



Compassion and Caring Beyond MCAS: Getting Comfortable with Dysautonomia

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Learning Objectives

Upon completion of this activity, participants should be able to...

- Identify conditions which may mimic MCAS
- Leverage primary care homes and multidisciplinary teams to provide the right care, at the right time, every time
- Discuss limitations of evidence and evidence in context
- Adopt a Holistic approach to evidence appraisal, with Open-minded patient partnership, and Willingness to engage in improving health



- *J.L. is an 18 year old woman with a history of Lyme disease and migraines who develops cough and dizziness 10 minutes after starting a dance routine during a class (3 hours after lunch fajita). Associated sx: splotchy rash on upper chest, flushed cheeks, and sense of throat tightness*
- *EMS transport: nebulized albuterol + IV line*
- *Vitals: T 36.7C, O₂ sat 98%, HR 120, RR 35, BP 105/70 mmHg*
- *PE: anxious, respiratory distress with coarse breath sounds, blotchy rash on upper chest*
- *Labs: Acute Tryptase: 8.4; Baseline Tryptase: 6.1*

Additional history:

- This has occurred several times in the past
- She has chronic pain, hypermobility, and easy bruising
- She is often dizzy, particularly when standing
- She has anxiety and depression as well as a diagnosis of irritable bowel syndrome

Is This Anaphylaxis?


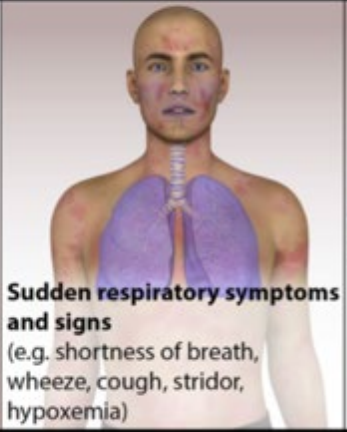

- An acute, potentially life-threatening systemic allergic reaction
- Diagnostic criteria are not perfect and fulfilling diagnostic criteria are not required for epinephrine use to treat an allergic reaction.
- Lifetime prevalence: 1.6% - 5.1%

Shaker M, Wallace D, Golden DBK, et al. JACI 2020. PMID 32001253


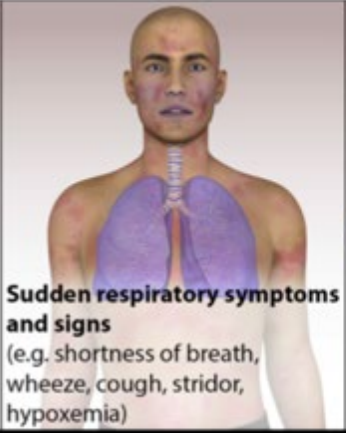


Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)



AND AT LEAST ONE OF THE FOLLOWING:

		
	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

OR 2 Two or more of the following that occur suddenly after exposure to a *likely allergen or other trigger** for that patient (minutes to several hours)

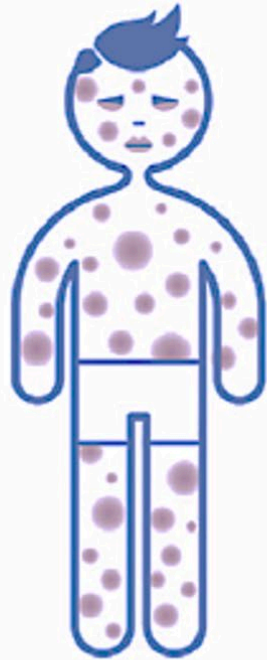
			
Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)	Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

OR 3 Reduced blood pressure (BP) after exposure to a *known allergen*** for that patient (minutes to several hours)

	Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP ***		Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
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1

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)



and at least one of the following



A. Airway/Breathing:
Respiratory compromise.

(e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)



B. Circulation: Reduced BP or associated symptoms of end-organ dysfunction.

(e.g. hypotonia [collapse], syncope, incontinence)



C. Other: Severe gastrointestinal symptoms.

(e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens)

- 2 Acute onset of **hypotension*** or **bronchospasm** or **laryngeal involvement** after exposure to a known or highly probable allergen for that patient (minutes to several hours), **even in the absence of typical skin involvement.**

Infants and children:
low systolic BP (age-specific)
or greater than 30% decrease
in systolic BP*



Adults:
systolic BP of less than 90
mm Hg or greater than 30%
decrease from that person's
baseline



or



Bronchospasm



Laryngeal
involvement

GA²FA 2024

GA²LEN Anaphylaxis and Food Allergy Conference

5th - 7th September 2024 Padua, Italy



2024 International Consensus Definition

46-member multidisciplinary panel of anaphylaxis experts

Anaphylaxis Clinical Support Tool

For Healthcare Professionals

Anaphylaxis is **likely** when any one of the following three criteria are fulfilled

- 1 No Known[†] Allergen Exposure**
Sudden onset of an illness (minutes to several hours) with **Skin / Mucosal** involvement AND either:
 - **Respiratory** involvement
 - **Cardiovascular** involvement
- 2 Likely or Known[†] Allergen Exposure**
Sudden onset of **two** or more of the following:
 - **Skin / Mucosal** involvement
 - **Respiratory** involvement
 - **Cardiovascular** involvement
 - Severe **Gastrointestinal** involvement ‡
- 3 Known[†] Allergen Exposure**
Sudden onset of either:
 - **Respiratory** involvement after exposure to a non-inhaled allergen
 - **Cardiovascular** involvement



Intramuscular Epinephrine / Adrenaline*

- Should be given immediately for suspected anaphylaxis
- Can be given for patients that do not yet fulfill the criteria, based on clinical judgement

Administer in the middle third of the anterolateral thigh; repeat every 5-15 minutes if the patient does not respond

Manual

- 0.01 mg/kg = 0.01 mL/kg of 1 mg/mL (1:1000) solution
- Max single dose 0.5 mg

Auto-injectors

- < 13 kg: 0.1 mg or 0.15 mg
- 13 to < 25 kg: 0.15 mg
- ≥ 25 kg: 0.3 mg (≥ 50 kg: 0.3 mg or 0.5 mg)

Anaphylaxis Organ Systems§



Skin

urticaria, flushing, erythema, facial swelling
Infants may also have mottling



Mucosal

lip, tongue, or oropharyngeal swelling,
severe throat tightness, difficulty swallowing
Infants may also have repetitive lip licking



Respiratory

wheezing, increased work of breathing[¶],
hypoxemia, cough, dyspnea
Laryngeal: stridor, voice change
Infants may also have a hoarse cry



Cardiovascular

hypotension, syncope, dizziness,
unexplained change in mental status
Infants may also have persistent
unexplained tachycardia



Gastrointestinal

severe crampy abdominal pain,
repetitive vomiting, diarrhea

Is this MCAS?

- Recurrent episodes r/t mast cell mediators
 - At least 2 organ systems
- Increases in tryptase
 - Or urinary mast cell mediators
 - Histamine
 - N-methylhistamine
 - Leukotriene E4
 - Prostaglandin D / 9 alpha
 - 11 beta-PGF2 metabolite
- Significant response to anti-mast cell therapy
 - H1 blocker, H2 blocker, LT modifier, cromolyn, or anti IgE

Variant of MCAS	Main Features	Anaphylaxis risk
Primary/Clonal/Monoclonal MCAS	+KIT D816V +/- mast cells with CD25 &/or CD30. May occur with (a) mastocytosis or (b) only 2 SM criteria	+++
Secondary MCAS	Secondary to IgE mediated allergy or immunologic disease	++
Combined MCAS	Meets criteria for both primary and secondary MCAS	+++
HaT+ MCAS	MCAS with HaT	variable
Idiopathic MCAS	No other criteria met	+

When is Tryptase Elevated? The Evolving Tryptase Rule

- Classic evidence of mast cell activation:
 - Acute tryptase 20% plus 2ng/ml over baseline
- Validated in perioperative anaphylaxis
 - **Sn 98%, Sp 44%**
 - PPV 98%, NPV 44%
- Variability limits rule
 - $\frac{1}{4}$ of individuals may exceed this variability on serial measures
- Alternative thresholds with the ratio of acute to baseline levels
- Ratio 1.685
 - Modeled **Sn 94.4%, Sp 94.4%**
- High vs. Low Clinical Suspicion
 - High: 1.374
 - Modeled **Sn 97.5%, Sp 76.5%**
 - Low: 1.868
 - Modeled **Sn 92.4%, Sp 97.5%**



National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):

6.1

Acute tryptase measurement* (ng/mL):

8.4

Clinical Suspicion

Possible

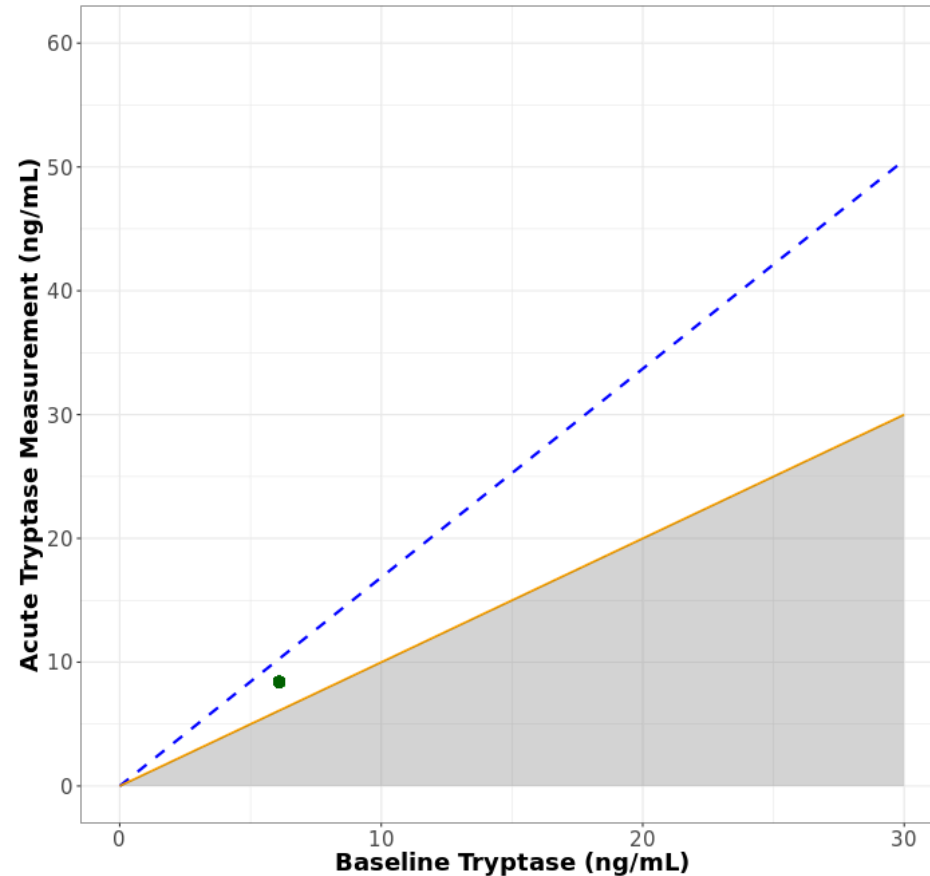
*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data

Reset

The change in total serum tryptase is NOT consistent with the clinical diagnosis of anaphylaxis.



Classic rule (Sn 98%; Sp 44%):

$(6.1 \text{ ng/mL} * 1.2) + 2 = 9.32 \text{ ng/mL} = \text{NO}$

Ratio threshold of 1.685 (Sn 94.4%; Sp 94.4%):

$8.4/6.1 = 1.377 = \text{NO}$

<https://triptase-calculator.niaid.nih.gov>



Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):

6.1

Acute tryptase measurement* (ng/mL):

8.4

Clinical Suspicion

Less Likely

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data

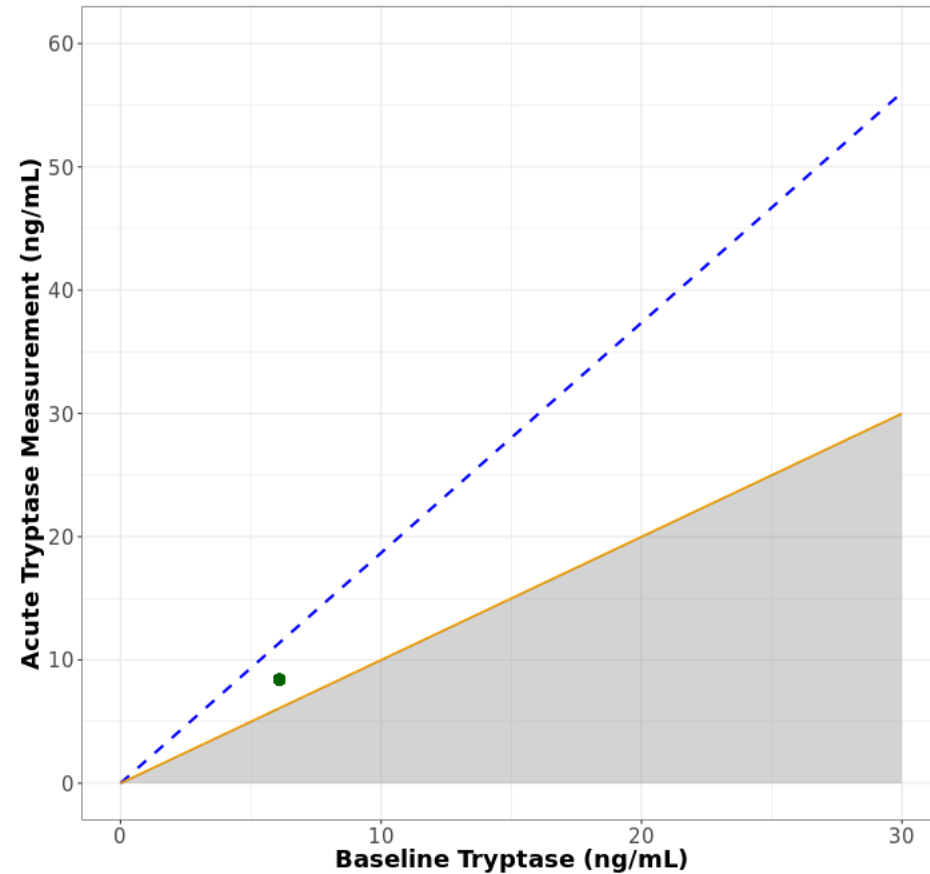
Classic rule (Sn 98%; Sp 44%):

$$(6.1 \text{ ng/mL} * 1.2) + 2 = 9.32 \text{ ng/mL} = \text{NO}$$

High ratio threshold of 1.868 (Sn 92.4%; Sp 97.5%):

$$8.4/6.1 = 1.37 = \text{NO}$$

The change in total serum tryptase is NOT consistent with the clinical diagnosis of anaphylaxis.



— Line of Identity - - Prediction Threshold • Your Patient

<https://triptase-calculator.niaid.nih.gov>



Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):

6.1

Acute tryptase measurement* (ng/mL):

8.4

Clinical Suspicion

Likely

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data

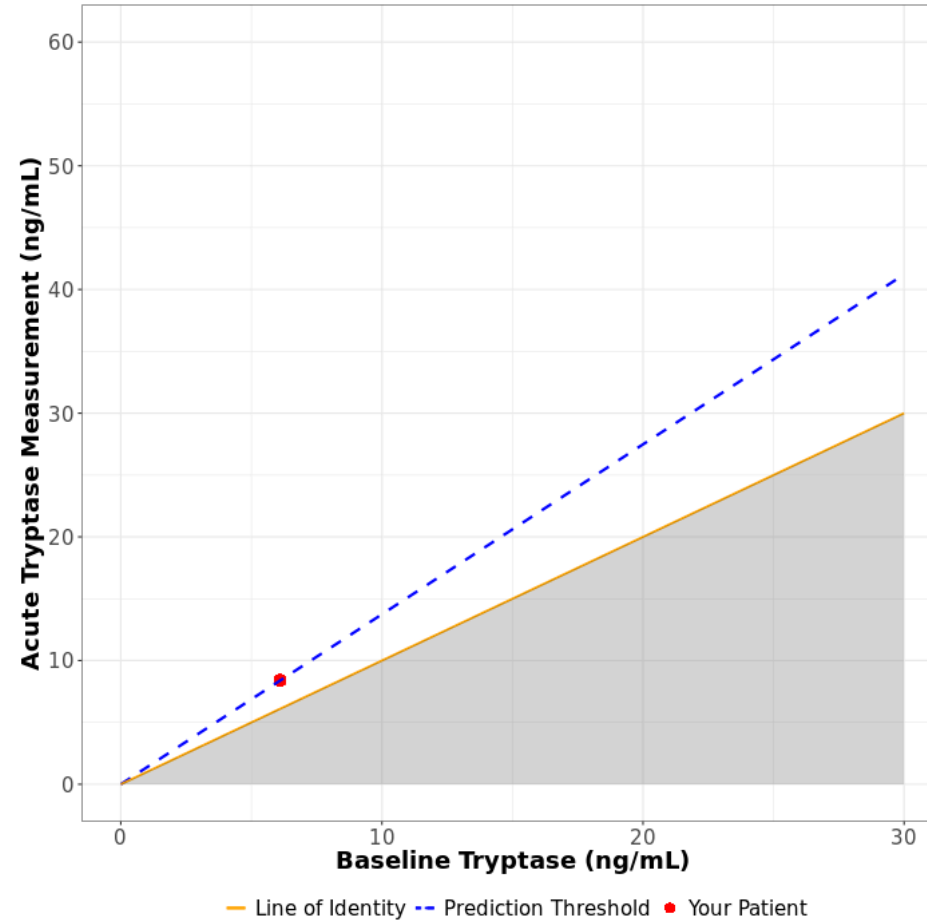
Classic rule (Sn 98%; Sp 44%):

$(6.1 \text{ ng/mL} * 1.2) + 2 = 9.32 \text{ ng/mL} = \text{NO}$

Low ratio threshold of 1.374 (Sn 97.5%; Sp 76.5%):

$8.4/6.1 = 1.377 = \text{YES}$

The change in total serum tryptase is consistent with the clinical diagnosis of ANAPHYLAXIS.



<https://triptase-calculator.niaid.nih.gov>

This tool was developed by [Translational Allergic Immunopathology Unit](#) in collaboration with [Bioinformatics and Computational Biosciences Branch \(BCBB\)](#). For any questions regarding this tool, please contact [Dr. Jonathan Lyons](#) or [Qinlu Wang](#).

Our manuscript describing the design and development of this tool can be found [here](#).

Is this Hereditary alpha Tryptasemia (HaT)?

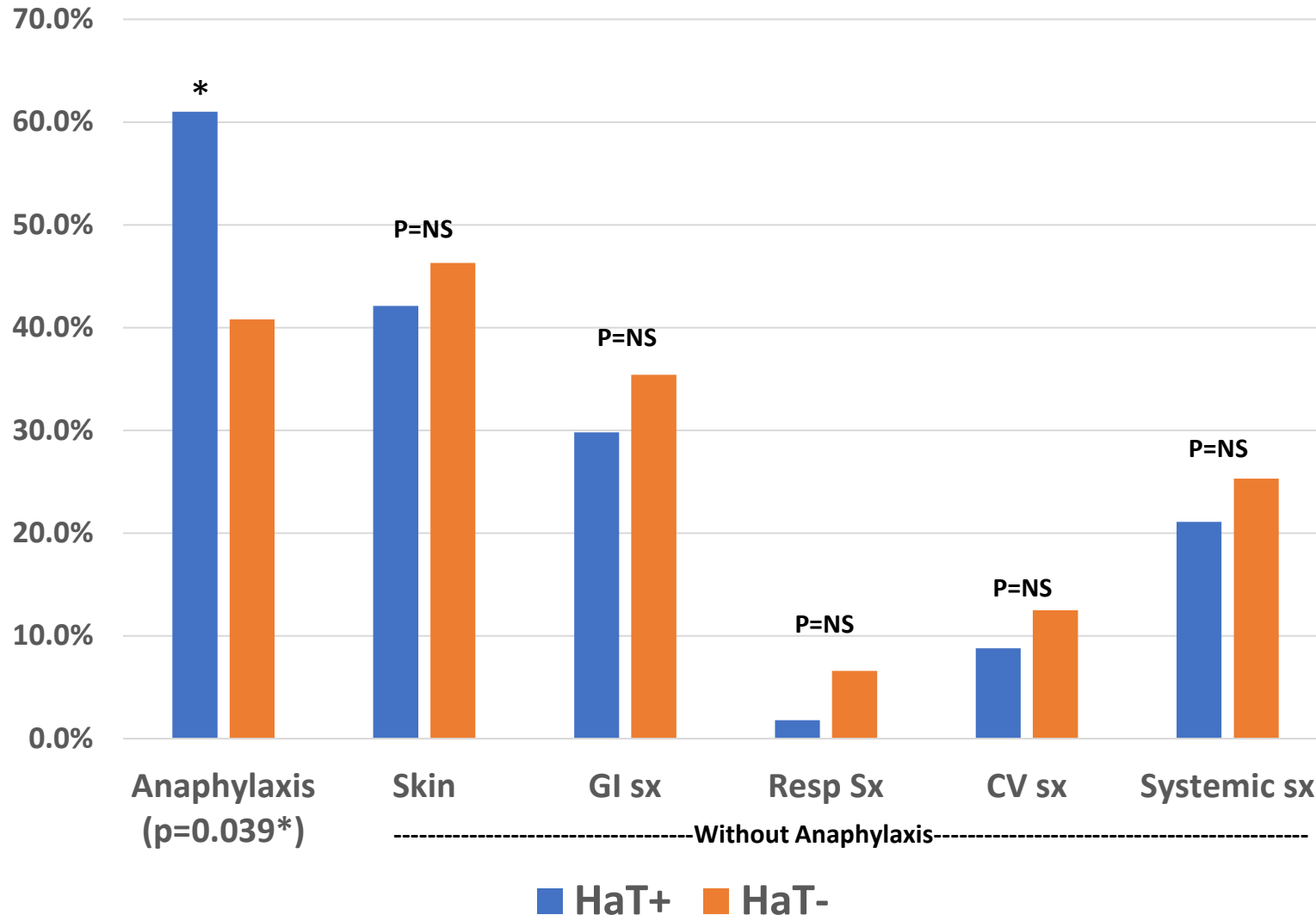
- May affect up to 6% of the population
- Increase in baseline tryptase
 - Alpha tryptase copies at TPSAB1 locus
 - Suspect if tryptase > 8 mg/ml
- May increase frequency and severity of allergic reactions
- Variable penetrance

Evolving understanding of extended associations
Prior theory that HaT led to flushing, bloating, pain, diarrhea, connective tissue disorder, and autonomic dysfunction is evolving
The theory was based on the idea that alpha-tryptase formed heterotetromers with beta tryptase to activate other molecules and enzymes, such as PAR2, which is present in several types of immune cells and involved in a variety of functions including coagulation, cytokine release, smooth muscle relaxation, and vasodilation

Does HaT cause Dysautonomia?

NO

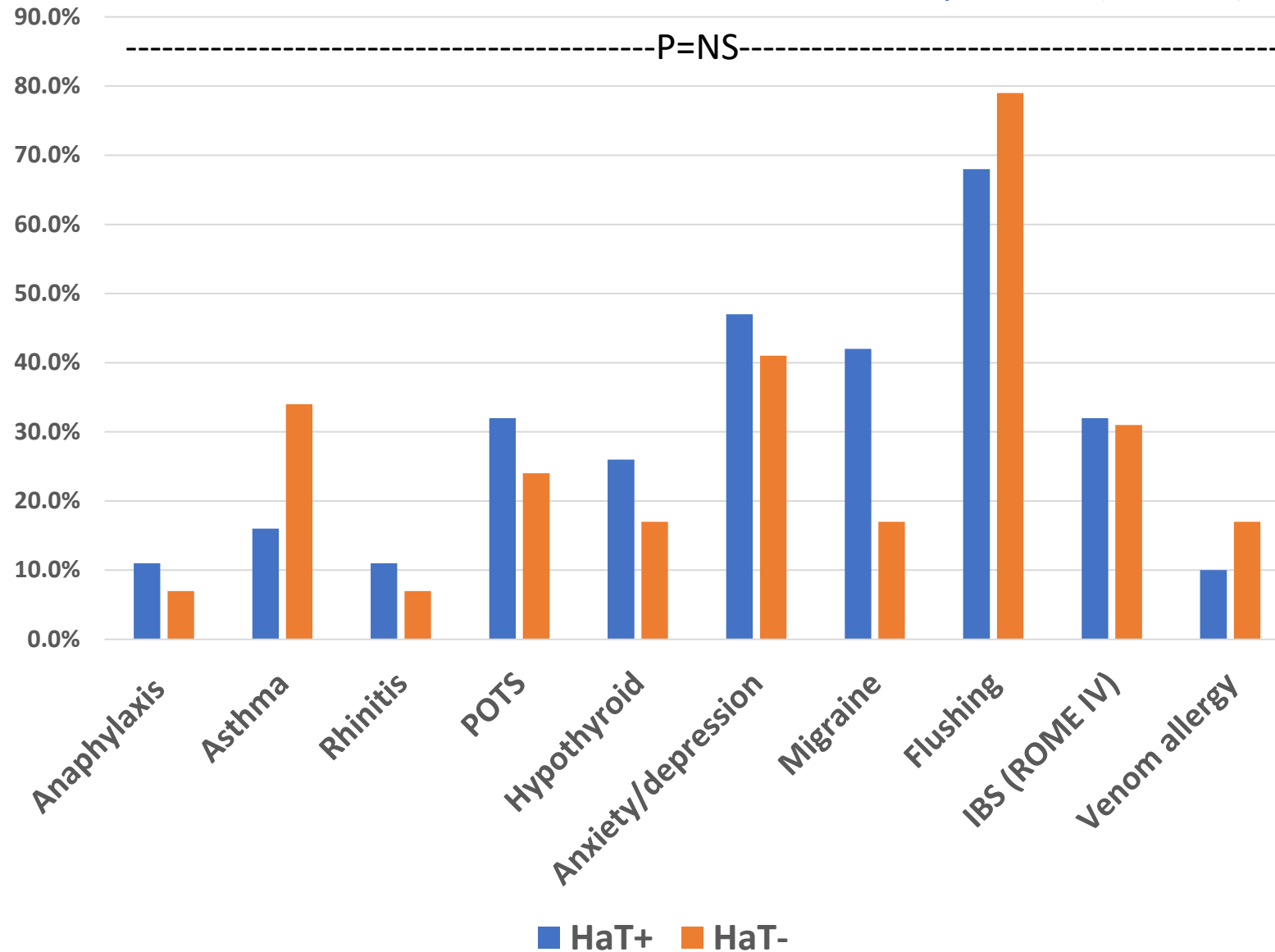
Patients with Mastocytosis or MMAS (n=444)



- Multicenter study
- Higher incidence of HaT in patients with mastocytosis (13.3%)
- Apart from anaphylaxis risk for other conditions was not significantly elevated

Does HaT cause Dysautonomia?

Patients with and without Mastocytosis (n=34)



NO

- No significant difference in comorbidities often considered associated with HaT either in patient with or without mastocytosis
- Limitations: small n

HaT may increase anaphylaxis frequency and severity in mastocytosis, venom allergy, and idiopathic anaphylaxis

Baseline Tryptase Elevations

TPSAB1 copy number can be used to interpret the baseline tryptase level

Additional TPSAB1 copy number	Basal serum tryptase (ng/mL), median (range)	Upper 95% predictive interval	Upper limit using (basal serum tryptase) / 1+copy equation
0	4.1 (0 - 10.4)	11.4	20
1	13.6 (6.5 - 33.9)	36.2	40
2	22.5 (10.5 - 39.5)	62.2	60
3	27.3 (23.4 - 40)	88.8	80
4	37 (25.5 - 62.7)	115.9	100
6	87 (N/A)	171.2	140
10	133 (110 - 156)	285.1	220

Mast cell Disorders and Anaphylaxis

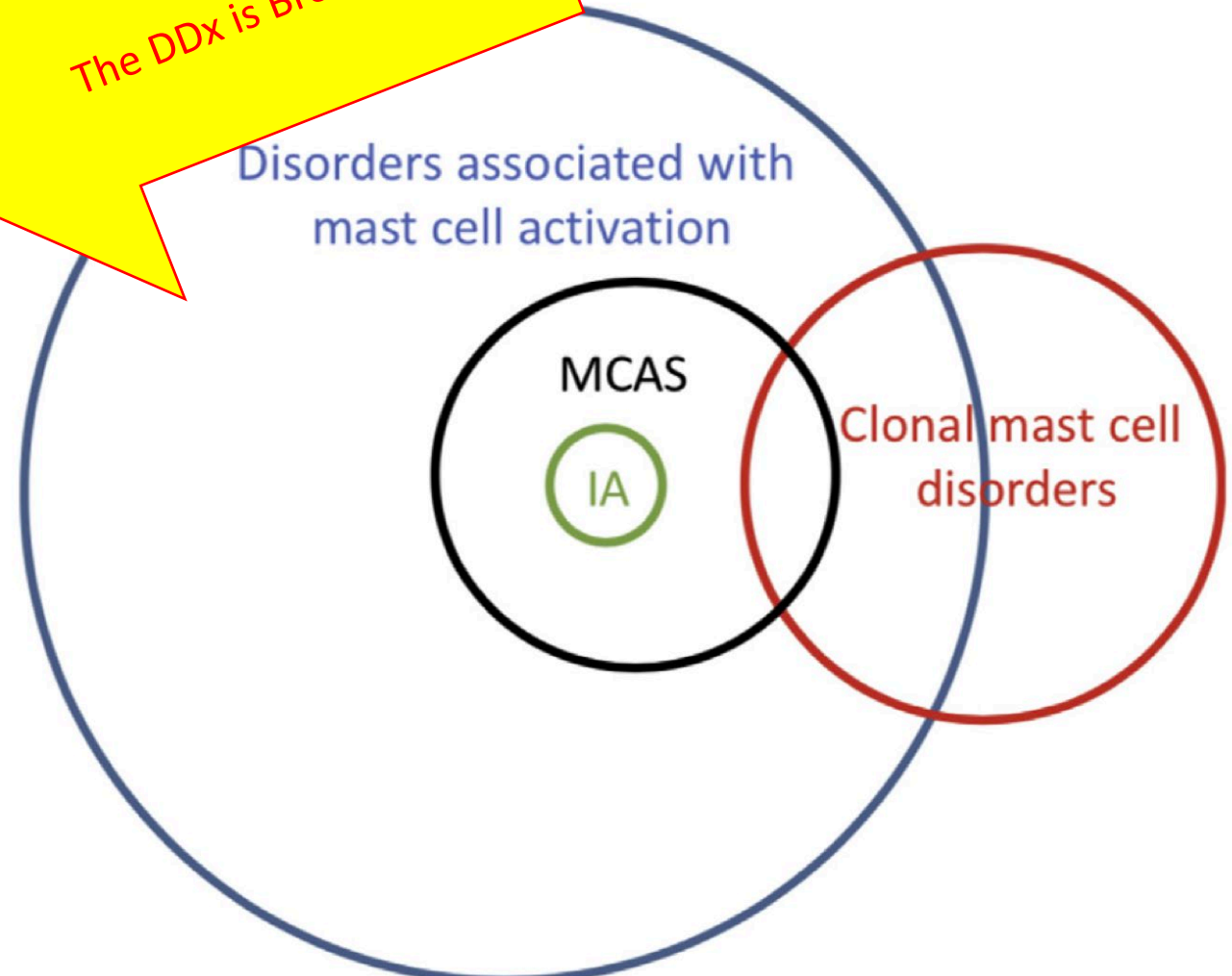
- Serum tryptase alone is not a sensitive enough marker for mastocytosis (s)
- Consider a bone-marrow evaluation in patients with a predictive REMA score (c)

	Variable	REMA score	NICAS score
Gender	Male	+1	+1
	Female	-1	-1
Clinical Symptoms During Attack	Absence of urticaria and angioedema	+1	--
	Presence of urticaria and/or angioedema	-2	--
	Presyncope or syncope	+3	
	Absence of angioedema	--	+1
	Flushing	--	-1
	Urticaria	--	+1
	Syncope	--	+3
Tryptase	< 15 ng/mL	-1	--
	>25 ng/ml	+2	---
	< 11.4 ng/mL	--	-1
	> 11.4 ng/mL	--	+3
Allele-specific PCR (D816V)	Negative	--	-1
	Positive	--	+3

Mast Cell Disorders

TABLE III. Selected differential diagnosis of IA

Anaphylaxis/MCDs	Nonanaphylactic disorders
Mastocytosis and other clonal MCDs	Vocal cord dysfunction
Nonclonal MCDs	Flushing disorders (pheochromocytoma, carcinoid, vasoactive intestinal peptide tumors)
Acute urticaria/angioedema	Somatoform disorders
Food allergy	Vasovagal syncope
	Panic attack
	Asthma exacerbation
	Myocardial infarction or other acute cardiac disorder
	Scrombroidosis



Neuropsychiatric symptoms may include short memory span, inability to concentrate, anxiety, depression, brain fog

FIGURE 1. Classification of mast cell disorders.

Total Patient Care

When it's not MCAS...

Consider....

- Cholinergic urticaria or other inducible hives,
- Chronic pain syndrome,
- Hypermobile Ehlers Danlos syndrome (hEDS),
- Postural orthostatic tachycardic syndrome (POTS) associated with dizziness, palpitations and flushing,
- Irritable bowel syndrome with bloating and diarrhea or constipation,
- Headaches,
- Mental Health,
- Environmental and medication intolerances.

MCAS Mast cell features across organ systems

Neuropsychiatric:

brain fog, depression, anxiety, short memory span, inability to concentrate, small fiber neuropathy.

Upper Respiratory:

sinonasal pruritus, nasal stuffiness, conjunctival infection

Lower Respiratory:

throat/chest tightness, dyspnea, wheezing

Skin:

urticaria, flushing, pruritus, angioedema

Cardiovascular:

hypotension, tachycardia, palpitations, chest pain

Gastrointestinal:

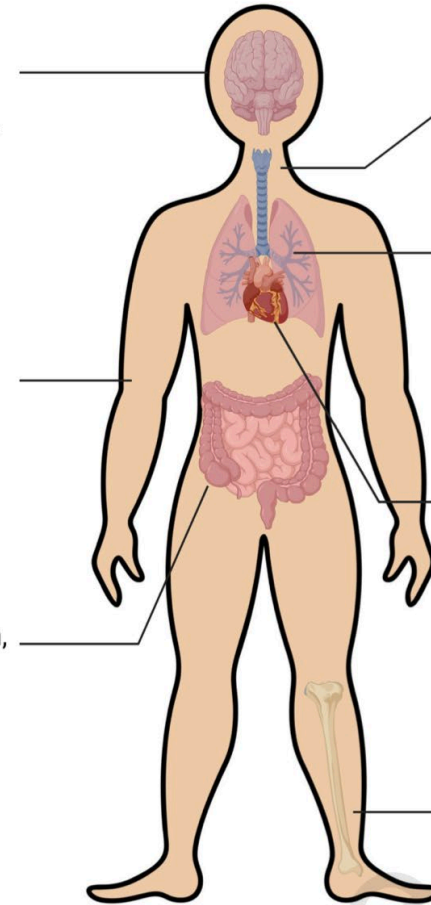
nausea, abdominal pain, bloating, cramping, diarrhea.

Musculoskeletal:

pain

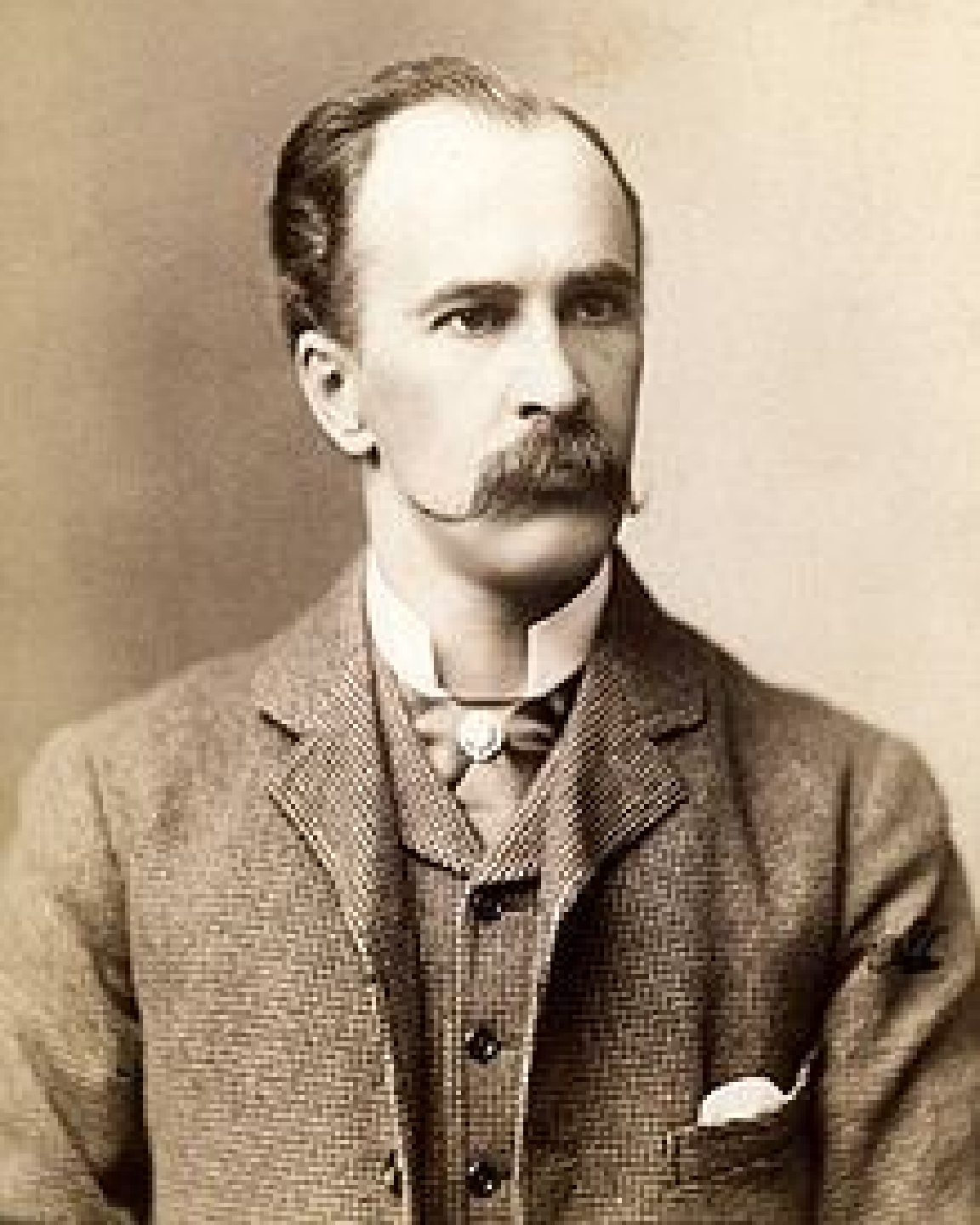
Systemic:

anaphylaxis, fatigue, dysautonomia.



TPC





“The good physician treats the disease; the great physician treats the patient who has the disease”

- Sir William Osler, 1849-1919

Beyond Confirmed Mast Cell Activation Syndrome: Approaching Patients With Dysautonomia and Related Conditions



Alexandra E. Conway, BA^a, Marylee Verdi, APRN, MSN^b, Marcus S. Shaker, MD, MS^{c,d,e}, Jonathan A. Bernstein, MD^f,
Claire C. Beamish, MD^g, Richard Morse, MD^{d,h}, Juliette Madan, MD^{i,j,k}, Michael W. Lee, PhD^l, Gordon Sussman, MD^m,
Amer Al-Nimr, MD^{d,n}, Matthew Hand, DO^{d,o}, and Daniel A. Albert, MD^{d,p} *Hanover and Lebanon, NH; Cincinnati, Ohio; and
Toronto, Ontario, Canada*

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Begins with

- Hearing
- Other
- People's
- Experiences

Allergic Diseases and Mental Health

Alexandra E. Conway, BA^a, Marylee Verdi, APRN, MSN^b, Navya Kartha, DO^c, Chaitanya Maddukuri, DO^d, Aikaterini Anagnostou, MD, PhD^e, Elissa M. Abrams, MD, MPH^f, Priya Bansal, MD^{g,h}, Don Bukstein, MDⁱ, Anna Nowak-Wegrzyn, MD, PhD^{j,k}, John Oppenheimer, MD^l, Juliette C. Madan, MD, MS^{m,n}, Sarah L. Garnaat, PhD^{o,p}, Jonathan A. Bernstein, MD^q, and Marcus S. Shaker, MD, MS^{r,s} *Hanover and Lebanon, NH; Akron and Cincinnati, Ohio; Houston, Texas; Winnipeg, MB, Canada; St. Charles, Ill; Milwaukee, Wis; New York, NY; Olsztyn, Poland; and Newark, NJ*

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Begins with

- **Hearing**
- **Other**
- **People's**
- **Experiences**

The Power of Validation

“As allergist-immunologists, even just the simple acknowledgement that mental health and inflammation are connected can have therapeutic value to our patients”

Allergic Diseases and Mental Health

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Some examples

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- Adolescents with AR have greater odds of depression (aOR 1.10) and suicide attempts (aOR 1.05)
- Children with AD have greater risks for ADHD (OR 1.87), depression (OR 1.81), and autism (OR 3.04)
- Emotional symptoms are more common in children with asthma (OR 1.34)
- Patients with CU more likely to have anxiety (OR 3.99) and depression (2.94)

HOPE & The Forgotten Rose

- In 1885, a young woman presented to the office of Dr. John Noland Makenzie
- CC: “allergy to roses”
 - The rose cold
 - Unable to sit in the same room with a rose
- During the interview, Dr. Makenzie produced a hidden rose and dramatic symptoms occurred

...but the rose was not a rose at all



Experience, Belief, and Disease

Of the mind and of the body

Perspective

Neuroimmune pathways and allergic disease

An overview

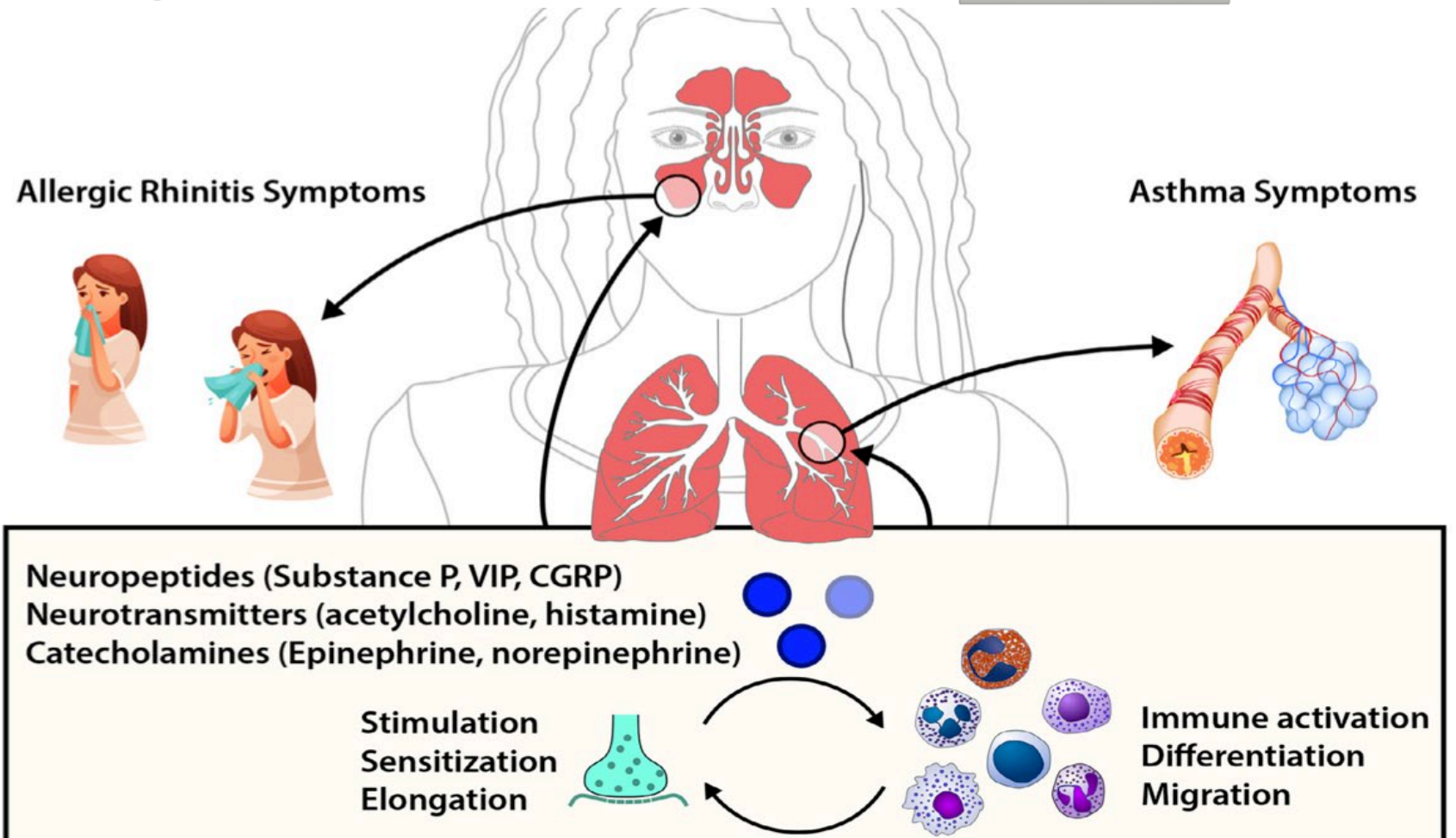
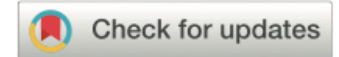
Andrew Long, PharmD^{*,†}; Jenika R. Sharon Chinthrajah, MD^{*}; Say

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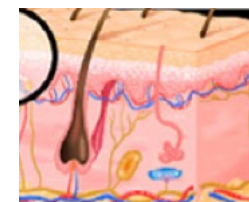
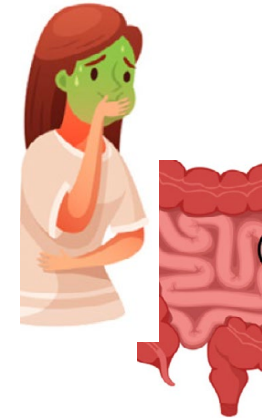
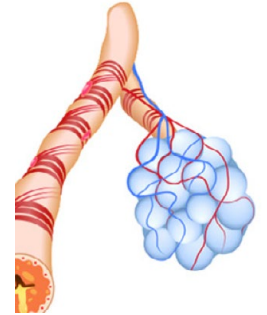
“the interactions between neurons and immune cells often result in a positive feedback loop in local tissues, amplifying robust immune responses, which may be responsible for persistent allergic symptoms”



Neuroimmunology

Some examples

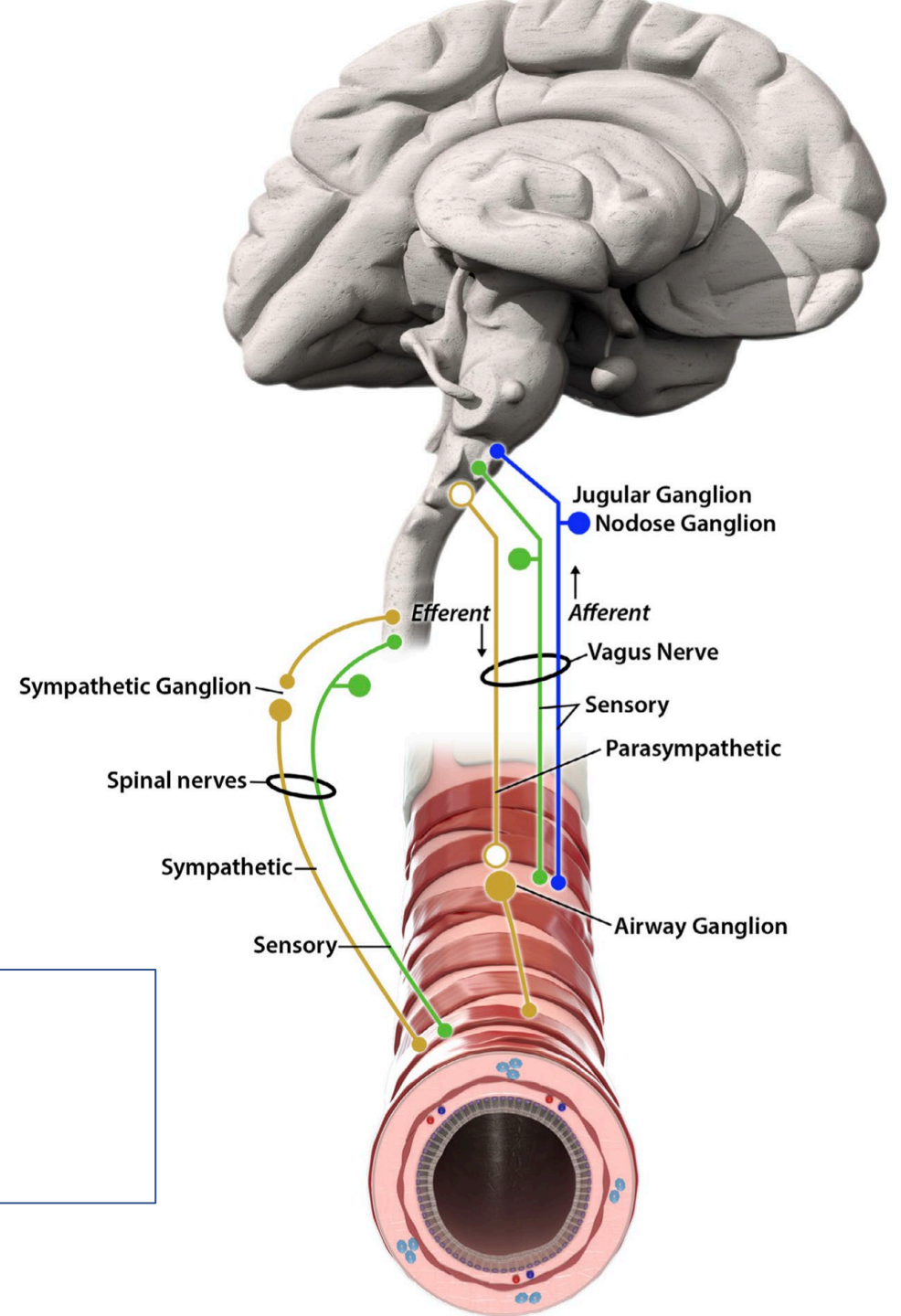
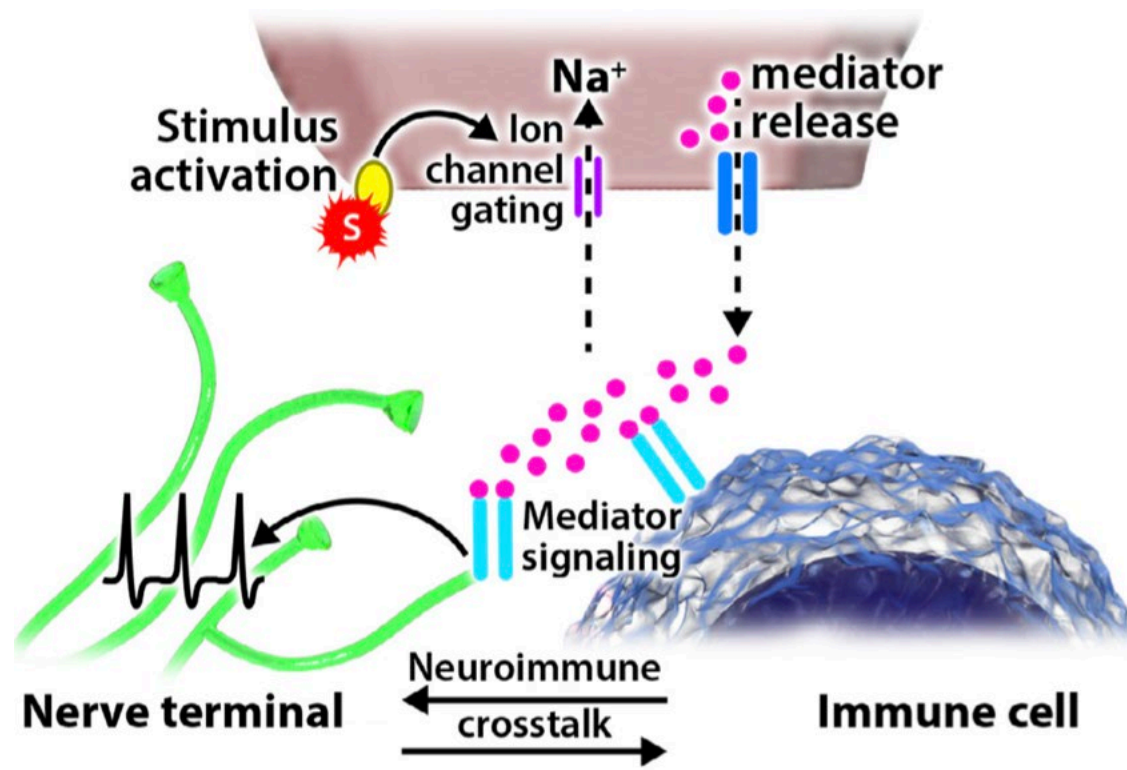
- AD itch-scratch cycle: epidermis and dermis of eczematous lesions contain a higher number of SP nerve and mast cells expressing their receptor (neuokinin 1). IL-4, IL-5, and IL-13 induce sensory nerve activation through neuropeptides such as SP
- Bronchospasm in asthma: smooth muscle is innervated by sympathetic and parasympathetic nerve fibers. Acetylcholine induces bronchoconstriction and mucous secretion by the M3 receptor
- Eosinophil derived major basic protein induces dysfunction in the M2 receptor, which may increase cholinergic activity



More Examples of Neuroimmune Cross-talk

Concept	Example(s)
Neuroimmune frameworks	
Neurons and immune cells share common and complementary signaling processes	<ul style="list-style-type: none">• Immune cells can express receptors for classic neurotransmitters, including neuropeptides, acetylcholine and noradrenaline• Nerve fibers express receptors for classic inflammatory mediators, including interferons, prostaglandins, and cytokines
Close spatial proximity between immune cells and airway nerve fibers facilitates bidirectional communication	<ul style="list-style-type: none">• Eosinophils shown to concentrate around airway nerves in patients with asthma
Specialized airway epithelial cells can facilitate neuroimmune interactions	<ul style="list-style-type: none">• Sensory neuropeptides modulate immune cells in airway mucosa• Airway brush cells sense bacterial stimuli and activate neurons through ATP and other mediators• Neuroendocrine cells forming neuroepithelial bodies (NEBs) positioned at airway branch sites and help regulate allergic inflammation through neuronal signaling
Sensory neural pathways	
Sensory neuropeptides can facilitate or inhibit inflammatory cell actions	<ul style="list-style-type: none">• Substance P and vasoactive intestinal peptide promote allergic inflammation• Calcitonin gene-related peptide negatively regulates ILC2s and neutrophils
Sensory neurons can respond to and become sensitized by tissue alarmins and pathogen-products	<ul style="list-style-type: none">• ATP binding to P2X receptors and HMGB1 binding to RAGE have actions on airway sensory neurons• Mycobacterium tuberculosis activates sensory neurons through cell wall-derived glycolipid, sulfolipid-1
Sensory ganglia can become inflamed during airway pathologies	<ul style="list-style-type: none">• Influenza infection shown to promote inflammatory cell recruitment and transcriptional changes in vagal ganglia• Patients with laryngeal dysfunction can show signs of vagal neuropathy
Sensory hypersensitivity contributes to disease morbidity	<ul style="list-style-type: none">• Chronic cough is associated with cough hypersensitivity syndrome, characterized by heightened sensitivity to a broad range of triggers• Sensory innervation to the airways is increased in patients with asthma and chronic cough
Autonomic neural pathways	
An anti-inflammatory reflex regulates systemic components of inflammation	<ul style="list-style-type: none">• The sympathetic nervous system suppresses systemic inflammation through splanchnic nerve innervation of the spleen and abdominal viscera• The anti-inflammatory reflex can be initiated through vagal sensory neuron stimulation
Common therapies targeting autonomic neural processes can modify inflammation	<ul style="list-style-type: none">• The muscarinic receptor antagonist tiotropium reduces cytokine and inflammatory mediator production/cell recruitment induced by different proinflammatory stimuli• Endogenous noradrenaline and dopamine, as well as beta-adrenergic therapies, suppress immune cells• Alpha 7 nicotinic acetylcholine receptor ($\alpha 7nAChR$) agonists attenuate hyperoxia-induced lung injury
Central nervous system	
A lung-brain axis may regulate neuroimmune interactions	<ul style="list-style-type: none">• Dedicated CNS circuits encode sensory inputs from the airways• CNS neuroinflammation can occur in models of airways disease• High brain processes for regulating immunologic memory have been described• Mood and cognitive comorbidities are common in patients with airways disease

Neuro-immune synapse



- **Close proximity**
- **Functional interactions**
- **Immune cells express neurotransmitter receptors**

Azelastine desensitizes transient receptor potential vanilloid 1 channels: explaining its therapeutic effect in allergic rhinitis

Umesh Singh¹, Jonathan A Bernstein

Affiliations + expand

PMID: 24980233 DOI: [10.2500/ajra.2014.28.4059](https://doi.org/10.2500/ajra.2014.28.4059).

We are regular contributors to the journal of Allergy and Clinical Immunology

Background: Capsaicin, a prototypic transient receptor potential vanilloid 1 (TRPV1) agonist, has been shown to be more clinically effective in the treatment of nonallergic rhinitis (NAR) compared with other rhinitis subtypes. Azelastine has also been found to be clinically effective in the treatment of NAR but its mechanism(s) of action is still poorly elucidated. This study was designed to determine, using in vitro cell lines, whether topical therapies including azelastine have activity on TRPV1 ion channels similar to capsaicin.

Methods: The effects of capsaicin (1 μ M), azelastine (30 μ M), bepotastine (10 μ M), olopatadine (10 μ M), and fluticasone (200 μ M) on TRPV1 channels using mice neuronal cells (Cath.a), as surrogates for submucosal sensory neurons, and human nasal epithelial cells (hNEC) were determined and compared. For azelastine, bepotastine, and capsaicin, which elicited an agonist effect on TRPV1, live cell $[Ca(2+)]$ signaling in Cath.a cells and hNECs expressing TRPV1 were performed in the absence and presence of capsazepine at 10 μ M (a TRPV1 antagonist) or using wild-type mouse embryonic fibroblasts (wtMEFs) that express TRPV1 ion channels and TRPV1 homozygous null mutant (TRPV1^{-/-}) knockout MEF cells as controls to establish TRPV1 channel selectivity. As azelastine has previously been found clinically effective in NAR, additional experiments were performed to determine its ability to desensitize TRPV1 ion channels and its effect on regulating intracellular calcium homeostasis.

Results: Cath.a cells treated with azelastine, bepotastine, or capsaicin showed a significant increase in TRPV1-dependant (Ca(2+)) specific cytosolic fluorescence. Continuous treatment with azelastine or capsaicin resulted in desensitization of TRPV1 channels. In hNECs, azelastine stimulation resulted in Ca(2+) shifts from the cytosol to mitochondria and overexpression of hematopoietic cell-specific Lyn substrate 1-associated protein X1, which may thus be effective in cytosolic Ca(2+) homeostasis.

Conclusion: Azelastine, similar to capsaicin, exhibits direct activity on TRPV1 ion channels that may represent a novel mechanistic pathway explaining its clinical efficacy in NAR.

Beyond Confirmed Mast Cell Activation Syndrome: Approaching Patients With **Dysautonomia** and Related Conditions



When it's not MCAS...

- Cholinergic urticaria or other inducible hives,
- Chronic pain syndrome,
- Hypermobile Ehlers Danlos syndrome (hEDS),
- Postural orthostatic tachycardic syndrome (POTS) associated with dizziness, palpitations and flushing,
- Irritable bowel syndrome with bloating and diarrhea or constipation,
- Headaches,
- Mental Health,
- Environmental and medication intolerances.

What is Dysautonomia?



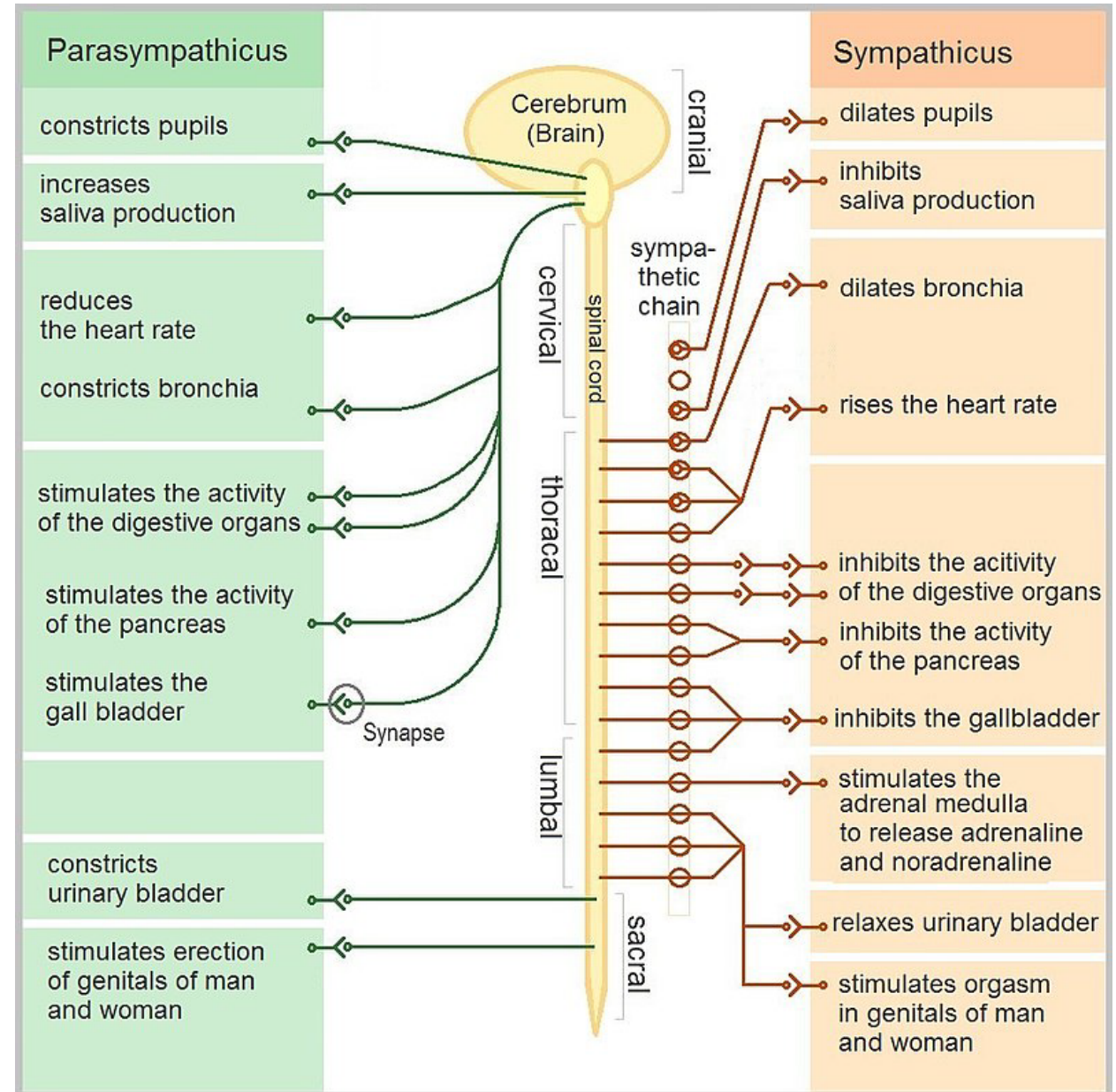
dysautonomia **noun**

dys·au·to·no·mia (dis-ŏt-ə-'nō-mē-ə)

: a disorder of the autonomic nervous system that causes disturbances in all or some autonomic functions and may result from the course of a disease (as diabetes) or from injury or poisoning

- A number of conditions can impact the autonomic nervous system
 - Parkinson's disease, multiple system atrophy, dementia with Lewy bodies, small fiber neuropathies (e.g, diabetes, autoimmune), hereditary forms
- Symptoms can overlap with MCAS
 - Brain fog, dizziness, difficulty swallowing, exercise intolerance, syncope, orthostasis

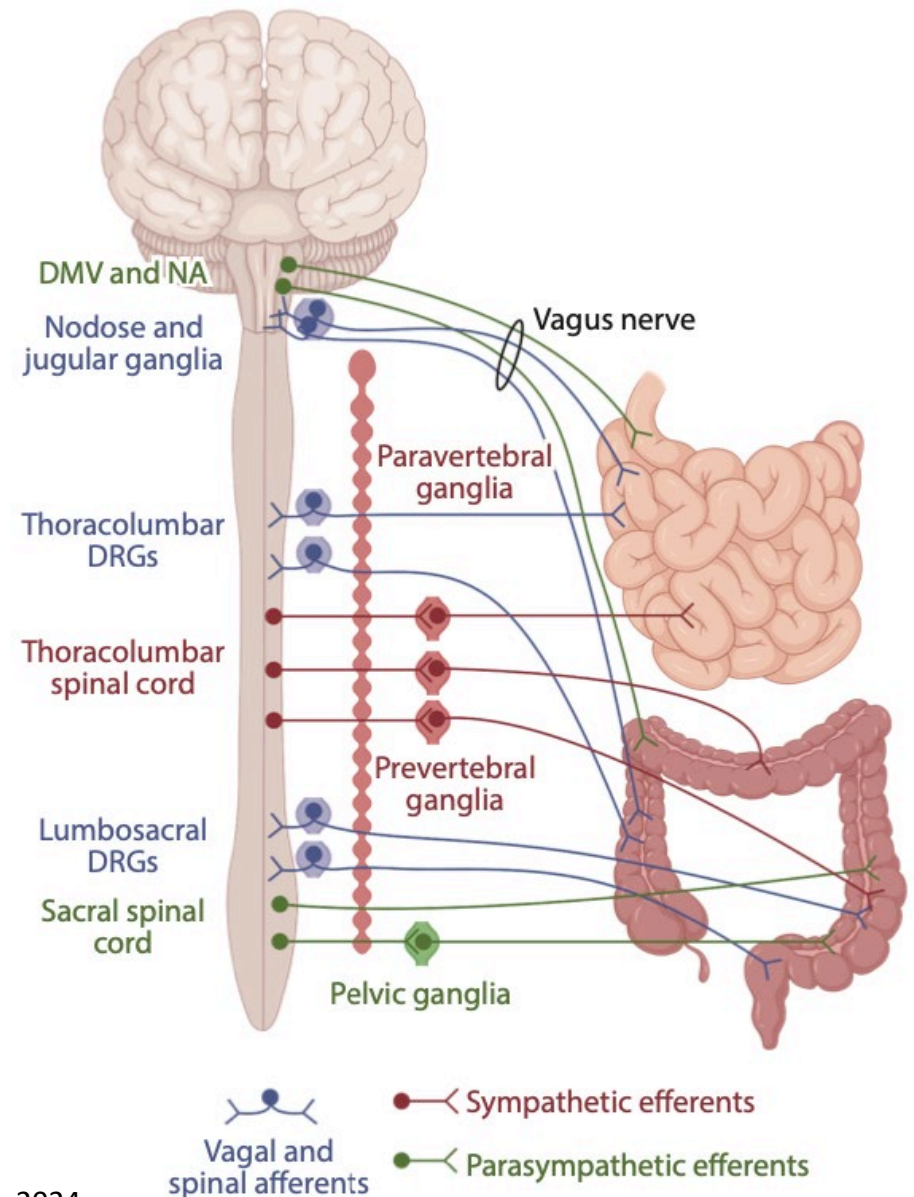
The autonomic nervous system (2/3)



What is Dysautonomia?

- Dysfunction of the sympathetic, parasympathetic, and enteric nervous systems can present in several ways
- Postural orthostatic tachycardia syndrome
- Irritable bowel syndrome
- Bladder dysfunction
- Evaluation may begin with measuring blood pressure in supine and standing positions to eval for orthostatic hypotension:
 - 20 mmHg drop in systolic BP
 - 10 mm Hg drop in diastolic BP

The enteric nervous system is the third arm of the autonomic nervous system (3/3)



POTS

- Mechanisms may include:
 - Hypovolemia and deconditioning, somatic hypervigilance, neuroendocrine hyperadrenergic state, small fiber neuropathy
- Sudomotor testing may be abnormal in up to 60% of patients
- Tilt table testing
- Patients are typically young (between 15 – 50 yo) and predominantly female
- Significant functional limitation
- Orthostatic symptoms include lightheadedness, palpitations, headache
- Associated cognitive dysfunction and GI disturbances, sleep and bladder disturbances

POTS

- Additional evaluation

- Plasma electrolytes, CBC, Thyroid function testing, ECG
- Consider: morning cortisol, echocardiogram, catecholamines, 24 hour urine sodium excretion, gastric motility testing

- Treatment

- **Water and salt:** Target 3L of water and 3-4 grams of sodium
- **Physical therapy and conditioning** with strength training
- **Counseling and lifestyle management:** Avoid further deconditioning, improved sleep, consider cognitive behavioral therapy to improve coping
- **Tight socks:** Compression stockings at 30-40 mmHg to prevent venous pooling
- **Individualized medications:** Low dose beta-blocker if not contraindicated. Additional considerations include midodrine, fludrocortisone, pyridostigmine, methylphenidate, and ivabradine

hEDS and Amplified Pain Syndrome

- Hypermobile EDS (hEDS) patients may also report orthostatic intolerance or autonomic symptoms
 - Up to 78% of patients with generalized joint hypermobility report autonomic symptoms
 - Connective tissue laxity may result in pain from joint instability and affect vascular wall compliance leading to venous pooling
- Hypermobility can be assessed with the Beighton score
- Treatment
 - Physical therapy, as in POTS
 - Selected pharmacotherapy: low dose amitriptyline, gabapentin
- Amplified Pain Syndrome (aka, fibromyalgia)
 - Address sleep and assess for comorbid anxiety and depression

hEDS and the Beighton score

TABLE III. Beighton score

Movement	Points
Pinky extends $\geq 90^\circ$ at metacarpophalangeal joint	+1 for each hand
Thumb bends to touch forearm	+1 for each hand
Elbow extends $\geq 190^\circ$	+1 for each arm
Knee extends $\geq 190^\circ$	+1 for each knee
Palms touch floor without bending at knees	+1
Total Beighton score (9 points possible)	

The cut-off to indicate generalized joint hypermobility varies by demographic. A score of ≥ 4 has been used with a sensitivity 0.8% and specificity 99.3%.²⁷ A higher cutoff may be appropriate for children.^{26,28}

hEDS and the Muldowny Physical Therapy Program

- Patient-physical therapist alliance
- False perceptions of tightness
- Precise order of exercises
- Strength, then function
- Eliminate triggers
- Body mechanics for activity of daily living
- Tools to enable strengthening
- When in doubt, refer out
- Do not give up

Mental Health Screening

Mental Health Screening

Anxiety: GAD-2

Anxiety: GAD-7

Depression: PHQ-2

Depression: PHQ-9

Generalized Anxiety Disorder 2-item (GAD-2) Share

The Generalized Anxiety Disorder 2-item (GAD-2) is a very brief and easy to perform initial screening tool for generalized anxiety disorder.¹

Over the **last 2 weeks**, how often have you been bothered by the following problems?

Not at all Several days More than half the days Nearly every day

1. Feeling nervous, anxious or on edge	<input type="radio"/> 0	<input type="radio"/> +1	<input type="radio"/> +2	<input type="radio"/> +3
2. Not being able to stop or control worrying	<input type="radio"/> 0	<input type="radio"/> +1	<input type="radio"/> +2	<input type="radio"/> +3

GAD-2 score obtained by adding score for each question (total points)



Interpretation:

A score of 3 points is the preferred cut-off for identifying possible cases and in which further diagnostic evaluation for generalized anxiety disorder is warranted. Using a cut-off of 3 the GAD-2 has a sensitivity of 86% and specificity of 83% for diagnosis generalized anxiety disorder.

Alternative screening tools are available for younger children (AAP mental health tools)

IBS

- Patients with dysautonomia, hEDS, and APS may also present with a functional gastrointestinal disorder that includes bloating, abdominal pain, and diarrhea or constipation
- Healthy eating patterns, involvement of a registered dietitian, and cognitive behavioral therapy can be helpful
- Individualized medication: Considerations may include antidiarrheal bulking agents or laxatives, antispasmodics, or low dose amitriptyline
- Integrative medicine approaches may mirror cognitive behavioral therapy, focusing on the mind-body connection of the neuroimmune axis

Vocal Cord Dysfunction / Inducible Laryngeal Obstruction

- Functional laryngeal disorder
- Female predominance
- Symptoms of throat tightness, choking sensation, dysphonia, cough
- Commonly evaluated and managed by allergist-immunologists
- Improved by speech / cognitive behavioral therapy
- May be associated with PTSD as well as dysautonomia
 - In one report, 44% of patients evaluated for VCD screened positive for PTSD

Adverse Childhood Experiences

- ACEs may influence dysautonomia and related conditions
- Elbers et al retrospectively reviewed 100 consecutive patients from a pediatric neurology clinic
 - At least 5 years old with at least 4 unexplained symptoms for at least 3 months
- Seventeen patients met inclusion criteria and were more likely to report at least one ACE (88% vs 33%, $p < 0.001$). These patients experienced:
 - Emotional dysregulation (100%)
 - Executive dysfunction (94%)
 - Autonomic dysregulation (76%)
 - Digestive problems (71%)

Severe Multiple Drug Intolerance Syndrome in Fibromyalgia and Irritable Bowel Syndrome



Alicia A. Alvarez, MD^a, Jayme M. Palka, PhD^b, and David A. Khan, MD^c *Sarasota, Fla; and Dallas, Texas*

What is already known about this topic? Multiple drug intolerance syndrome (MDIS) describes patients with multiple nonimmunologically mediated adverse reactions to medications. MDIS, fibromyalgia, and irritable bowel syndrome (IBS) overlap in patient characteristics and interactions with health care.

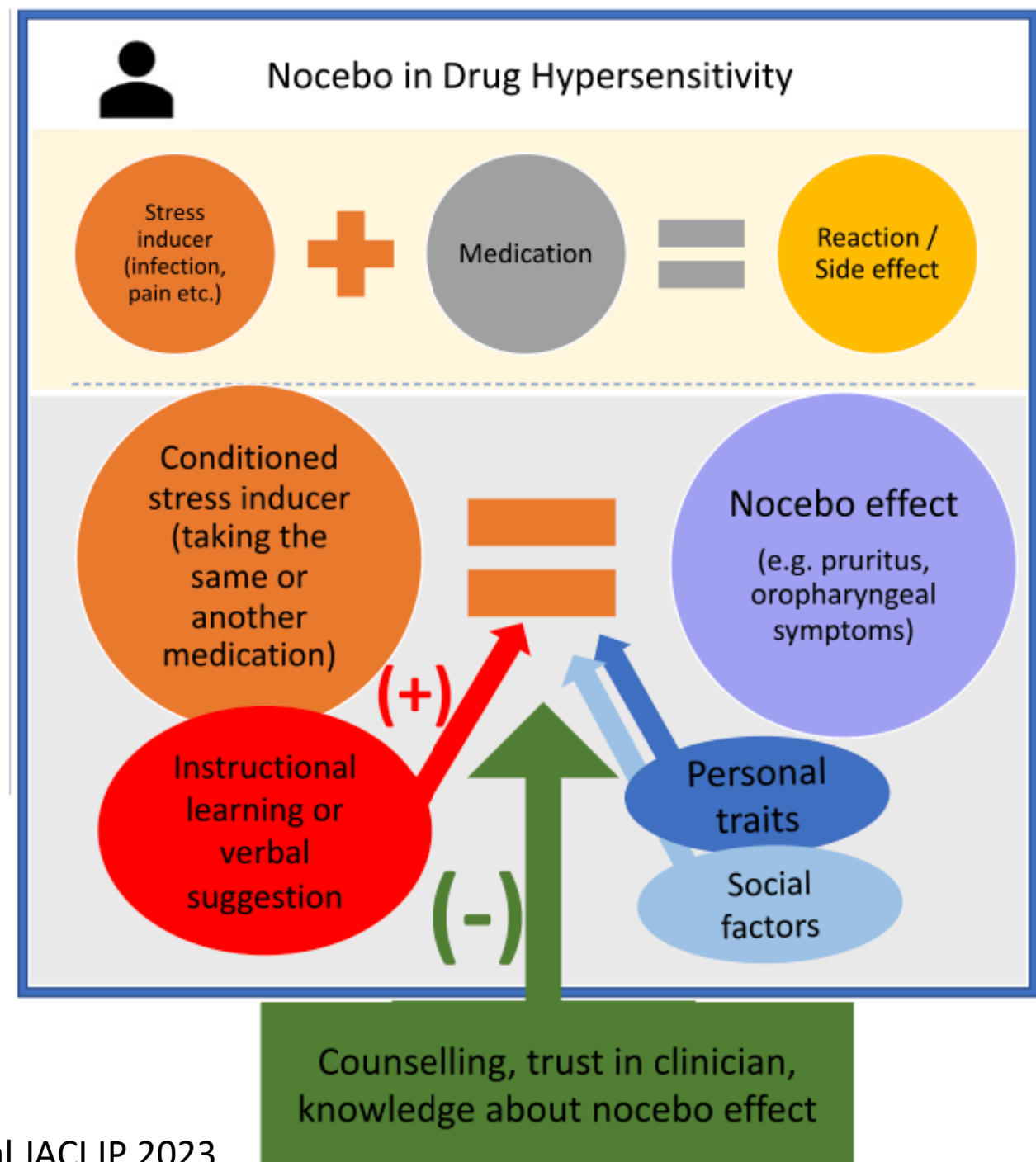
What does this article add to our knowledge? Patients with fibromyalgia and IBS have significantly higher rates of severe MDIS. This was associated with polypharmacy in both groups. Patients with IBS more often reported gastrointestinal symptoms as adverse medication reactions.

How does this study impact current management guidelines? Fibromyalgia and IBS should be noted during the evaluation of drug allergy labels. These findings highlight the need for therapeutic options for patients with MDIS and delabeling strategies for patients with multiple comorbidities.

Patients with fibromyalgia and IBS were 12 and 3 times more likely to have severe MDIS

Nocebo effect

- Another mind-body example, where negative expectations are fulfilled with a placebo
- In a study of 228 patients with reliable drug allergy histories
 - 60% had reactions to placebo
 - 12% of nocebo reactions were objective
 - 43% urticaria
 - 24% flushing



Multiple Chemical Sensitivity & Fear-Based Models of Treatment

Odors eliciting fear: A conditioning approach to Idiopathic Environmental Intolerances

Arne Leer^{a,*}, Monique A.M. Smeets^a, Patricia J. Bultsing^b, Marcel A. van den Hout^a

^aDepartment of Clinical & Health Psychology, Utrecht University, P.O. Box 80140, 3508 TC Utrecht, The Netherlands

^bUnilever, Vlaardingen, The Netherlands

- IEI triggered by harmless odors resulting in multiple organ system complaints
- Example of an adverse conditioning response may play some role
- Fear responses can be extinguished over time, suggesting a role for cognitive behavioral therapy

- **False**
- **Evidence**
- **Appearing**
- **Real**

‘Known Knowns’

How do we understand, explain, and apply evidence to patients?

‘Known Unknowns’

‘Unknown Unknowns’

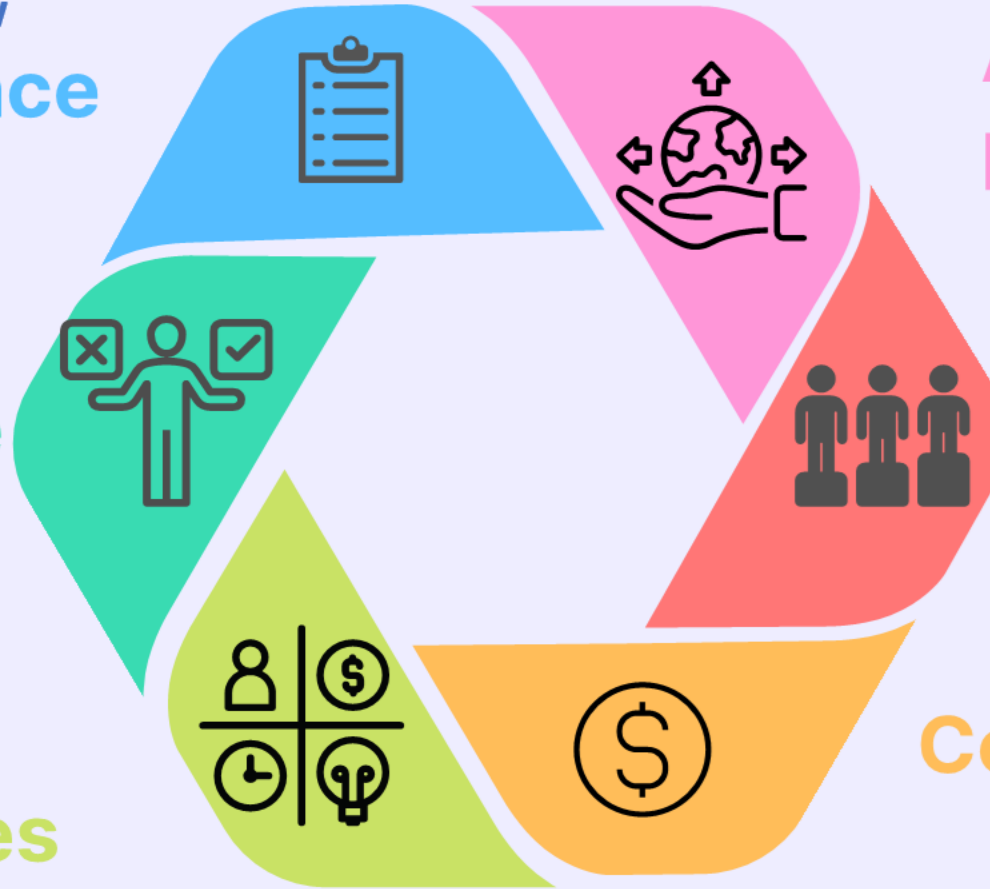
Holistic appraisal of evidence in context

High, Moderate, Low, or Very Low
Certainty of Evidence

RCT vs cohort? Risk of bias?
Imprecision? Inconsistency?
Indirectness? Publication bias? Effect
size? Dose-response? Confounding?

Patient Preference

Resources



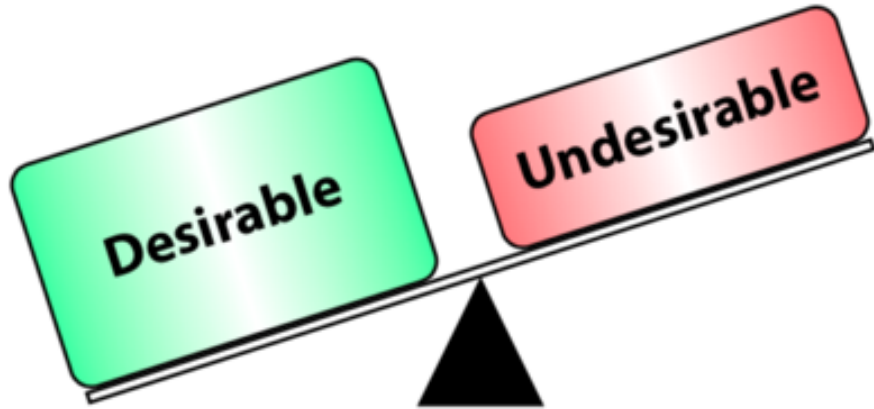
Acceptability and Feasibility

Equity

Cost-Effectiveness

Guideline Recommendations Must Consider

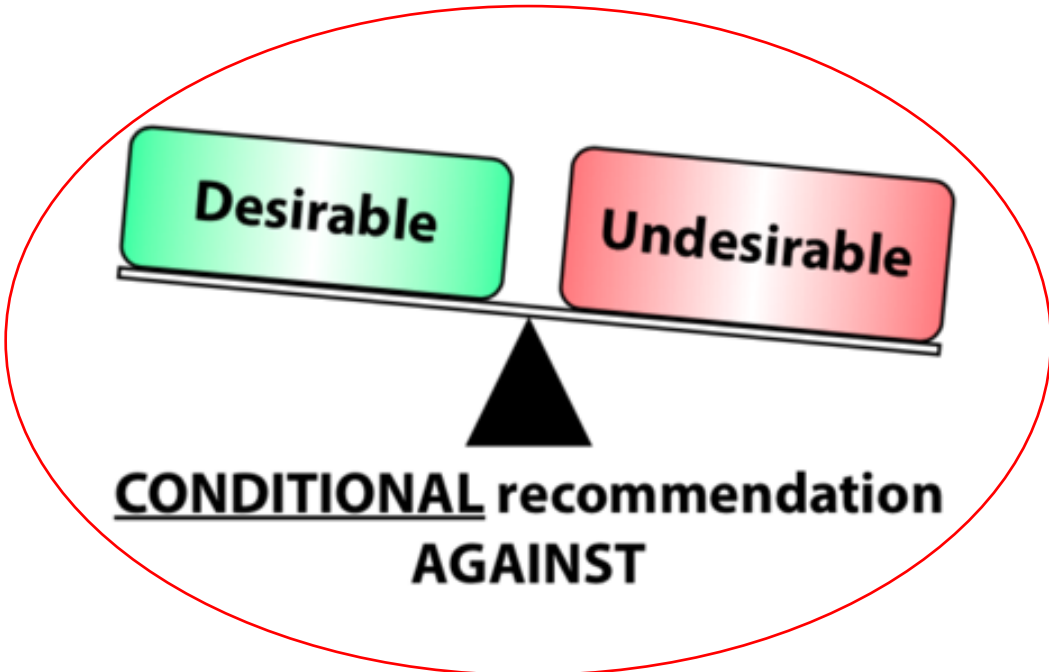
Holistic appraisal of evidence in context



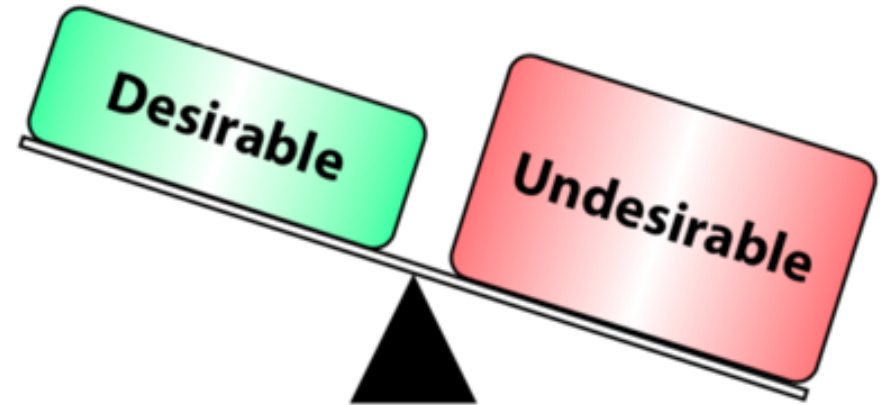
**STRONG recommendation
IN FAVOR**



**CONDITIONAL recommendation
IN FAVOR**



**CONDITIONAL recommendation
AGAINST**



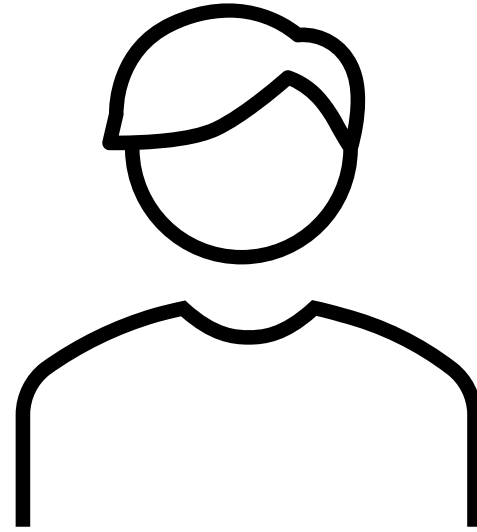
**STRONG recommendation
AGAINST**

Conditional Recommendations are Navigational Signals for Shared Decision Making

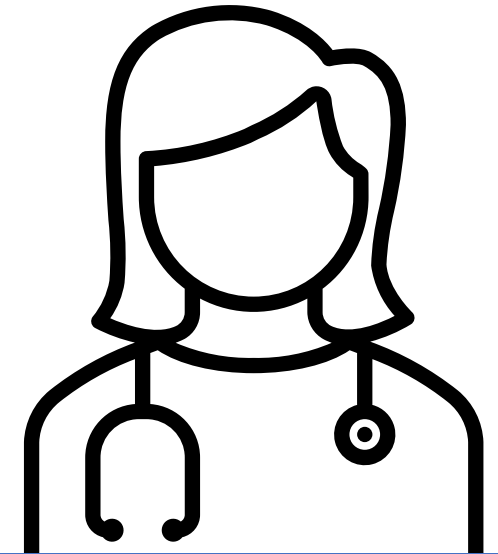


Shared Decision Making

Patients and clinicians work together to share the best possible evidence of clinical science, expertise, values, and preferences to deliver bespoke care in situations of clinical equipoise or conditional recommendations



Patient
Expertise in their
Values and
Preferences



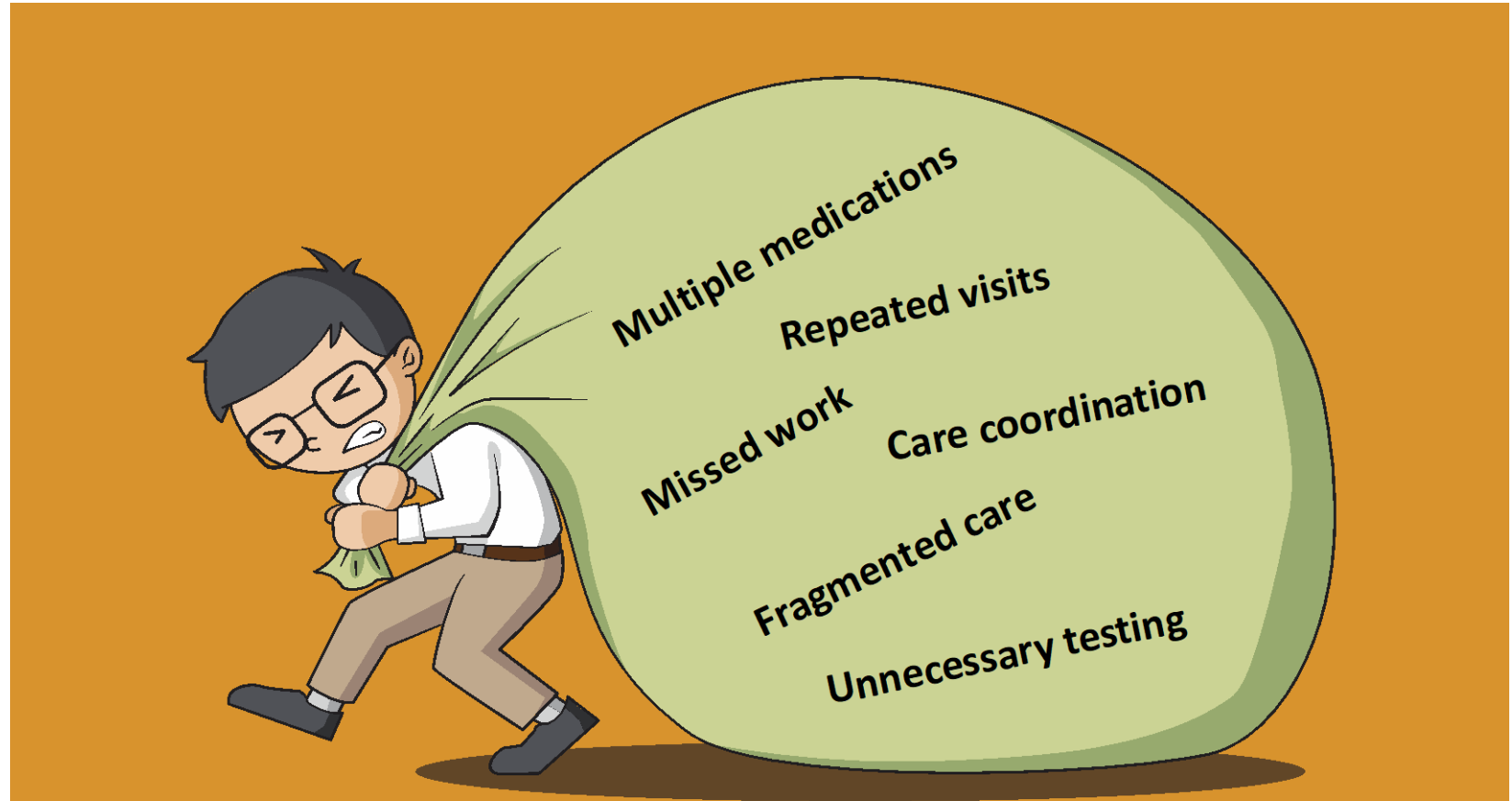
Clinician
Expertise and
Experience in
Clinical Science

Equipoise



Minimally Disruptive Medicine & Shared Decisions

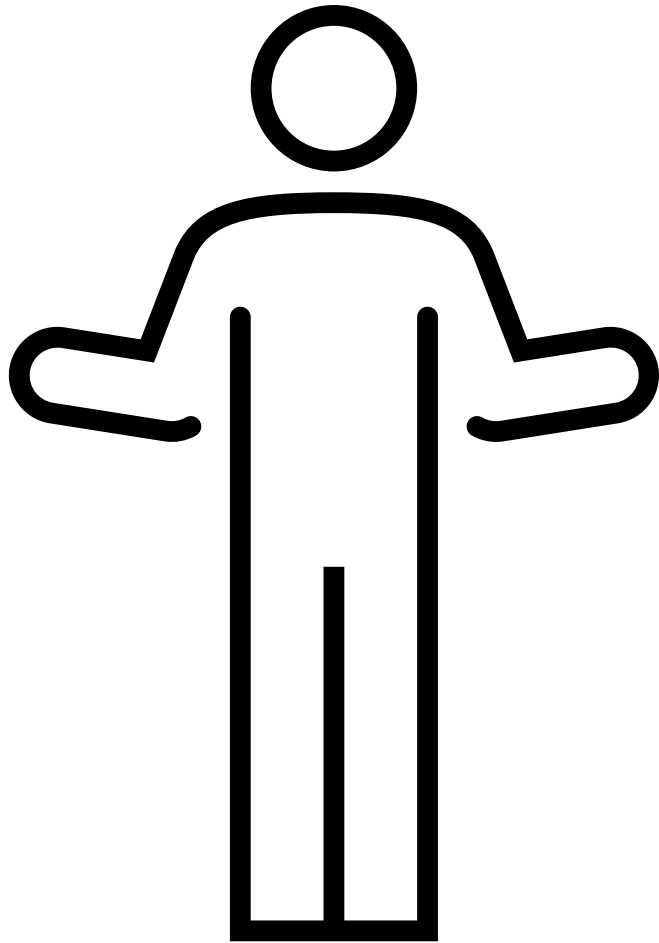
- Awareness of patient burdens can help to maximize their collaborative capacity



Overwhelmed patients may be less able to partner in their own care

Willingness to serve as a partner and guide

Willingness requires appreciation of the entire person



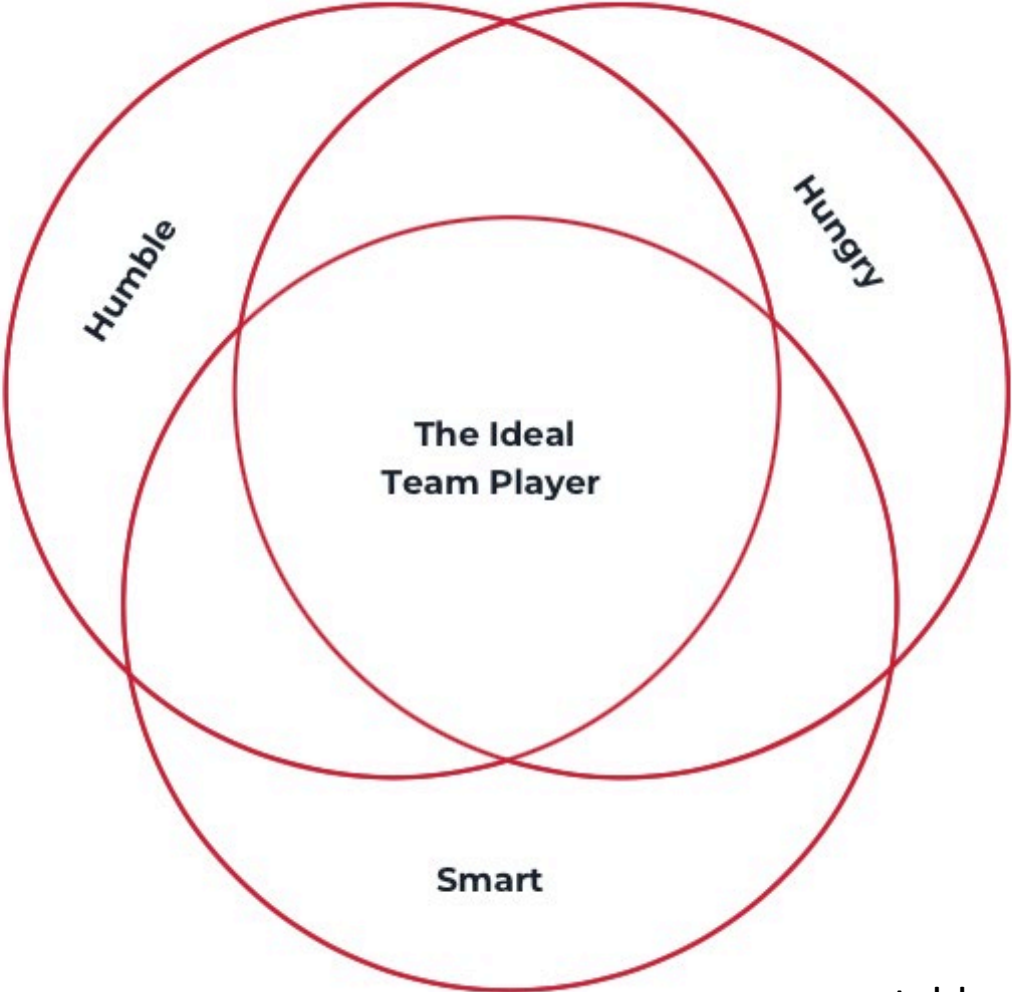
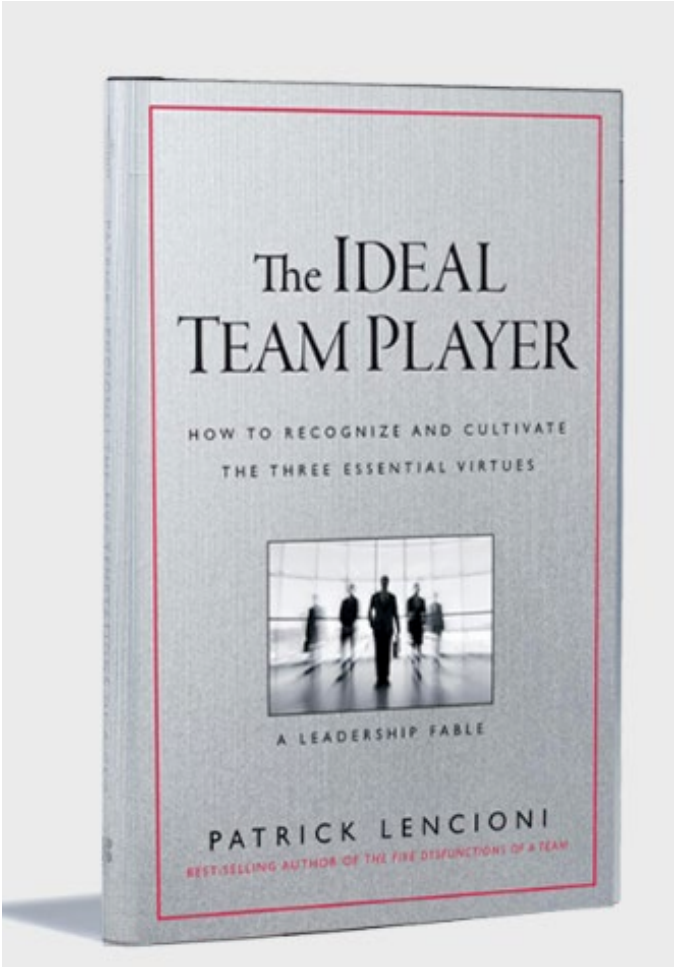
Mind

Body

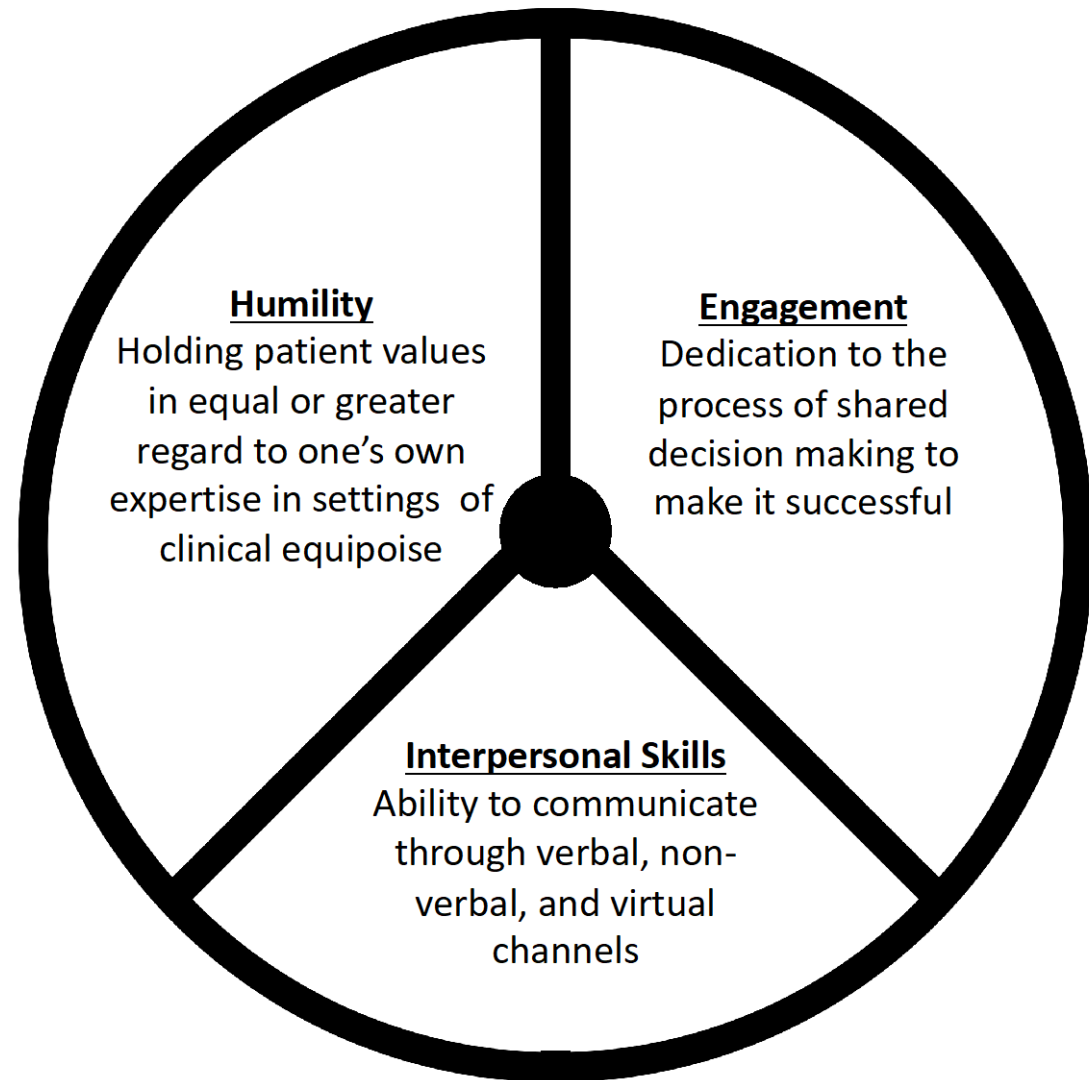
Spirit

Experience
of illness and
integration
into self,
family,
community

Partnerships



The Ideal Team Player in Medicine

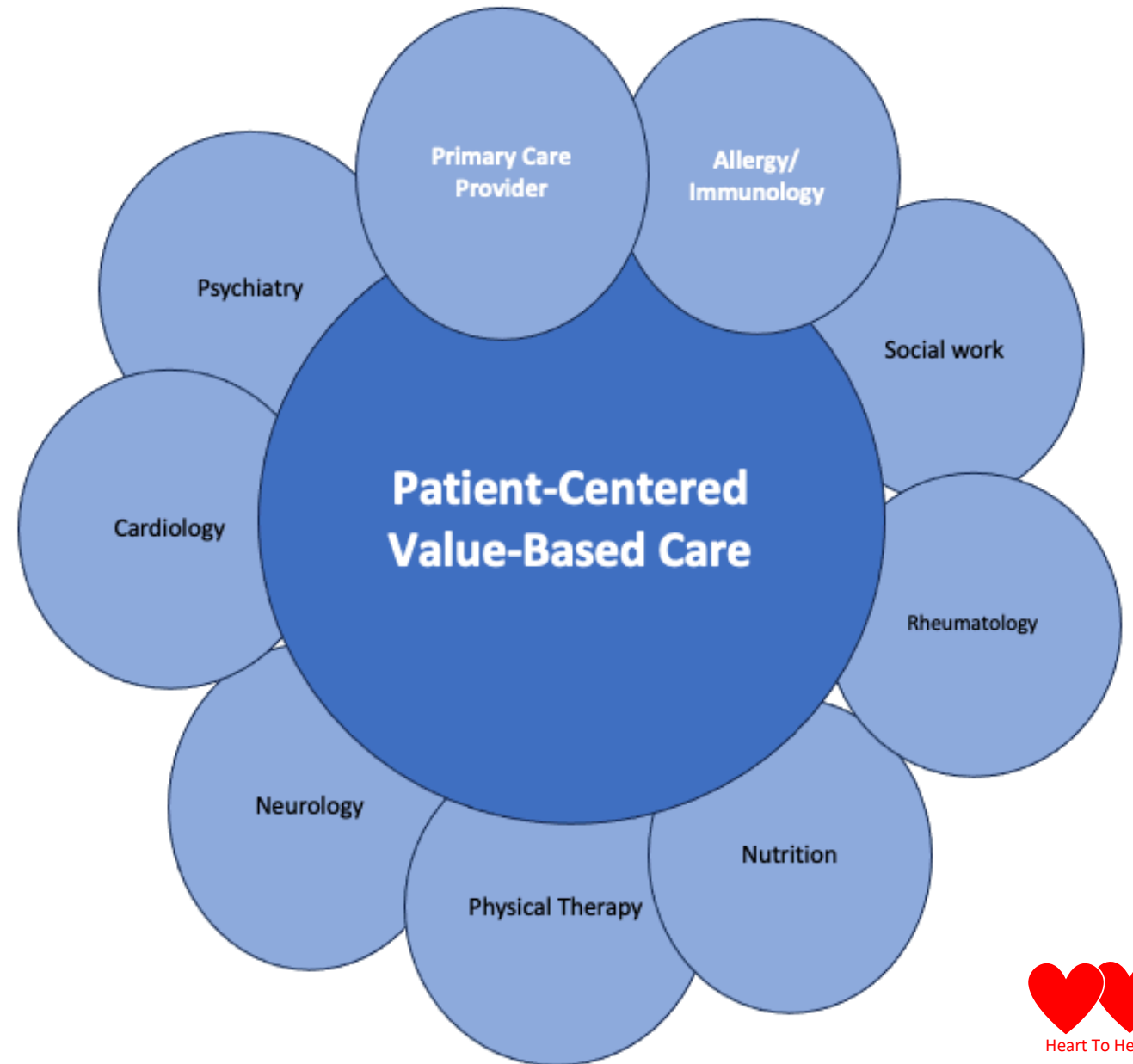


Total Patient Care

When it's not MCAS...

Consider....

- Cholinergic urticaria or other inducible hives,
- Chronic pain syndrome,
- Hypermobile Ehlers Danlos syndrome (hEDS),
- Postural orthostatic tachycardic syndrome (POTS) associated with dizziness, palpitations and flushing,
- Irritable bowel syndrome with bloating and diarrhea or constipation,
- Headaches,
- Mental Health,
- Environmental and medication intolerances.



Providing Total Patient Care



Heart To Heart


Medical Reductionism & Compartmentalism

Qualitative Health Research
OnlineFirst
© The Author(s) 2023, Article Reuse Guidelines
<https://doi.org/10.1177/10497323231216346>

Sage Journals

Research Article

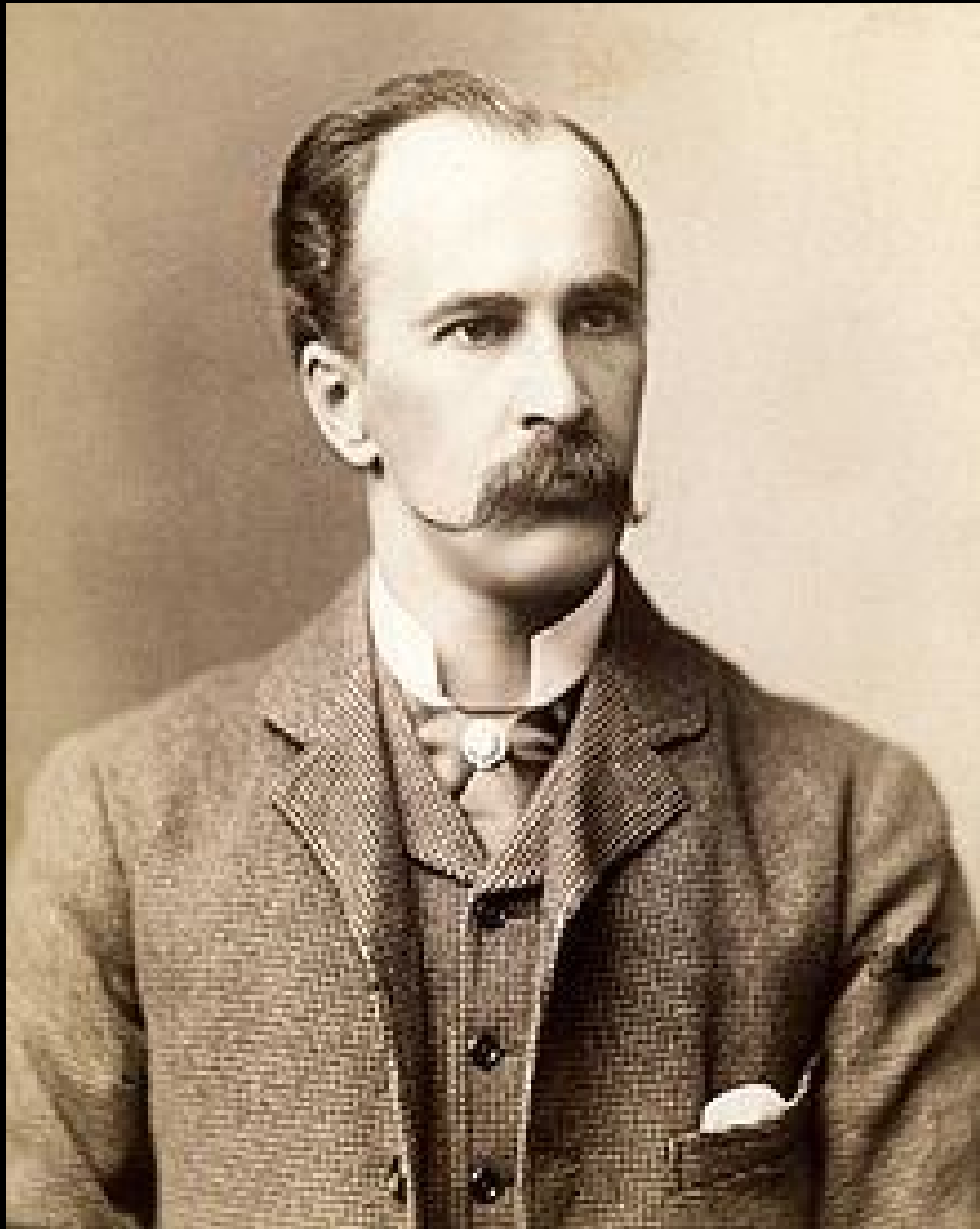
“Somewhere Between an Actual Disease and a Disease”: A Grounded Theory Study on Diagnosing Functional Neurological Disorders From a Multi-Informant Perspective

Francesca Sireci¹, Valentina Moretti², Francesco Cavallieri¹, Silvia Ferrari^{3,4}, Valentina Minardi¹, Francesca Ferrari¹, Giulietta Luul Balestra⁵, Luca Ghirotto ⁵, and Franco Valzania¹

Abstract

Functional Neurological Disorders are characterized by sensory-motor or cognitive symptoms. Recent research has revealed their complex nature involving biological, psychological, and social factors. Care requires a multidisciplinary approach, which, to date, has yet to be considered. A Constructivist Grounded Theory study was conducted to understand the reasons behind this, exploring Functional Neurological Disorders diagnosis, communication, and understanding from multiple perspectives (patients and healthcare professionals). The core category was “negotiating Functional Neurological Disorders meanings and care amid a dissatisfying dichotomy,” with sub-categories: i) seeking to “word” the disease, ii) exposing reductionism, and iii) a pluralist vision emerging. Diagnosing and communicating Functional Neurological Disorders is a process of negotiating meanings and care that hinges on participants’ diverse ontological perspectives regarding the condition. Results highlight the difficulty in finding common ground and achieving mutual understanding among the various viewpoints, creating a challenge in establishing a unified approach to Functional Neurological Disorders care. In this context, only a few healthcare professionals emphasized the potential benefits of increased integration. A shift is required from a reductionist to an integrated biopsychosocial perspective to develop a more cohesive approach. Defining a medical paradigm through dialogue with teams and patients is essential in addressing Functional Neurological Disorders effectively. Furthermore, the required interdisciplinary approach holds the potential to mitigate the dissatisfaction arising from fragmented and compartmentalized care (the “dissatisfying dichotomy”) experienced by our participants. It signifies a comprehensive strategy that could address the concerns of all involved parties and enhance the overall quality of care provided.





“The practice of medicine is an art, not a trade; a calling, not a business; a calling in which your heart will be exercised equally with your head”

Sir William Osler, 1849-1912



Take Home Points

Multiple conditions can present with symptoms similar to MCAS

Dysautonomia, POTS, hEDS, IBS, Amplified Pain Syndrome, Anxiety, Depression can interwoven

Holistic evidence appraisal, Open-minded partnership, and Willingness to engage are HOW we can help!



Thank You