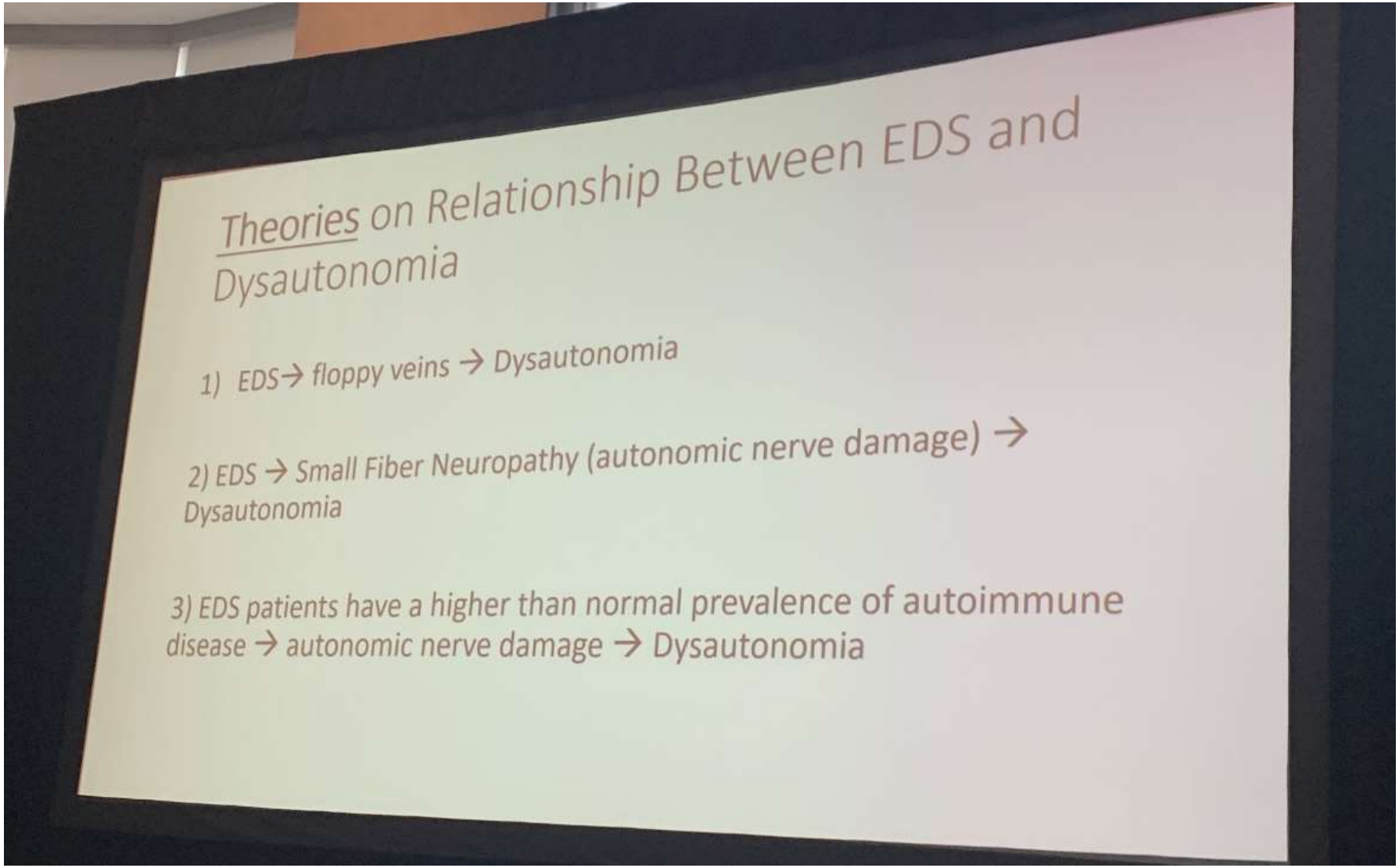
The 3 Orthostatic Syndromes

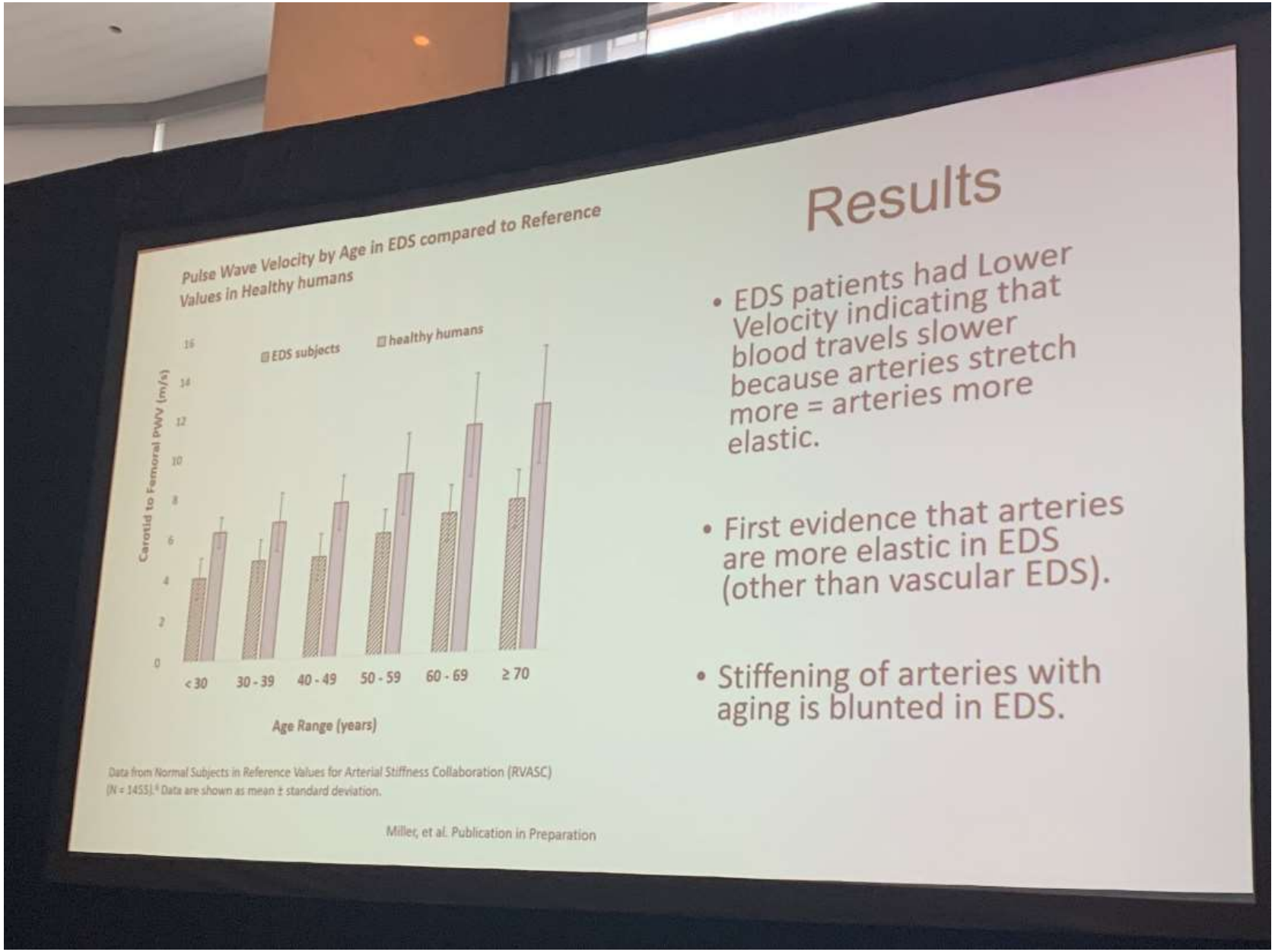
	Orthostatic Hypotension	Postural Tachycardia	Reflex Syncope
Definition	Gradual, Sustained ↓sBP>20 or ↓dBP>10	↑HR>30 1st 10' up; no ↓ BP	Sudden ↓BP & HR
BP Pattern			
Physiology	Arterial denervation – main impact ***diastole***	Venous return impact ***systole***	Brainstem ***threshold***
CV reflexes	Usually abnormal	Usually normal	Usually nl
Associated Dysauton.	Disease-based Poor prognosis	Syndromic Good Prognosis	Syndromic
SFN Type	**Severe, Diffuse**	**Mild, Focal**	**None**

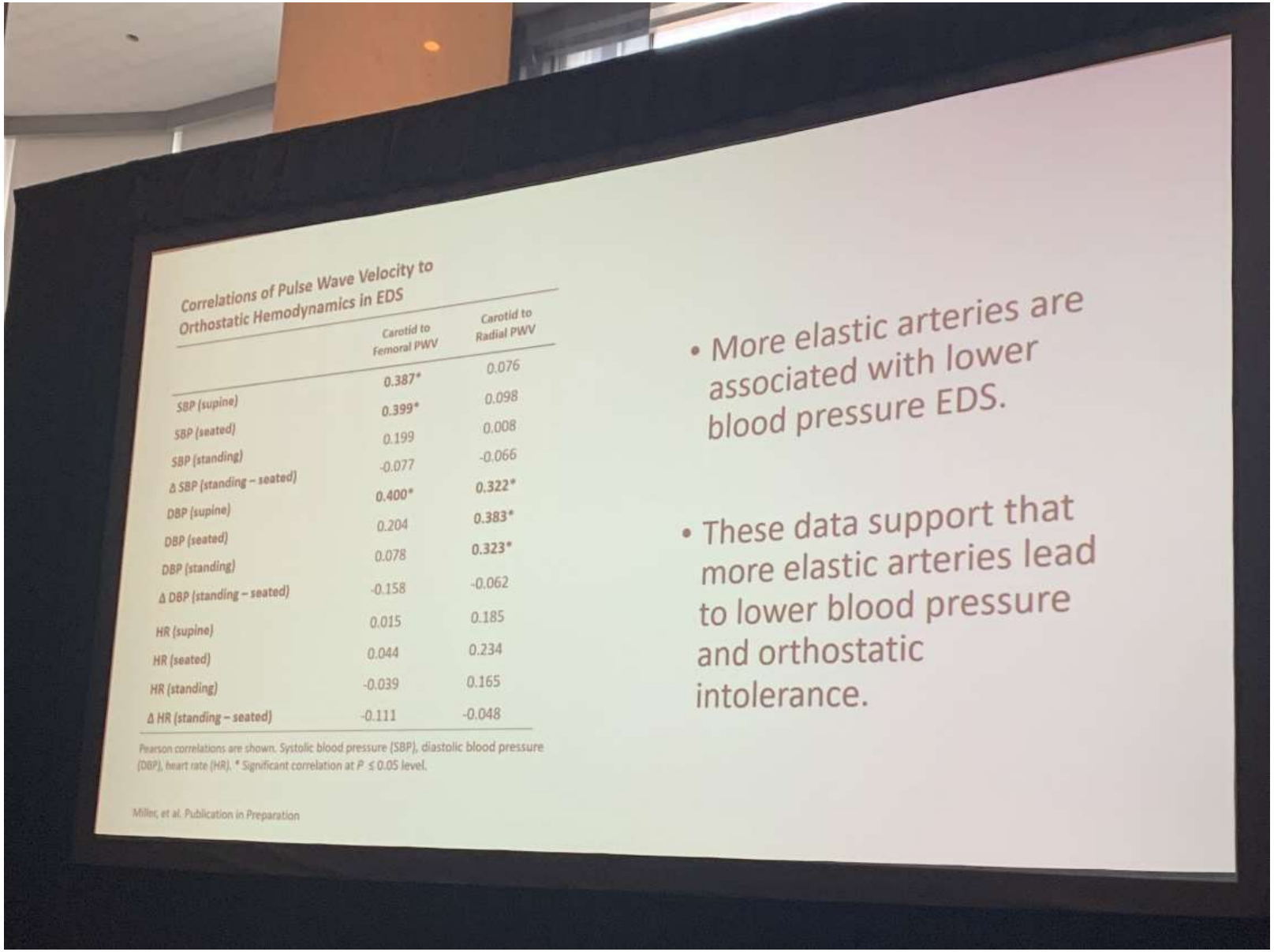

Typical Multi-factorial Process
Neuraxis diagnosis itself unclear
True small fiber neuropathy?
Confluent polyradiculopathy?
Combination?
Glucose intolerance; ? early diabetes
Inflammatory disorders
Lupus; Sjogren's

Ehlers-Danlos Syndrome, Cognition & Dysautonomia – Dr. Amanda Miller

- 2018 Research Study found that brain fog in POTS is not only experienced when standing; experienced just as much laying down
- There is no gene associated with hEDS
- In 2017, new diagnostic criteria came out which is more stringent and many people who were previously diagnosed with hEDS are now diagnosed with Hypermobility Spectrum Disorder
- Dr. Miller performed a study to show that those with hEDS had “floppy veins” which could make them more prone to POTS


Theories on Relationship Between EDS and Dysautonomia
1) EDS→ floppy veins → Dysautonomia
2) EDS → Small Fiber Neuropathy (autonomic nerve damage) → Dysautonomia
3) EDS patients have a higher than normal prevalence of autoimmune disease → autonomic nerve damage → Dysautonomia


Pulse Wave Velocity by Age in EDS compared to Reference Values in Healthy humans
EDS subjects
healthy humans
Carotid to Femoral PWV (m/s)
0
2
4
6
8
10
12
14
16
< 30
30 - 39
40 - 49
50 - 59
60 - 69
≥ 70
Age Range (years)
Data from Normal Subjects in Reference Values for Arterial Stiffness Collaboration (RVASC) (N = 1455).[4] Data are shown as mean ± standard deviation.
Miller, et al. Publication in Preparation
Results
• EDS patients had Lower Velocity indicating that blood travels slower because arteries stretch more = arteries more elastic.
• First evidence that arteries are more elastic in EDS (other than vascular EDS).
• Stiffening of arteries with aging is blunted in EDS.



Correlations of Pulse Wave Velocity to Orthostatic Hemodynamics in EDS

	Carotid to Femoral PWV	Carotid to Radial PWV
SBP (supine)	**0.387***	0.076
SBP (seated)	**0.399***	0.098
SBP (standing)	0.199	0.008
Δ SBP (standing – seated)	-0.077	-0.066
DBP (supine)	**0.400***	**0.322***
DBP (seated)	0.204	**0.383***
DBP (standing)	0.078	**0.323***
Δ DBP (standing – seated)	-0.158	-0.062
HR (supine)	0.015	0.185
HR (seated)	0.044	0.234
HR (standing)	-0.039	0.165
Δ HR (standing – seated)	-0.111	-0.048

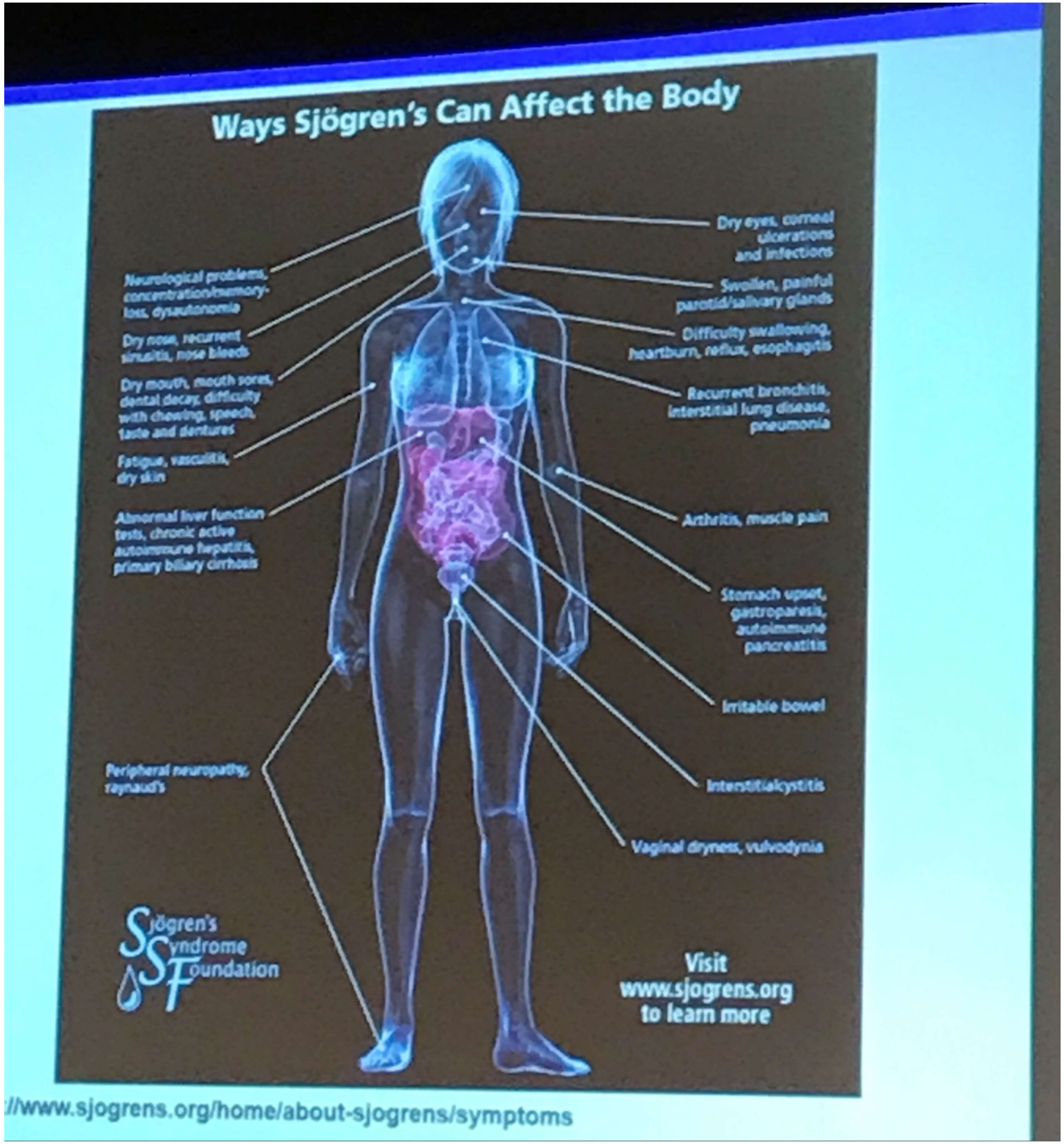
Pearson correlations are shown. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR). * Significant correlation at $P \leq 0.05$ level.

Miller, et al. Publication in Preparation

- More elastic arteries are associated with lower blood pressure EDS.
- These data support that more elastic arteries lead to lower blood pressure and orthostatic intolerance.

Sjogren's Syndrome and the Autonomic Nervous System – Dr. Brent Goodman

- Diagnostic testing for SS is horrendous
- "Autonomic dysfunction in SS is typically mild" is a myth as he believes 50% show autonomic symptoms
- Common for autonomic disorders to sweat less in legs/feet and more in forearm/head
- SS commonly with non-length dependent neuropathies
- SS prevalence much higher in elderly; could be that it takes that long to diagnose
- SSA – low % coincidence with SS
- GI symptoms are common
- Dry eyes, dry mouth doesn't commonly occur initially
- Lip biopsy is negative for 27% of those that have SS


Ways Sjögren's Can Affect the Body
Dry eyes, corneal ulcerations and infections
Swollen, painful parotid/salivary glands
Difficulty swallowing, heartburn, reflux, esophagitis
Recurrent bronchitis, interstitial lung disease, pneumonia
Arthritis, muscle pain
Stomach upset, gastroparesis, autoimmune pancreatitis
Irritable bowel
Interstitialcystitis
Vaginal dryness, vulvodynia
Peripheral neuropathy, raynaud's
Neurological problems, concentration/memory-loss, dysautonomia
Dry nose, recurrent sinusitis, nose bleeds
Dry mouth, mouth sores, dental decay, difficulty with chewing, speech, taste and dentures
Fatigue, vasculitis, dry skin
Abnormal liver function tests, chronic active autoimmune hepatitis, primary biliary cirrhosis
Sjögren's Syndrome Foundation
Visit www.sjogrens.org to learn more
://www.sjogrens.org/home/about-sjogrens/symptoms

MAYO CLINIC

Table 3 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: The classification of primary Sjögren's syndrome (SS) applies to any individual who meets the inclusion criteria,* does not have any of the conditions listed as exclusion criteria,† and has a score of ≥4 when the weights from the five criteria items below are summed

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥1 foci/4 mm^2‡	3
Anti-SSA/Ro-positive	3
Ocular Staining Score ≥5 (or van Bijsterveld score ≥4) in at least one eye§¶	1
Schirmer's test ≤5 mm/5 min in at least one eye§	1
Unstimulated whole saliva flow rate ≤0.1 mL/min§**	1

*These inclusion criteria are applicable to any patient with at least one symptom of ocular or oral dryness, defined as a positive response to at least one of the following questions: (1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (2) Do you have a recurrent sensation of sand or gravel in the eyes? (3) Do you use tear substitutes more than three times a day? (4) Have you had a daily feeling of dry mouth for more than 3 months? (5) Do you frequently drink liquids to aid in swallowing dry food? or in whom there is suspicion of Sjögren's syndrome (SS) from the European League Against Rheumatism SS Disease Activity Index questionnaire (at least one domain with a positive item).

†Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: (1) history of head and neck radiation treatment, (2) active hepatitis C infection (with confirmation by PCR), (3) AIDS, (4) sarcoidosis, (5) amyloidosis, (6) graft-versus-host disease, (7) IgG4-related disease.

‡The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using the protocol described by Daniels *et al*.[10]

§Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness.

¶Ocular Staining Score described by Whitcher *et al*;[11] van Bijsterveld score described by van Bijsterveld.[9]

**Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar.[12]

hiboski CH, Shiboski SC, eror R, et al 2016 American ollege of heumatology/European ague Against Rheumatism assification criteria for imary Sjögren's syndrome nals of the Rheumatic seases 2017;76:9-16.

MAYO CLINIC

Treatment of Autonomic Dysfunction in SS – My Approach

Stabilize ANS

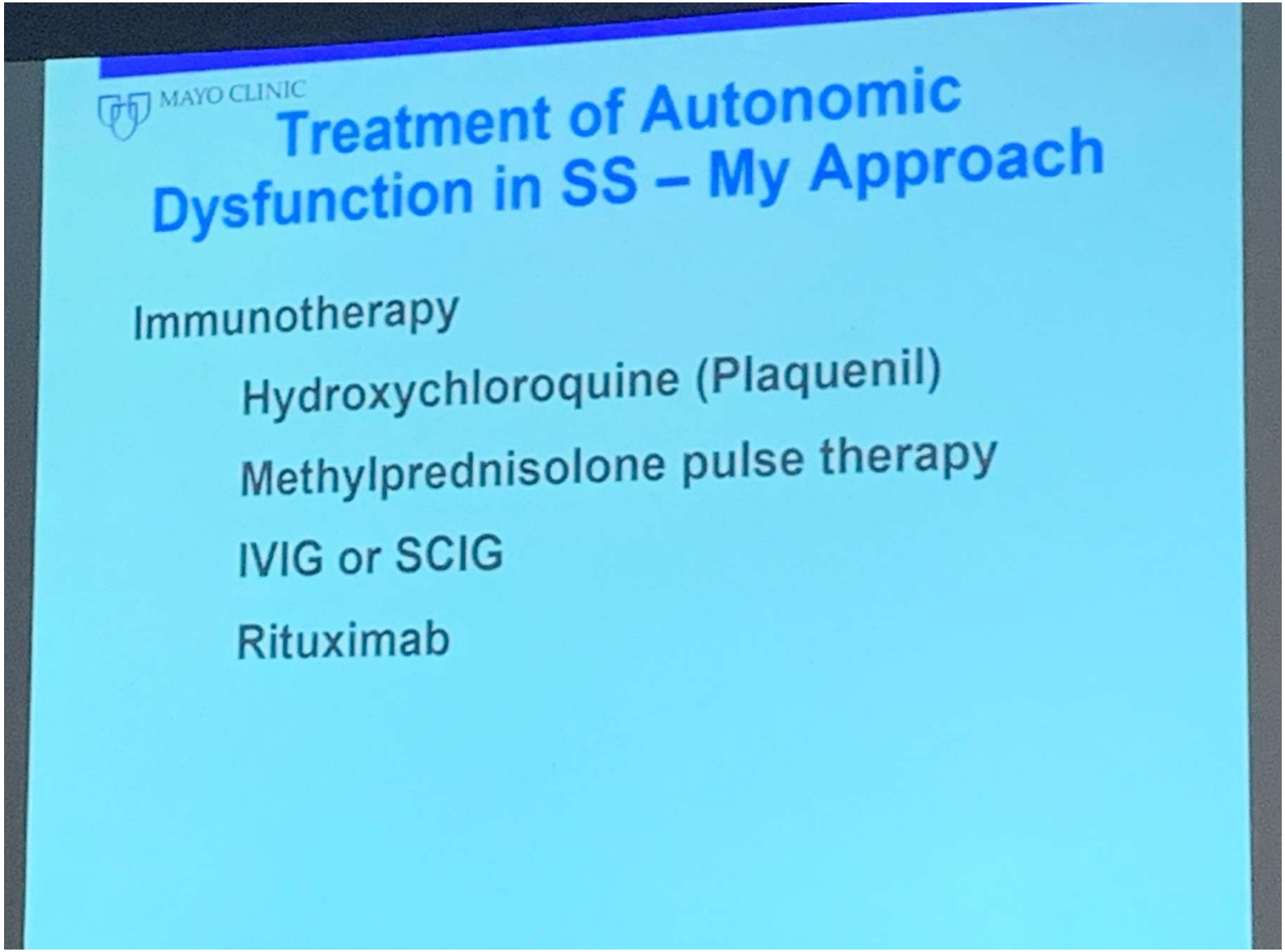
diet, lifestyle, pharmacotherapy

Stabilize Mast Cell Pathways

With refractory signs/symptoms…

With evidence of Autonomic Neuropathy and/or GI dysmotility ...

Weigh Pros & Cons of Immunotherapy

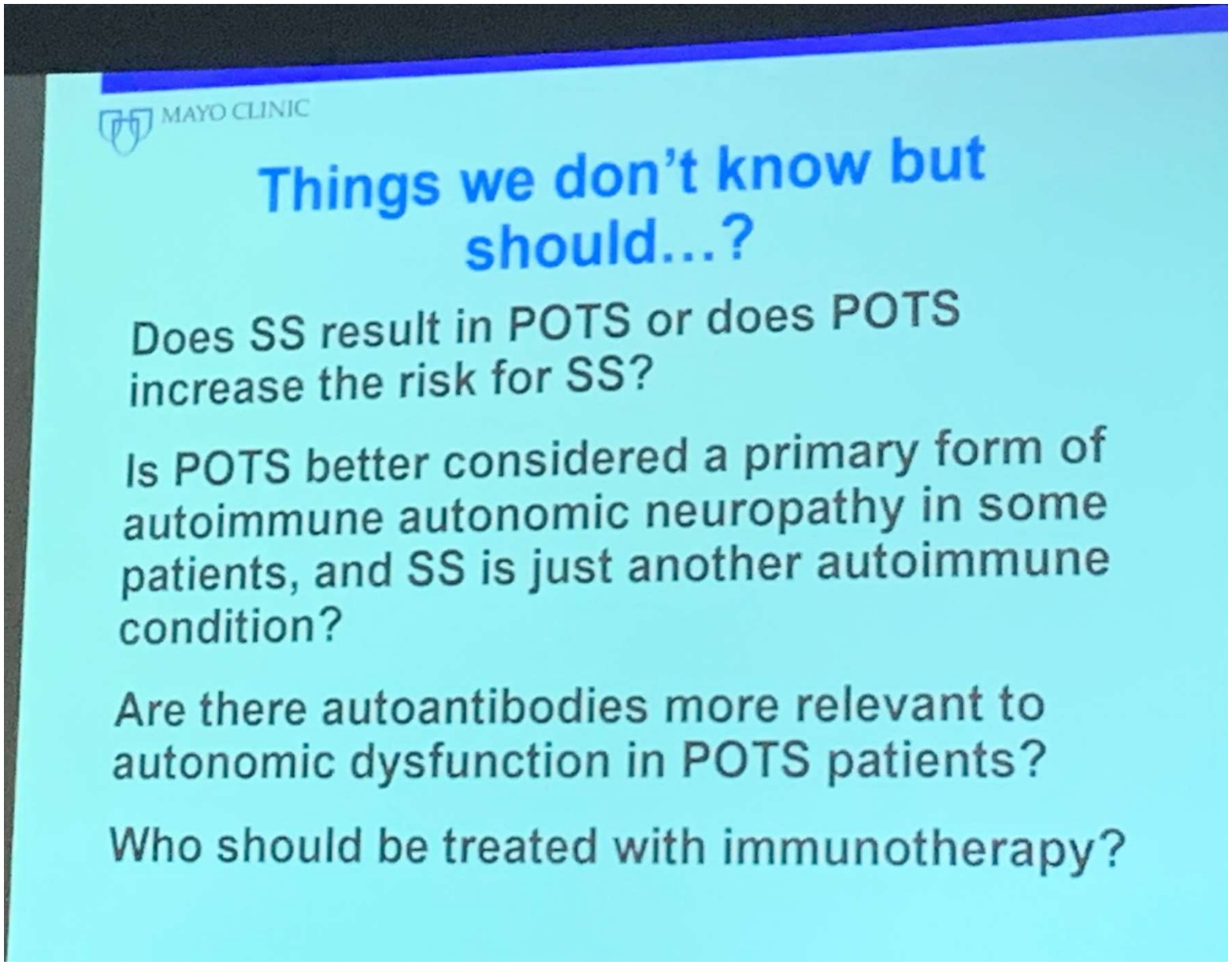

MAYO CLINIC
Treatment of Autonomic Dysfunction in SS – My Approach
Immunotherapy
Hydroxychloroquine (Plaquenil)
Methylprednisolone pulse therapy
IVIG or SCIG
Rituximab

MAYO CLINIC

Things I suspect …

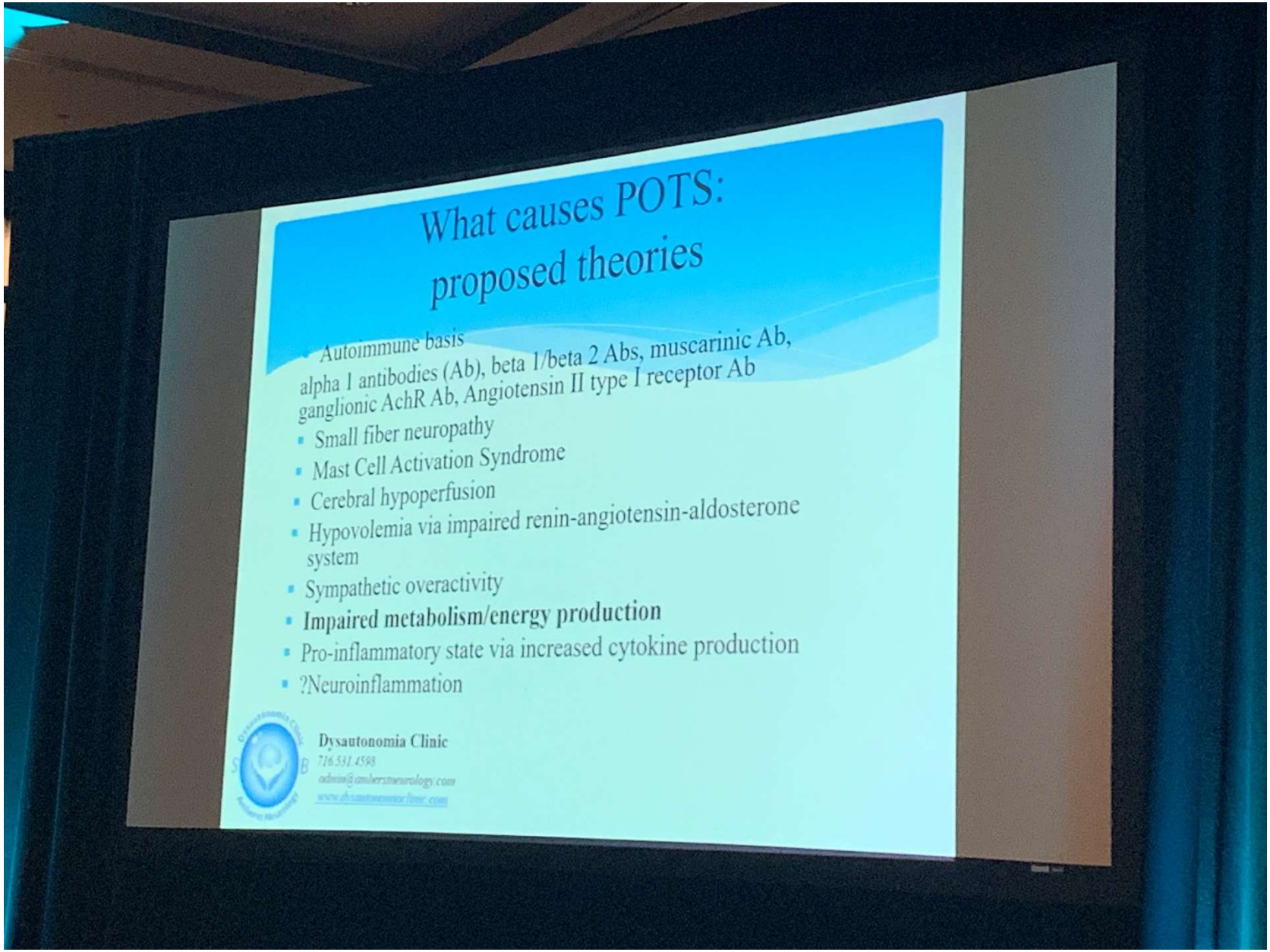
SS may be the cause of Autonomic and systemic symptoms in some % of POTS patients

Autonomic symptoms in POTS patients may be immunoresponsive


MAYO CLINIC
Things we don't know but should…?
Does SS result in POTS or does POTS increase the risk for SS?
Is POTS better considered a primary form of autoimmune autonomic neuropathy in some patients, and SS is just another autoimmune condition?
Are there autoantibodies more relevant to autonomic dysfunction in POTS patients?
Who should be treated with immunotherapy?

Vitamin Deficiencies and POTS: The Tip of the Iceberg – Dr. Svetlana Blitshteyn

- Vitamin B6 can cause neuropathy when too low and too high
- Vitamin C – mast cell stabilizer and recommended for those with EDS
- Vitamin B12, Iron, and Vitamin D are the most common deficiencies in POTS patients
- Vitamin B1 (Thiamin) – depletion can occur within 14 days. You can especially become deficient if you don't eat grains, dairy, and meat. Deficiency symptoms may mimic or worsen POTS symptoms
- Had a patient with a slightly lower B1 level and saw miraculous improvement with a B1 supplement in just days\
- Thiamine Hydrochloride dosage – 100mg/day for 4 weeks
- Whole blood vitamin B1 test is more accurate than serum; normal values are 78-185; however improvement is seen with this supplement for those that are just marginally below normal levels (72-76)
- Approximately 6% of POTS have a thiamin deficiency, which is a higher prevalence than non-POTS population
- Thiamine modulates the release of acetylcholine; a deficiency leads to less acetylcholine in the brain which can lead to memory loss
- Even though you may be in the "low normal" range, a supplement may help
- MTHFR – not important to know
- B12 can also cause issues if the value is too high


What causes POTS:
proposed theories
Autoimmune basis
alpha 1 antibodies (Ab), beta 1/beta 2 Abs, muscarinic Ab, ganglionic AchR Ab, Angiotensin II type I receptor Ab
Small fiber neuropathy
Mast Cell Activation Syndrome
Cerebral hypoperfusion
Hypovolemia via impaired renin-angiotensin-aldosterone system
Sympathetic overactivity
Impaired metabolism/energy production
Pro-inflammatory state via increased cytokine production
?Neuroinflammation
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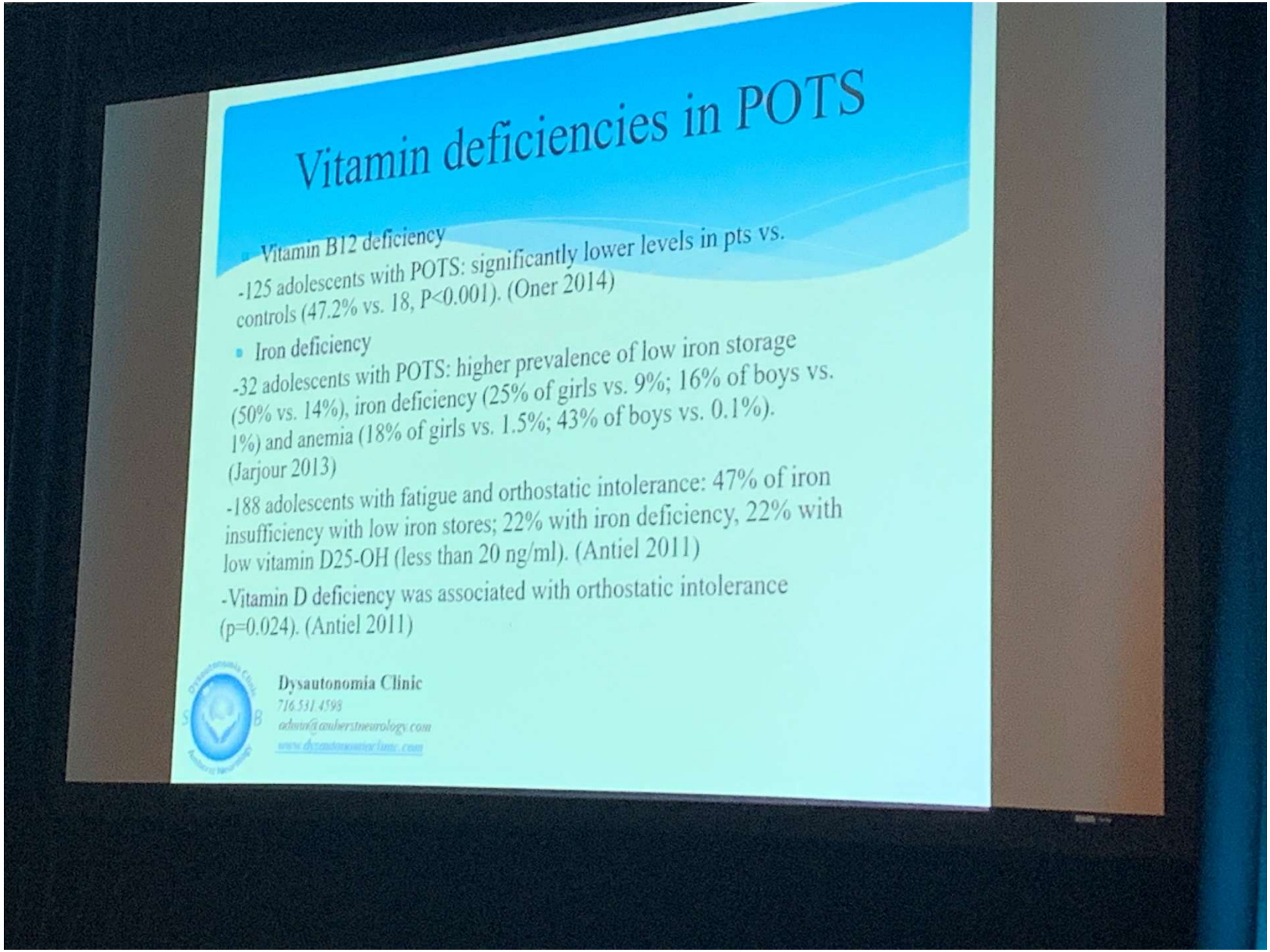
Vitamin deficiencies in POTS
Vitamin B12 deficiency
-125 adolescents with POTS: significantly lower levels in pts vs. controls (47.2% vs. 18, P<0.001). (Oner 2014)
Iron deficiency
-32 adolescents with POTS: higher prevalence of low iron storage (50% vs. 14%), iron deficiency (25% of girls vs. 9%; 16% of boys vs. 1%) and anemia (18% of girls vs. 1.5%; 43% of boys vs. 0.1%). (Jarjour 2013)
-188 adolescents with fatigue and orthostatic intolerance: 47% of iron insufficiency with low iron stores; 22% with iron deficiency, 22% with low vitamin D25-OH (less than 20 ng/ml). (Antiel 2011)
-Vitamin D deficiency was associated with orthostatic intolerance (p=0.024). (Antiel 2011)
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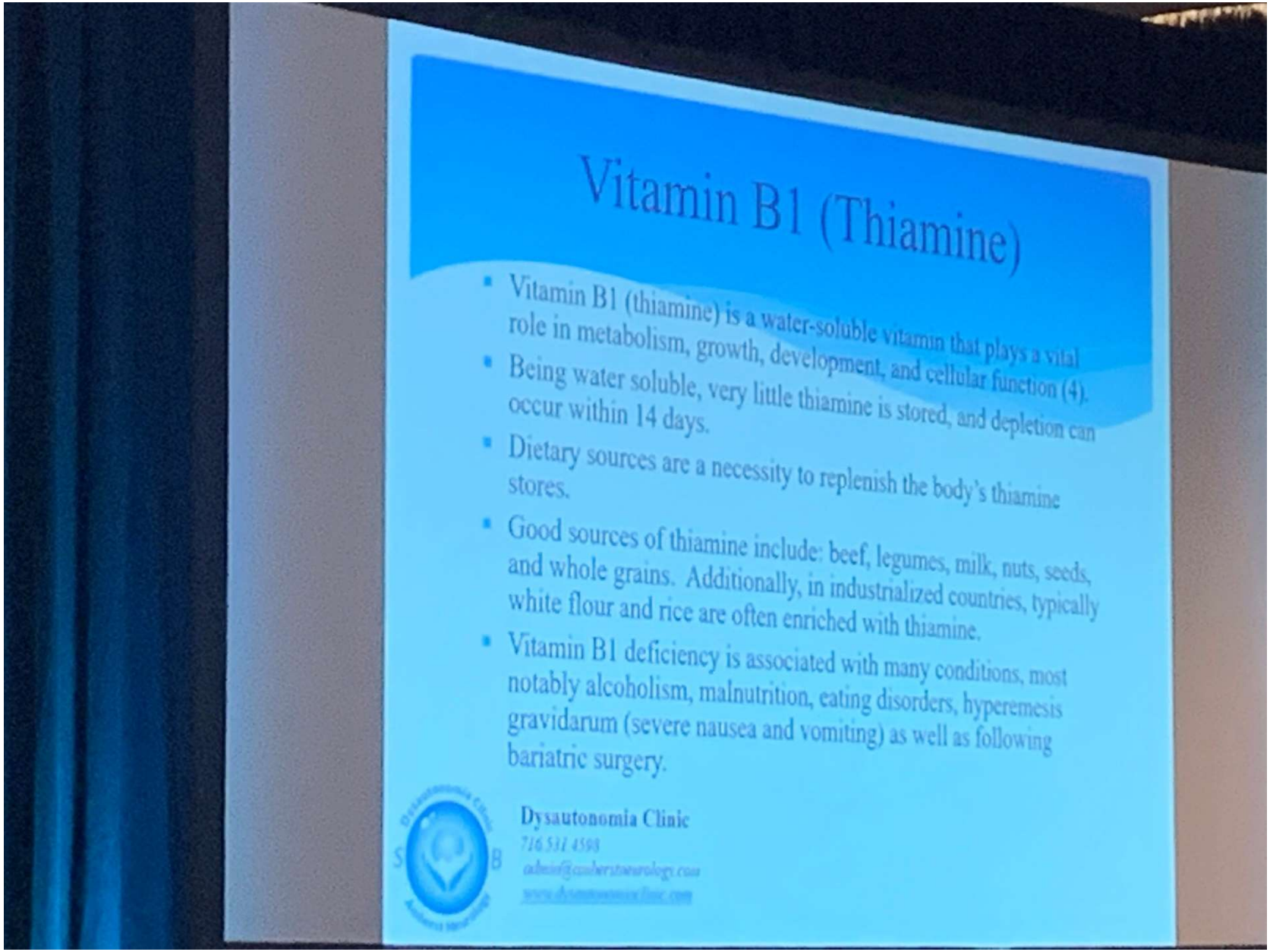
Vitamin B1 (Thiamine)
Vitamin B1 (thiamine) is a water-soluble vitamin that plays a vital role in metabolism, growth, development, and cellular function (4).
Being water soluble, very little thiamine is stored, and depletion can occur within 14 days.
Dietary sources are a necessity to replenish the body's thiamine stores.
Good sources of thiamine include: beef, legumes, milk, nuts, seeds, and whole grains. Additionally, in industrialized countries, typically white flour and rice are often enriched with thiamine.
Vitamin B1 deficiency is associated with many conditions, most notably alcoholism, malnutrition, eating disorders, hyperemesis gravidarum (severe nausea and vomiting) as well as following bariatric surgery.
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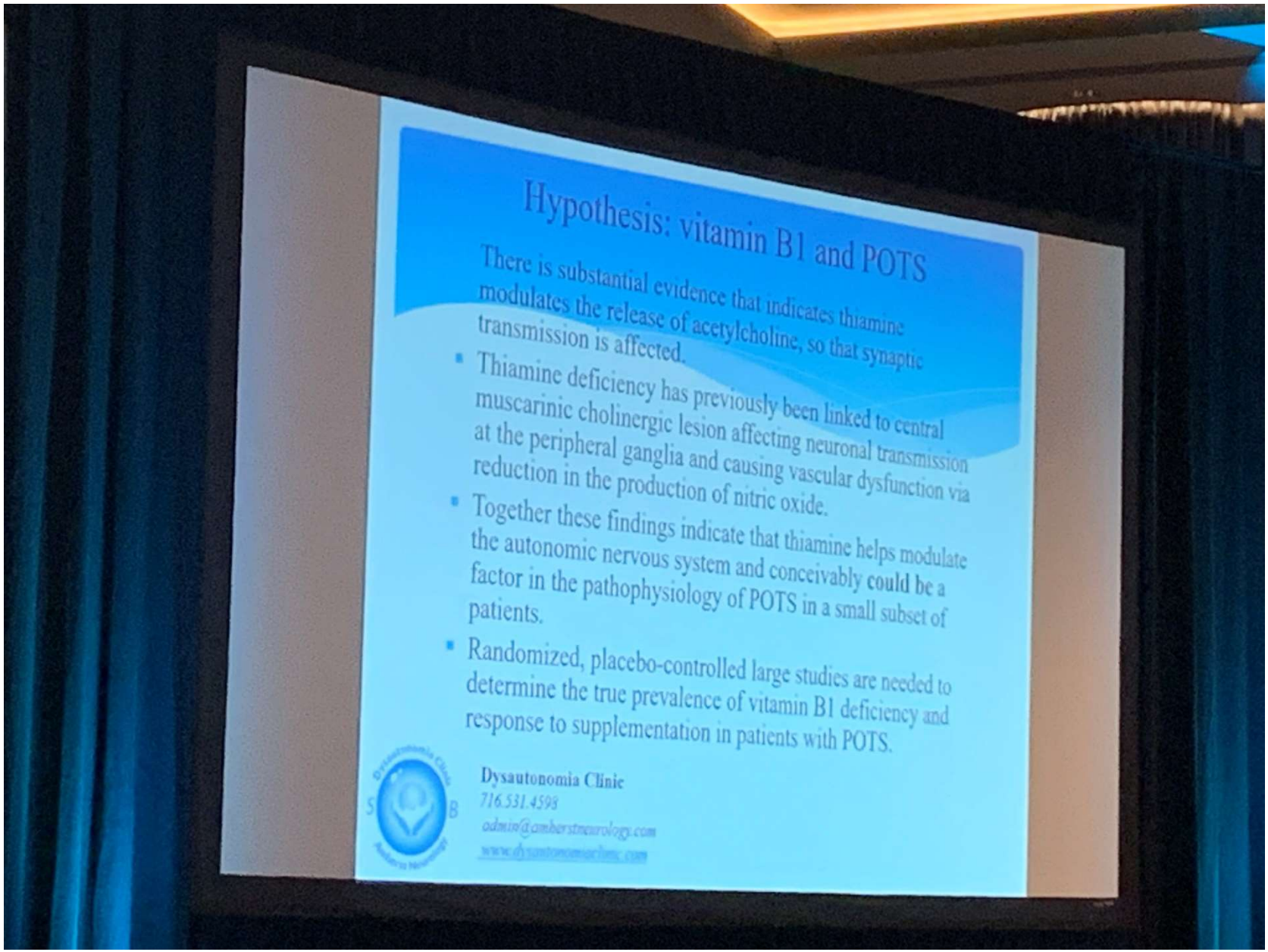
Hypothesis: vitamin B1 and POTS
There is substantial evidence that indicates thiamine modulates the release of acetylcholine, so that synaptic transmission is affected.
Thiamine deficiency has previously been linked to central muscarinic cholinergic lesion affecting neuronal transmission at the peripheral ganglia and causing vascular dysfunction via reduction in the production of nitric oxide.
Together these findings indicate that thiamine helps modulate the autonomic nervous system and conceivably could be a factor in the pathophysiology of POTS in a small subset of patients.
Randomized, placebo-controlled large studies are needed to determine the true prevalence of vitamin B1 deficiency and response to supplementation in patients with POTS.
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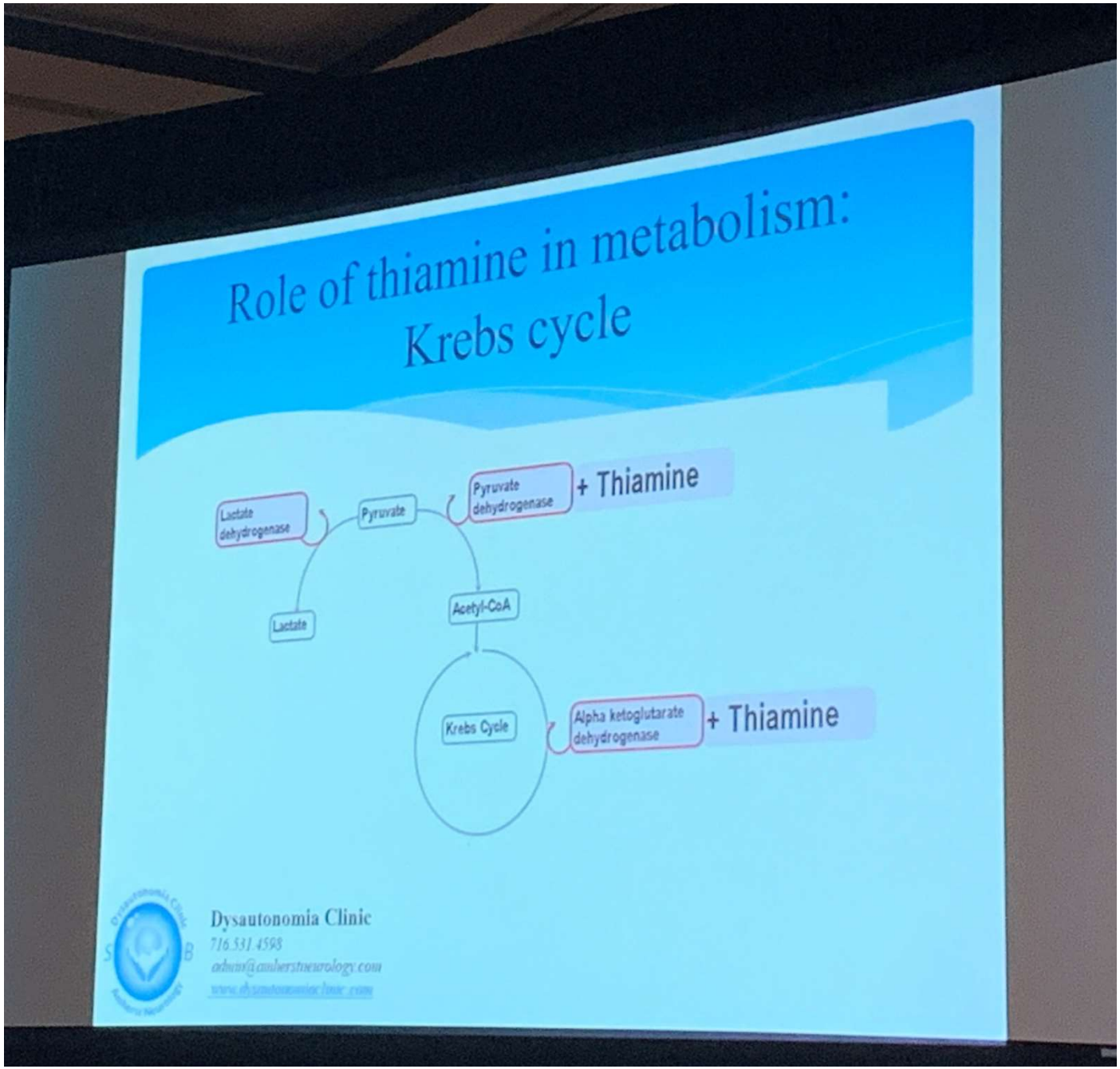
Role of thiamine in metabolism:
Krebs cycle
Lactate dehydrogenase
Pyruvate
Pyruvate dehydrogenase
+ Thiamine
Lactate
Acetyl-CoA
Krebs Cycle
Alpha ketoglutarate dehydrogenase
+ Thiamine
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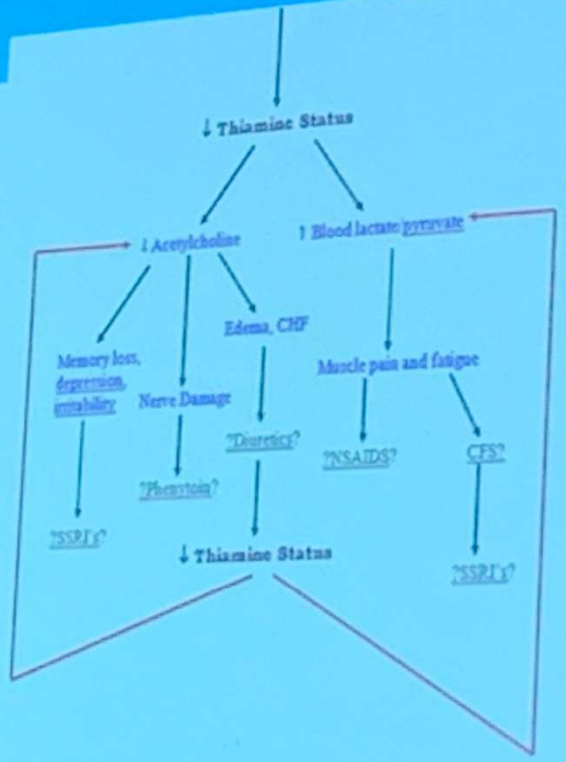
Thiamine deficiency: how



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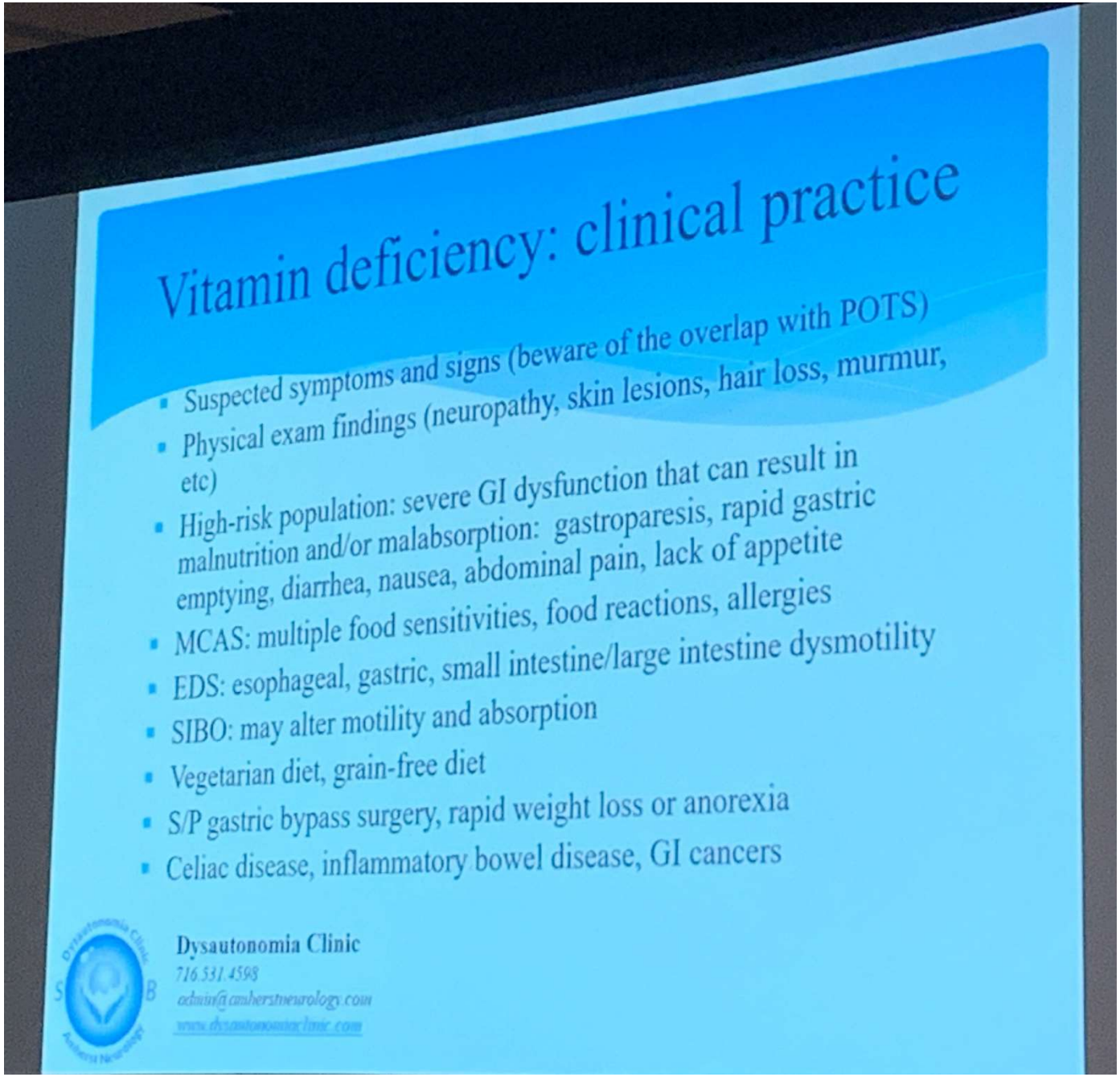
Vitamin deficiency: clinical practice
Suspected symptoms and signs (beware of the overlap with POTS)
Physical exam findings (neuropathy, skin lesions, hair loss, murmur, etc)
High-risk population: severe GI dysfunction that can result in malnutrition and/or malabsorption: gastroparesis, rapid gastric emptying, diarrhea, nausea, abdominal pain, lack of appetite
MCAS: multiple food sensitivities, food reactions, allergies
EDS: esophageal, gastric, small intestine/large intestine dysmotility
SIBO: may alter motility and absorption
Vegetarian diet, grain-free diet
S/P gastric bypass surgery, rapid weight loss or anorexia
Celiac disease, inflammatory bowel disease, GI cancers
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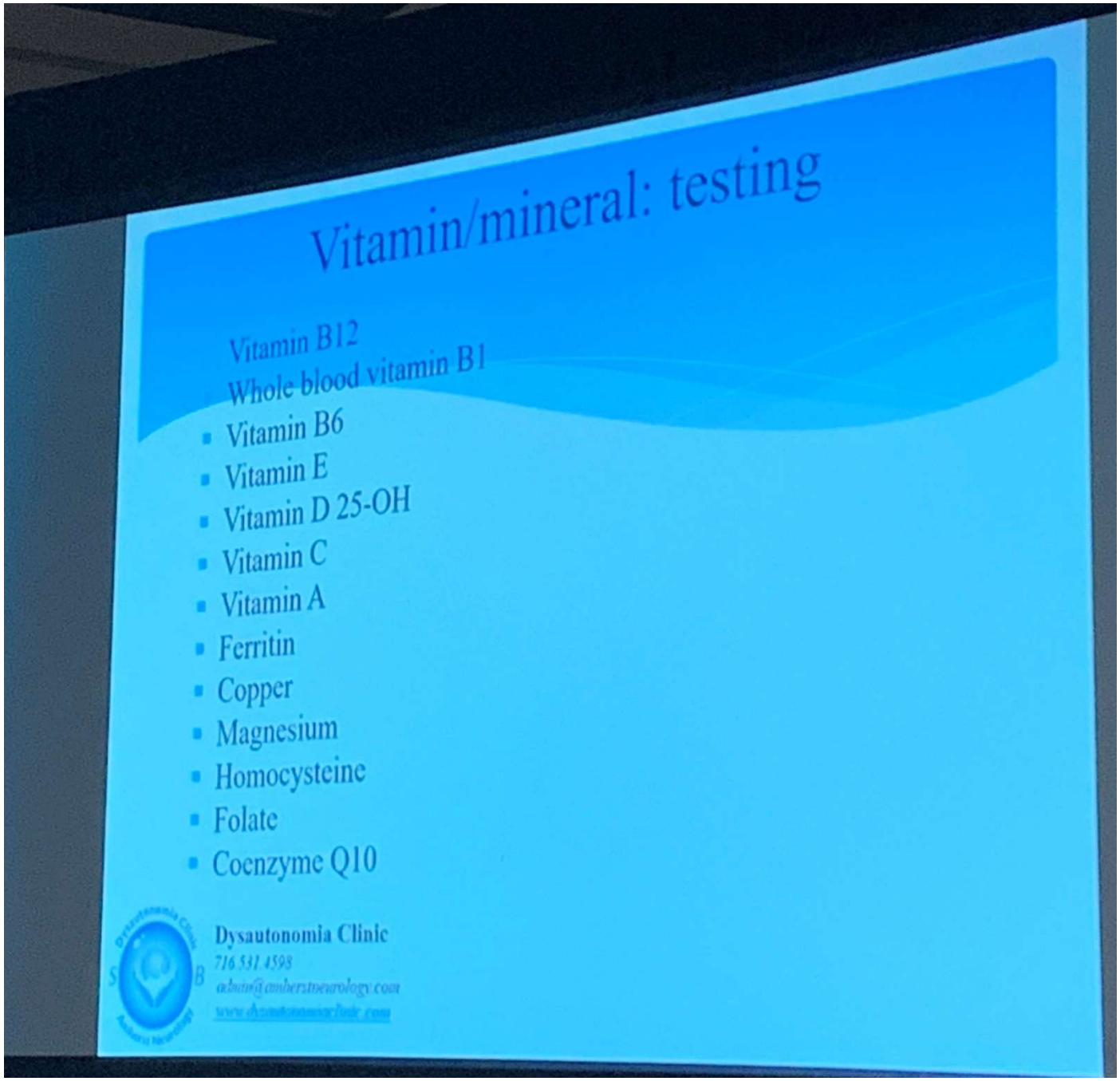
Vitamin/mineral: testing
Vitamin B12
Whole blood vitamin B1
Vitamin B6
Vitamin E
Vitamin D 25-OH
Vitamin C
Vitamin A
Ferritin
Copper
Magnesium
Homocysteine
Folate
Coenzyme Q10
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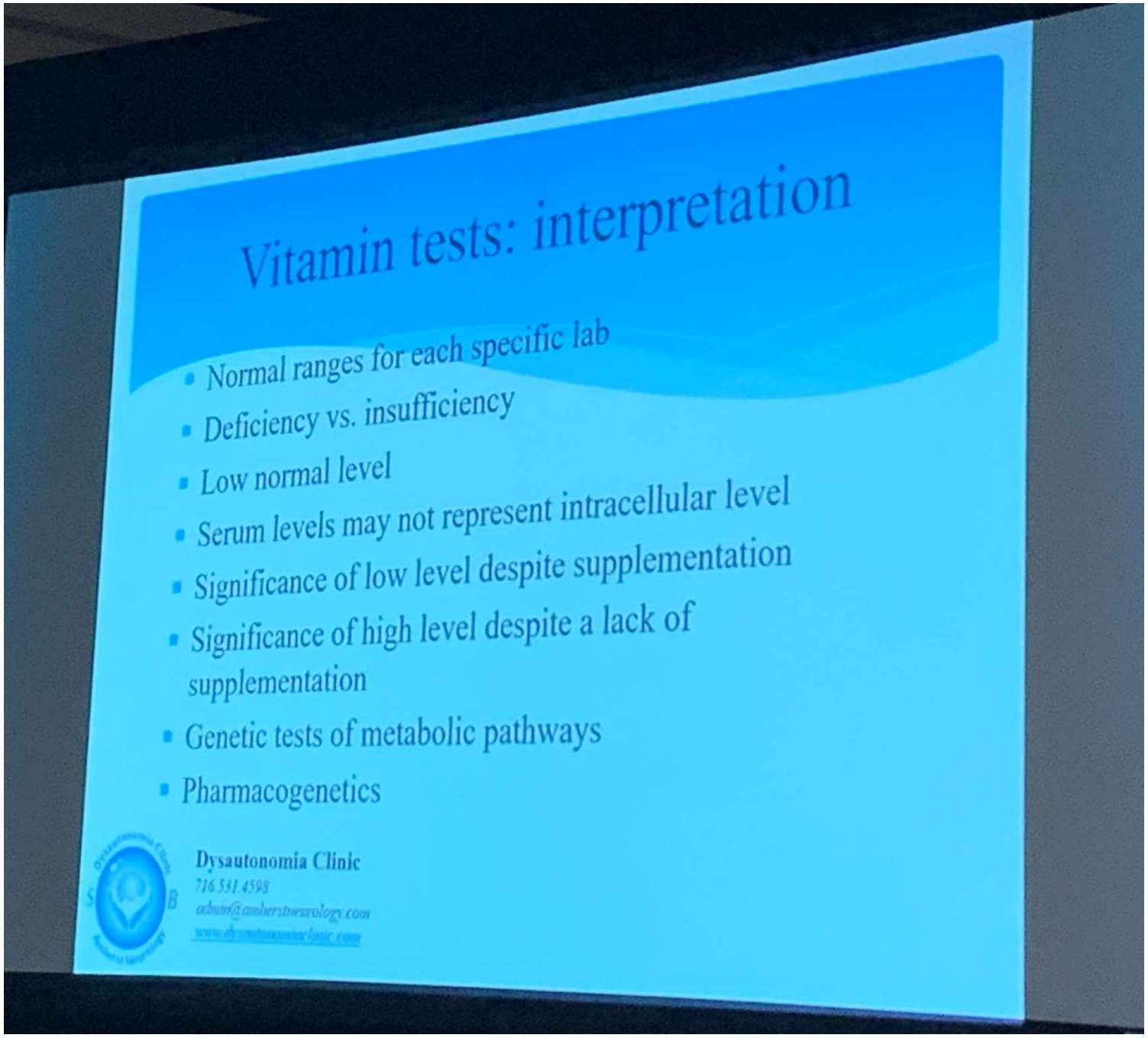
Vitamin tests: interpretation
Normal ranges for each specific lab
Deficiency vs. insufficiency
Low normal level
Serum levels may not represent intracellular level
Significance of low level despite supplementation
Significance of high level despite a lack of supplementation
Genetic tests of metabolic pathways
Pharmacogenetics
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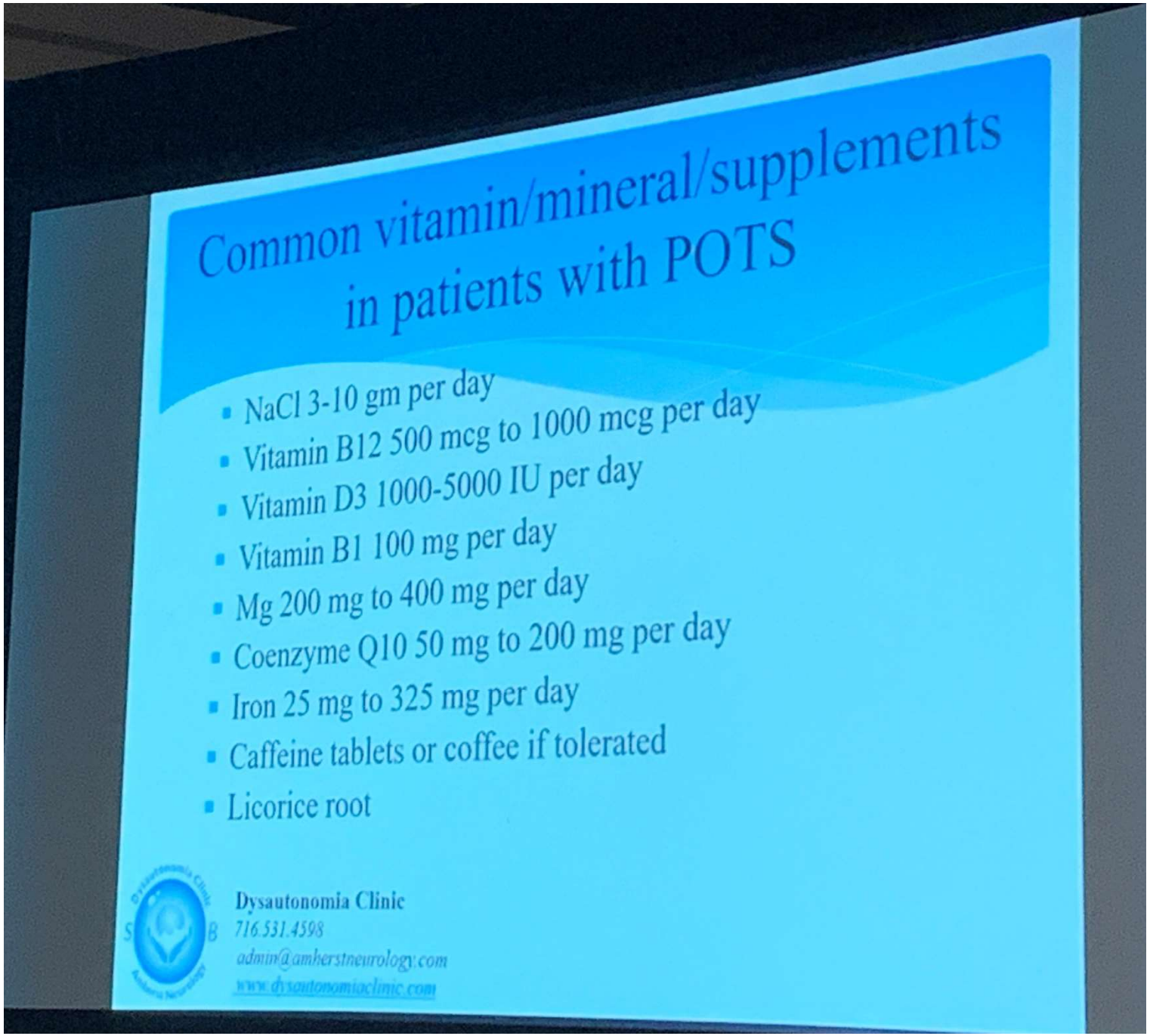
Common vitamin/mineral/supplements in patients with POTS
NaCl 3-10 gm per day
Vitamin B12 500 mcg to 1000 mcg per day
Vitamin D3 1000-5000 IU per day
Vitamin B1 100 mg per day
Mg 200 mg to 400 mg per day
Coenzyme Q10 50 mg to 200 mg per day
Iron 25 mg to 325 mg per day
Caffeine tablets or coffee if tolerated
Licorice root
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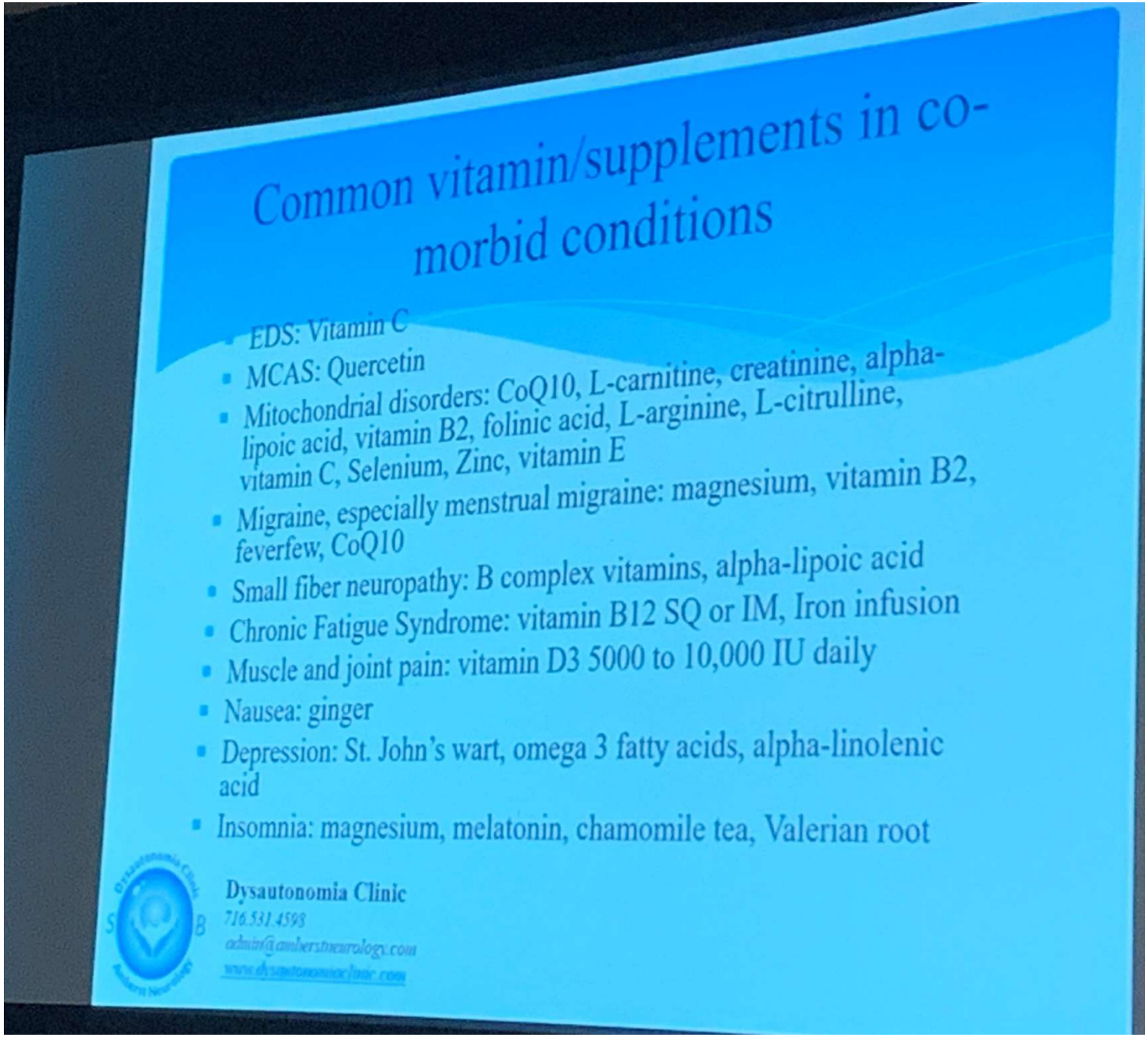
Common vitamin/supplements in co-morbid conditions
EDS: Vitamin C
MCAS: Quercetin
Mitochondrial disorders: CoQ10, L-carnitine, creatinine, alpha-lipoic acid, vitamin B2, folinic acid, L-arginine, L-citrulline, vitamin C, Selenium, Zinc, vitamin E
Migraine, especially menstrual migraine: magnesium, vitamin B2, feverfew, CoQ10
Small fiber neuropathy: B complex vitamins, alpha-lipoic acid
Chronic Fatigue Syndrome: vitamin B12 SQ or IM, Iron infusion
Muscle and joint pain: vitamin D3 5000 to 10,000 IU daily
Nausea: ginger
Depression: St. John's wart, omega 3 fatty acids, alpha-linolenic acid
Insomnia: magnesium, melatonin, chamomile tea, Valerian root
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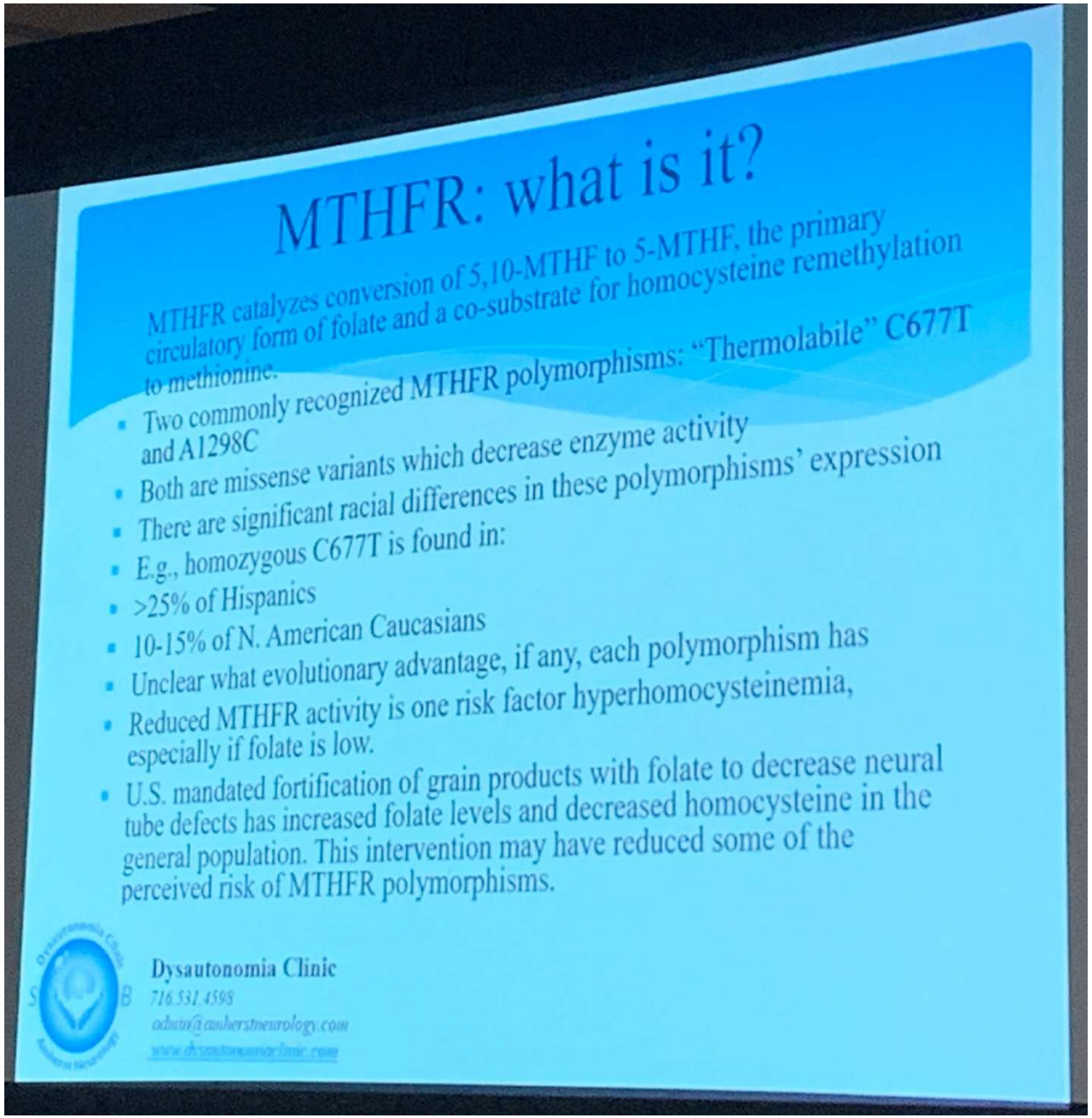
MTHFR: what is it?
MTHFR catalyzes conversion of 5,10-MTHF to 5-MTHF, the primary circulatory form of folate and a co-substrate for homocysteine remethylation to methionine.
Two commonly recognized MTHFR polymorphisms: "Thermolabile" C677T and A1298C
Both are missense variants which decrease enzyme activity
There are significant racial differences in these polymorphisms' expression
E.g., homozygous C677T is found in:
>25% of Hispanics
10-15% of N. American Caucasians
Unclear what evolutionary advantage, if any, each polymorphism has
Reduced MTHFR activity is one risk factor hyperhomocysteinemia, especially if folate is low.
U.S. mandated fortification of grain products with folate to decrease neural tube defects has increased folate levels and decreased homocysteine in the general population. This intervention may have reduced some of the perceived risk of MTHFR polymorphisms.
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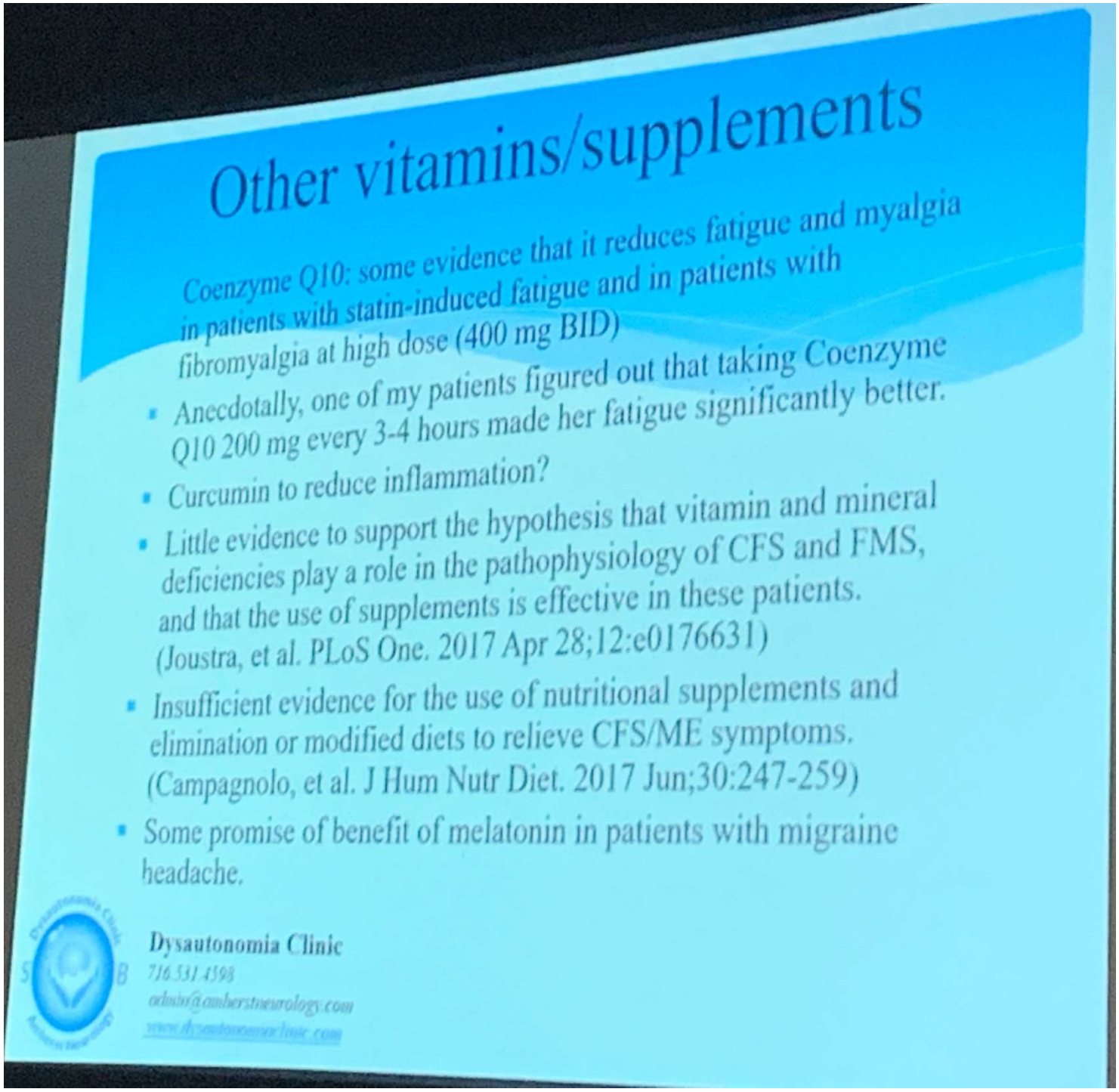
Other vitamins/supplements
Coenzyme Q10: some evidence that it reduces fatigue and myalgia in patients with statin-induced fatigue and in patients with fibromyalgia at high dose (400 mg BID)
Anecdotally, one of my patients figured out that taking Coenzyme Q10 200 mg every 3-4 hours made her fatigue significantly better.
Curcumin to reduce inflammation?
Little evidence to support the hypothesis that vitamin and mineral deficiencies play a role in the pathophysiology of CFS and FMS, and that the use of supplements is effective in these patients. (Joustra, et al. PLoS One. 2017 Apr 28;12:e0176631)
Insufficient evidence for the use of nutritional supplements and elimination or modified diets to relieve CFS/ME symptoms. (Campagnolo, et al. J Hum Nutr Diet. 2017 Jun;30:247-259)
Some promise of benefit of melatonin in patients with migraine headache.
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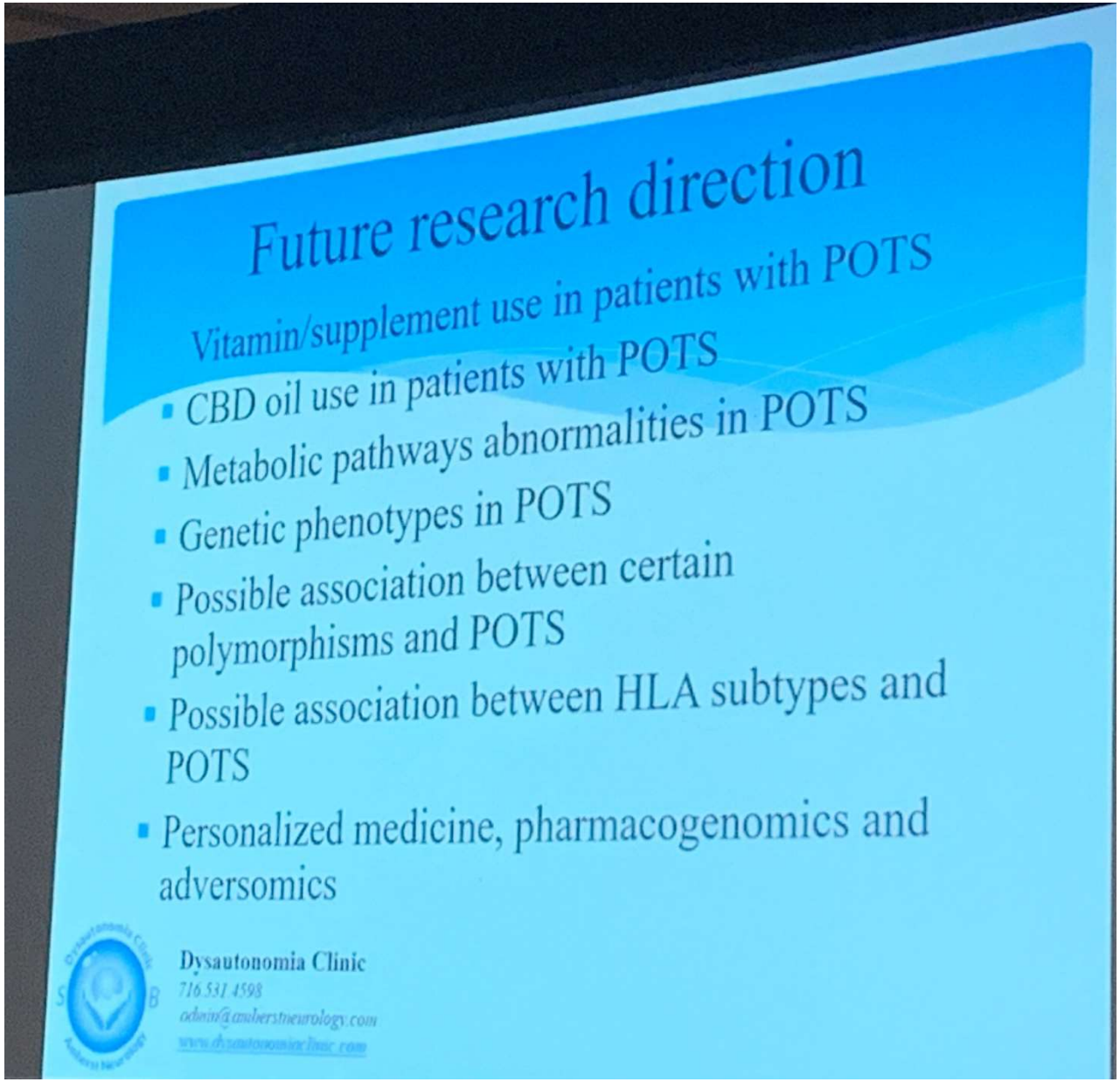
Future research direction
Vitamin/supplement use in patients with POTS
CBD oil use in patients with POTS
Metabolic pathways abnormalities in POTS
Genetic phenotypes in POTS
Possible association between certain polymorphisms and POTS
Possible association between HLA subtypes and POTS
Personalized medicine, pharmacogenomics and adversomics
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Overview of Orthostatic Disorders – Dr. Julian Stewart

- To respond to dizziness, clench glutes
- 25-50% POTS patients experience hyperventilation

Definitions

Orthostatic Intolerance

The presence of symptoms - lightheadedness, dizziness, nausea, breathlessness, body warmth, sweating, vision change, pallor, hypotension, excessive tachycardia, H.A.

linked specifically to assuming or maintaining upright posture, and symptoms and signs must abate once supine

Acute/Episodic Orthostatic Intolerance: Recurrent or periodic

– Postural vasovagal syncope,

Initial Orthostatic Hypotension (IOH)

Chronic Orthostatic Intolerance: Orthostatic Intolerance on a day-to-day basis for at least 3 months

Orthostatic Hypotension (OH)

Postural Tachycardia Syndrome (POTS)

Chronic Bed Rest Syndrome*

Caloric Restriction Syndrome*

Postural Hyperventilation*

"OI alone" Orthostatic Cerebral Hypoperfusion Syndrome (OCHOS)

*=less often considered OI

Specific Forms of OI

- Initial Orthostatic Hypotension (IOH)
- Orthostatic Hypotension (OH)
- Postural Vasovagal Syncope (VVS)

  → DOH
- Postural Tachycardia Syndrome (POTS)
- Orthostatic Cerebral Hypoperfusion Syndrome
- Chronic Bed Rest Syndrome/Microgravity Deconditioning
- Hypocaloric Weight Loss Syndrome
- Postural Hyperpnea

Orthostatic Cerebral Hypoperfusion Syndrome => Impaired Cerebral Autoregulation

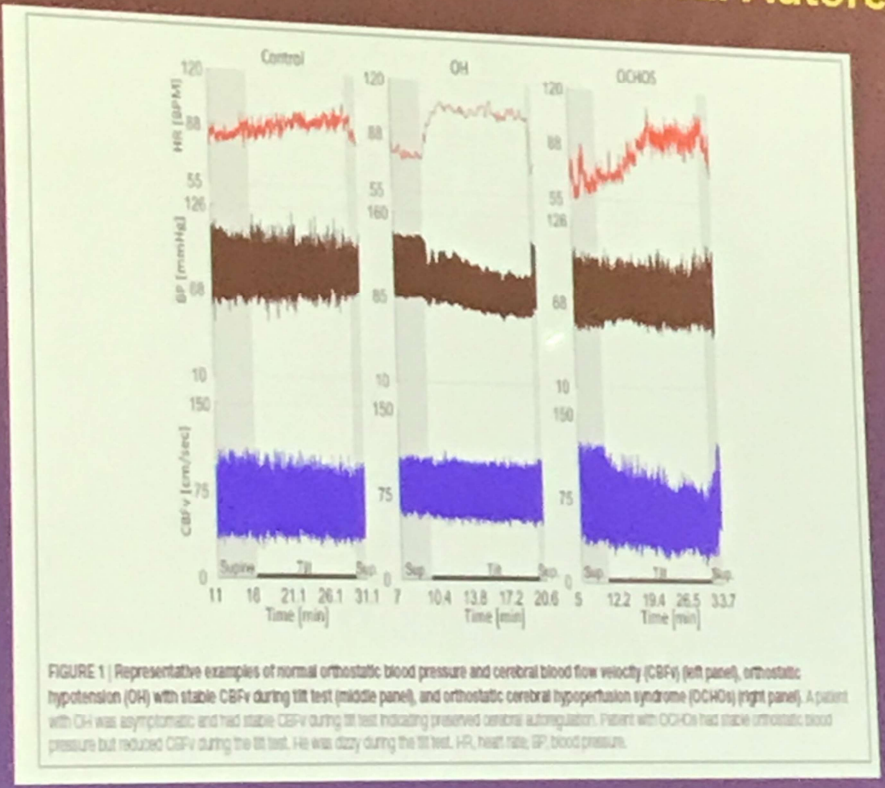


FIGURE 1 | Representative examples of normal orthostatic blood pressure and cerebral blood flow velocity (CBFv) (left panel), orthostatic hypotension (OH) with stable CBFv during tilt test (middle panel), and orthostatic cerebral hypoperfusion syndrome (OCHOs) (right panel). A patient with OH was asymptomatic and had stable CBFv during tilt test indicating preserved cerebral autoregulation. Patient with OCHOs had stable orthostatic blood pressure but reduced CBFv during the tilt test. He was dizzy during the tilt test. HR, heart rate; BP, blood pressure.

Novak P (2016) Orthostatic Cerebral Hypoperfusion Syndrome. Front. Aging Neurosci. 8:22

A Valid Definition

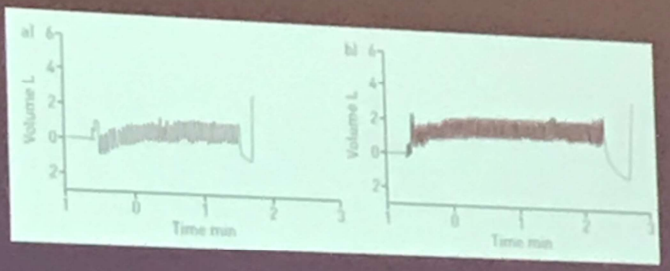
Hyperventilation (AKA overbreathing) occurs **when the rate or tidal volume of breathing eliminates more carbon dioxide than the body can produce.** This leads to hypocapnia, a reduced concentration of carbon dioxide dissolved in the blood. The blood becomes alkaline, a condition called respiratory alkalosis.

Modified from Wikipedia

Hyperventilation Syndrome and Dysfunctional Breathing

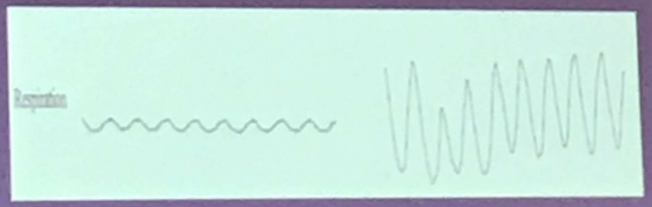
Examples show tachypnea with minimal hypernea in the "Hyperventilation Syndrome"

- Tachypnea in HV Syndrome



- HV is often considered a form of **"Dysfunctional Breathing"** or a **"Breathing Pattern Disorder"** result in dyspnea and other symptoms in the absence of or in excess of physiological respiratory or cardiac disease. This is often treated with **Breathing Exercises** (U.K. and Commonwealth) with unclear efficacy – Cochrane Review.

- Hyperpnea in POTS?



Consequences of Hypocapnia

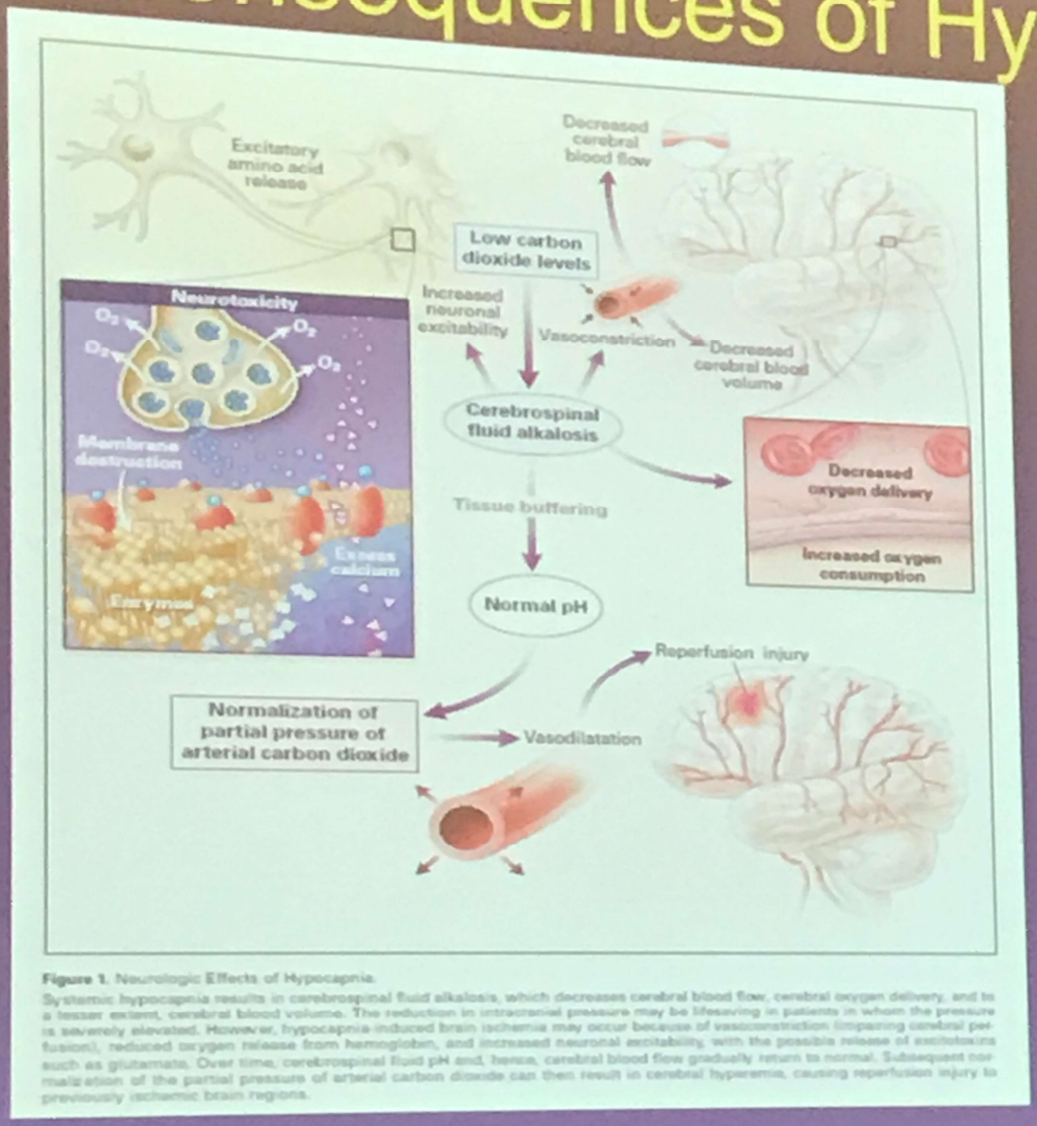


Figure 1. Neurologic Effects of Hypocapnia.

Systemic hypocapnia results in cerebrospinal fluid alkalosis, which decreases cerebral blood flow, cerebral oxygen delivery, and to a lesser extent, cerebral blood volume. The reduction in intracranial pressure may be lifesaving in patients in whom the pressure is severely elevated. However, hypocapnia-induced brain ischemia may occur because of vasoconstriction (impairing cerebral perfusion), reduced oxygen release from hemoglobin, and increased neuronal excitability, with the possible release of excitotoxins such as glutamate. Over time, cerebrospinal fluid pH and, hence, cerebral blood flow gradually return to normal. Subsequent normalization of the partial pressure of arterial carbon dioxide can then result in cerebral hyperemia, causing reperfusion injury to previously ischemic brain regions.

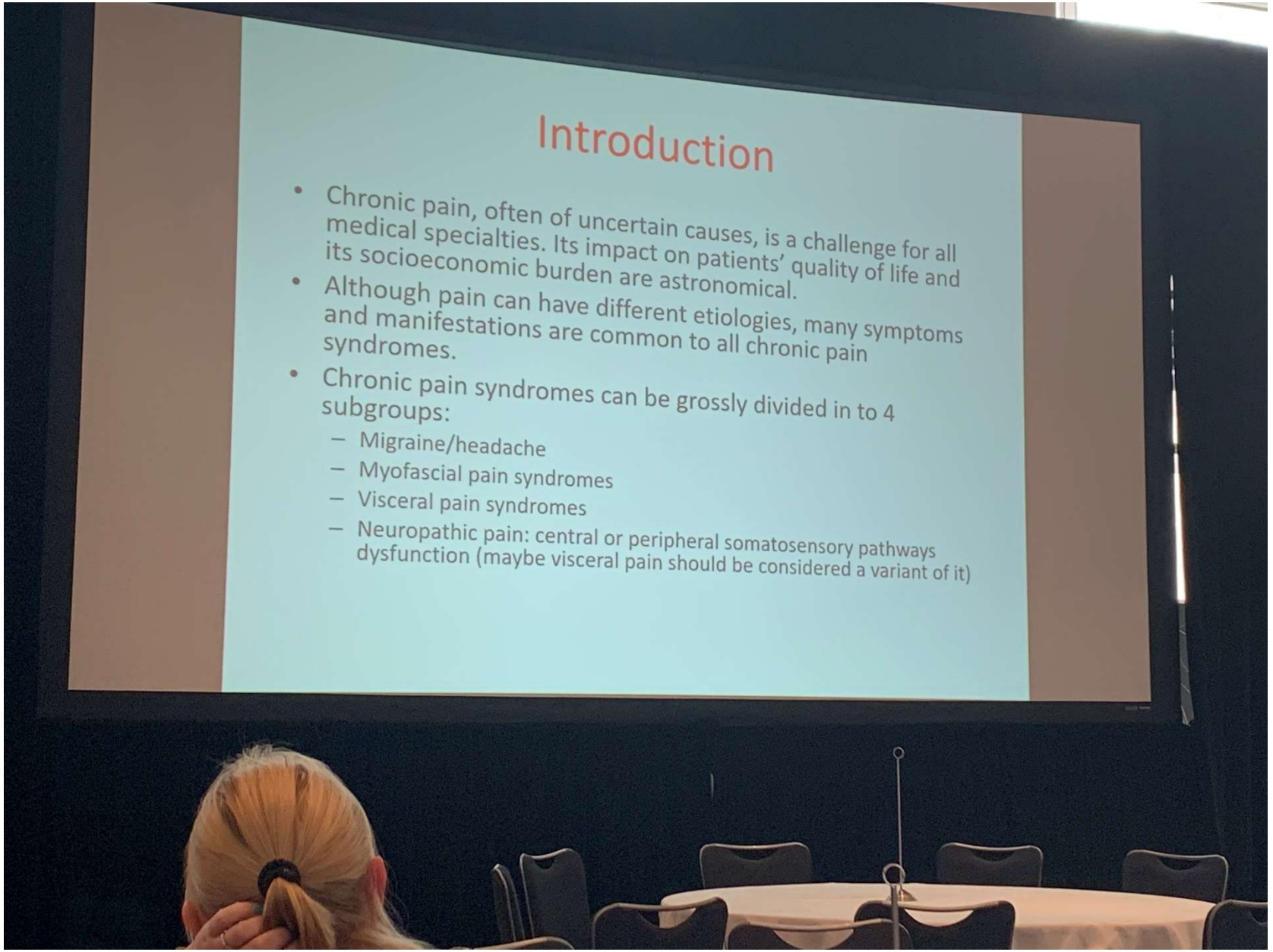
Cerebral and coronary arterial vasoconstriction – cerebral and myocardial ischemia
->lightheaded, chest pain, cognitive loss, Ultimate Brainstem anoxia

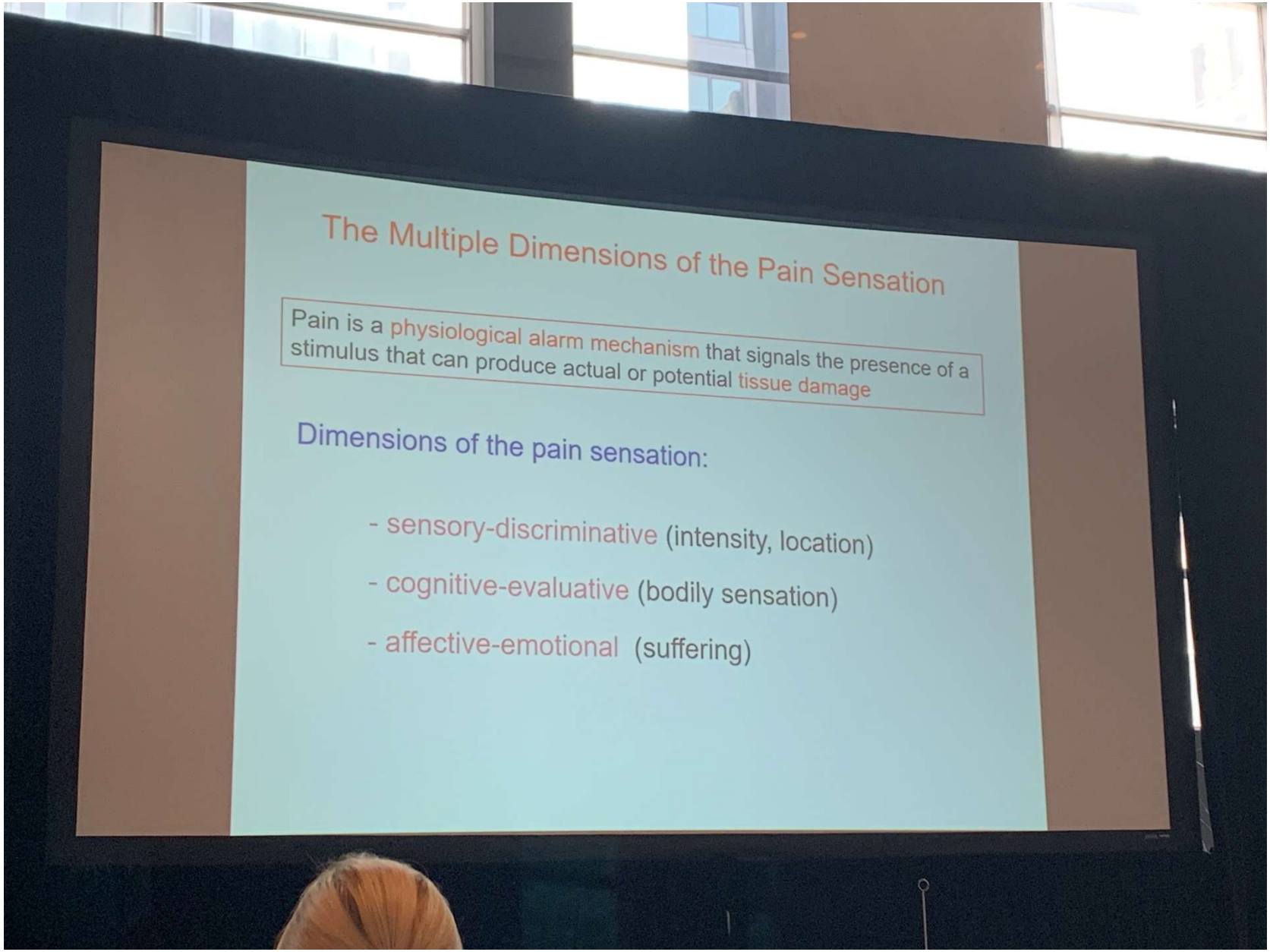
Increased metabolic demand
-> Fatigue, Exercise Intolerance

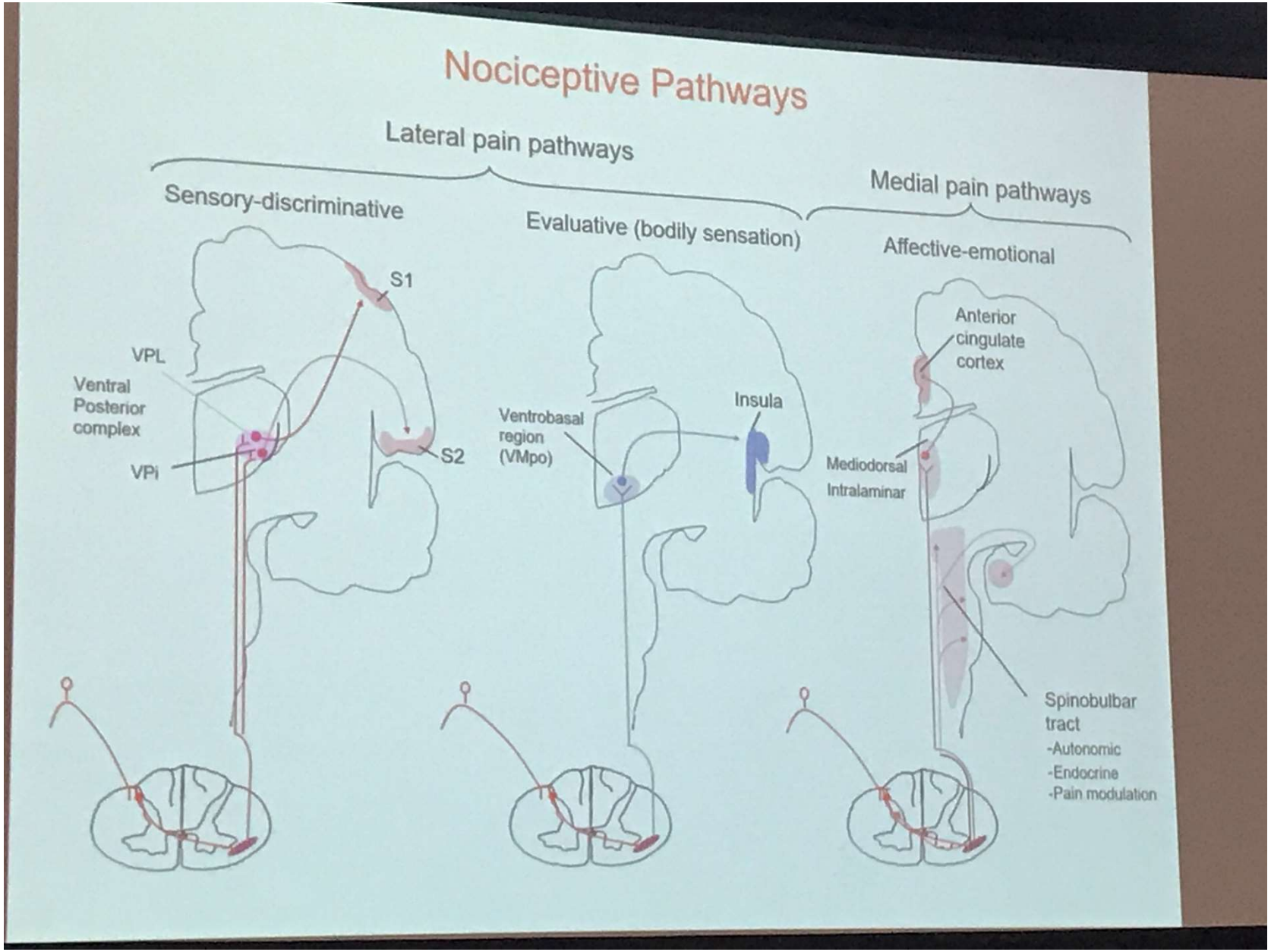
Paresthesias and Numbness

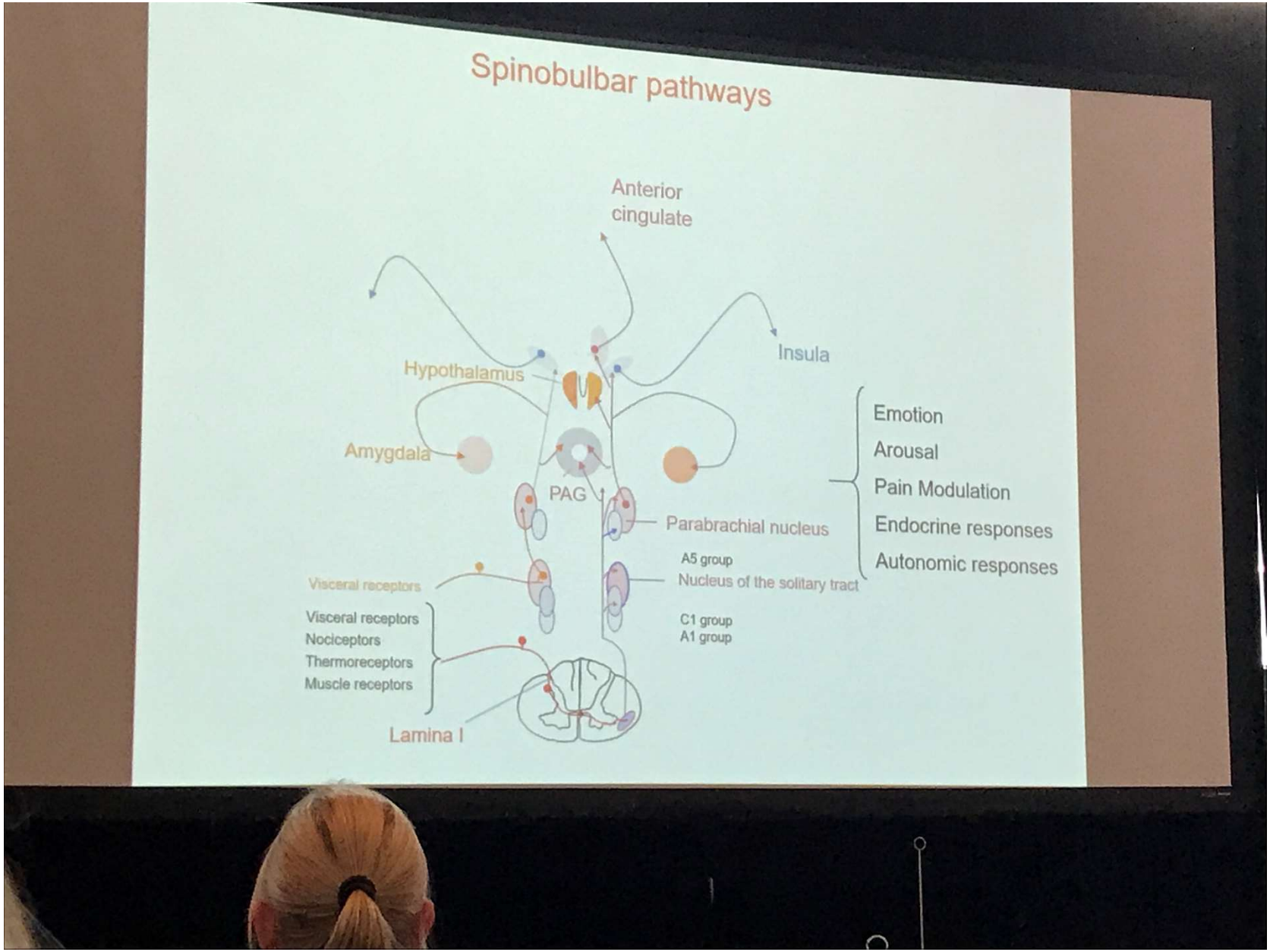
Nausea, reduced gastrointestinal motility

Managing CRPS, Fibromyalgia & Chronic Pain – Dr. Paola Sandroni


Introduction
Chronic pain, often of uncertain causes, is a challenge for all medical specialties. Its impact on patients' quality of life and its socioeconomic burden are astronomical.
Although pain can have different etiologies, many symptoms and manifestations are common to all chronic pain syndromes.
Chronic pain syndromes can be grossly divided in to 4 subgroups:
Migraine/headache
Myofascial pain syndromes
Visceral pain syndromes
Neuropathic pain: central or peripheral somatosensory pathways dysfunction (maybe visceral pain should be considered a variant of it)


The Multiple Dimensions of the Pain Sensation
Pain is a physiological alarm mechanism that signals the presence of a stimulus that can produce actual or potential tissue damage
Dimensions of the pain sensation:
- sensory-discriminative (intensity, location)
- cognitive-evaluative (bodily sensation)
- affective-emotional (suffering)

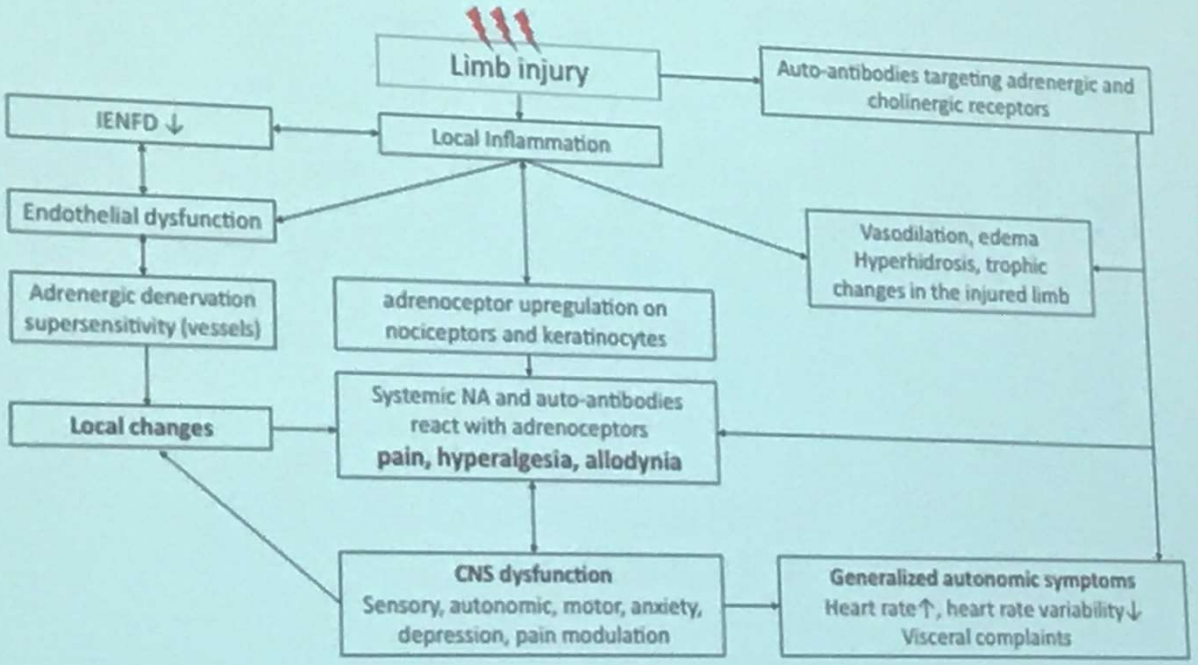

Nociceptive Pathways
Lateral pain pathways
Medial pain pathways
Sensory-discriminative
Evaluative (bodily sensation)
Affective-emotional
S1
VPL
Ventral
Posterior
complex
VPi
S2
Ventrobasal
region
(VMpo)
Insula
Anterior
cingulate
cortex
Mediodorsal
Intralaminar
Spinobulbar
tract
-Autonomic
-Endocrine
-Pain modulation


Spinobulbar pathways
Anterior cingulate
Insula
Hypothalamus
Amygdala
PAG
Parabrachial nucleus
A5 group
Nucleus of the solitary tract
C1 group
A1 group
Visceral receptors
Visceral receptors
Nociceptors
Thermoreceptors
Muscle receptors
Lamina I
Emotion
Arousal
Pain Modulation
Endocrine responses
Autonomic responses

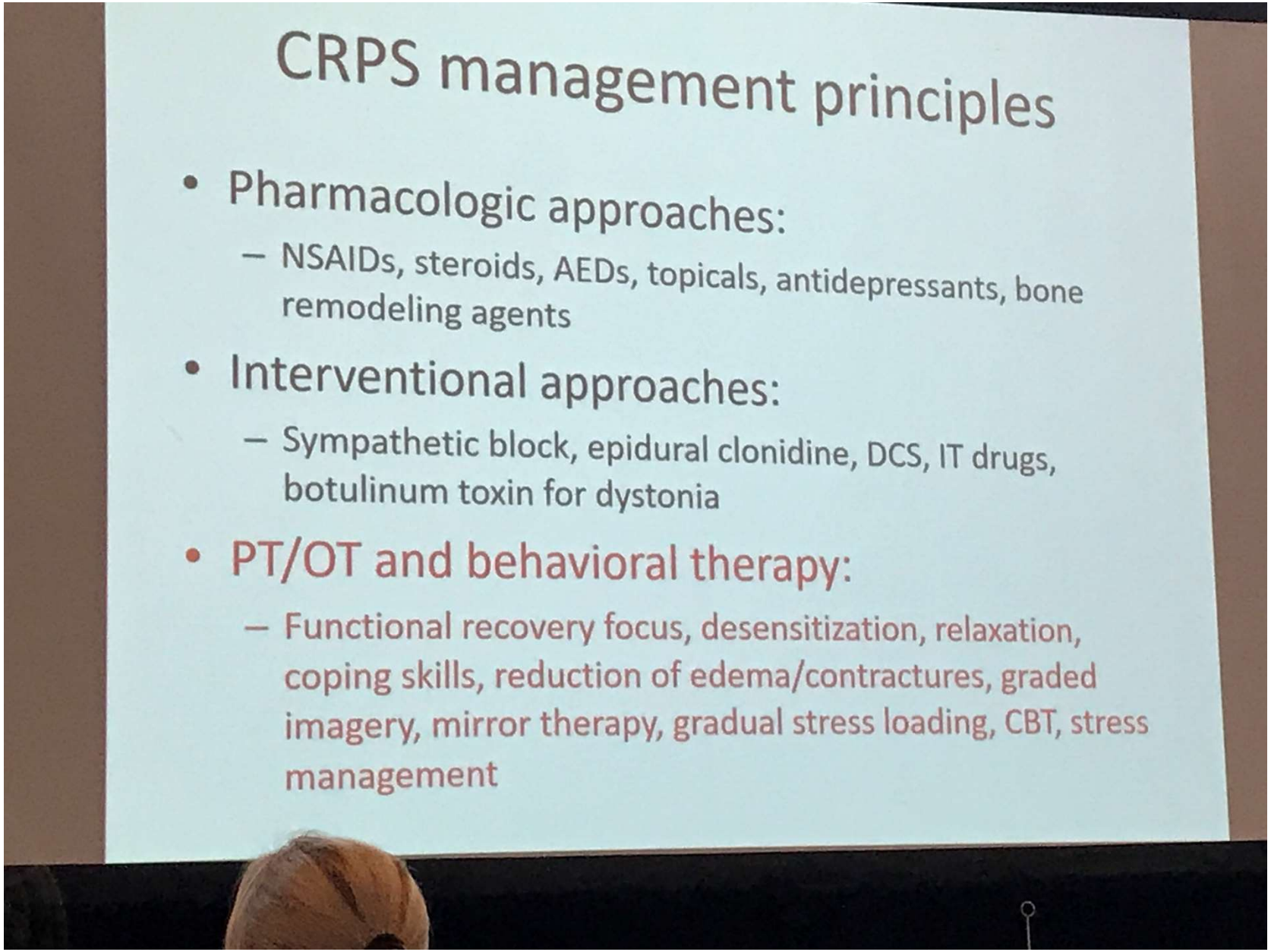
Peripheral Sensitization of Nociceptors

- Spontaneous activity of normally "silent" C- and Aδ nociceptors
- Ectopic firing at the level of the DRG
- Uninjured nerves participate in pain signaling
- Increased activity and / or expression of
  - $Na_v1.7$, $Na_v1.8$. $Na_v1.9$, $Na_v1.3$
  - TRPV1, TRPV4, TRPM8
  - α_1 and α_2 adrenoreceptors
- Important role of inflammation
  - 5-HT, ATP, PgE2, bradykinin
  - TNF-α
  - IL-6
  - NGF

CRPS



Knudsen et al. 2019


CRPS management principles
• Pharmacologic approaches:
– NSAIDs, steroids, AEDs, topicals, antidepressants, bone remodeling agents
• Interventional approaches:
– Sympathetic block, epidural clonidine, DCS, IT drugs, botulinum toxin for dystonia
• PT/OT and behavioral therapy:
– Functional recovery focus, desensitization, relaxation, coping skills, reduction of edema/contractures, graded imagery, mirror therapy, gradual stress loading, CBT, stress management

Fibromyalgia 2019 criteria

New Clinical Fibromyalgia Diagnostic Criteria – Part 1.

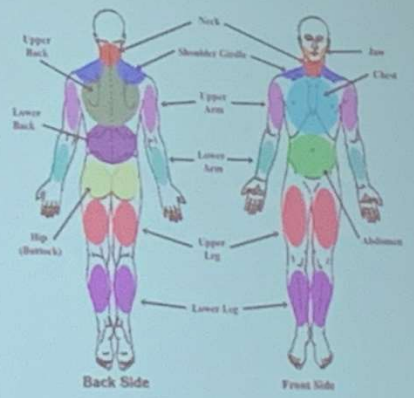
To answer the following questions, patients should take into consideration

- how you felt the **past week**.
- while taking your current therapies and treatments, and
- exclude your pain or symptoms from other known illnesses such as arthritis, Lupus, Sjogren's, etc.

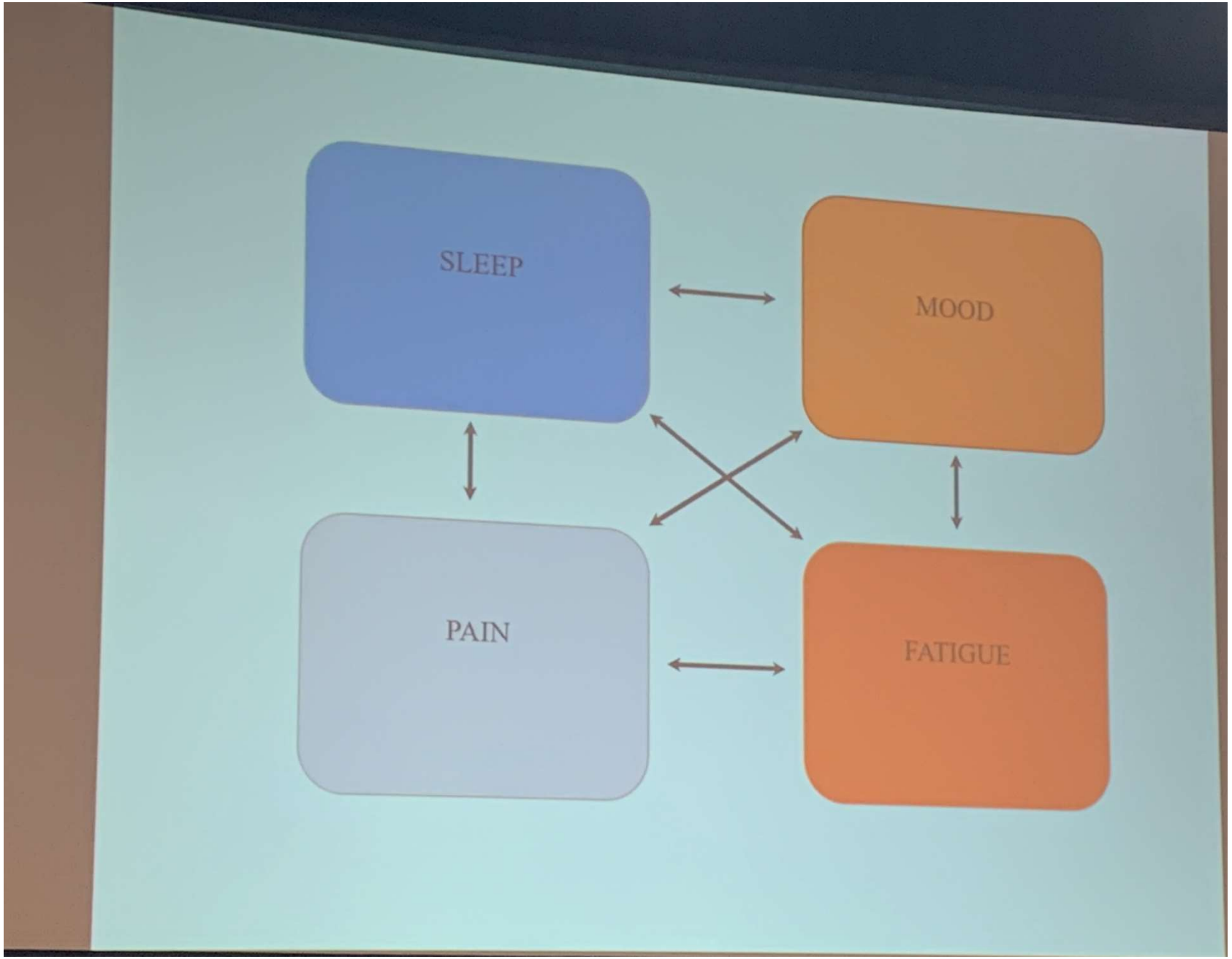
Check each area you have felt pain in over the past week.

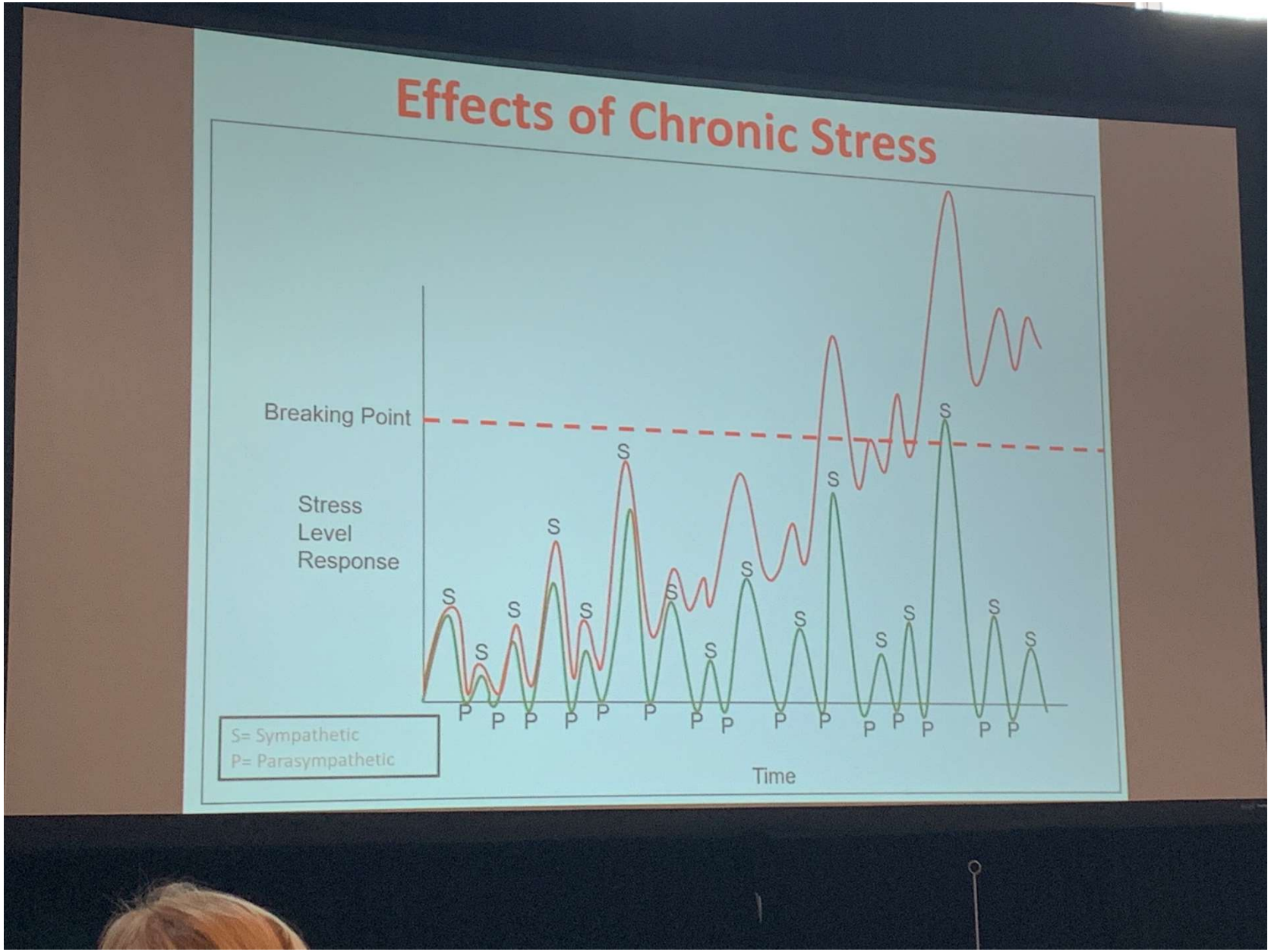
- ☐ Shoulder girdle, left
- ☐ Shoulder girdle, right
- ☐ Upper arm, left
- ☐ Upper arm, right
- ☐ Lower arm, left
- ☐ Lower arm, right
- ☐ Hip (buttock) left
- ☐ Hip (buttock) right
- ☐ Upper leg left
- ☐ Upper leg right
- ☐ Lower leg left
- ☐ Lower leg right
- ☐ Jaw left
- ☐ Jaw right
- ☐ Chest
- ☐ Abdomen
- ☐ Neck
- ☐ Upper back
- ☐ Lower back
- ☐ None of these areas

Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.



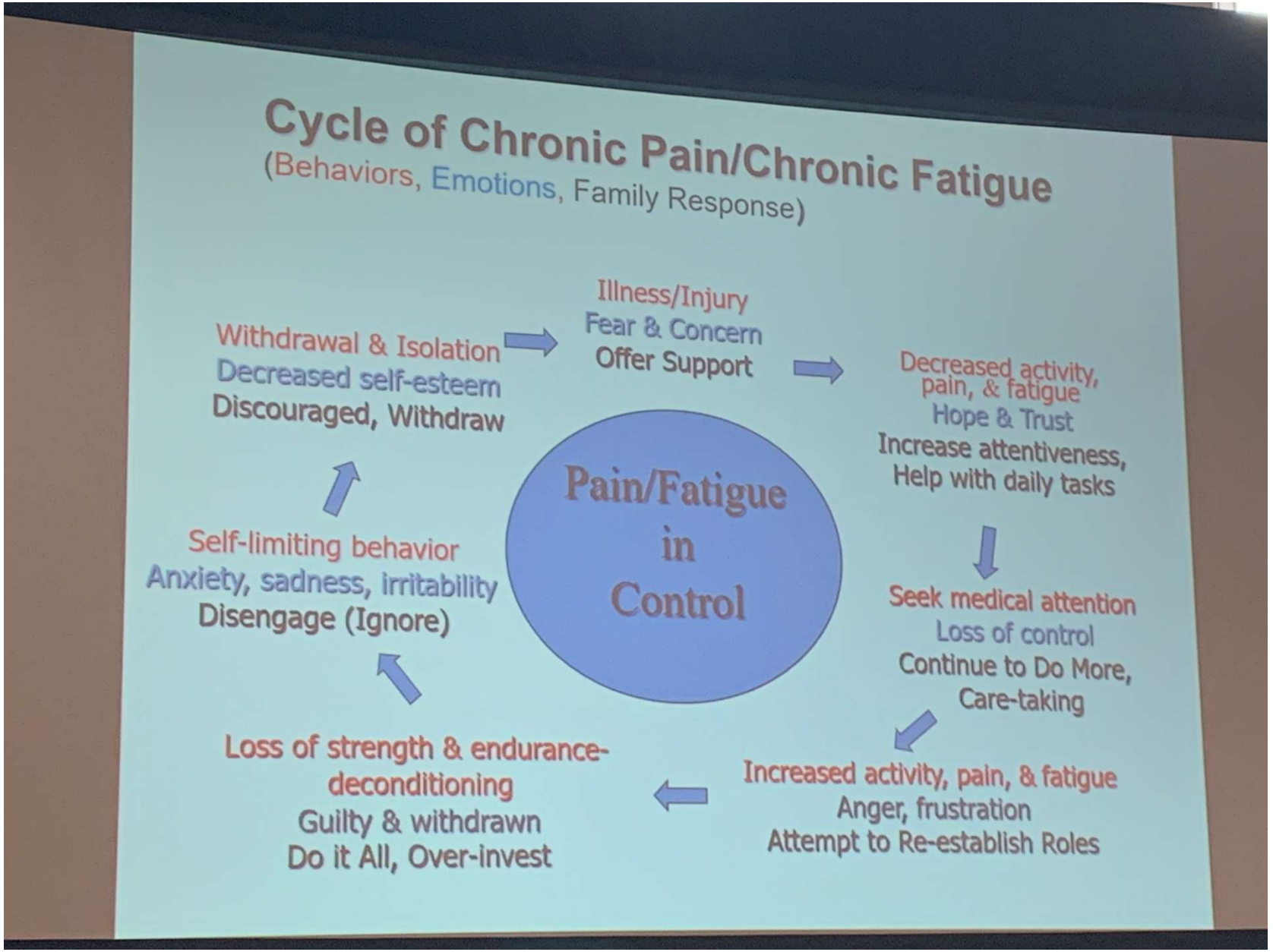
Count up the number of areas checked and enter your Widespread Pain Index or WPI score score here _____.


SLEEP
MOOD
PAIN
FATIGUE


Effects of Chronic Stress
Breaking Point
Stress Level Response
S= Sympathetic
P= Parasympathetic
Time

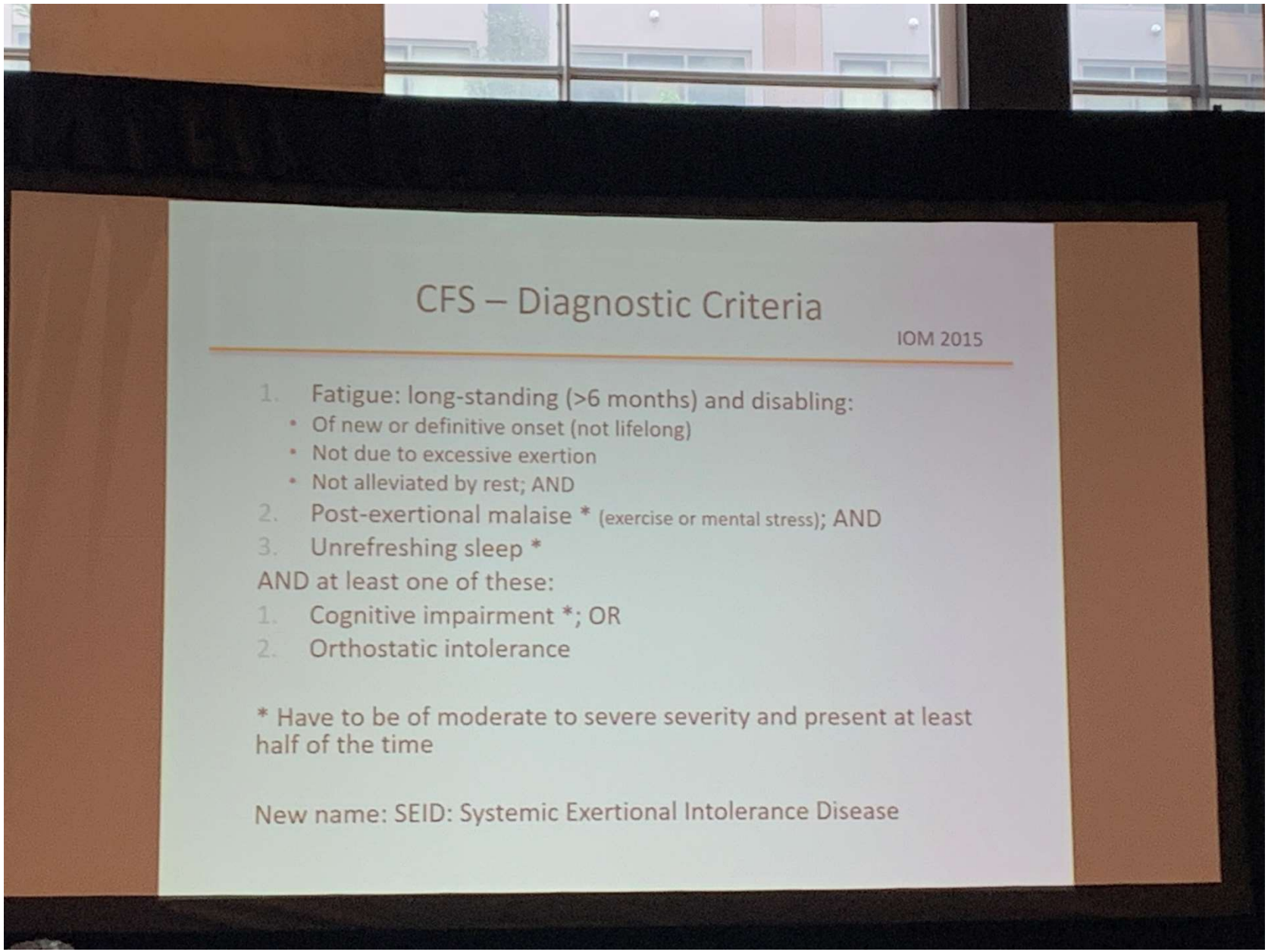
Stress Signals

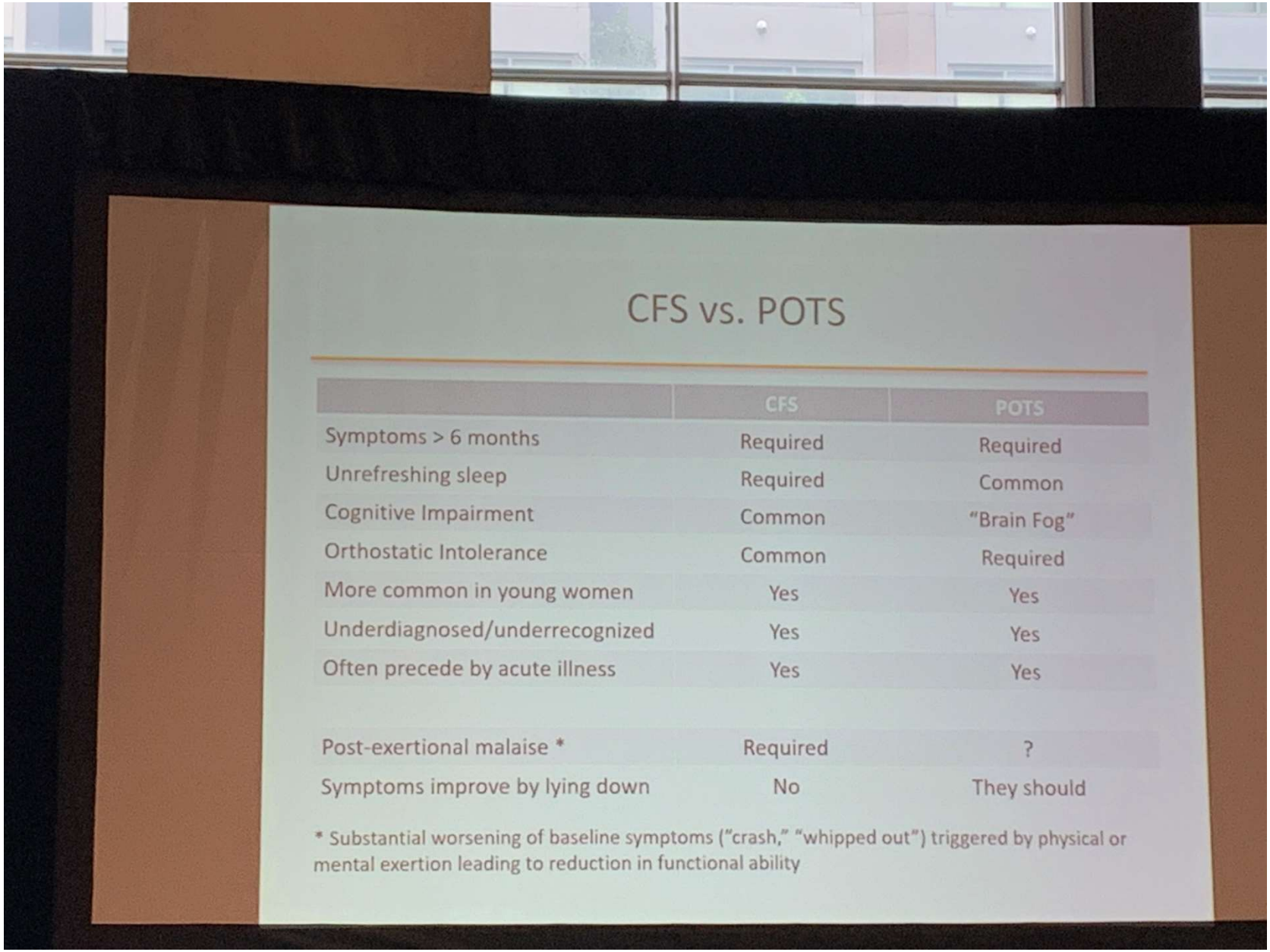
Physical	Emotional	Cognitive	Behavioral
*increased sweating	*anxiety	poor concentration	unhealthy eating patterns
*increased heart rate	*nervousness	memory lapse	sleeping habits change
*increased blood pressure	*feeling overwhelmed	forgetfulness	increased focus on symptoms
palpitations	crying easily	confusion	negative attitude
*short, shallow respirations	mood swings	difficulty with word find	negative thoughts
*muscle tension	impatience	"fogginess"	irritability
body aches	irritability		no longer fun to be with
*clench jaw/teeth	sensitivity		withdrawal/isolation
TMJ symptoms	anger		decreased activity and/or exercise
headaches	depression		scattered activity
*change in appetite	worry		procrastination
irritable bowel	guilt		unrealistic expectations
irritable bladder	fear		spend more hours doing less work
insomnia			increased chemical use
constantly tired			(meds, caffeine, alcohol, nicotine)
fatigue			addictive behaviors
weight loss/gain			neglecting appearance
decrease sexual desire/function			
skin changes			
Sensitivities			
Dizziness/lightheadedness			
Sense of imbalance			


Cycle of Chronic Pain/Chronic Fatigue
(Behaviors, Emotions, Family Response)
Illness/Injury
Fear & Concern
Offer Support
Decreased activity, pain, & fatigue
Hope & Trust
Increase attentiveness, Help with daily tasks
Seek medical attention
Loss of control
Continue to Do More, Care-taking
Increased activity, pain, & fatigue
Anger, frustration
Attempt to Re-establish Roles
Loss of strength & endurance-deconditioning
Guilty & withdrawn
Do it All, Over-invest
Self-limiting behavior
Anxiety, sadness, irritability
Disengage (Ignore)
Withdrawal & Isolation
Decreased self-esteem
Discouraged, Withdraw
Pain/Fatigue in Control

Overlap Between POTS and Chronic Fatigue Syndrome – Dr. Italo Biaggioni

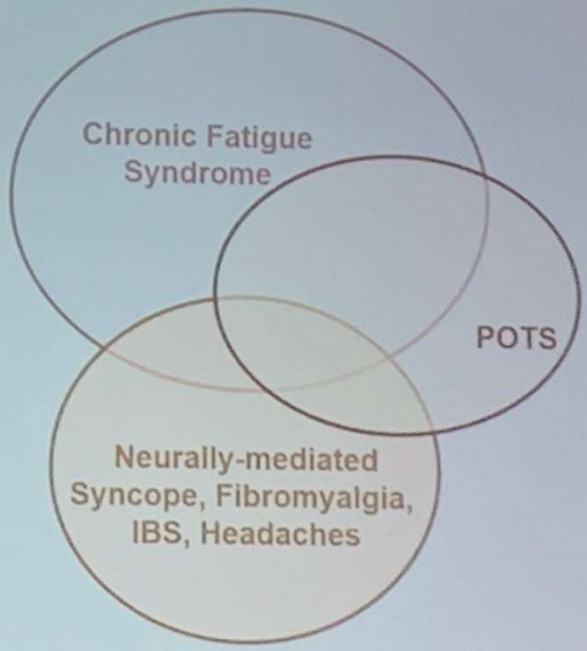
- 50-65% POTS patients meet criteria for CFS
- Greater sympathetic activation in CFS-POTS
- Patients may respond to medications such as methyldopa, guanfacine; although there is an issue with sedation in an already fatigued patient
- About to start a clinical trial with moxonidine, which is non-sedating
- When looking at exercise, you need to determine the balance; exercise is probably better but there may be exceptions
- “Patients don’t have POTS because they are deconditioned; they are deconditioned because they have POTS”
- He prefers methyldopa over clonidine
- Question was asked if you can take propanol and corlanor and he said yes
- “Yellow” Glasses or screen protectors that filter blue light may be useful if electronics must be used at night


CFS – Diagnostic Criteria
IOM 2015
1. Fatigue: long-standing (>6 months) and disabling:
• Of new or definitive onset (not lifelong)
• Not due to excessive exertion
• Not alleviated by rest; AND
2. Post-exertional malaise * (exercise or mental stress); AND
3. Unrefreshing sleep *
AND at least one of these:
1. Cognitive impairment *; OR
2. Orthostatic intolerance
* Have to be of moderate to severe severity and present at least half of the time
New name: SEID: Systemic Exertional Intolerance Disease

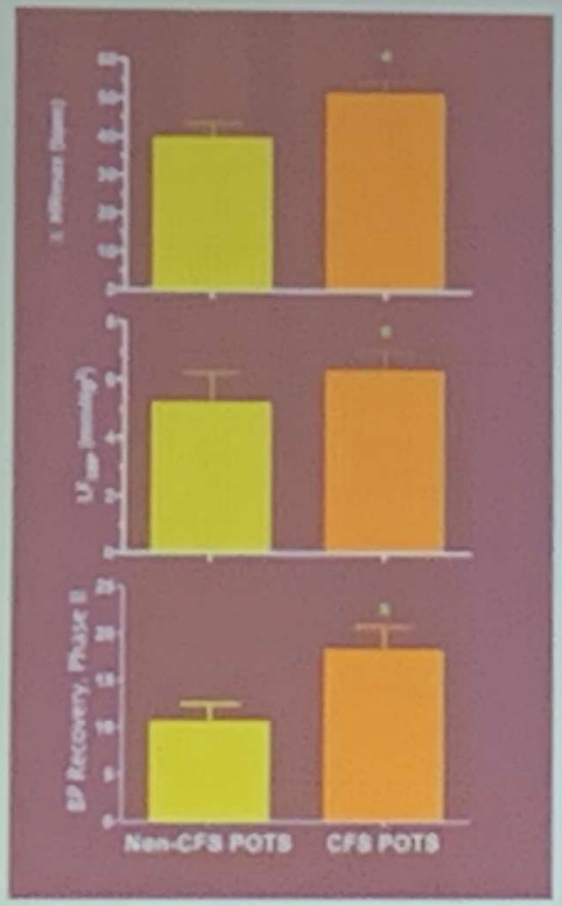

CFS vs. POTS
CFS
POTS
Symptoms > 6 months
Required
Required
Unrefreshing sleep
Required
Common
Cognitive Impairment
Common
"Brain Fog"
Orthostatic Intolerance
Common
Required
More common in young women
Yes
Yes
Underdiagnosed/underrecognized
Yes
Yes
Often precede by acute illness
Yes
Yes
Post-exertional malaise *
Required
?
Symptoms improve by lying down
No
They should
* Substantial worsening of baseline symptoms ("crash," "whipped out") triggered by physical or mental exertion leading to reduction in functional ability

Overlap Between POTS and CFS

- ~27% of CFS patients have POTS (Streeten, Thomas & Bell, 2000) (Range 7-50%)
- 50-65% of our POTS patients meet criteria for CFS
- This association appears to be even higher in adolescents with POTS



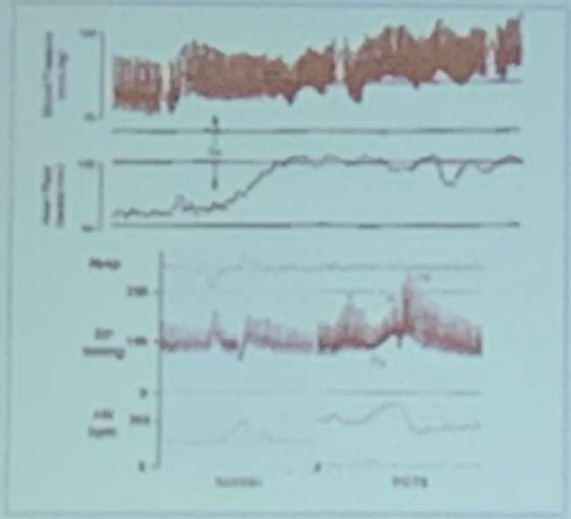
Greater Sympathetic Activation in CFS-POTS

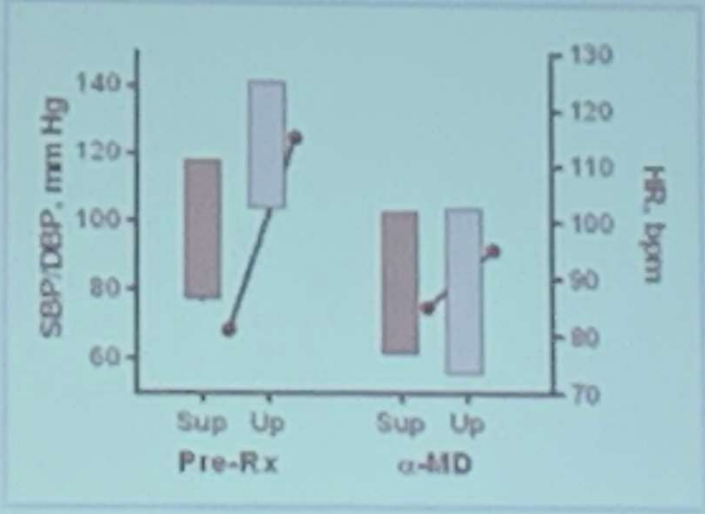


- Increased Postural Tachycardia
- Increased Low Frequency BP Variability
- Increased BP Recovery During Phase II Valsalva

Greater Sympathetic Activation in CFS-POTS

- Some patients have "adrenaline rushes" with hypertension, tachycardia, flushing followed by "post exertional malaise"
- These patients may respond to "central sympatholytics" (methyl dopa, guanfacine) to reduce sympathetic activity
- About to start a clinical trial with moxonidine (non-sedating)





Impact of CFS in POTS – Q&A

What if I don't meet criteria for CFS or for POTS

What if my HR increases only 28 bpm not 30

What if I only have symptoms for 5 months not 6

- Who cares? "Diagnostic Criteria" are designed for investigators to classify patients and by coders for billing/insurance.
- Patients that do not "meet criteria" should be treated as appropriate. Criteria should be used to guide treatment, not to deny treatment

Impact of CFS in POTS – Q&A

- What if I don't meet criteria for CFS or for POTS?
- How to treat CFS patients with tachycardia, or POTS patients with fatigue? → the same
  - If ↑ HR → beta blockers, mestinon, verapamil, cornalor
  - If ↓ BP → midodrine, fludrocortisone, mestinon
  - If ↑ BP → consider methyl-dopa, guanfacine

  - Fatigue, sleep, brain fog

Impact of CFS in POTS – Q&A

- What if I don't meet criteria for CFS or for POTS?
- How to treat CFS with tachycardia, or POTS with fatigue?
- Will beta-blockers make fatigue worse? → maybe
  - Use low dose short acting 10-20 mg propranolol
  - Use alternatives to control tachycardia (mestinon, verapamil, cornalor)

Impact of CFS in POTS – Q&A

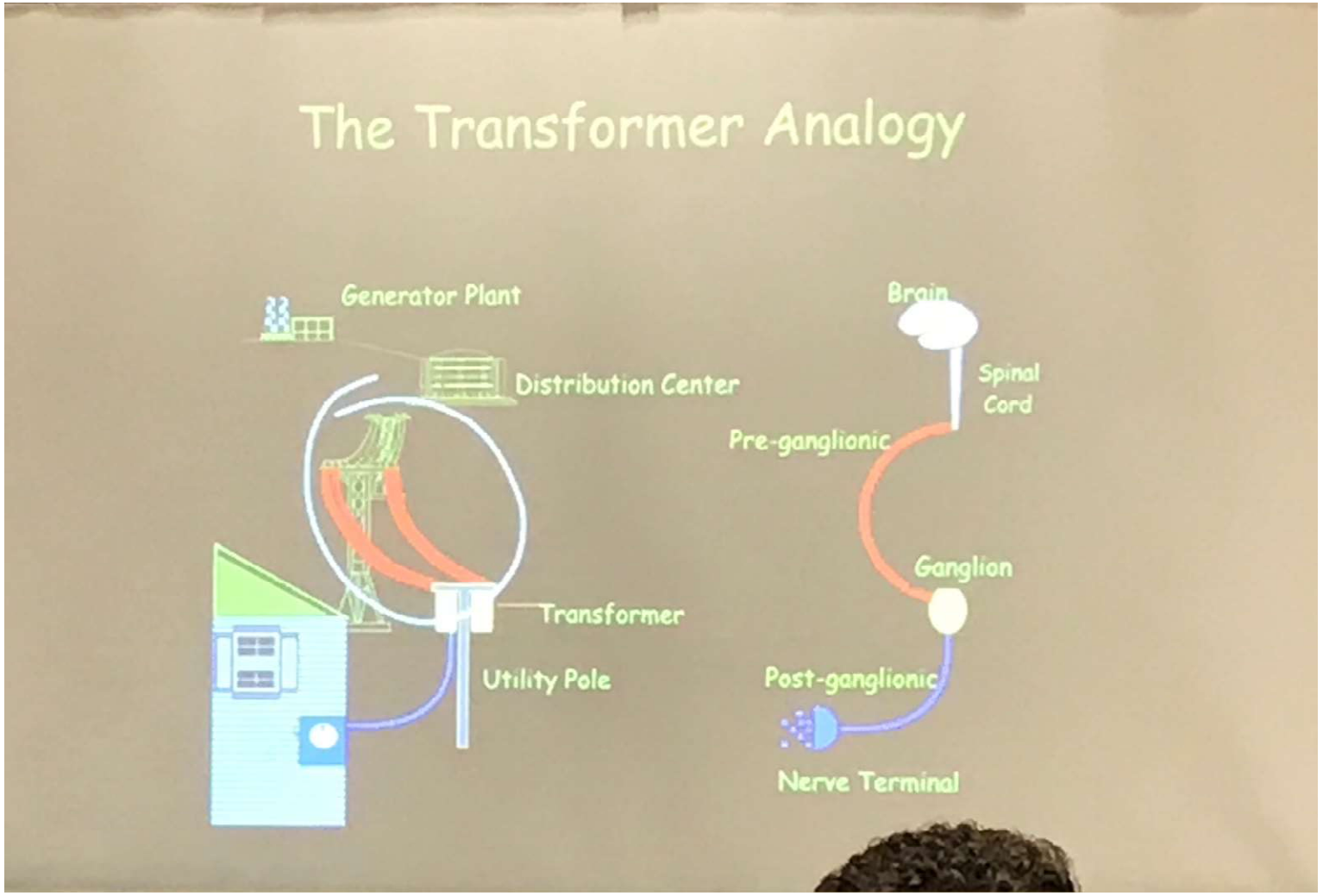
- What if I don't meet criteria for CFS or for POTS?
- How to treat CFS with tachycardia, or POTS with fatigue?
- Will beta-blockers make fatigue worse?
- Will exercise make fatigue worse?
  - It may (post exercise malaise), but not exercising is pro ably worse
  - Most of the "cures" we see involve some kind of exercise program
  - Try gradual exercise, add propranolol

Sleep & POTS

- Do not stay in bed during the day
- Exercise in the afternoon
- Go to sleep at the same time
- "Wind down" before; DO NOT use electronics with screens (blue light)
- Read a boring book
- Dark, cold room

Overview of the Autonomic Nervous System – Dr. David Goldstein

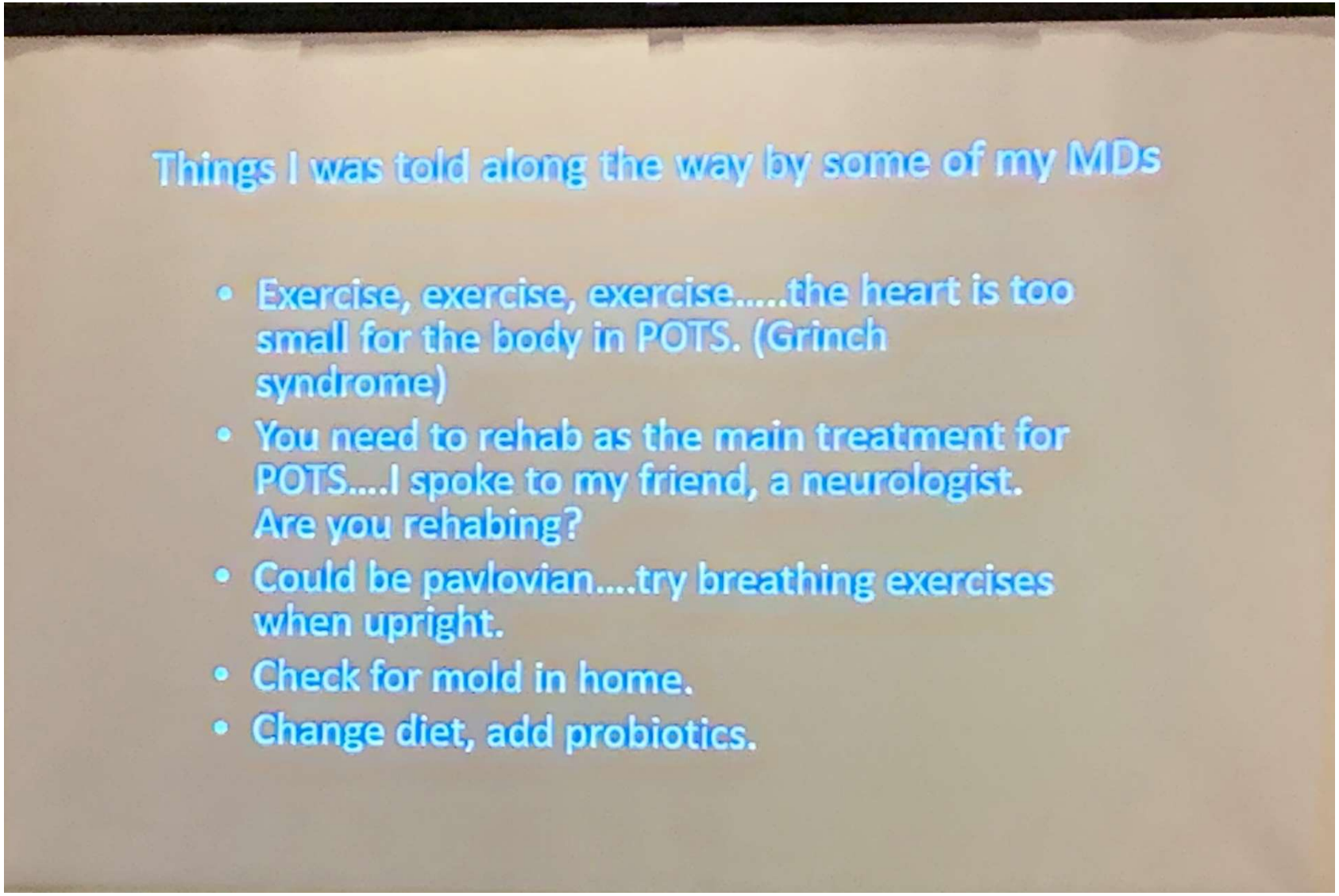
- ANS is not autonomous; there is a “central command”
- Detailed paper of his presentation is here: https://neuroscience.nih.gov/publications/PrinciplesofAutonomicMedicine30.pdf



From Doctor to Patient: An Immunologist's Experience with POTS, EDS, and CSF leaks – Dr. Taylor Doherty

(A touching presentation; would highly recommend watching as he can relate with so many of us)

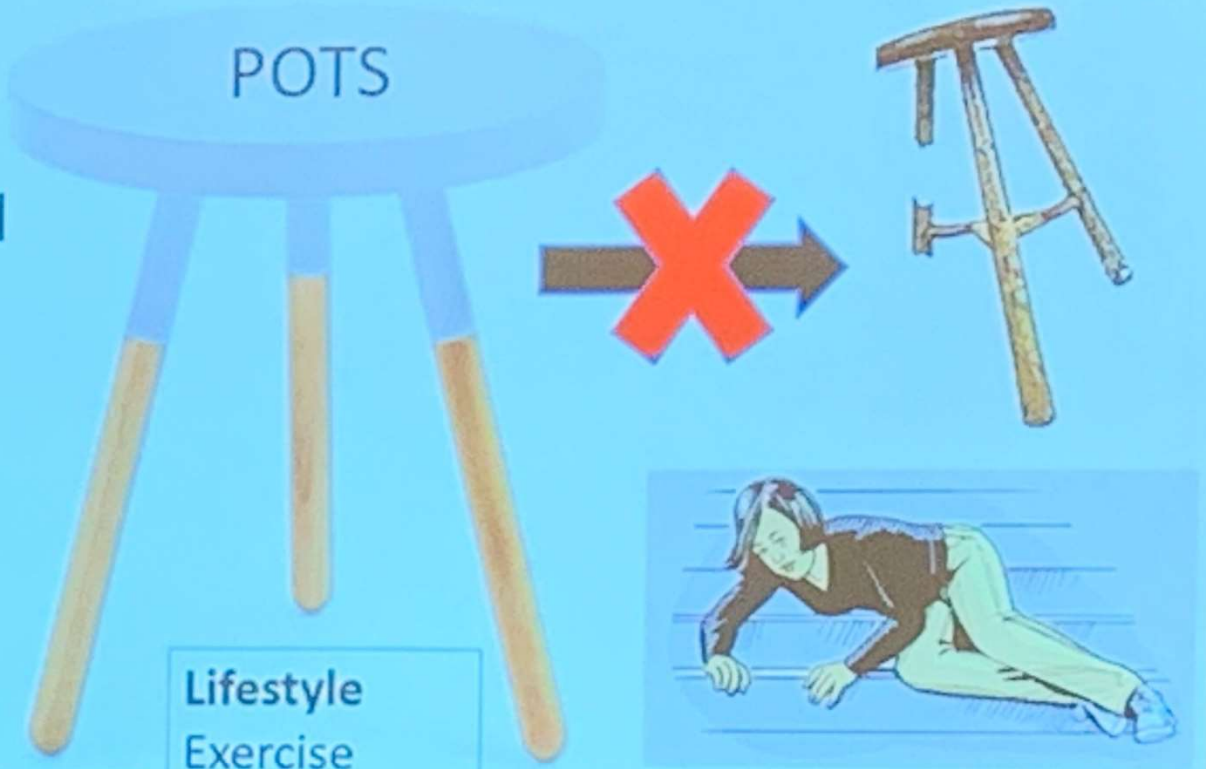
- "The eyes do not see what the mind does not Know" is a quote so true when doctors see patients with POTS
- He tried IVIG but couldn't tolerate
- He got blood patches for a possible CSF Leak but did not help
- Rituximab wipes away B Cells
- Done Plasmapheresis 3x a week for 1 year


Things I was told along the way by some of my MDs
• Exercise, exercise, exercise.....the heart is too small for the body in POTS. (Grinch syndrome)
• You need to rehab as the main treatment for POTS....I spoke to my friend, a neurologist. Are you rehabing?
• Could be pavlovian....try breathing exercises when upright.
• Check for mold in home.
• Change diet, add probiotics.

NO MATTER HOW MUCH IT HURTS, HOW DARK IT GETS, OR HOW HARD YOU FALL... YOU ARE NEVER OUT OF THE FIGHT.

-MARCUS LUTTRELL

Three leg stool model for POTS Treatment



Symptomatic Meds
Volume expanders
Vasoconstrictors
Chronotropic
Other

Lifestyle
Exercise
Diet
Salt
Compression
Sleep
Other

Underlying causes & assoc dz
Autoimmune
Metabolic
Structural
Other
MCAS
EDS
Infections

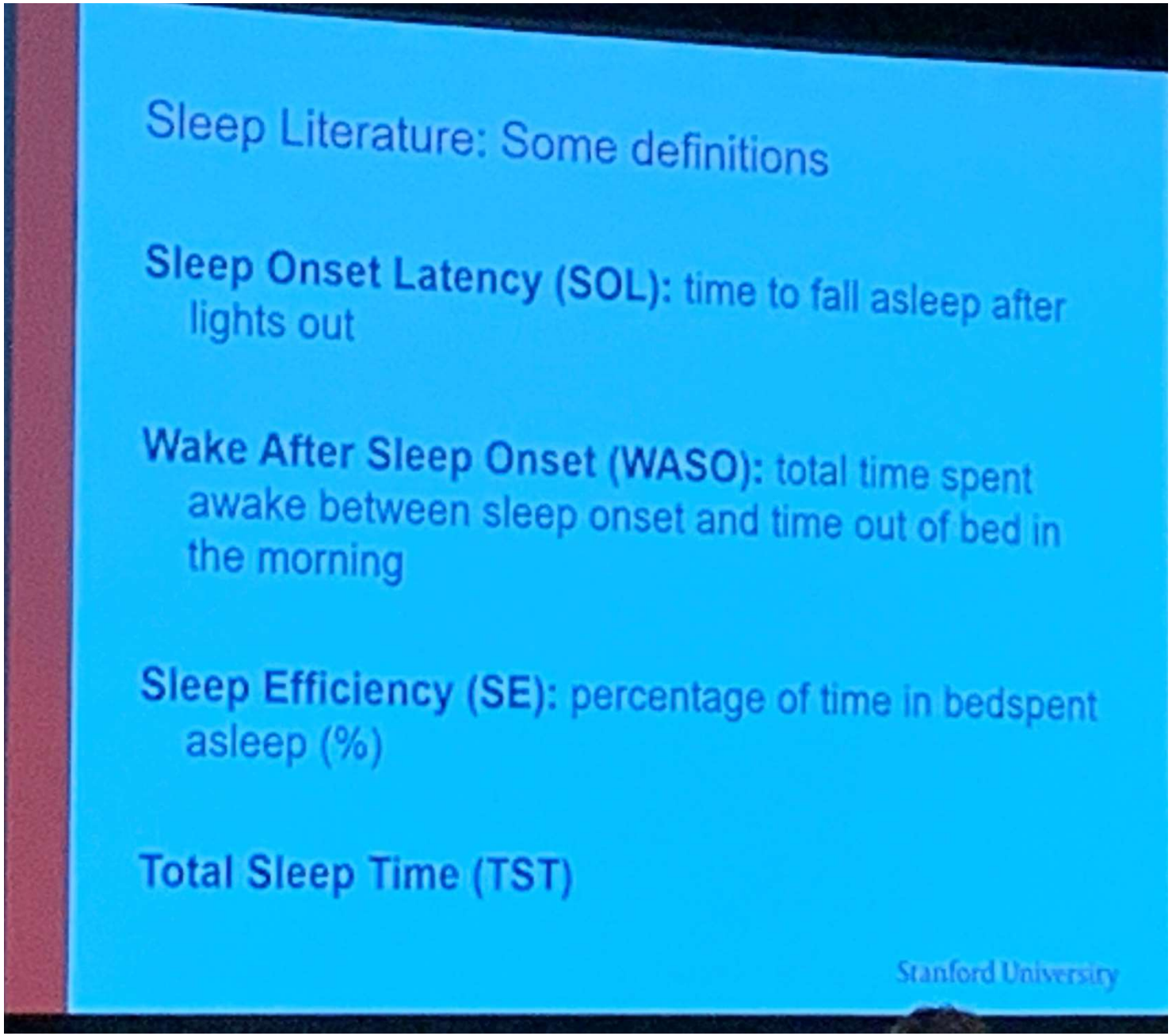
Sleep Dysfunction in POTS – Dr. Mitchell Miglis

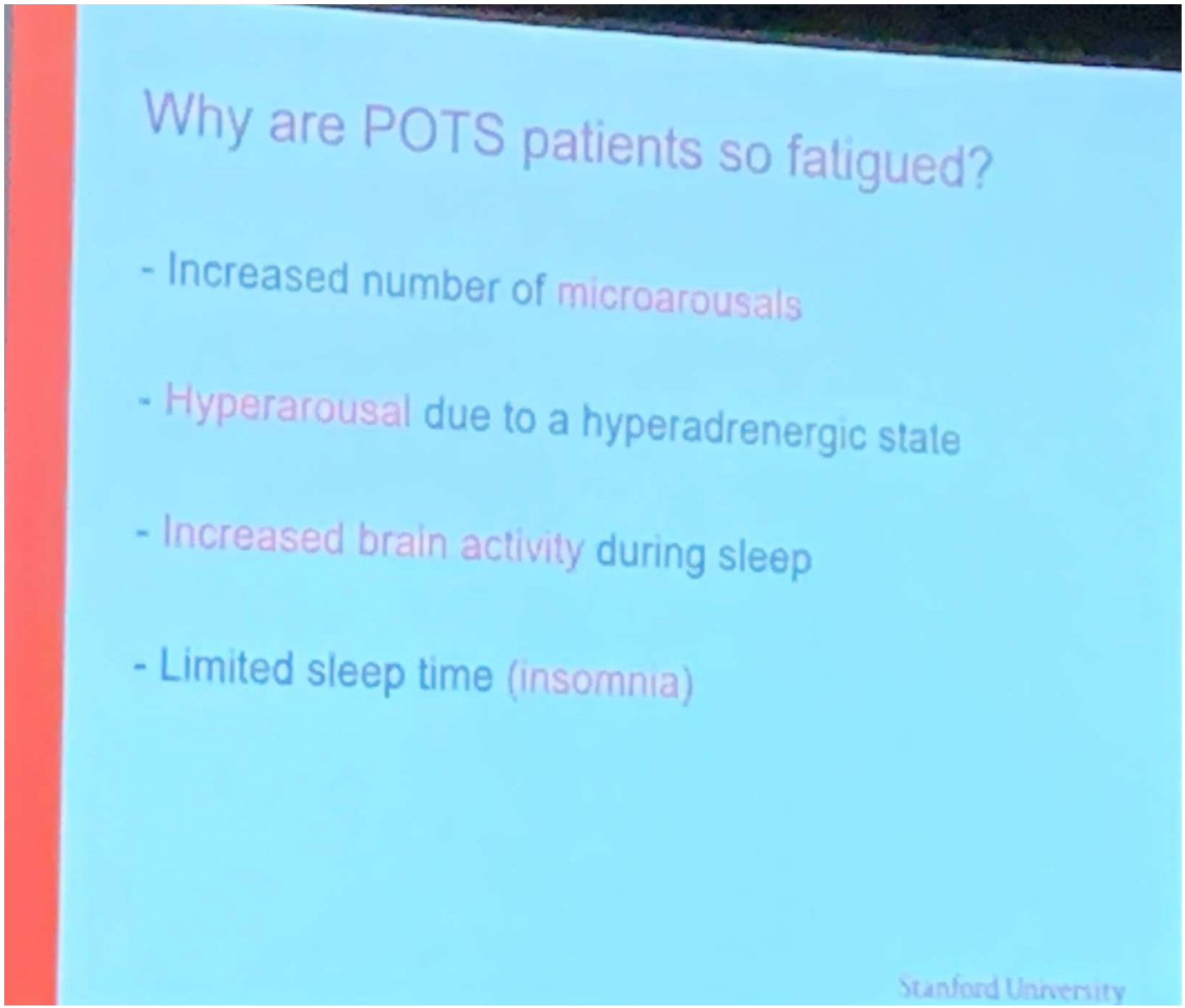
- Sleepiness – Propensity to fall asleep
- Fatigue – feeling depleted/exhausted
- POTS patients tend to have a delayed sleep phase
- Most POTS patients have mild sleep apnea
- POTS patients are fatigued because they have
    - Increased microarousals
    - Hyperarousal due to hyperadrenergic state
- Elevated cortisol is suspected; however, it's hard to measure cortisol accurate so typically don't do it
- Beta blockers may inhibit melatonin secretion
- Recommend Melatonin 3mg ~ 30 min before bedtime
- Can also take ½ mg 6 hours before going to bed to change circadian rhythm
- Restless Leg Syndrome is easily treatable (gabapentin, dopamine); 25% of women have this
- Low ferratin can also cause Restless Leg Syndrome
- Most POTS patients spend too much time in bed. Limit to 8 hours
- VA path to Better Sleep
- For Sleep apnea, CPAPs are best, although can be hard to tolerate. Dental appliances are bad for those with EDS because of TMJ
- Central alpha blockers can help with night sweats

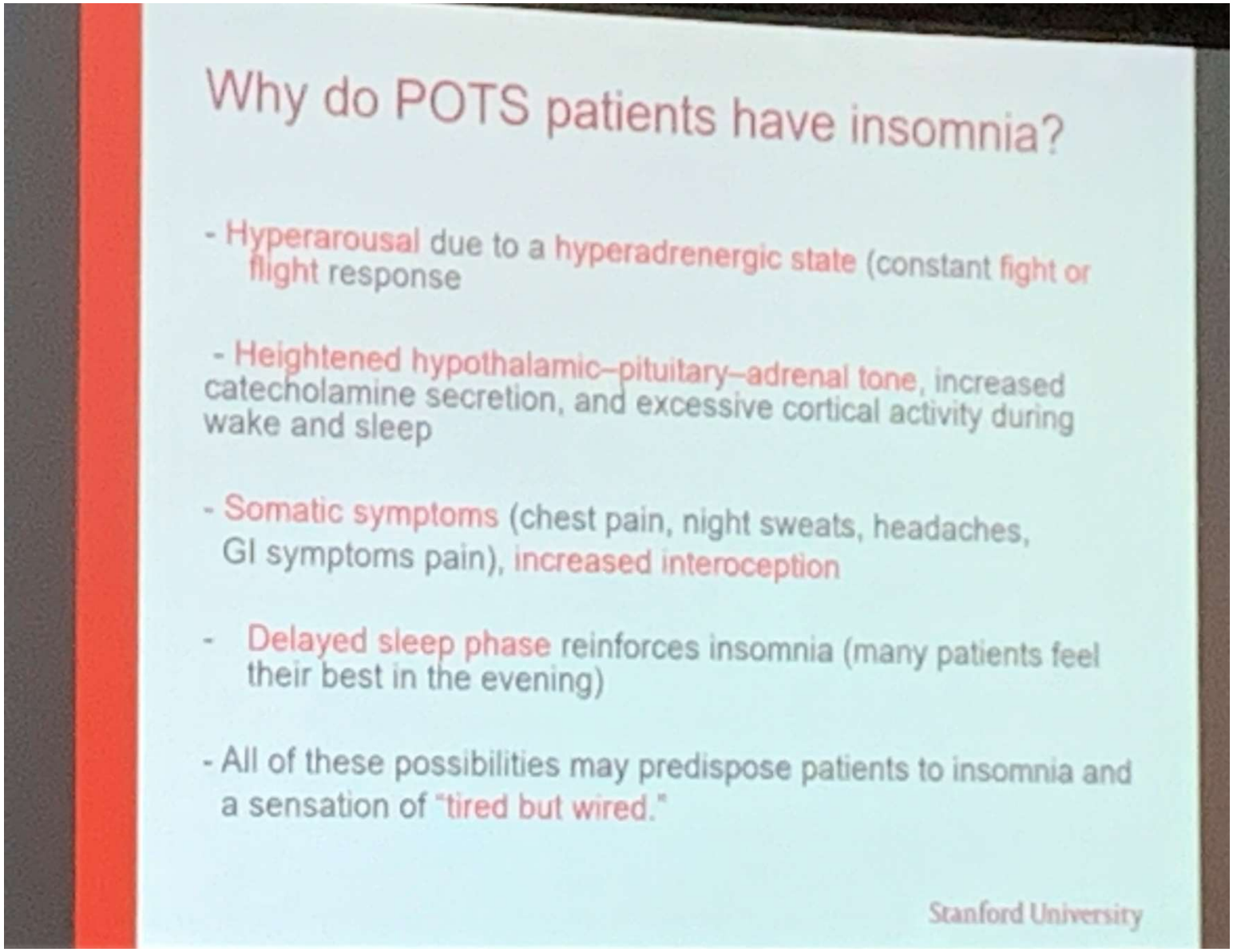
Fatigue v. Sleepiness

	SYMPTOMS	CAUSES
SLEEPINESS	"Propensity to fall asleep" • Breathing slows • Eyes get heavy • Head nods	"One main reason" • Sleep loss • Sedating medication • Cold, flu or other illness
FATIGUE	"Feeling depleted/exhausted" • Low physical energy • Low mental energy • Need to de-stress	"Dozens of reasons" • Physical/mental exertion • Medical illness • Deconditioning

Stanford University


Sleep Literature: Some definitions
Sleep Onset Latency (SOL): time to fall asleep after lights out
Wake After Sleep Onset (WASO): total time spent awake between sleep onset and time out of bed in the morning
Sleep Efficiency (SE): percentage of time in bedspent asleep (%)
Total Sleep Time (TST)
Stanford University


Why are POTS patients so fatigued?
- Increased number of microarousals
- Hyperarousal due to a hyperadrenergic state
- Increased brain activity during sleep
- Limited sleep time (insomnia)
Stanford University


Why do POTS patients have insomnia?
- Hyperarousal due to a hyperadrenergic state (constant fight or flight response
- Heightened hypothalamic–pituitary–adrenal tone, increased catecholamine secretion, and excessive cortical activity during wake and sleep
- Somatic symptoms (chest pain, night sweats, headaches, GI symptoms pain), increased interoception
- Delayed sleep phase reinforces insomnia (many patients feel their best in the evening)
- All of these possibilities may predispose patients to insomnia and a sensation of "tired but wired."
Stanford University

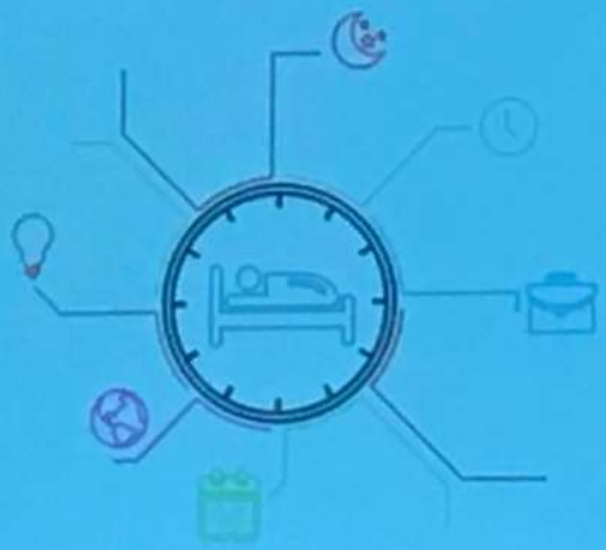
Restless Legs Syndrome: URGE (Willis-Ekbom disease)

- An unpleasant sensation and Urge to move
- Worse with Rest
- Gets better with movement
- Worse in the Evening (circadian rhythmicity)

Stanford University

Support Sleep-Wake Routines

- Consistent sleep schedule
- Consistent bedtime routine
- Protected sleep environment
- Regularly timed meals
- Appropriately timed exercise and activities
- Appropriate use of caffeine, alcohol and other substances



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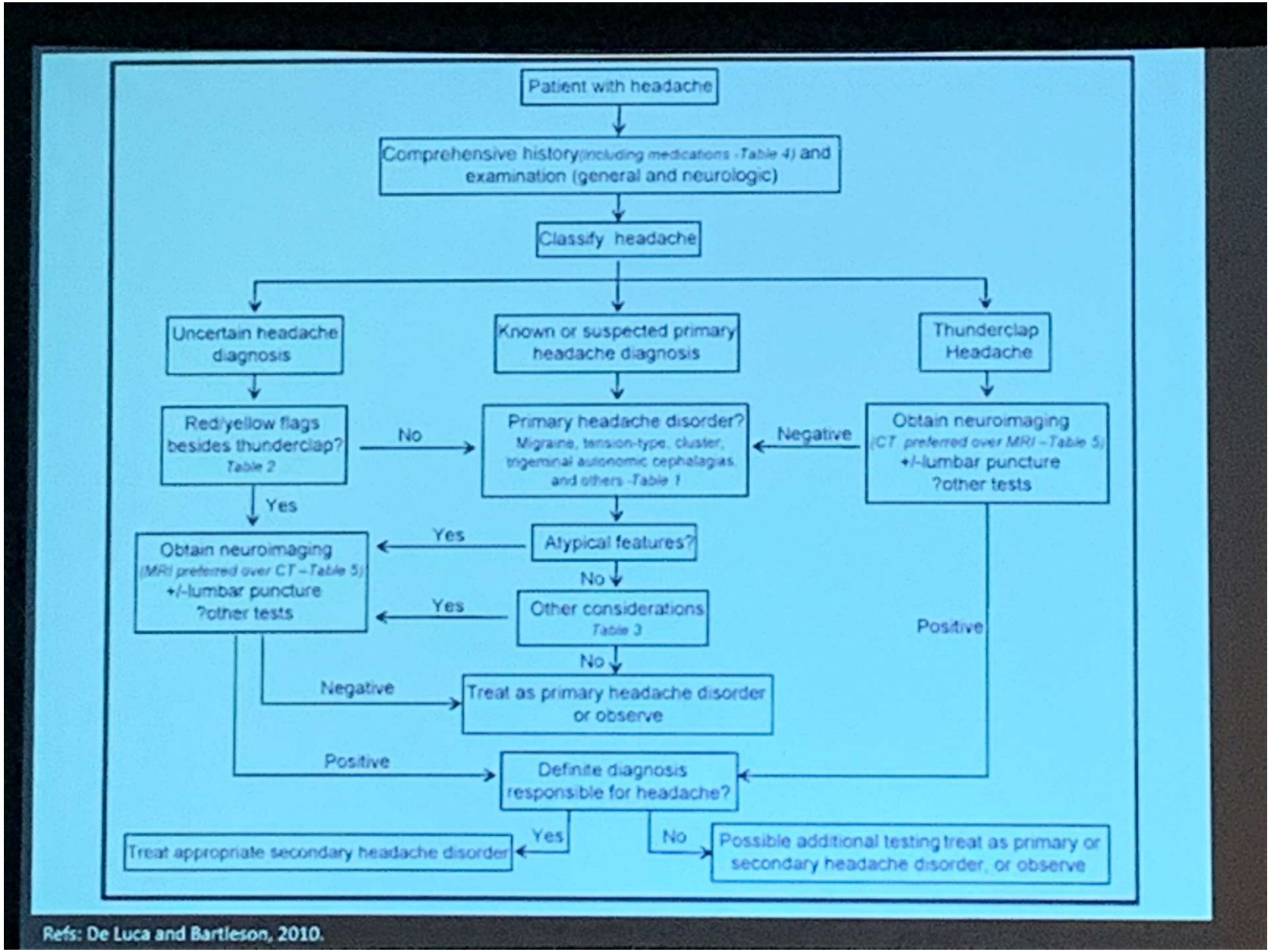
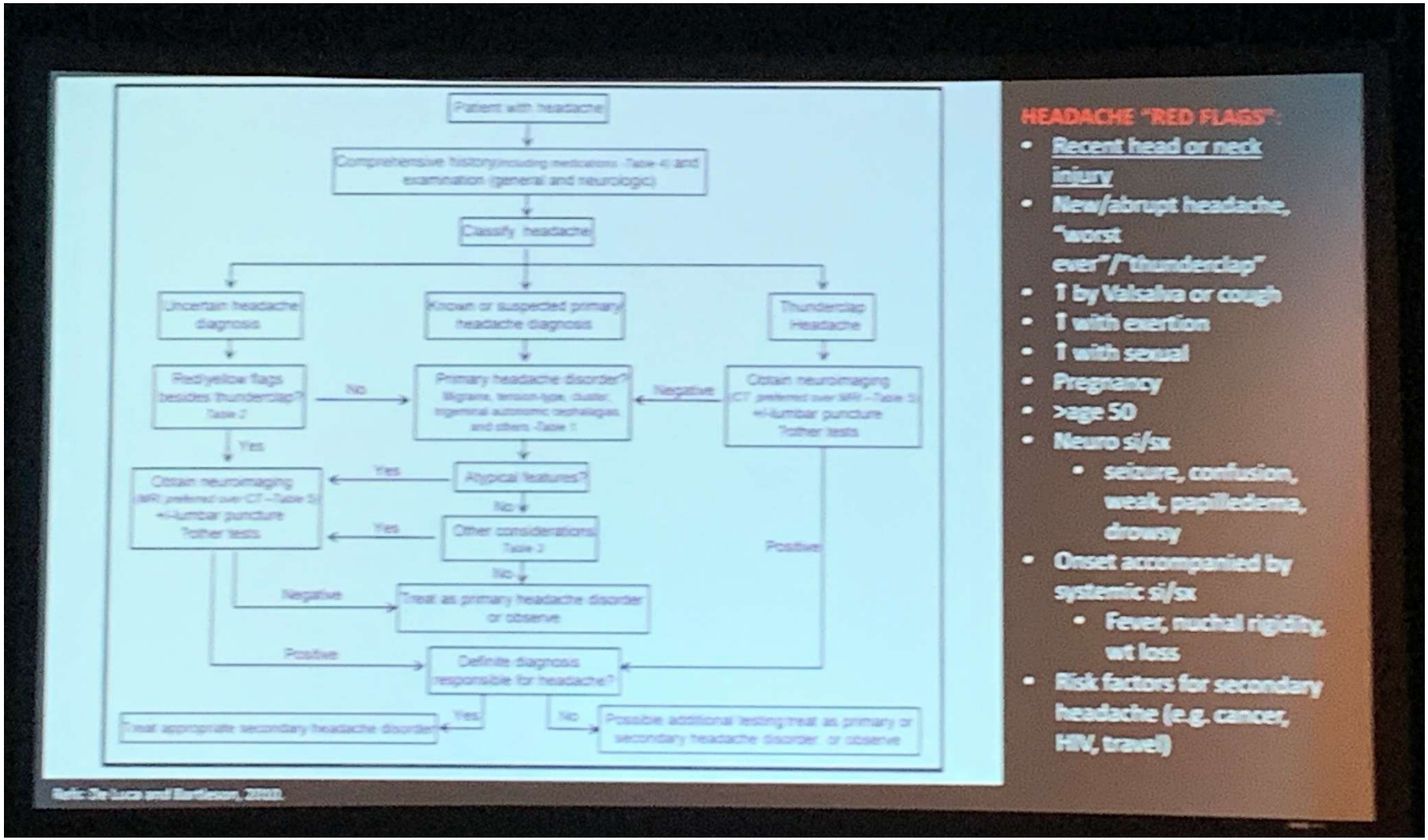
Meditation Apps
CBT-i
HEADSPACE
Calm
ACT
10% HAPPIER
MEDITATION FOR FIDGETY SKEPTICS
Insight Timer
Stanford University

Headaches & Migraines in POTS

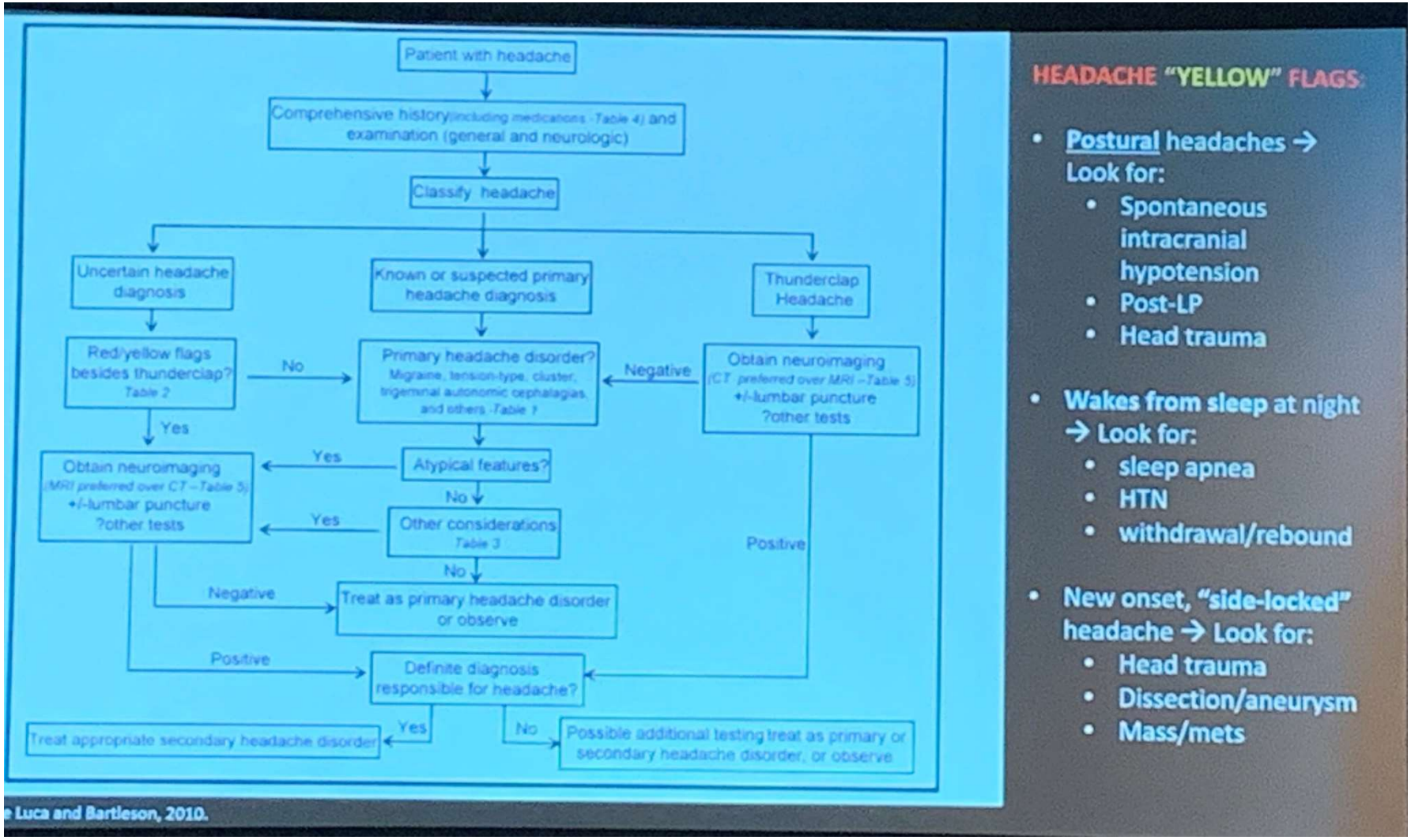
(Missed much of presentation but captured a few slides)


Patient with headache
Comprehensive history (including medications -Table 4) and examination (general and neurologic)
Classify headache
Uncertain headache diagnosis
Known or suspected primary headache diagnosis
Thunderclap Headache
Red/yellow flags besides thunderclap? Table 2
No
Primary headache disorder? Migraine, tension-type, cluster, trigeminal autonomic cephalagias, and others -Table 1
Negative
Obtain neuroimaging (CT preferred over MRI – Table 5) +/-lumbar puncture ?other tests
Yes
Obtain neuroimaging (MRI preferred over CT – Table 5) +/-lumbar puncture ?other tests
Yes
Atypical features?
No
Yes
Other considerations Table 3
No
Positive
Negative
Treat as primary headache disorder or observe
Positive
Definite diagnosis responsible for headache?
Yes
No
Treat appropriate secondary headache disorder
Possible additional testing treat as primary or secondary headache disorder, or observe
Refs: De Luca and Bartleson, 2010.



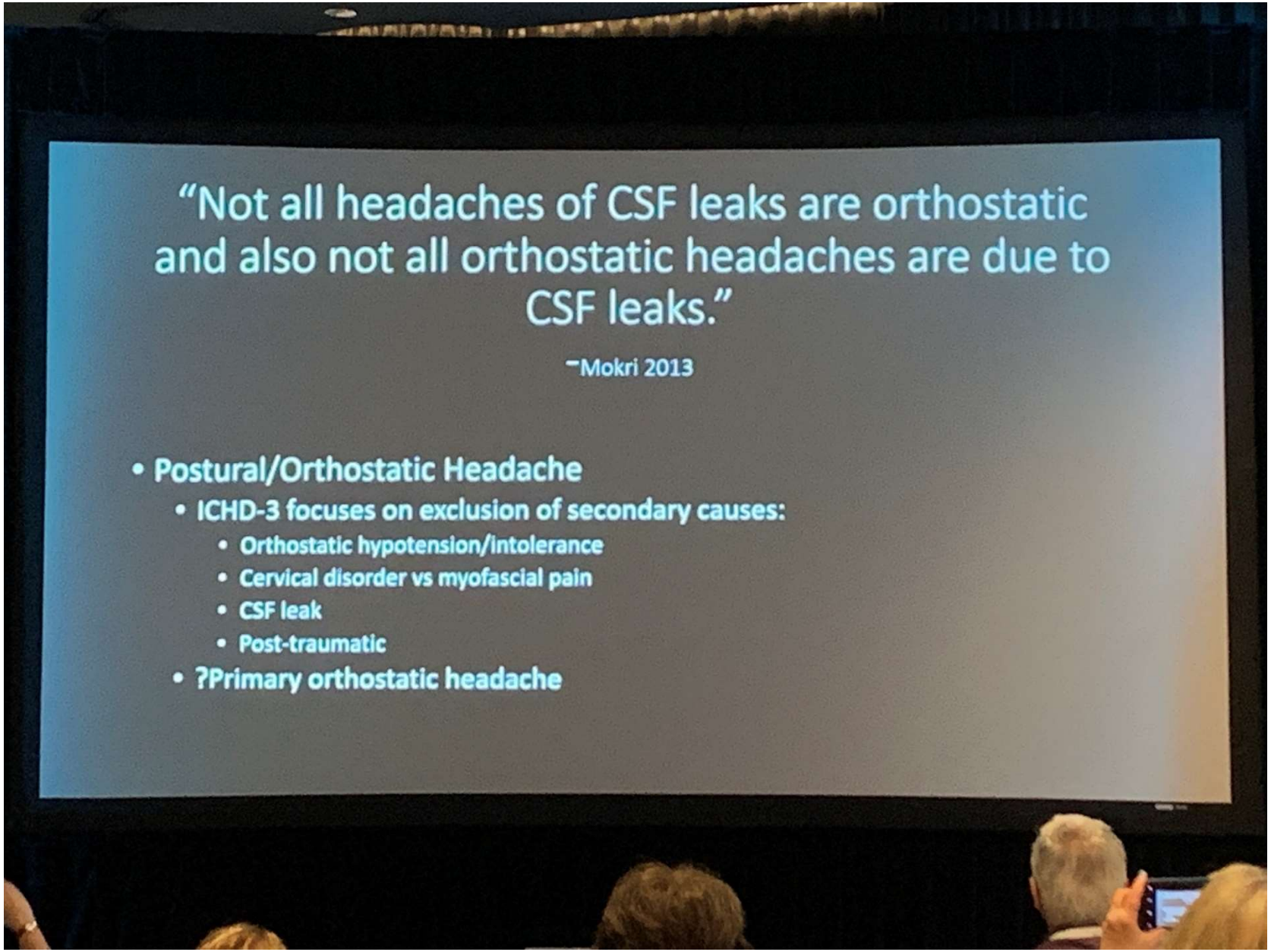
HEADACHE "RED FLAGS":

- Recent head or neck injury
- New/abrupt headache, "worst ever"/"thunderclap"
- ↑ by Valsalva or cough
- ↑ with exertion
- ↑ with sexual
- Pregnancy
- >age 50
- Neuro si/sx
  - seizure, confusion, weak, papilledema, drowsy
- Onset accompanied by systemic si/sx
  - Fever, nuchal rigidity, wt loss
- Risk factors for secondary headache (e.g. cancer, HIV, travel)



HEADACHE "YELLOW" FLAGS:

- **Postural** headaches → Look for:
  - Spontaneous intracranial hypotension
  - Post-LP
  - Head trauma
- Wakes from sleep at night → Look for:
  - sleep apnea
  - HTN
  - withdrawal/rebound
- New onset, "side-locked" headache → Look for:
  - Head trauma
  - Dissection/aneurysm
  - Mass/mets

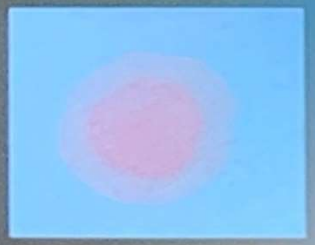

"Not all headaches of CSF leaks are orthostatic and also not all orthostatic headaches are due to CSF leaks."
-Mokri 2013
• Postural/Orthostatic Headache
• ICHD-3 focuses on exclusion of secondary causes:
• Orthostatic hypotension/intolerance
• Cervical disorder vs myofascial pain
• CSF leak
• Post-traumatic
• ?Primary orthostatic headache

CSF Leak and Orthostatic Headache

- Cerebral Spinal Fluid (CSF) Leak Epidemiology
  - All ages
  - 3 types:
    - **post-traumatic** – most within 2 days, most heal spontaneously (rare persistent up to years)
    - **non-traumatic** – nontraumatic pathologies such as tumors, infections, and congenital cephaloceles
    - **spontaneous** – fistulas; obese, middle age women with signs of intracranial hypertension (IIH)
  - Most common symptom = CSF rhinorrhea ("runny nose")
    - Increases with Valsalva/head down maneuvers (Reservoir Test)
    - "Halo sign" – pillow in AM
    - Gold standard: Beta-2 transferrin immunofixation (92% sn, 80% sp), then MRI
  - **Suspected/occult:**
    - Lumbar puncture of less than <6 cm H2O (?normal in 25%)
    - Brain MRI features of craniospinal hypotension
    - CT (gold standard)/MR (test of choice) Cisternography (~equivalent Sn, sp)
    - Rapid leaks need dynamic CT myelography

Refs: Vemuri et al 2017. Mathias et al 2016. Starling et al 2013. Mokri 2013. Wang et al 2009.

CSF Leak and Orthostatic Headache

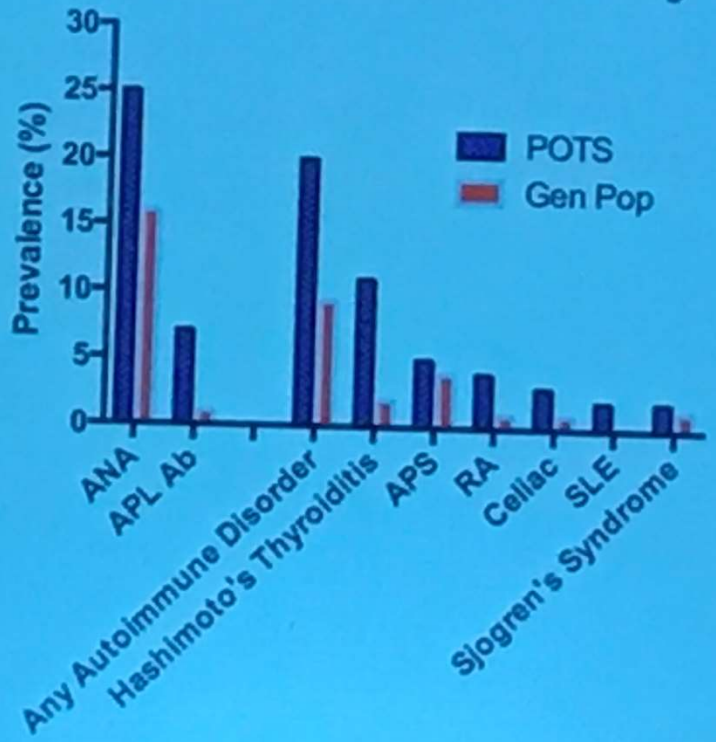


- Cerebral Spinal Fluid (CSF) Leak Epidemiology
  - All ages
  - 3 types:
    - post-traumatic – most within 2 days, most heal spontaneously (rare persistent up to years)
    - non-traumatic – nontraumatic pathologies such as tumors, infections, and congenital cephaloceles
    - spontaneous – fistulas; obese, middle age women with signs of intracranial hypertension (IIH)
  - Most common symptom = CSF rhinorrhea ("runny nose")
    - Increases with Valsalva/head down maneuvers (Reservoir Test)
    - "Halo sign" – pillow in AM
    - Gold standard: Beta-2 transferrin immunofixation (92% sn, 80% sp), then MRI
  - Suspected/occult:
    - Lumbar puncture of less than <6 cm H2O (?normal in 25%)
    - Brain MRI features of craniospinal hypotension
    - CT (gold standard)/MR (test of choice) Cisternography (~equivalent Sn, sp)
    - Rapid leaks need dynamic CT myelography

Refs: Vemuri et al 2017. Mathias et al 2016. Starling et al 2013. Mokri 2013. Wang et al 2009.

Adrenergic Antibodies in POTS: 2014 Conference Study Update – Dr. Satish Raj

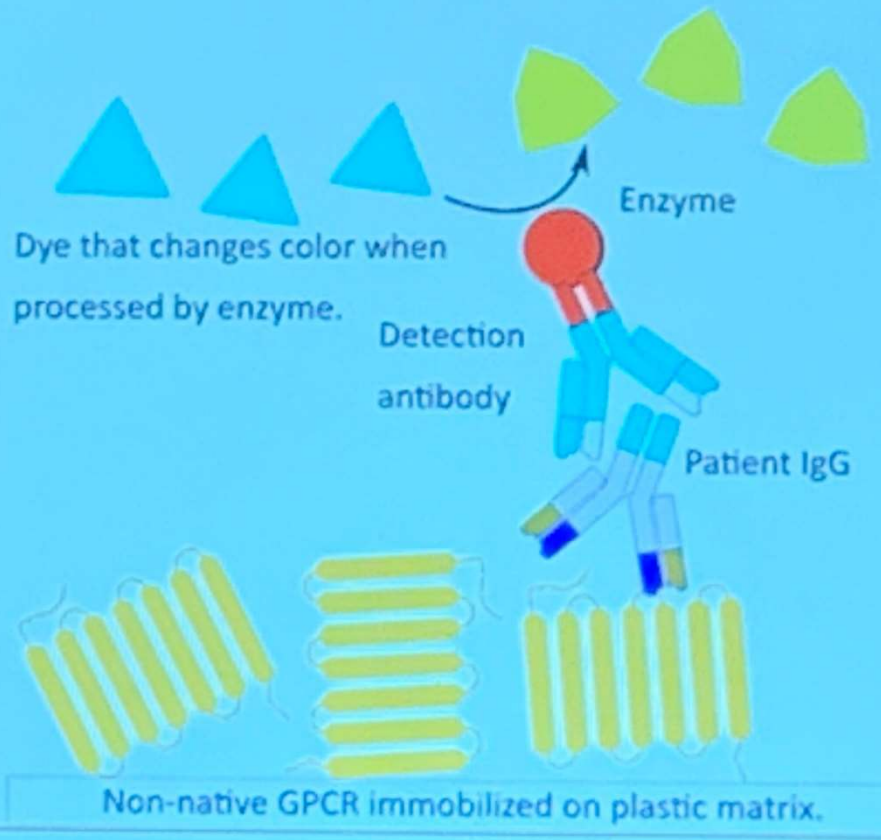
POTS patients have lots of Antibodies…more of everything



S Blitshteyn, Lupus 2015

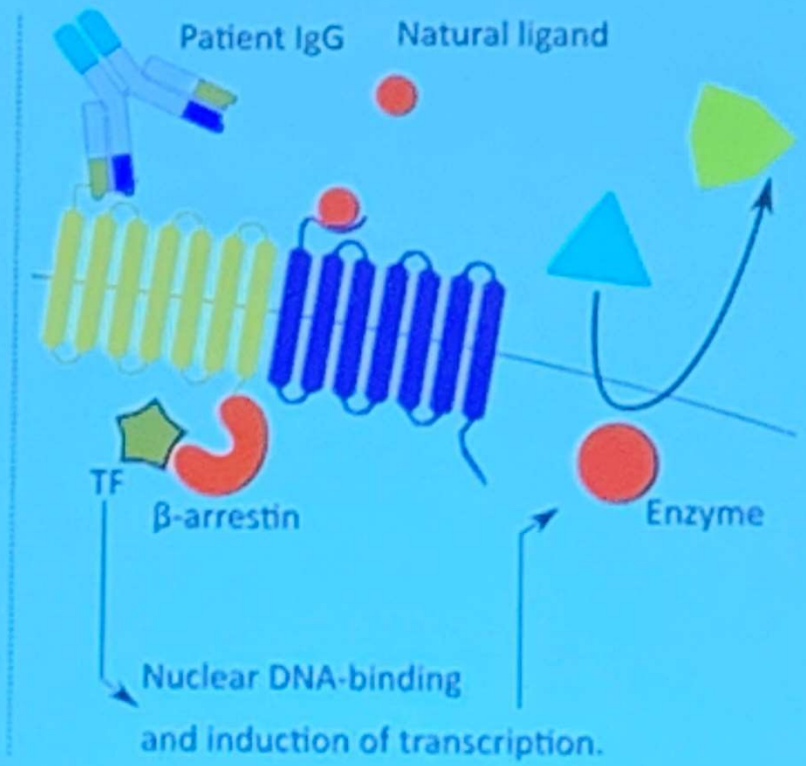
POTS Ab Assessment - ELISA

Is an Ab or Ab-fragment Present?



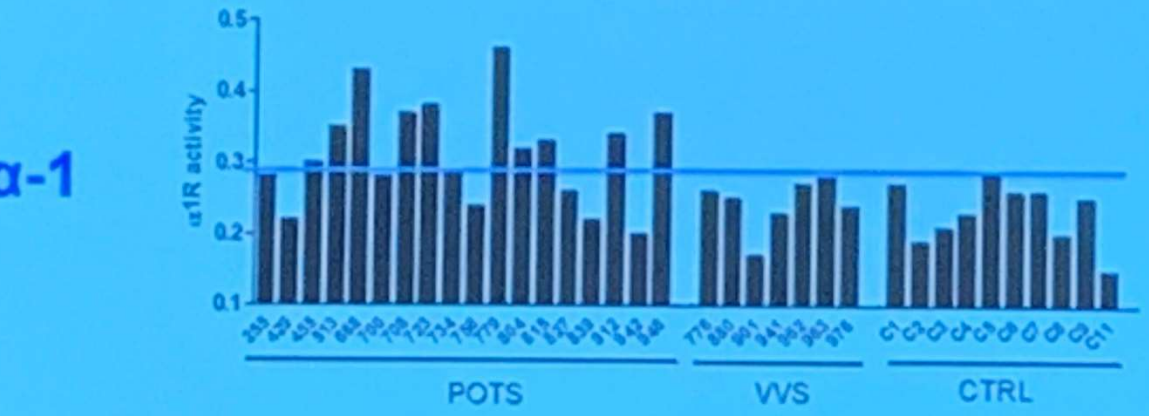
POTS Ab Assessment - TANGO

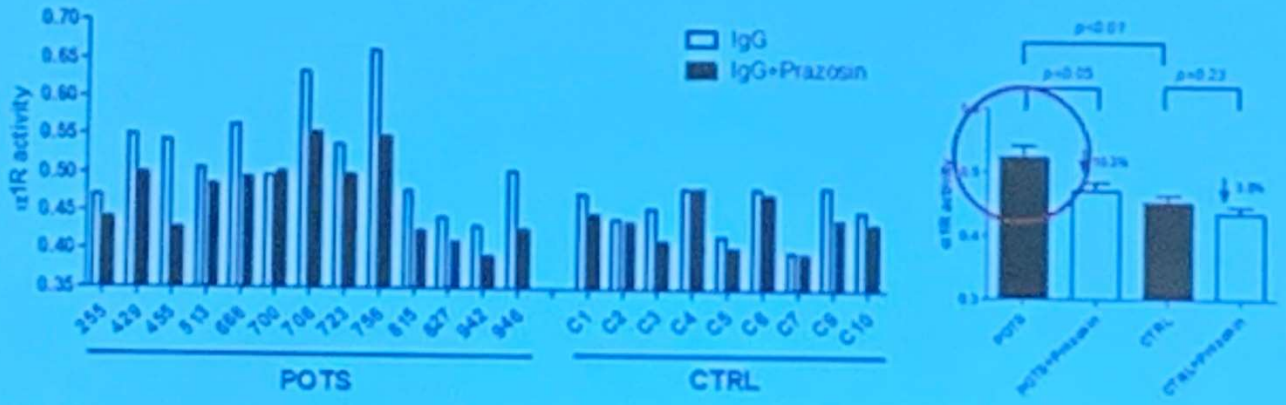
Do Ab or Ab-fragment Stimulate Cell Receptors?



POTS Adrenergic Ab 2 –α_1 blocker

α-1



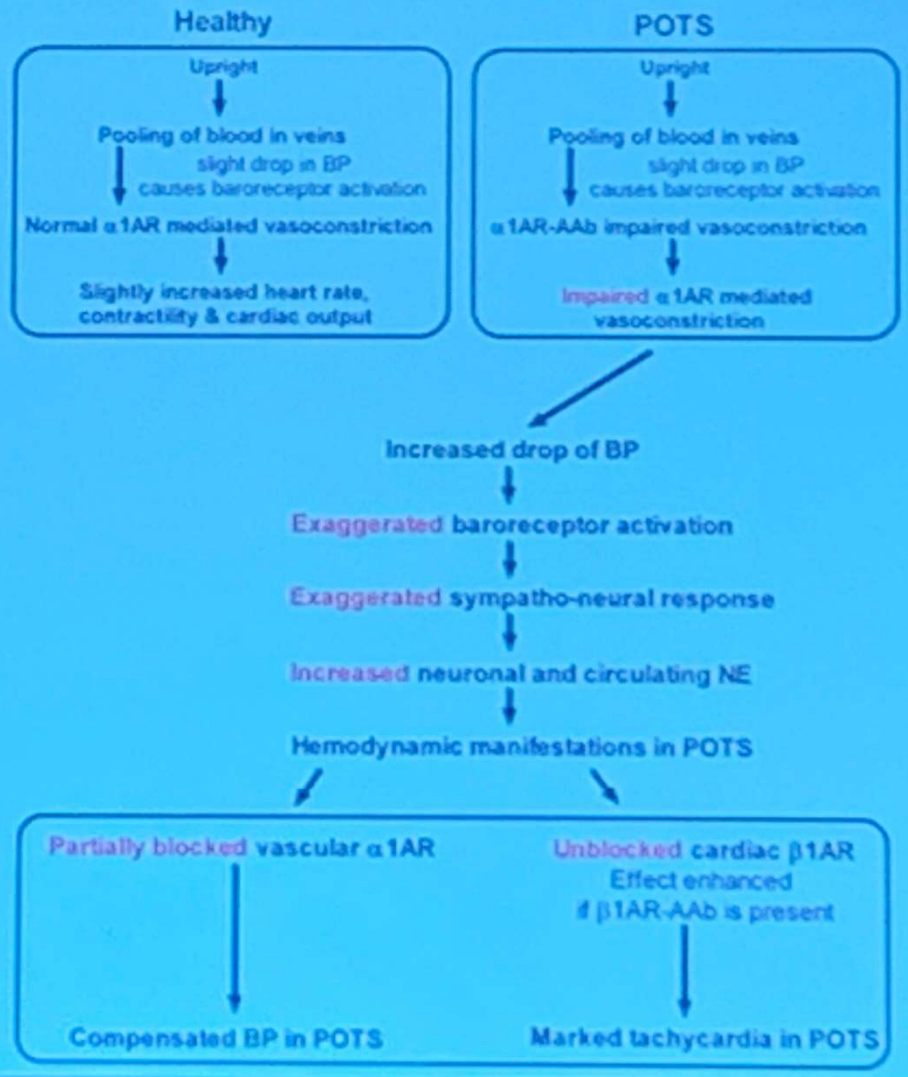


High α-1 activity in POTS IgG; blocked with α-1 blocker

Fedorowski/Kem et al

POTS Adrenergic Ab - The Model

How could the Ab contribute to the POTS phenotype?

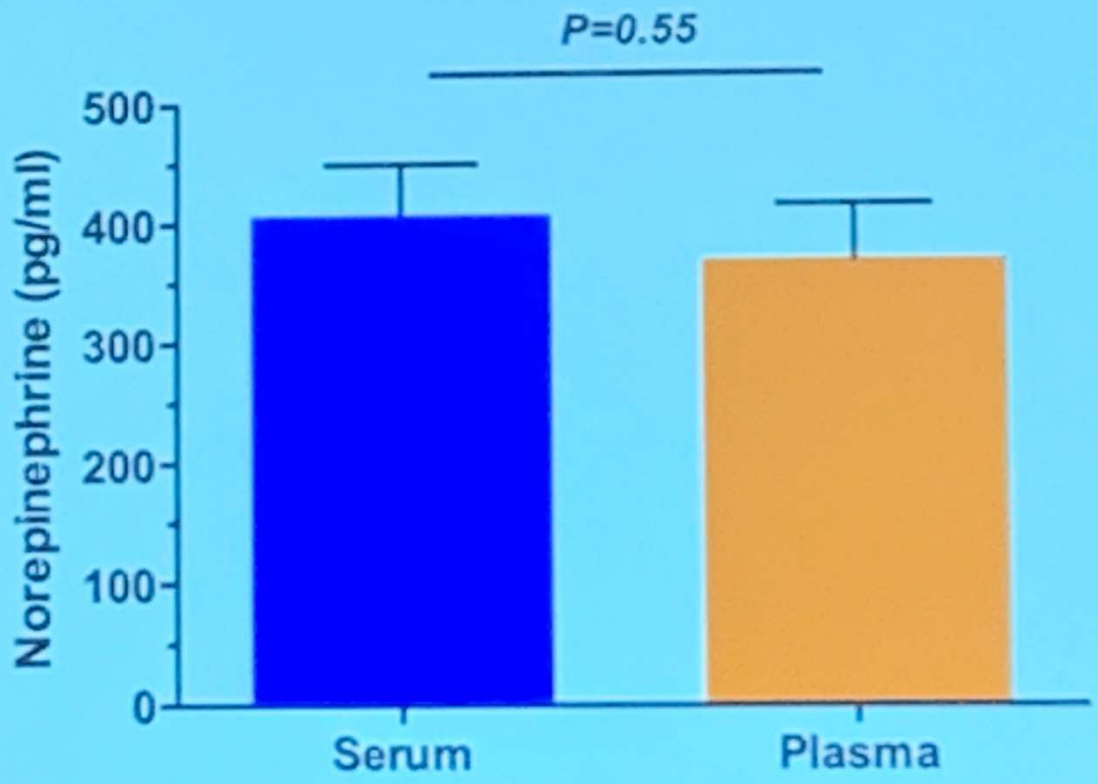


H Li et al., JAHA 2014; 3(1):e000755.

POTS Adrenergic Ab 2 - Summary

- In a different Swedish Cohort of IgG of POTS patients earlier findings were reproduced
- POTS IgG ***in vitro*** has:
  - Alpha-1 Partial Agonist
  - Beta-1 Agonist
  - Beta-2 Agonist
- Do these antibodies have activity ***in vivo***?
  - Next set of planned studies

Norepinephrine Survives in Unpreserved Serum



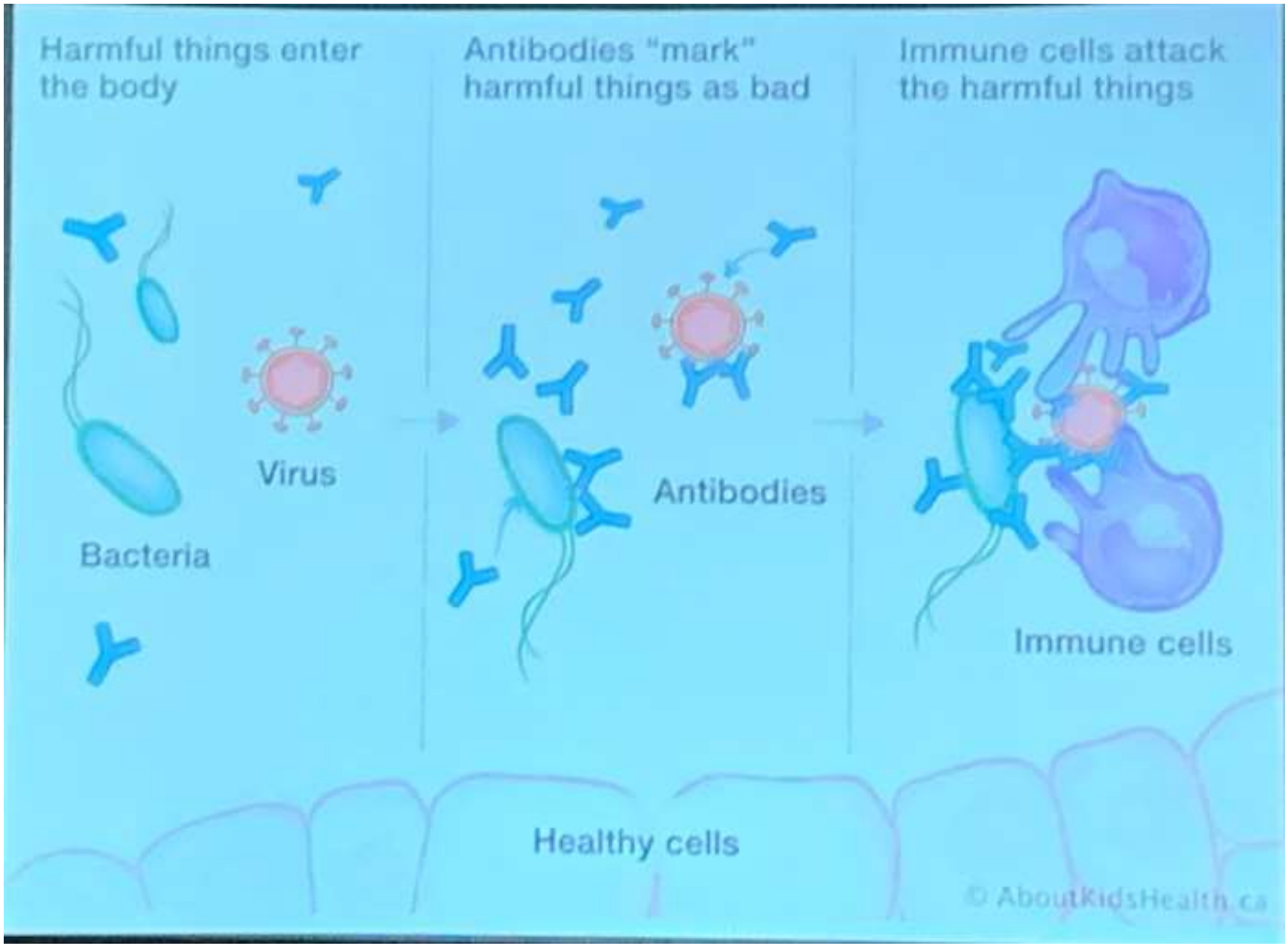
T Badiudeen et al., J Tranlat Autoimmunity 2019; https://doi.org/10.1016/j.jtauto.2019.100006

Conclusions

- Different Information from ELISA vs. Functional Assays
- Norepinephrine can linger in frozen serum samples
  - Can affect alpha-1 and beta-1 AR stimulation assays
- Assays can eliminate the NE

- Alpha-1 and Beta-1 AR Activity is HIGH in POTS

Adrenergic & Muscarinic Antibodies in POTS – Dr. Blair Grubb

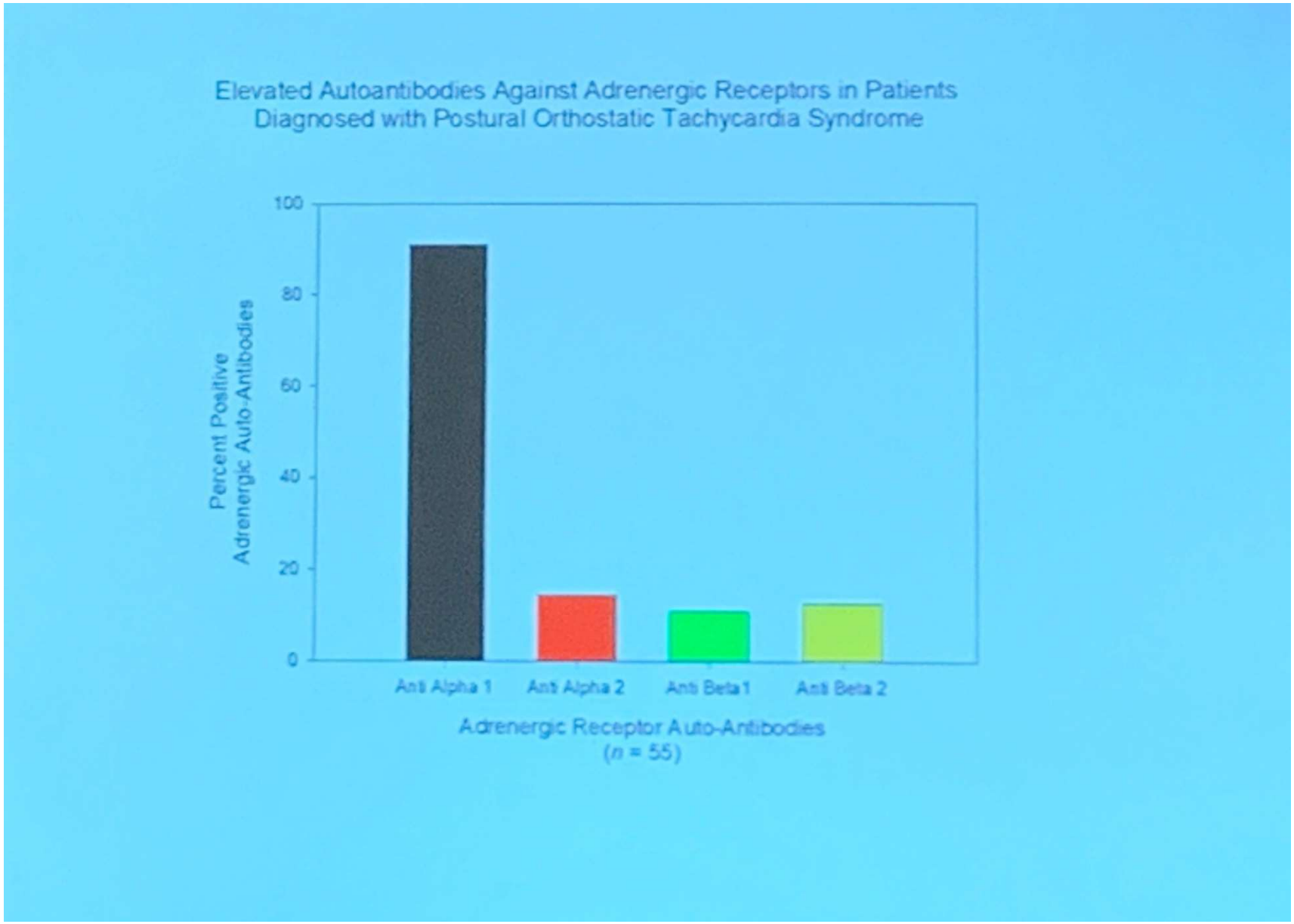

Harmful things enter the body
Antibodies "mark" harmful things as bad
Immune cells attack the harmful things
Virus
Bacteria
Antibodies
Immune cells
Healthy cells
© AboutKidsHealth.ca

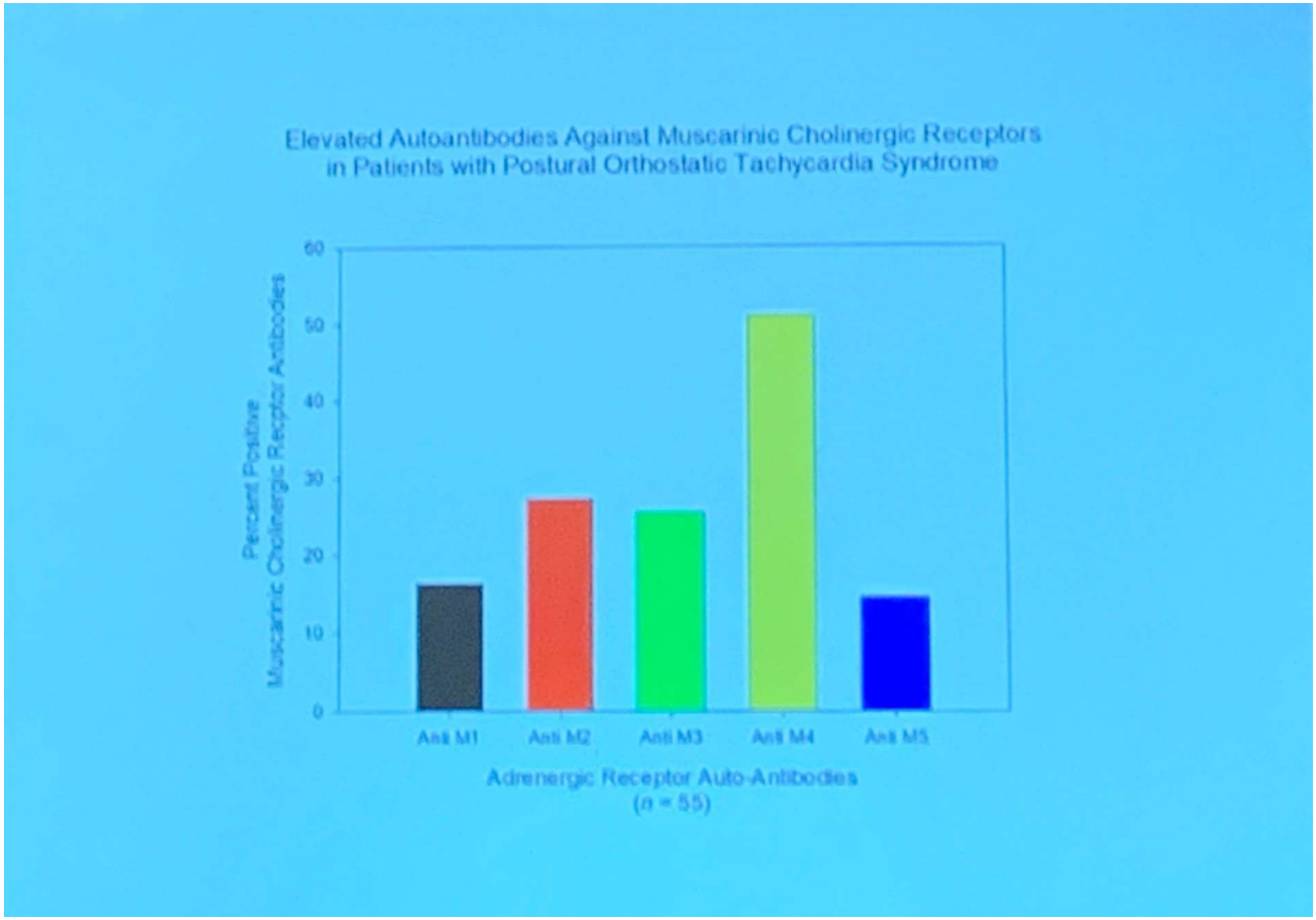

Immune system starts creating antibodies against healthy cells
Antibodies "mark" healthy cells as bad
Immune cells attack the healthy cells
Immune cells
Antibodies
Healthy cells

Alpha and Beta Receptors

Table 1. Alpha and beta adrenergic receptors and their main physiological effects.

Receptor	Location	Physiological activity upon stimulation
α1A	Blood vessels mainly skin and GI tract	Smooth muscle contraction leading to vasoconstriction
α2A	Brain, presynaptic sympathetic nerves	Decrease blood pressure and lower plasma norepinephrine
α2B	Kidney	Water retention and vasoconstriction
α2C	Skin vasculature	Cold induced vasoconstriction
β1AR	Heart	Increase heart rate and stroke volume
	Juxtaglomerular cells of the kidney	Increase renin release causing fluid retention and water restriction
β2AR	Heart	Increase heart rate and stroke volume
	Blood vessels mainly skeletal muscles	Smooth muscle relaxation leading to vasodilation


Elevated Autoantibodies Against Adrenergic Receptors in Patients Diagnosed with Postural Orthostatic Tachycardia Syndrome
Percent Positive Adrenergic Auto-Antibodies
100
80
60
40
20
0
Anti Alpha 1
Anti Alpha 2
Anti Beta 1
Anti Beta 2
Adrenergic Receptor Auto-Antibodies
(n = 55)


Elevated Autoantibodies Against Muscarinic Cholinergic Receptors
in Patients with Postural Orthostatic Tachycardia Syndrome
Percent Positive
Muscarinic Cholinergic Receptor Antibodies
60
50
40
30
20
10
0
Anti M1
Anti M2
Anti M3
Anti M4
Anti M5
Adrenergic Receptor Auto-Antibodies
(n = 55)

Auto-Antibody Summary

- 89% of patients (49/55) had elevated Alpha 1 adrenergic receptor autoantibodies
  - 31% (17/55) had only elevated Alpha 1 autoantibodies
  - 18% (10/55) had 2 or more adrenergic receptor auto-abs
- 5.4% (3/55) of the patients had elevated autoantibodies against all 4 adrenergic and all 5 muscarinic cholinergic receptors; 3.6% (2/55) had 8/9 elevated autoantibodies
- 11% (6/55) of the POTS patients had no elevation of any of the 9 autoantibodies assayed
- Controls had no elevation of autoantibodies

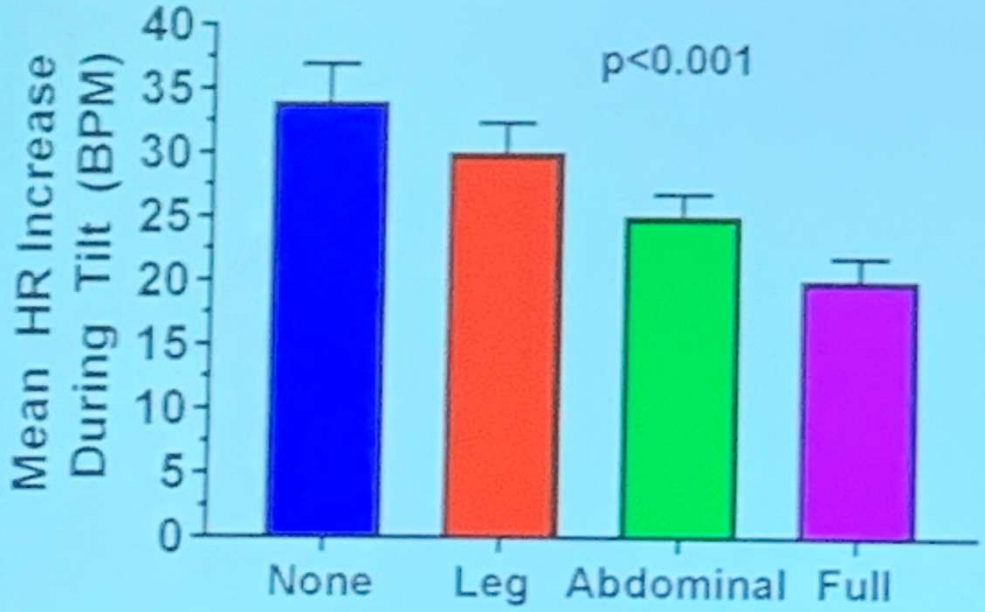
Auto-Antibody Summary (Continued)

- Elevation of muscarinic cholinergic receptor autoantibodies was ***dependent*** upon elevation of adrenergic receptor antibodies
- All POTS patients with elevated muscarinic cholinergic receptor autoantibodies had at least 1 elevated adrenergic receptor antibody
  - 56% (31/55) had elevation of at least one muscarinic autoantibody
  - Muscarinic cholinergic M4 receptor autoantibodies were elevated in 53% (29/55)
  - 31% (17/55) had 2 or more muscarinic cholinergic receptor auto-abs

Do Compression Garments Work in POTS? – Kate Bourne, BSc

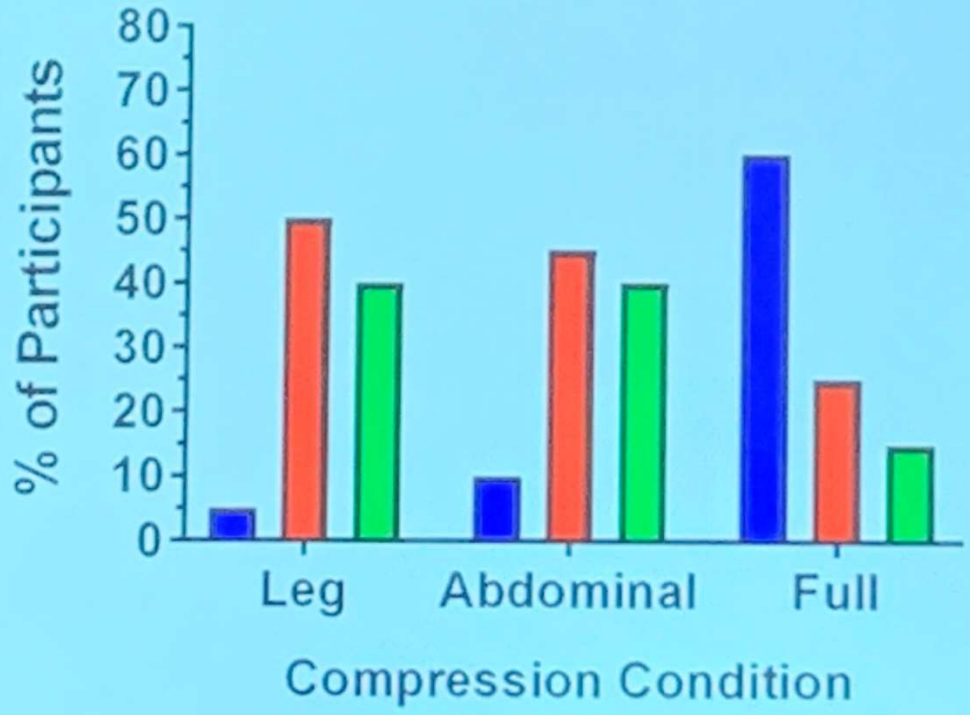
- Study Compared Patients using full (Abs & Legs), Abdominal, Leg, and No Compression
- Study results showed that from Best to Worst:
  1. Full (Abs & Legs)
  2. Abs
  3. Legs
  4. No compression

Mean Heart Rate Increase During Tilts



Compression Condition	Δ Heart Rate (BPM)
None	34
Leg	30
Abdominal	25
Full	20

What did participants experience?



20 study participants responded