POTS and PANS: The Condition and Cases

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BRB CE Group

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Disclosures

- on the Medical Advisory group for NFH. This is a paid position.
- a co-founder of Exceptional ND, an education platform for NDs. This is a for profit company
- a board member for Canadian Association of Naturopathic Doctors. Not for profit
- on the Membership Engagement Taskforce for the OAND. Not for profit

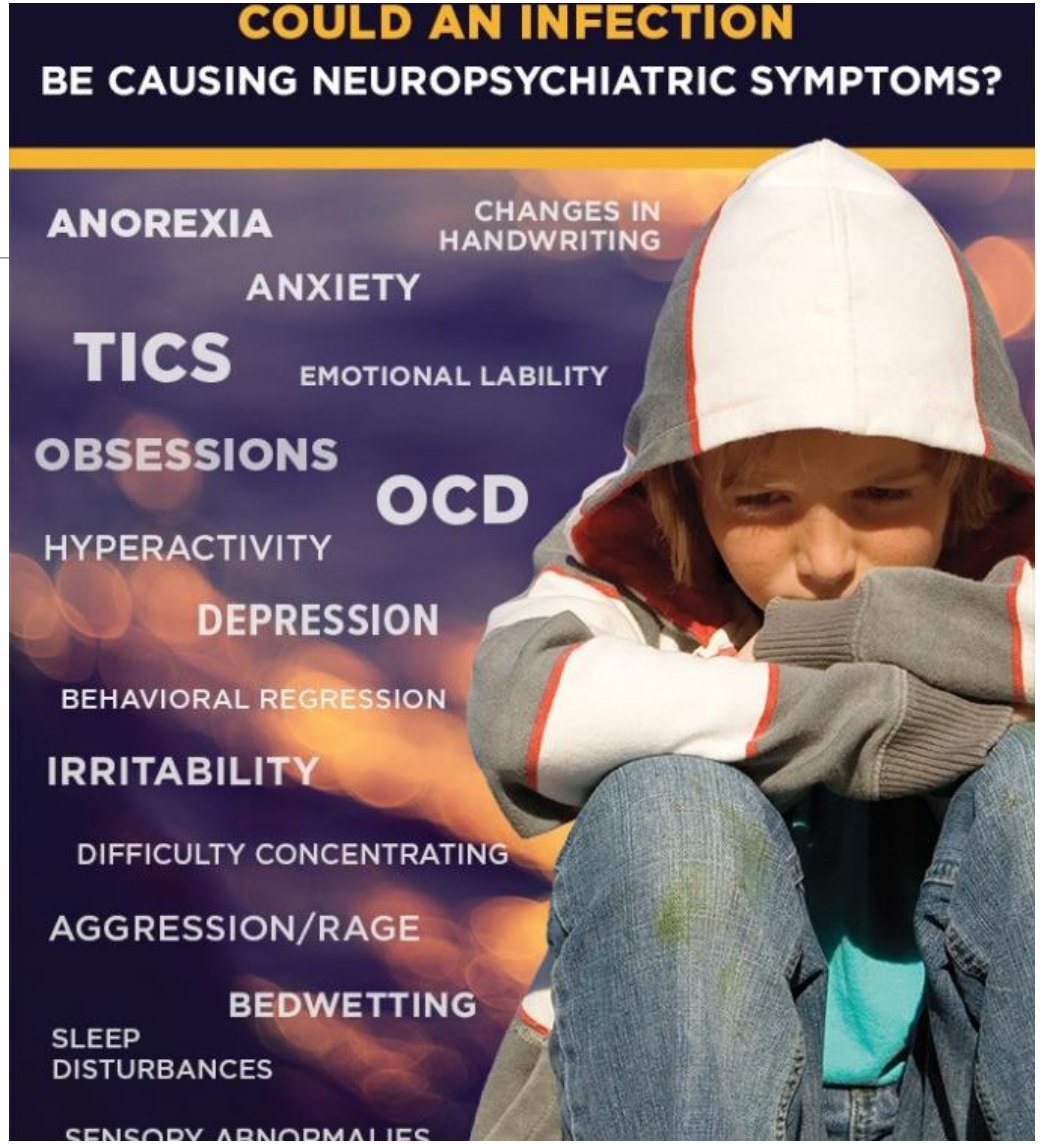
POTS AND PANS

2 complex conditions that need to be looked at during complex cases

PANDAS/PANS

Firstly, PANDAS stands for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus.

Similarly, PANS stands for Pediatric Acute-onset Neuropsychiatric Syndrome



PANDAS

PANDAS was identified by Dr Susan E. Swedo.

She has retired but was a researcher in the field of pediatrics and neuropsychiatry as the Chief of Pediatrics and Developmental Neuroscience Branch at the US National Institute of Health.

In 1994, Swedo was lead author on a paper describing pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)

This was a controversial hypothesis proposing a link between Group A streptococcal infection in children and some rapid-onset cases of obsessive-compulsive disorder (OCD) or tic disorders such as Tournette syndrome

PANDAS: The old way to diagnose…

- Presence of OCD, a tic disorder, or both
- Pediatric onset of symptoms (i.e., age 3 to puberty)
- Episodic course of symptom severity (see information below)
- Association with group A Beta-hemolytic strep infection, such as a positive throat culture for strep or history of scarlet fever
- Association with neurological abnormalities, such as physical hyperactivity or unusual, jerky movements that are not in the child's control
- Very abrupt onset or worsening of symptoms
- If the symptoms have been present for more than a week, blood tests may be done to document a preceding strep infection.

https://neuroimmune.org/susan-swedo-pandas-interview

PANDAS

Handwriting samples documenting dysgraphia during acute illness.

Before symptom onset

During acute episode

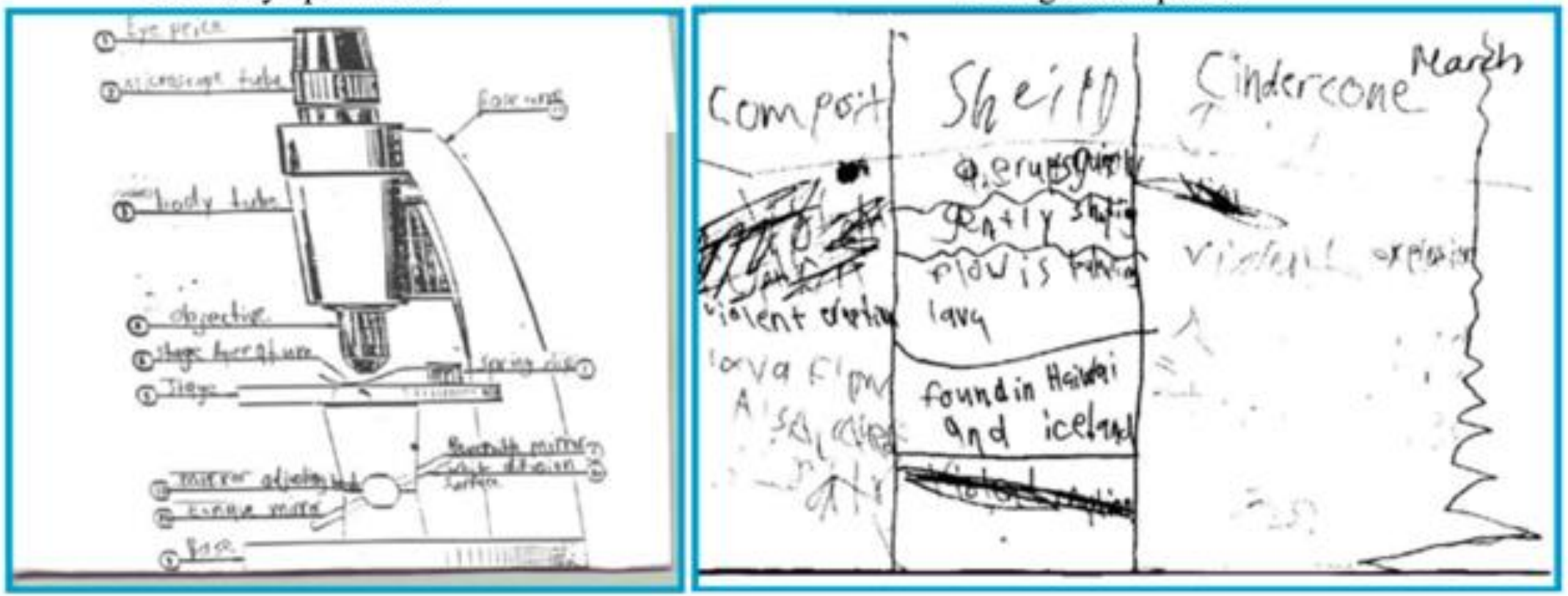


Figure 3: Drawings that Demonstrate Loss of Fine Motor Skills During Acute Illness.

https://www.longdom.org/open-access-pdfs/from-research-subgroup-to-clinical-syndrome-modifying-the-pandas-criteria-to-describe-pans-pediatric-acute-onset-neuropsychiatr.pdf

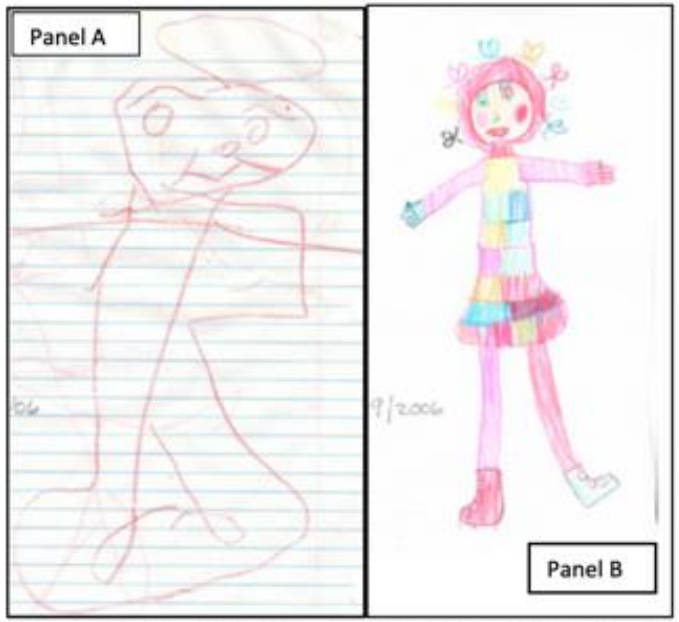
PANDAS PATIENT

Drawing samples taken before an episode, during and after a symptomatic episode.

https://www.longdom.org/open-access-pdfs/from-research-subgroup-to-clinical-syndrome-modifying-the-pandas-criteria-to-describe-pans-pediatric-acute-onset-neuropsychiatr.pdf

PANDAS PATIENT

Hand writing samples show before and after IVIG therapy.



Panel A– Drawing produced during an acute exacerbation of OCD and other symptoms of PANDAS which appears quite messy and immature.

Panel B – Age-appropriate picture drawn after treatment with IVIG and symptomatic improvement.

Figure 2: Handwriting Samples Showing Behavioral Regression During Symptomatic Episode.

https://www.longdom.org/open-access-pdfs/from-research-subgroup-to-clinical-syndrome-modifying-the-pandas-criteria-to-describe-pans-pediatric-acute-onset-neuropsychiatr.pdf

Mechanism of PANDAS

Anti-dopamine receptor antibodies might be relevant to both Sydenham's chorea (SC)—the prototypical post-streptococcal neuropsychiatric disorder and some rare forms of encephalitis targeting the basal ganglia specifically, but studies exploring their association with children fulfilling Swedo's criteria for PANDAS have been inconclusive.

Moreover, we lack evidence in favor of the efficacy of antibiotic prophylaxis or tonsillectomy in patients fulfilling Swedo's criteria for PANDAs

https://neuroimmune.org/susan-swedo-pandas-interview

PANS: THE NEW WAY TO THINK…

Obsessive-compulsive disorder (OCD) can have an unusually abrupt onset of symptoms, accompanied by a variety of comparably severe and acute neuropsychiatric symptoms.

Thus the use of acute onset in the name…Pediatric Acute-onset Neuropsychiatric Syndrome (PANS).

Stopping PANDAS criteria would allow new criteria to be involved in investigation and treatment

Swedo et al., Pediatr Therapeut 2012, 2:2
DOI: 10.4172/2161-0665.1000113

Pediatrics & Therapeutics

Research Article Open Access

From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)

Susan E. Swedo[1]*, James F. Leckman[2] and Noel R. Rose[3]

[1]*Pediatrics & Developmental Neuroscience Branch, National Institute of Mental Health, National Institutes of Health, Bethesda MD, USA*
[2]*Child Study Center, Yale University, New Haven CT, USA*
[3]*Center for Autoimmune Disease Research, Johns Hopkins School of Medicine, Baltimore MD, USA*

https://www.longdom.org/open-access-pdfs/from-research-subgroup-to-clinical-syndrome-modifying-the-pandas-criteria-to-describe-pans-pediatric-acute-onset-neuropsychiatr.pdf

PANS is a clinical diagnosis requiring OCD and/or restrictive food intake...

restricted intake

...as well as two or more of the following symptoms:

OCD

emotional lability

aggression

depression

irritability

deterioration in school work

oppositional behaviors

urinary frequency

anxiety

sleep disturbances

regression

sensory abnormalities

enuresis

https://neuroimmune.org/patient-and-family-resources/what-are-pans-pandas/

PANS

erion	Description
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or sev restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, similarly severe and acute onset, from at least two of the followi seven categories (see text for full description):
	1. Anxiety
	2. Emotional lability and/or depression
	3. Irritability, aggression and/or severely oppositional behaviors
	4. Behavioral (developmental) regression
	5. Deterioration in school performance
	6. Sensory or motor abnormalities
	7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or m disorder, such as Sydenham chorea, systemic lupus erythemat Tourette disorder or others.
	Note: The diagnostic work-up of patients suspected of PANS m comprehensive enough to rule out these and other relevant disc The nature of the co-occurring symptoms will dictate the necess assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

le 2: Diagnostic Criteria Proposed for Pediatric Acute-onset Neuropsy drome (PANS).

PANS

More criteria to look at and assess for PANS and not just treat the infection

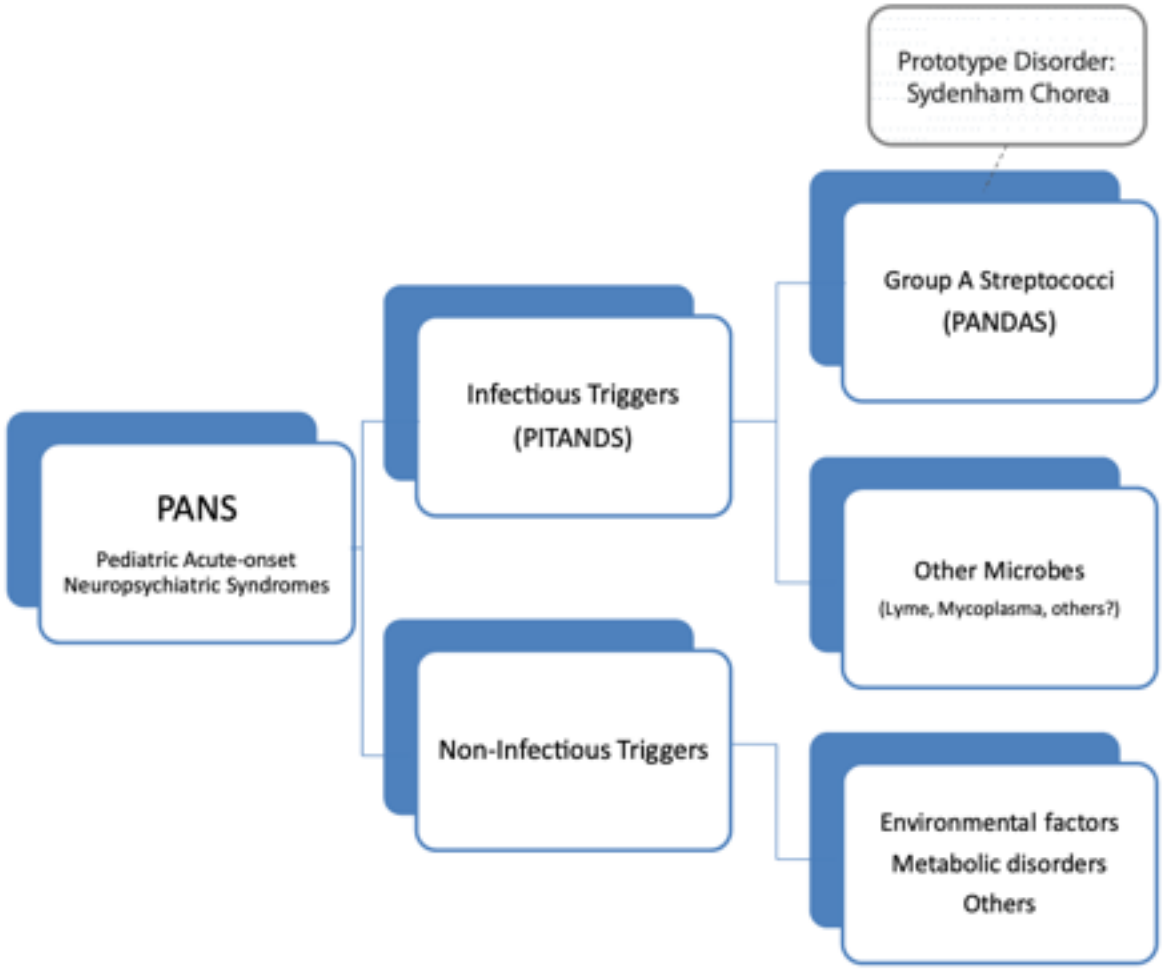


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

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PANS

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 27, Number 7, 2017

Pp. 562–565
DOI: 10.1089/cap.2017.0042

Introduction

Overview of Treatment of Pediatric Acute-Onset Neuropsychiatric Syndrome

Susan E. Swedo, MD,[1] Jennifer Frankovich, MD, MS,[2,3] and Tanya K. Murphy, MD, MS[4]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610386/pdf/cap.2017.0042.pdf

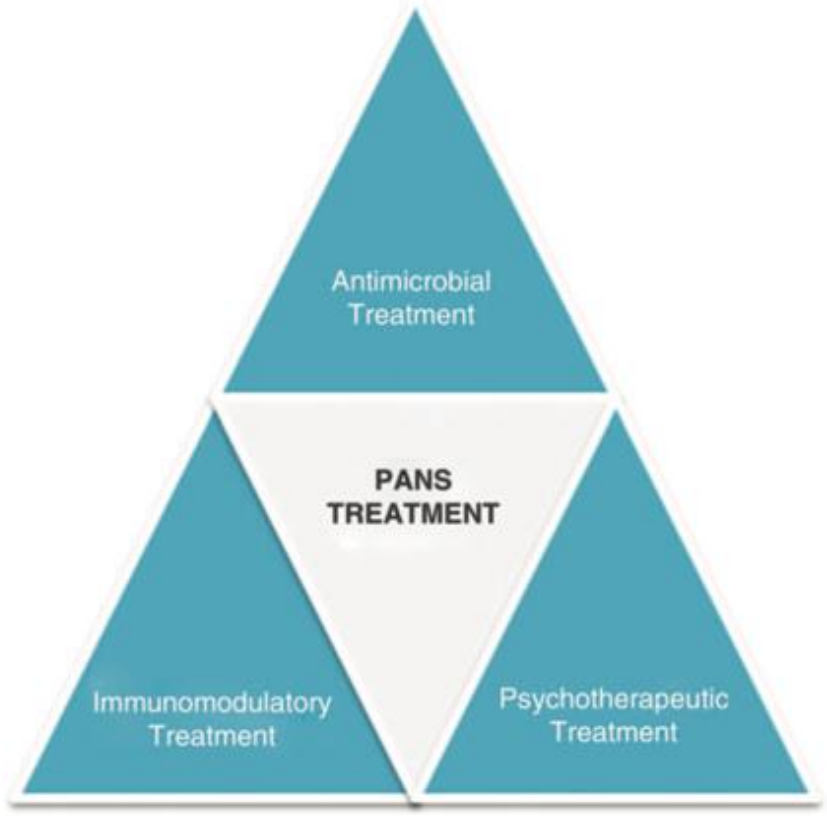


FIG. 1. The PANS treatment triangle. PANS, pediatric acute-onset neuropsychiatric syndrome. Color images available online at www.liebertpub.com/cap

TABLE 1. GENERAL PRINCIPLES FOR TREATING PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

1. Establish that PANS is the correct "diagnosis of exclusion" by completing a comprehensive diagnostic evaluation (Chang et al. 2015).
2. Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and interference (Thienemann et al. 2017).
3. Treat underlying infections and consider use of therapeutic or prophylactic antibiotics (Cooperstock et al. 2017).
4. Treat symptoms resulting from neuroinflammation or postinfectious autoimmunity with anti-inflammatory or immunomodulatory therapies, chosen on the basis of symptom severity and disease trajectory (Frankovich et al. 2017).
5. Evaluate effectiveness of the treatment regimen at frequent intervals, making modifications as warranted by improvement or worsening of symptoms.
6. Treatment can be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again at some point in the future, given the relapsing–remitting nature of PANS symptoms.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5610386/pdf/cap.2017.0042.pdf

THE DIFFERENCE BETWEEN PANS AND PANDAS

- PANDAS is when specifically strep is connected to the sudden onset of OCD and/or tics along with other listed clinical symptoms.
- PANS removes the emphasis of the etiologic factor and concentrates on the clinical symptoms. PANS can be triggered by any infectious agent (NOT only strep) in addition to non-infectious triggers which are yet to fully determined but may include metabolic disorders and environmental factors.
- Symptoms cannot be explained by any other neurological or medical disorder.

http://www.pandasnetwork.org/understanding-pandaspans/what-is-pans/

PANS is defined by the following criteria:

Abrupt, dramatic onset of OCD or severely restricted food intake; symptoms are not better explained by a known neurologic or medical disorder; and the addition of at least 2 of the "accompanying" symptoms:

- Anxiety
- Emotional lability and/or depression
- Irritability, aggression and/or severely oppositional behaviors
- Behavioral (developmental) regression
- Deterioration in school performance
- Sensory or motor abnormalities
- Somatic signs including sleep disturbances, enuresis or urinary frequency

The onset of PANS may start with infectious agents other than strep. It also includes onset from environmental triggers or immune dysfunction.

PANDAS is defined by the following criteria:

Clinical diagnosis of PANDAS includes 5 criteria:

- Presence of significant obsessions, compulsions and/or tics
- Abrupt onset of symptoms or a relapsing-remitting course of symptom severity
- Prepubertal onset
- Association with streptococcal infection
- Association with other neuropsychiatric symptoms (includes any of the PANS "accompanying" symptoms)

http://www.pandasnetwork.org/understanding-pandaspans/what-is-pans/

Test for PANs/PANDAS: Rhomberg Test

Abnormal movements: Motor or phonic tics are common in patients with PANS. Choreiform movements (piano playing fingers) may be present.

These movements can be elicited with a Romberg test in which the child stands with the hands outstretched and eyes closed for 60 seconds.

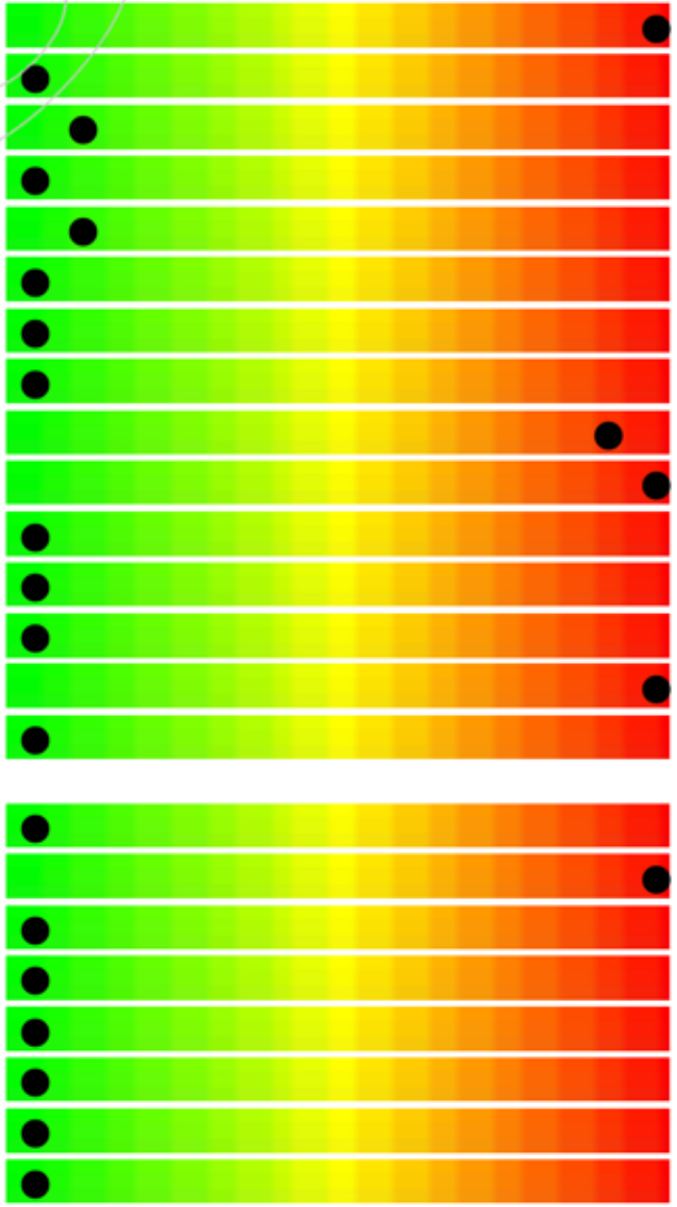
Hand movements are considered abnormal in children >8 years.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340805/

Tests for PANS/PANDAS

- Rapid Strep Antigen Testing
- Strep culture.
- Streptolysin O (ASO) and anti-DNase B titers.
- responses to immunomodulatory therapies
- Cross-reactive antineuronal antibodies such as IgG autoantibodies against four neuronal autoantigens (tubulin, lysoganglioside G_{M1}, and dopamine receptors D1 and D2) (The Cunningham Panel)
- The antibody titers against human brain enolase (AE) and Streptococcal proteins (AS)
- Nucleic acid amplification tests (NAATs)

Opportunistic Bacteria/Overgrowth	Result	Range	Units
Bacillus species.	1.70 *H	< 1.00	x10^4 CFU/g
Enterococcus faecalis	0.30	< 1.00	x10^5 CFU/g
Enterococcus faecium	0.50	< 1.00	x10^5 CFU/g
Morganella species	<dl	< 1.00	x10^5 CFU/g
Pseudomonas species	0.50	< 1.00	x10^4 CFU/g
Pseudomonas aeruginosa.	<dl	< 3.00	x10^4 CFU/g
Staphylococcus species	<dl	< 1.00	x10^3 CFU/g
Staphylococcus aureus	2.00	< 5.00	x10^3 CFU/g
Streptococcus agalactiae.	4.20 *H	< 3.00	x10^6 CFU/g
Streptococcus anginosus.	6.70 *H	< 3.00	x10^6 CFU/g
Streptococcus mutans.	<dl	< 3.00	x10^6 CFU/g
Streptococcus oralis.	<dl	< 3.00	x10^6 CFU/g
Streptococcus salivarius.	<dl	< 3.00	x10^6 CFU/g
Methanobrevibacter smithii	6.60 *H	< 3.50	x10^5 CFU/g
Desulfovibrio piger	<dl	< 18.00	x10^7 CFU/g
Potential Autoimmune Triggers			
Citrobacter species.	<dl	< 5.00	x10^4 CFU/g
Citrobacter freundii.	55.00 *H	< 5.00	x10^4 CFU/g
Klebsiella species	<dl	< 5.00	x10^3 CFU/g
Klebsiella pneumoniae.	<dl	< 5.00	x10^5 CFU/g
Prevotella copri	<dl	< 1.00	x10^9 CFU/g
Proteus species	<dl	< 5.00	x10^5 CFU/g
Proteus mirabilis.	<dl	< 1.00	x10^4 CFU/g
Fusobacterium species	1.70	< 10.00	x10^4 CFU/g



PHYSICAL EXAM

Heart rate lying down, blood pressure and oxygen lying and standing.

Greater than 30 may indicate POTS. (Postural Orthostatic Hypotension).

Modified Romberg Test. 2 minutes. Eyes closed. Head up. Legs shoulder length apart.

Oxygen seated, lying down and standing

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340805/

THE STORY OF ROWAN

- Always moving even in my sister's belly
- Hard time to sleep
- Speech delayed
- Hyper-fixated
- So smart, so engaged and dynamic
- Bright light in a room

Life just got harder

- Head banding
- Only like wearing PJs
- Sensory issues
- Always wanted to run, climb and play
- Transition issues
- Tantrum to beat all tantrums

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4340805/

THE STORY OF ROWAN

- Trichotillomania
- Peeled lips
- Rashes
- Nightmares
- Anxiety
- Immune trigger…family got sick...he got behaviour issues
- He was in pain

https://www.youtube.com/watch?v=yUxujbXNnow

When in doubt, clear it out….

- Clear outs can be up to 10,000-20,000mg Magnesium oxide
- Dr. Sonya ND started treating PANS patient with a modified version of an autism protocol and it worked!
- Dr. Sonya ND's Core 4 for Autism. B12 injection, paleo diet, CLO (cod liver oil) and multi-vitamin and mineral
- Note: spring rage, regression in spring and fall
- Rage, anxiety, insomnia, nightmares, transition, clingy, tics

Sudden onset and the immune roller coaster. Strep infection stopped the behaviour and pain

When he actually got a strep infection then he was in remission

When did get sick, had high fevers and limp and a noodle for a day

Concepts in pans: Sudden on set

Antibiotic roller coaster

- Sonya went to MAPS and learned about the diagnosis from Dr. Susan Swedo
- The severity didn't match Sonya's patient...so Sonya asked Dr. Swedo about the prevalence and severity
- Dr. Swedo said that more minor issues are what Swedo calls micro-pandas

Consistent Treatment

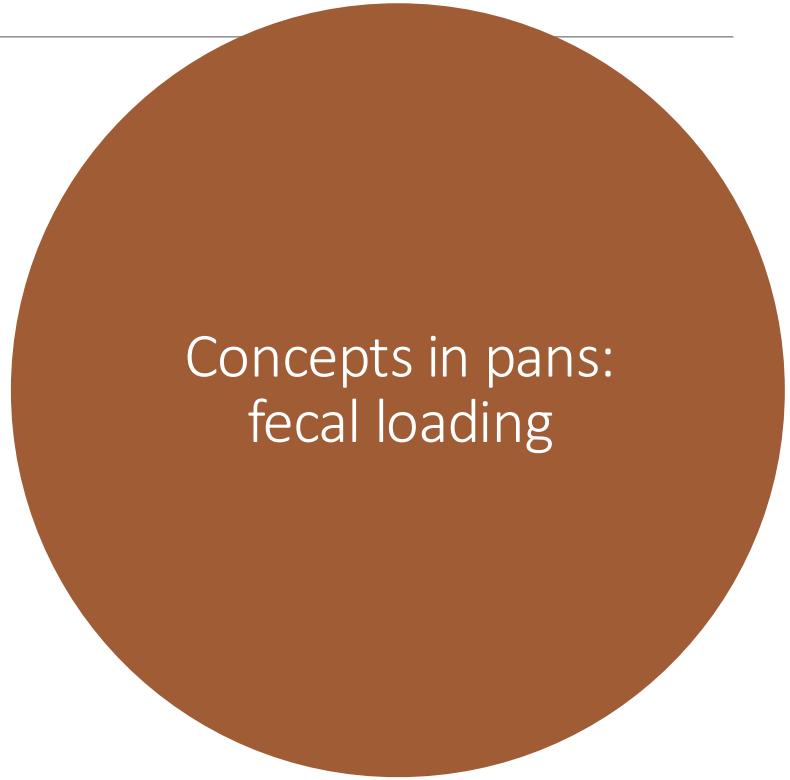
Stolen childhood documentary…then Dr. Sonya ND got a whole lot of sick PANS kids

Rowan said he has Seasonal Schizophrenia Disorder. SSD

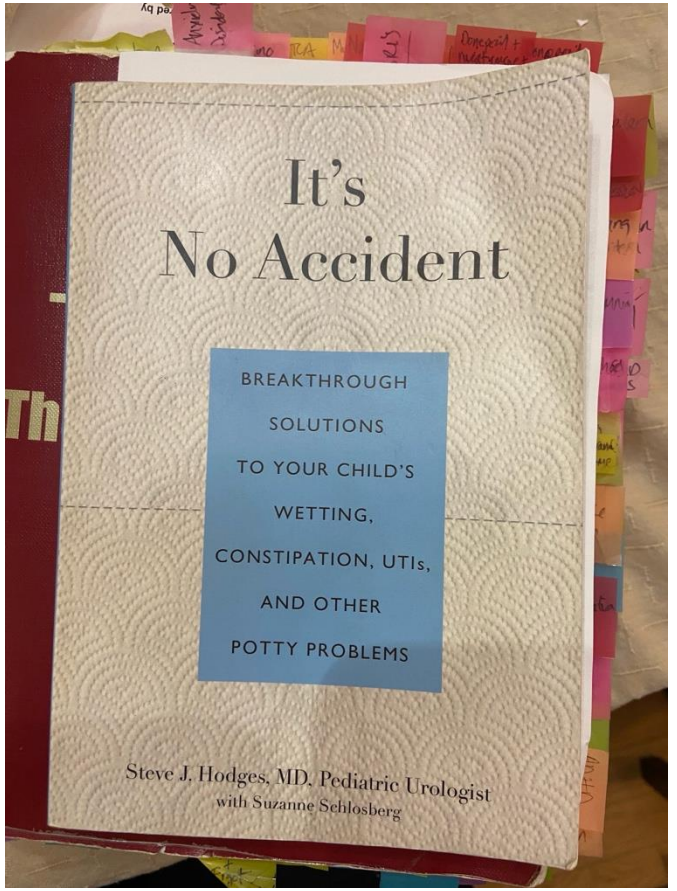
Nausea, Phlegm

Biofilm

Why would there be incontinence in some cases?



Incontinence is almost always constipation



PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report

Timothy Buie, Daniel B. Campbell, George J. Fuchs, III, Glenn T. Furuta, Joseph Levy, Judy VandeWater, Agnes H. Whitaker, Dan Atkins, Margaret L. Bauman, Arthur L. Beaudet, Edward G. Carr, Michael D. Gershon, Susan L. Hyman, Pipop Jirapinyo, Harumi Jyonouchi, Koorosh Kooros, Rafail Kushak, Pat Levitt, Susan E. Levy, Jeffery D. Lewis, Katherine F. Murray, Marvin R. Natowicz, Aderbal Sabra, Barry K. Wershil, Sharon C. Weston, Lonnie Zeltzer and Harland Winter

Pediatrics 2010;125;S1-S18
DOI: 10.1542/peds.2009-1878C

https://publications.aap.org/pediatrics

TABLE 2 Behaviors That May Be Markers of Abdominal Pain or Discomfort in Individuals With ASDs

Vocal Behaviors	Motor Behaviors[a]	Changes in Overall State
Frequent clearing of throat, swallowing, tics, etc	Facial grimacing	Sleep disturbances: difficulty getting to sleep, difficulty staying asleep
Screaming	Gritting teeth	Increased irritability (exaggerated responses to stimulation)
Sobbing "for no reason at all"	Wincing	Noncompliance with demands that typically elicit an appropriate response (oppositional behavior)
Sighing, whining	Constant eating/drinking/swallowing ("grazing" behavior)	
Moaning, groaning	Mouthing behaviors: chewing on clothes (shirt sleeve cuff, neck of shirt, etc), pica	
Delayed echolalia that includes reference to pain or stomach (eg, child says, "Does your tummy hurt?" echoing what mother may have said to child in the past)	Application of pressure to abdomen: leaning abdomen against or over furniture or kitchen sink, pressing hands into abdomen, rubbing abdomen	
Direct verbalizations (eg, child says "tummy hurts" or says "ouch," "ow," "hurts," or "bad" while pointing to abdomen)	Tapping behavior: finger tapping on throat	
	Any unusual posturing, which may appear as individual postures or in various combinations: jaw thrust, neck torsion, arching of back, odd arm positioning, rotational distortions of torso/trunk, sensitivity to being touched in abdominal area/flinching	
	Agitation: pacing, jumping up and down	
	Unexplained increase in repetitive behaviors	
	Self-injurious behaviors: biting, hits/slaps face, head-banging, unexplained increase in self-injury	
	Aggression: onset of, or increase in, aggressive behavior	

A functional behavioral assessment would be useful in interpreting these behaviors.

[a] Motor behaviors also may be markers of pain or discomfort arising in other parts of the body.

https://publications.aap.org/pediatrics

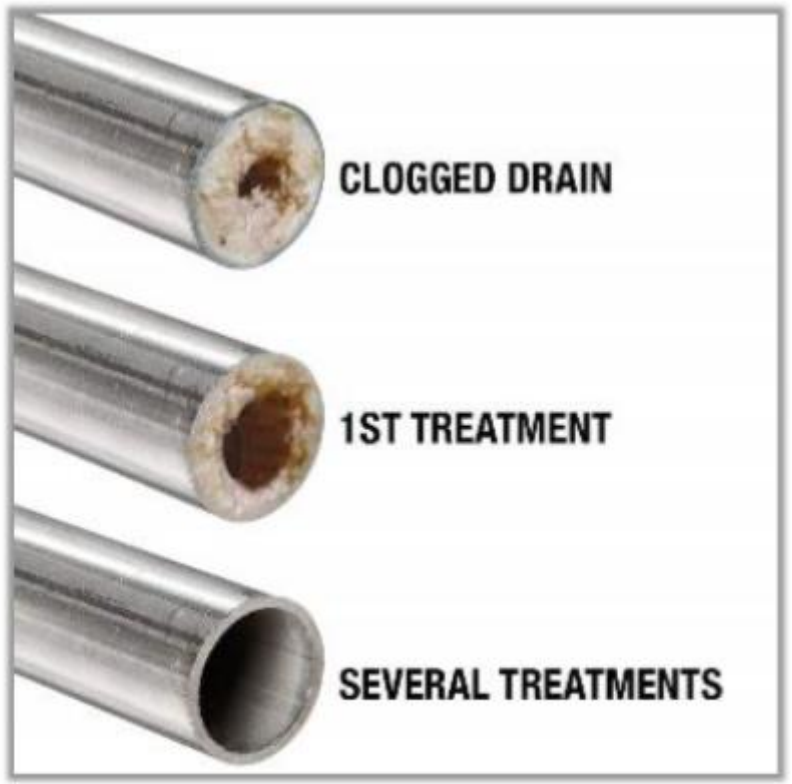
Diagnosis

Constipation is diagnosed by clinical history and examination.

A physical examination should include an abdominal examination to assess the degree of faecal loading, as well as neurological assessment of the spine and lower limbs.

It is important to watch for growth failure, 'overflow diarrhea with blood and/or mucus, pallor or fatigue, or failure to respond to conventional treatment during the course of management and be prepared to re-evaluate.

Children with inflammatory bowel conditions (with or without anal involvement) and coeliac disease may present with constipation.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143086/#B27

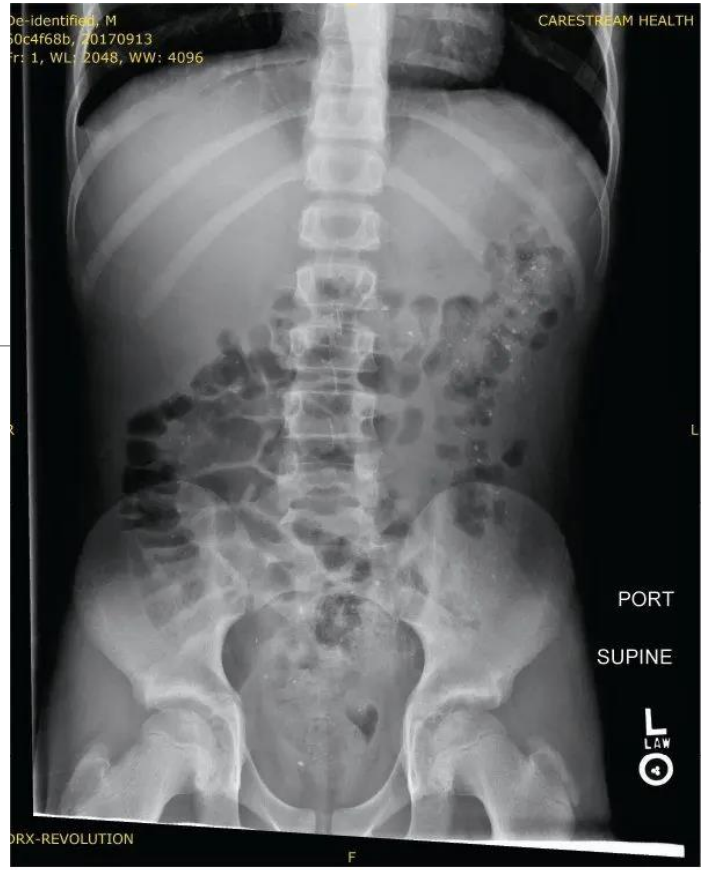
https://www.nice.org.uk/guidance/CG99

Diagnosis

Plain abdominal x-ray as presence of firm, packed hard stool in the rectum correlates closely with radiological evidence of fecal retention, with sensitivity and positive predictive values exceeding 90%.

KUB (kidneys, ureters, and bladder) x-ray can be done to diagnose fecal loading

Transit time test. Eat beets or purple dragon fruit ½ to 1 beet or ½ purple dragon fruit. 3 days later eat corn cup to ¼ corn. Transit time should be 8-18 hours. Last time see food is transit time.



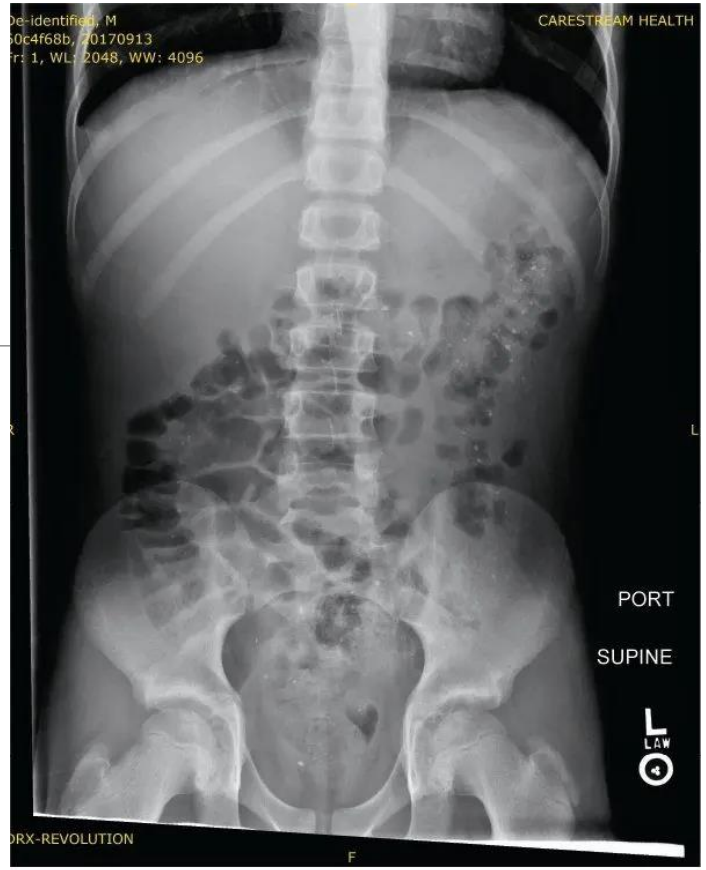
▲ FIGURE **Abdominal single-view x-ray shows punctate opacities throughout the patient's colon suggestive of ingested material, moderate amount of stool in the rectosigmoid region, and nonobstructive bowel gas pattern.**

Diagnosis

Typical Reaction protocol:

Adult: Magnesium oxide (clear out test) : Take 1500mg and what happens?

Typical response is diarrhea after 1 hour and 2-5 loose stool lasting only 6 hours.



▲ FIGURE **Abdominal single-view x-ray shows punctate opacities throughout the patient's colon suggestive of ingested material, moderate amount of stool in the rectosigmoid region, and nonobstructive bowel gas pattern.**

Treatment

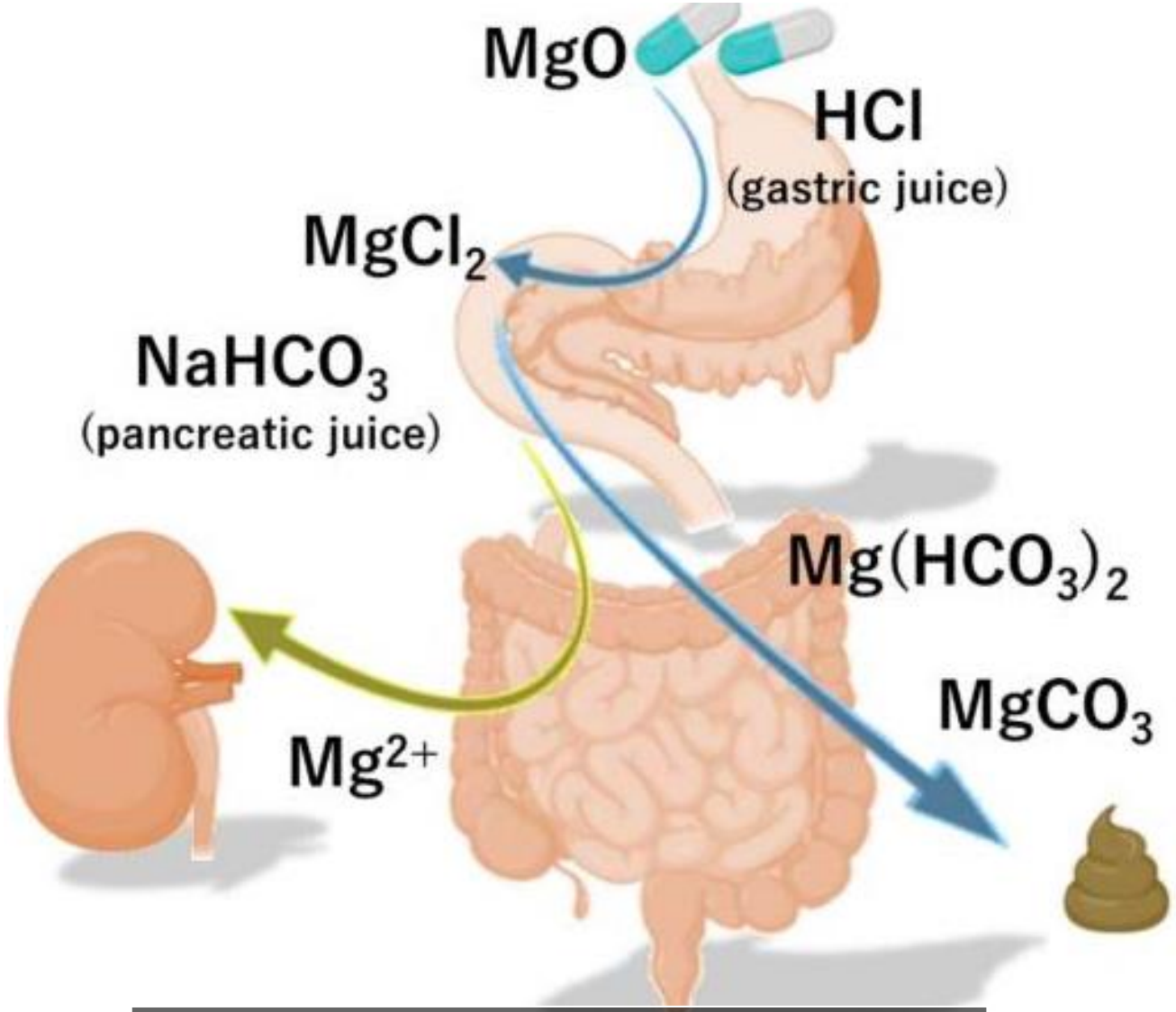
Disimpaction, clear out the old stool. An excessive dose of stimulant risks precipitating acute abdominal pain in cases of impaction. Diarrhea in a constipated child is likely

Maintenance therapy. Once disimpaction has taken place, the aim of treatment, should be to keep the child, symptom free with regular soft bowel actions and should be commenced.

This may last 6 months to a year to return the tone and elasticity back to the digestive system.

Examples of two of the possible signs of constipation that could be overlooked: posturing and a distended, bloated stomach.

https://www.nice.org.uk/guidance/cg99/resources/2018-exceptional-surveillance-of-constipation-in-children-diagnosis-and-management-nice-guideline-cg99-4899678301/chapter/Surveillance-decision?tab=evidence



Magnesium oxide

Although magnesium oxide use can lead to hypermagnesemia, this is rare.

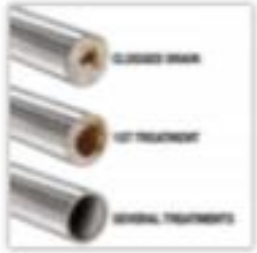
No severe treatment-related adverse events were observed using magnesium oxide in research

Standard dosing for complaint-based constipation

For adults, take 2 g of the active ingredient in 3 divided doses a day before or after meals, or once before bedtime.

A starting dose of approximately 1 g taken as two or three divided doses a day is used, and adjusted appropriately according to symptoms

PEDIATRIC MAGNESIUM CLEAR-OUT PROTOCOL



Options include:

- Any form of magnesium but magnesium oxide powder is preferred (Now Brand, or any other)
- Pico Salax and PurgOdan - available over counter at pharmacies. Note that the pharmacist will inform you this product is not to be used for constipation.

Instructions:

- PLEASE STOP ALL SUPPLEMENTS DURING THIS TIME.
- If more than 48 hours have passed and there is still no loose stool, continue this protocol but bring supplements back in
- FOOD IS NOT RESTRICTED but it is important to continue your child's recommended diet
- DRINK LOTS OF WATER ALONG AND OTHER LIQUIDS to maximize effectiveness of the bowel clear-out. Ideally drinking body weight equivalent in ounces (60 lbs = 60 oz)
- MAKE SURE TO REPLENISH ELECTROLYTES. Brands include Metagenics, BioSteel, Emergen-C, LMNT

Frequency of Rounds:_____

*For many of our patients experiencing chronic constipation, it can take several days or repeated rounds of Magnesium Oxide in order to empty the bowel completely. Once you have achieved liquid stools for one whole day, give Magnesium Oxide two more times, and then stop.

Dosing information:

- 9am mix: _____ of Magnesium Oxide in 8oz or one glass of water.
- 11am mix: _____ of Magnesium Oxide in 8oz or one glass of water.

Other important information:

- Repeat daily until your child has two full days of loose, water, brown stool
- Please email the clinic if your child is experiencing diarrhea for more than 4 days
- Give your child electrolytes if diarrhea occurs for more than 3 days

Chronic Constipation Protocol

Any form of magnesium can be used. Here are some of the supplements we recommend. Keep in mind which flavour your child may prefer. Supplements come in liquid, powder and capsules.

Treatment:

- Starting dose: 100 mg
- Give magnesium twice daily (ideally morning and before bed)
- Increase the dose slowly (by 50 mg to 100 mg every few days)
- There is no safety issue with any dose of magnesium
- Your child's maximum daily dose is when your child gets loose, watery stool
- When you reach the dose of magnesium that causes loose stools, lower the dose
- The first goal is a daily bowel movement that is no looser than soft serve ice cream
- The second goal is to remove old stool that is stuck in the intestine (FECAL LOADING)
- Even if your child has daily bowel movements, fecal loading means that stool is stuck to the intestinal wall
- Magnesium is an osmotic laxative which brings water into the intestine which softens the old stool
- Aim for the highest dose of magnesium you can get to without causing loose, watery stool
- You want to aim for the higher amount of magnesium because the more water that comes into the intestine, the faster the old stool can be removed

Please note: If you have loose stools anytime during the raising of magnesium, then stop increasing the dose**. This protocol may cause accidents.**

No grains, no dairy

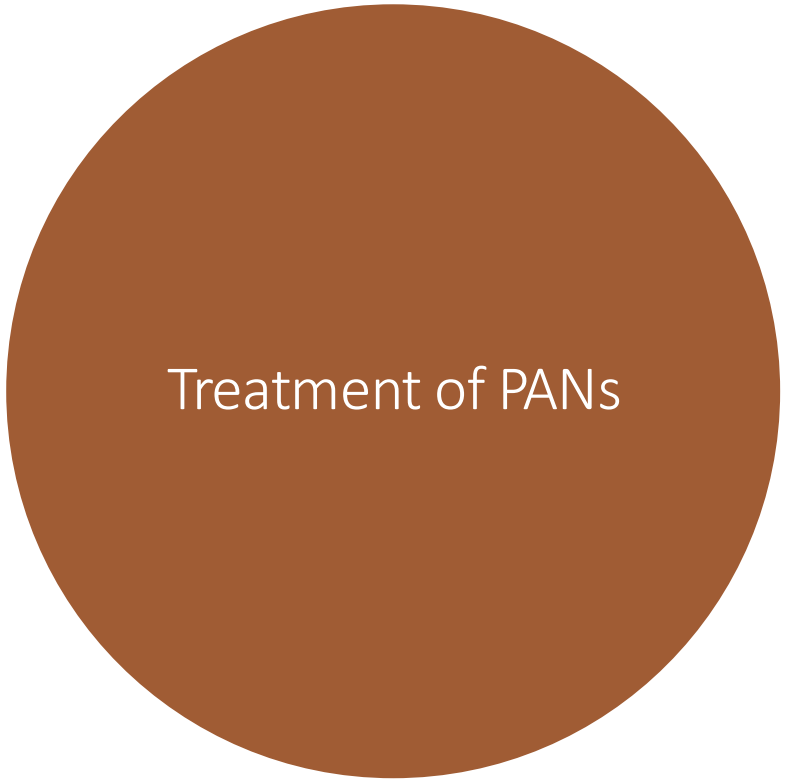
B6 200-400mg/day with 100-200mg Magnesium bisglycinate

NAC 900mg

Mercurius solubis 30CH 3 pellets a day

Assess and treat for fecal loading

When patient shows signs up a true physical strep infection….treat it. We use goldenseal 500mg 1-2 capsules every hour.



POTS and PANS: Chronic Strep infection

frontiers | Frontiers in Neurology

ORIGINAL RESEARCH
published: 26 April 2022
doi: 10.3389/fneur.2022.819636

Check for updates

Children With PANS May Manifest POTS

Avis Chan[1,2], *Jaynelle Gao*[1,2], *Madison Houston*[2,3], *Theresa Willett*[1,2], *Bahare Farhadian*[1,2], *Melissa Silverman*[2,4], *Paula Tran*[2,4], *Safwan Jaradeh*[5], *Margo Thienemann*[2,4†] *and Jennifer Frankovich*[1,2*†]

[1] *Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA, United States,* [2] *Stanford PANS/Immune Behavioral Health Clinic and PANS Research Program at Lucile Packard Children's Hospital, Palo Alto, CA, United States,* [3] *Department of Human Biology, Stanford University School of Humanities and Sciences, Stanford, CA, United States,* [4] *Division of Child and Adolescent Psychiatry and Child Development, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA, United States,* [5] *Autonomic Disorders Program, Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Palo Alto, CA, United States*

POTS: Postural Orthostatic Tachycardia

Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous multifactorial disorder characterized by orthostatic tachycardia and intolerance, which significantly impairs quality of life.

Theories of POTS pathophysiology include heightened sensitivity of cardiac beta-adrenoreceptors, cardiovascular deconditioning, peripheral neuropathy, autoimmunity and immune dysregulation

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455430/

https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2024.1297964/full

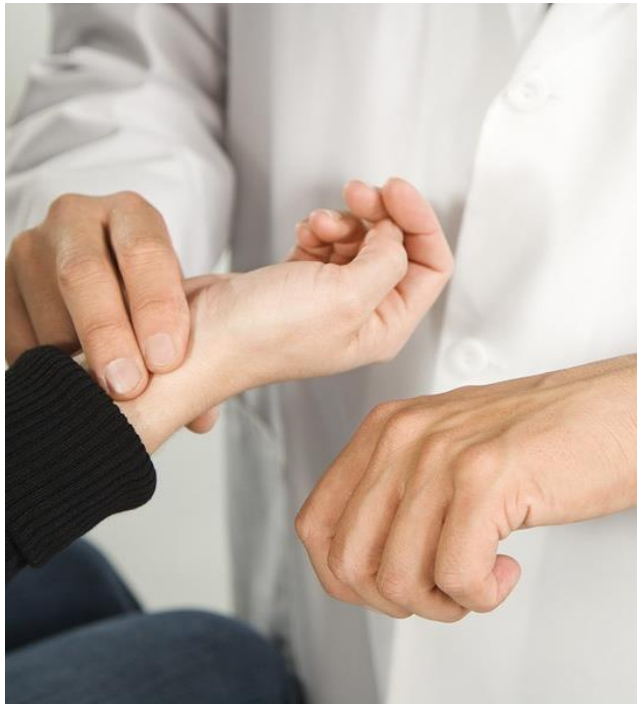
Clinical Definition of POTS

A sustained HR increment of no less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; and

An absence of orthostatic hypotension (i.e. no sustained systolic blood pressure [BP] drop of 20 mmHg or more); and

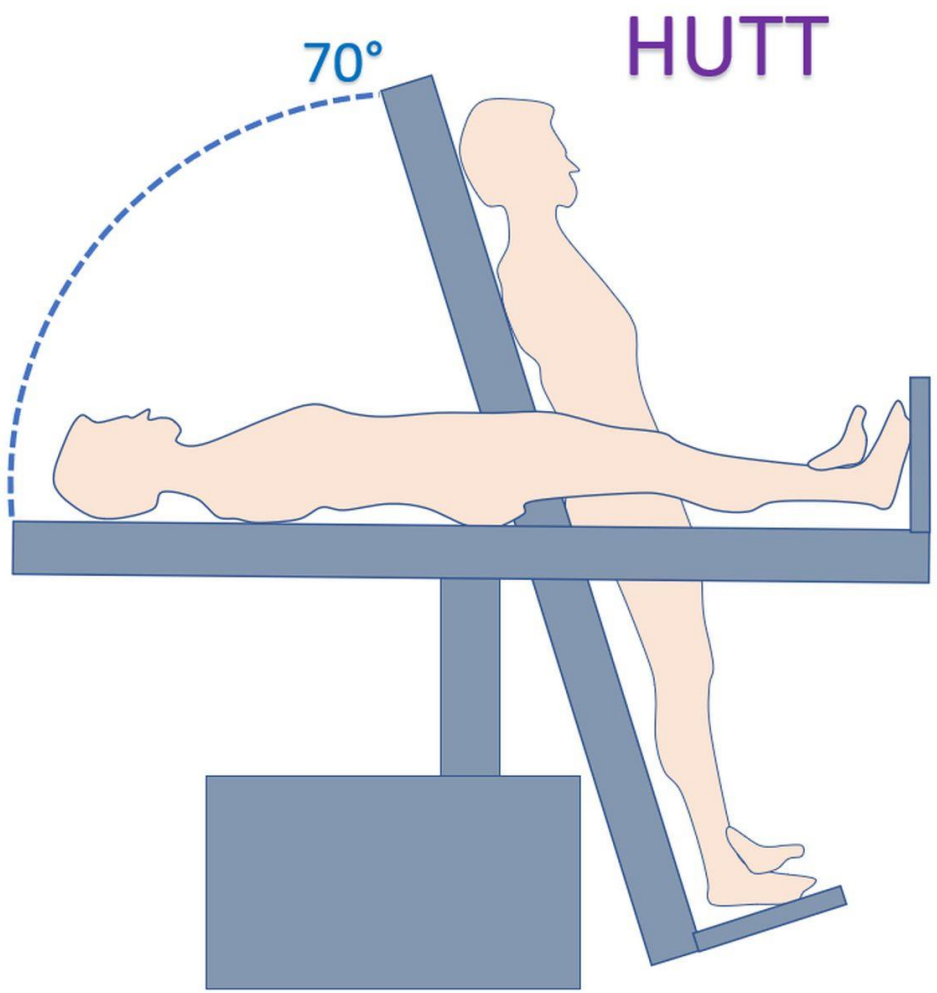
Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and

Duration of symptoms for at least 3 months



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5267948/

How to assess for POTS

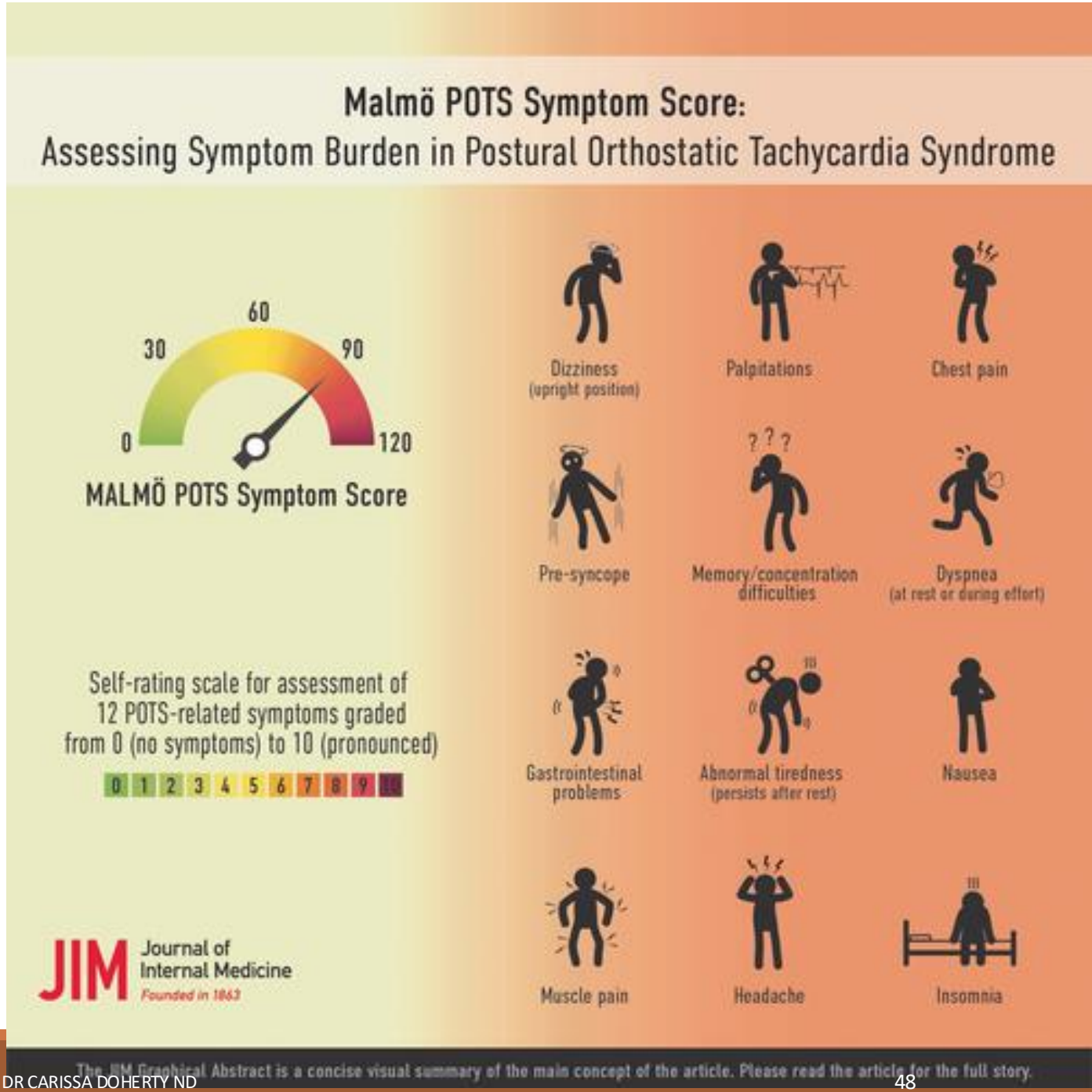


- A tilt table test, sometimes known as a passive head-up tilt test (HUTT).
- This procedure is used to record both blood pressure and heart rate each minute, while the patient is tilted on a table at varying levels.
- IV takes blood to measure adrenaline.
- Blood pressure cuff on both arms and electrical activity of the heart are taken.

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

Malmö POTS Symptom Score (MAPS)

- Most people would have a score of 14
- Max score is 120
- Most POTS patients have a score of 80



Malmö POTS Symptom Score (MAPS)

JIM Original Article

doi: 10.1111/joim.13566

Malmö POTS symptom score: Assessing symptom burden in postural orthostatic tachycardia syndrome

Jasmina Medic Spahic[1,2], Viktor Hamrefors[1,3], Madeleine Johansson[1,2], Fabrizio Ricci[1,4], Olle Melander[1,3], Richard Sutton[1,5] & Artur Fedorowski[1,6,7]

From the [1]Department of Clinical Sciences, Lund University, Malmö, Sweden; [2]Department of Cardiology, Skåne University Hospital, Malmö, Sweden; [3]Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden; [4]Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy; [5]National Heart and Lung Institute, Imperial College, London, UK; [6]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; and [7]Department of Medicine, Karolinska Institute, Stockholm, Sweden

Abstract. Spahic JM, Hamrefors V, Johansson M, Ricci F, Melander O, Sutton R, et al. Malmö POTS symptom score: Assessing symptom burden in pos-

Results. POTS patients showed significantly higher total MAPS score (78 ± 20 vs. 14 ± 12, $p < 0.001$), higher baseline systolic blood pressure (BP), dias-

https://onlinelibrary.wiley.com/doi/10.1111/joim.13566

Malmö POTS Symptom Score (MAPS)

Your average symptoms for the past week. If you haven't experienced symptoms described below, circle zero (0).

1. **Dizziness in upright position or while standing up**
2. **Dizziness, feeling that you are going to faint**
3. **Palpitations, high pulse, or feeling heart beating irregularly**
4. **Difficult breathing/dyspnoea, both at effort and rest**
5. **Chest pain**
6. **Headache**
7. **Concentration difficulties and/or problems with thinking**
8. **Muscle pain**
9. **Nausea**
10. **Gastrointestinal problems (stomach-ache, diarrhea, constipation)**
11. **Abnormal tiredness that persists after rest**
12. **Insomnia**

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fjoim.13566&file=joim13566-sup-0001-SuppMat.pdf

Symptoms of POTS

Table 1: Commonly Reported Symptoms of Postural Orthostatic Tachycardia Syndrome

System	Complaint
Cardiovascular	Palpitations, syncope, pre-syncope, tremor, diaphoresis, chest pain, limb edema, venous pooling, Raynaud's phenomenon
Respiratory	Shortness of breath
Gastrointestinal	Nausea, vomiting, diarrhea, bloating, abdominal pain, constipation, gastroparesis
Genitourinary	Increased urinary frequency, nocturia, bladder dysfunction
Musculoskeletal	Muscle weakness, muscle pain, joint pain, joint dislocation/ hypermobility
Neurological	Lightheadedness, dizziness, vertigo, headache, weakness, visual blurring, brain fog/cognitive disturbance, fatigue, sleep disturbance
Endocrine	Heat intolerance, menorrhagia, PCOS
Psychiatric	Anxiety, ADHD

ADHD = attention deficit/hyperactivity disorder; PCOS = polycystic ovary syndrome.

https://assets.radcliffecardiology.com/s3fs-public/article/2023-09/e13_table_1.jpg?VersionId=jbZJAh5oMLw3aOjpmpxGQfEd0B8LwU7v&_gl=1*scpr8e*_up*MQ..*_ga*OTQzNzc4Mzg3LjE3NDIxNTI4MjY.*_ga_04TB49QXXL*MTc0MjE1MjgyNS4xLjAuMTc0MjE1MjgyNS4wLjAuMA..

Table 4 *Symptom profile*

Symptoms	Number	Total number*	% Total
Cardiovascular symptoms			
Lightheadedness	3992	4034	99
Tachycardia	3901	4032	97
Presyncope	3789	4032	94
Shortness of breath	3562	4032	88
Palpitations	3033	4031	87
Chest pain	3164	4032	79
Low blood pressure	2864	4033	71
Syncope	1452	4033	36

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

Gastrointestinal symptoms			
Nausea	3618	4032	90
Stomach pains	3357	4032	83
Bloating	3184	4031	79
Constipation	2845	4032	71
Diarrhoea	2783	4032	69

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

Neurological symptoms – head and brain			
Headache	3797	4032	94
Difficulty concentrating	3794	4032	94
Memory problems	3538	4032	87
Tremulousness	3124	4039	78
Neurological symptoms – eyes and ears			
Blurred vision	3015	4032	75
Dry mouth	2662	4031	66
Dry eyes	2383	4030	60
Neurological symptoms – extremities			
Muscle pains	3374	4029	84
Foot coldness	3377	4030	84
Muscle weakness	3344	4030	83
Hand coldness	3311	4029	82
Hand tingling	3060	4029	76
Foot tingling	2701	4028	67
Hand numbness	2627	4029	65
Foot numbness	2350	4029	58

Treat POTS

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

Skin symptoms			
Skin flushing	2774	4029	69
Bladder symptoms			
Frequent urination	2733	4031	68

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

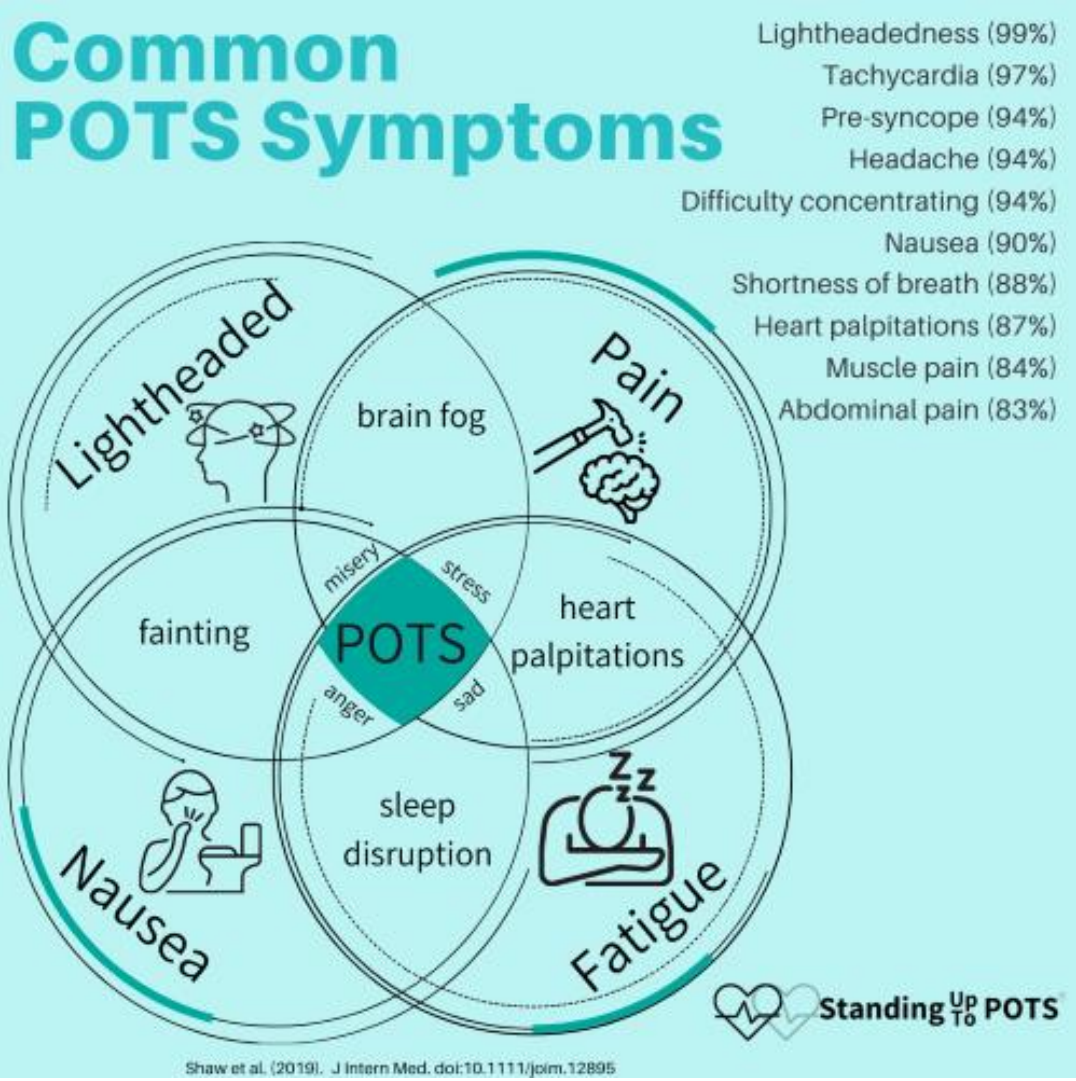
Symptoms of POTS

Pain Related to POTS

Neuropathic pain

Abdominal pain

Hypersensitivity (skin, light, sound)



Treat POTS

https://www.standinguptopots.org/livingwithpots/pots-symptoms

POTS: The current estimate on numbers

Experts have estimated that up to 3,000,000 Americans could be affected, and potentially 70 million worldwide.

Canadian Statistics: United States—often used as a rough benchmark—suggest that **0.1% to 1.0%** of the general population may have POTS. Extrapolating this to Canada (with a population of about 40 million) suggests a possible **40,000 to 400,000** individuals in Canada might be affected—but this is speculative rather than evidence-based.

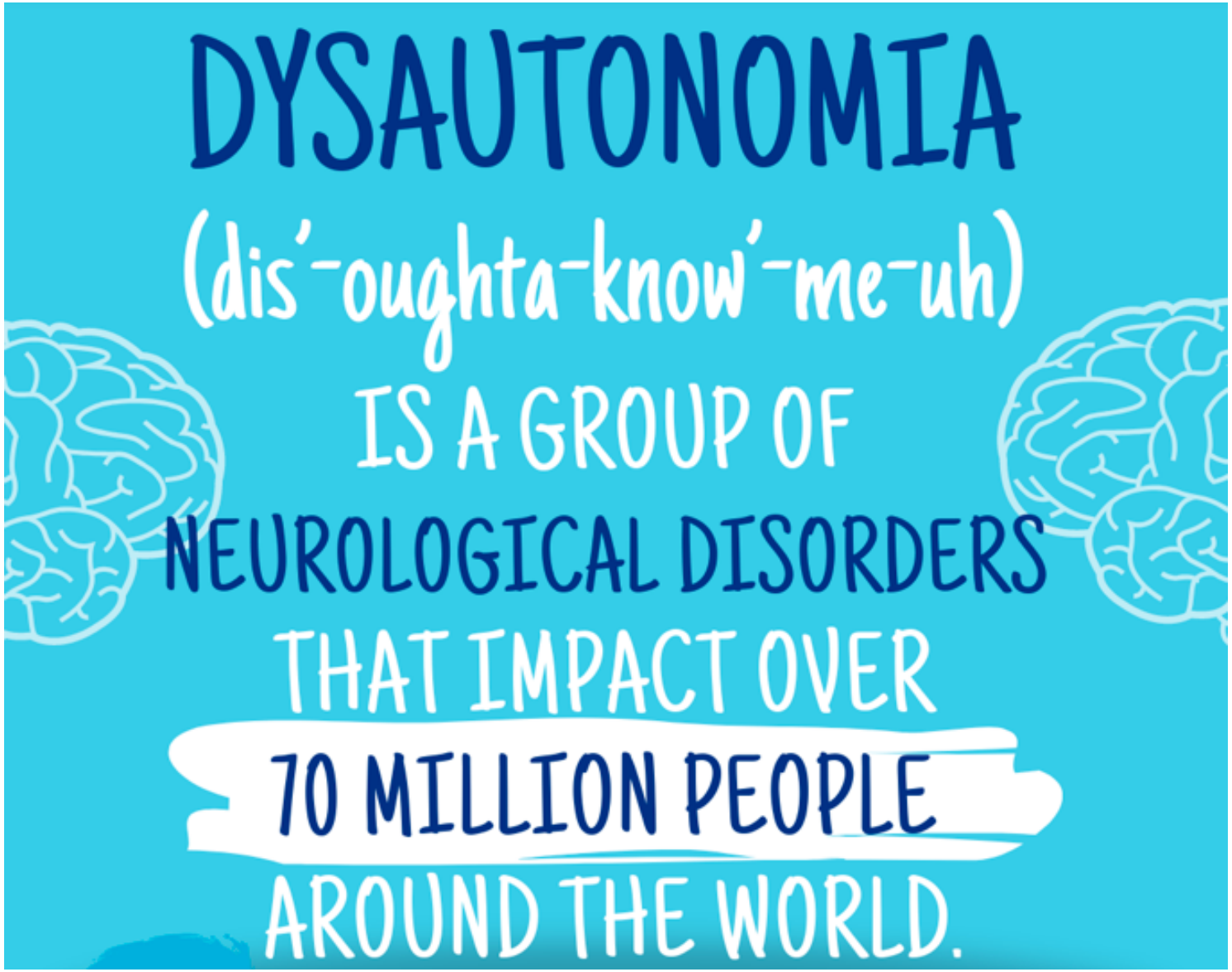
One study in China reported 6.8% of adolescents met clinical criteria for POTS

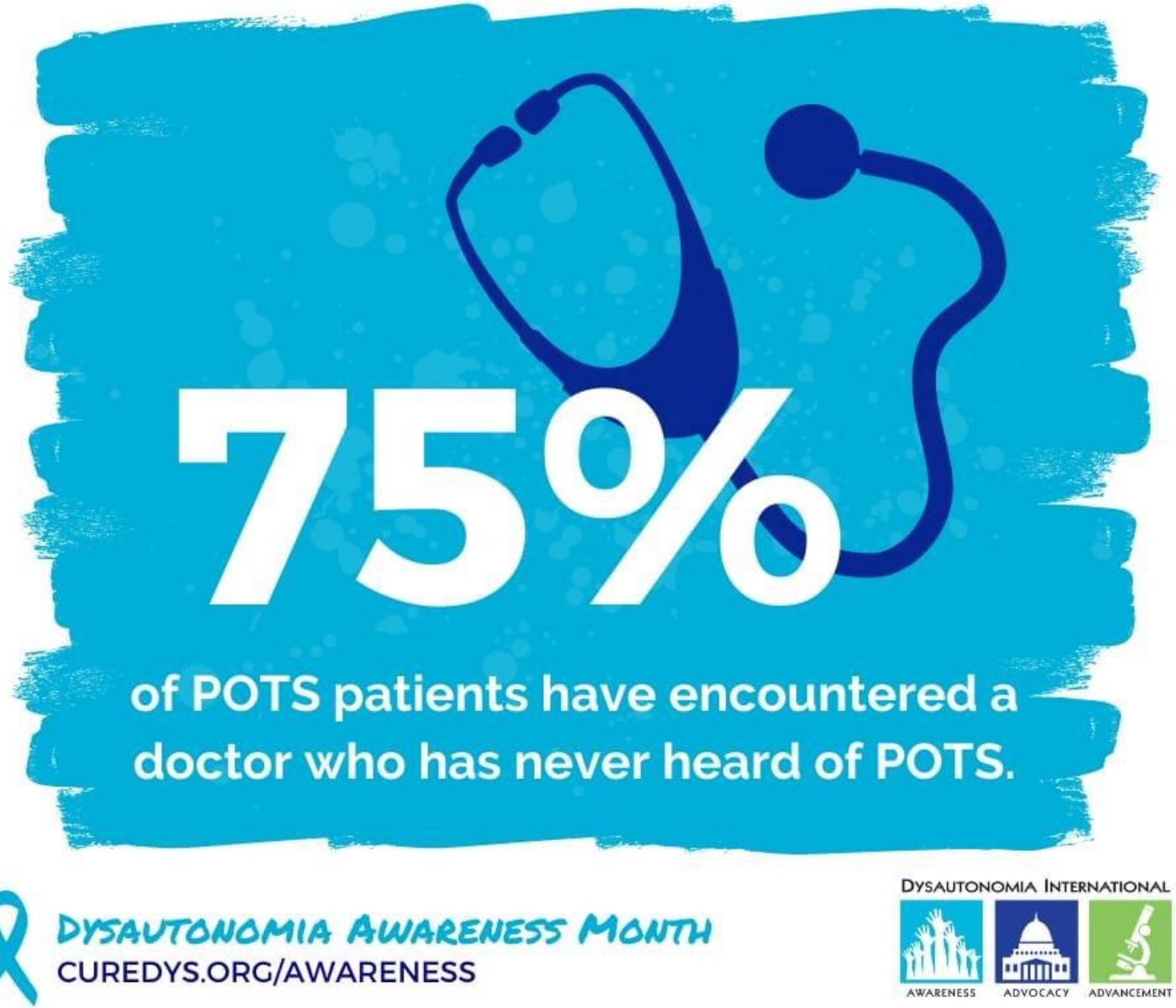
POTS is a common neurocardiovascular disease, representing approximately 32.2% of all corresponding syncope cases

POTS is one of the most common forms of autonomic dysfunction.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455430/
https://pubmed.ncbi.nlm.nih.gov/25474569/
https://pubmed.ncbi.nlm.nih.gov/28286247/

Treat POTS





A PATIENT WILL SEE AN AVERAGE OF

7 DOCTORS

BEFORE RECEIVING A POTS DIAGNOSIS.

What if its not POTS?

Sinus tachycardia causes that are not POTS:

- Iron deficiency
- anorexia nervosa
- **primary anxiety disorders**
- **Hyperventilation**
- Anemia
- Fever
- Pain
- Infection

- Dehydration
- Hyperthyroidism
- pheochromocytoma,
- use of cardioactive drugs (e.g. sympathomimetics, anticholinergics) or
- severe deconditioning caused by prolonged bed rest.

What is the pathophysiology of POTS?

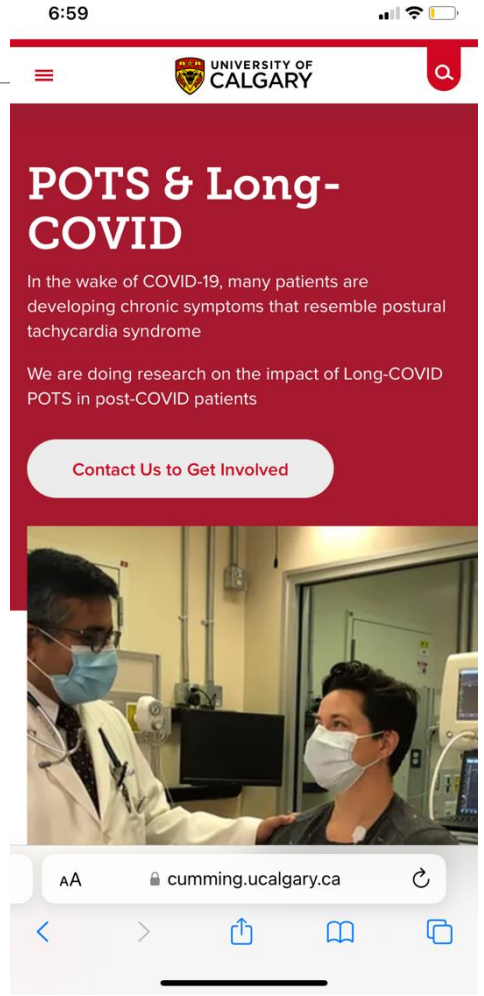
Postural orthostatic tachycardia syndrome may have an immunological cause.

Many patients describe a post-viral onset, **and** 15%–20% of patients with POTS report a history of an autoimmune disorder such as Hashimoto thyroiditis, rheumatoid arthritis or Sjögren's syndrome.

https://www.heartrhythmcasereports.com/article/S2214-0271(21)00223-2/fulltext
https://www.sciencedirect.com/science/article/pii/S0002934321004721

Why do I care now? POTS is famous

- Recent reports indicate that 2%-14% of coronavirus disease 2019 (COVID-19) survivors develop POTS and 9%-61% experience POTS-like symptoms, such as tachycardia, orthostatic intolerance, fatigue, and cognitive impairment within 6-8 months of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- post–acute sequelae of SARS-CoV-2 syndrome," "post–coronavirus disease 2019 (COVID-19) syndrome," "long-haul COVID," or "long COVID" and are usually defined as symptoms that persist for >4 weeks from acute illness.



https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10065129/

CTV NEWS

CORONAVIRUS | News

Doctors warn of possible rise of debilitating nervous-system disorder in patients with long COVID-19

UNIVERSITY OF CALGARY

POTS & Long-COVID

In the wake of COVID-19, many patients are developing chronic symptoms that resemble postural tachycardia syndrome

We are doing research on the impact of Long-COVID POTS in post-COVID patients

Contact Us to Get Involved

https://cumming.ucalgary.ca/labs/calgary-autonomic-investigation/pots-long-covid

Can J Cardiol. Author manuscript; available in PMC 2022 Oct 1. PMCID: PMC9402394
Published in final edited form as: NIHMSID: NIHMS1831162
Can J Cardiol. 2021 Oct; 37(10): 1683–1684. PMID: 34371119
Published online 2021 Aug 8. doi: 10.1016/j.cjca.2021.07.017

Patients with Postural Orthostatic Tachycardia Syndrome have different experiences in Healthcare in Canada and USA

Juliette Hall,[1] Kate M. Bourne, [illegible] heldon, MD PhD,[1]
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Alfredo C. Gamboa, MD MSCI [illegible]ni, MD,[4]
David Robertson, MD,[4] and Sa[illegible]

Kate M Bourne
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What is the pathophysiology of POTS?

POTS is a disorder of the autonomic nervous system, marked by an abnormally high heart rate when standing, without a major drop in blood pressure. The cause is complex and multifactorial.

1. Hypovolemia (Low Blood Volume)

2. Excess Sympathetic Nervous System Activity

3. Neuropathic POTS: involves damage to the small nerve fibers (peripheral neuropathy) that control blood vessel constriction, particularly in the legs and abdomen.

4. Impaired Baroreflex Function

5. Autoimmune Mechanisms

6. Mast Cell Activation

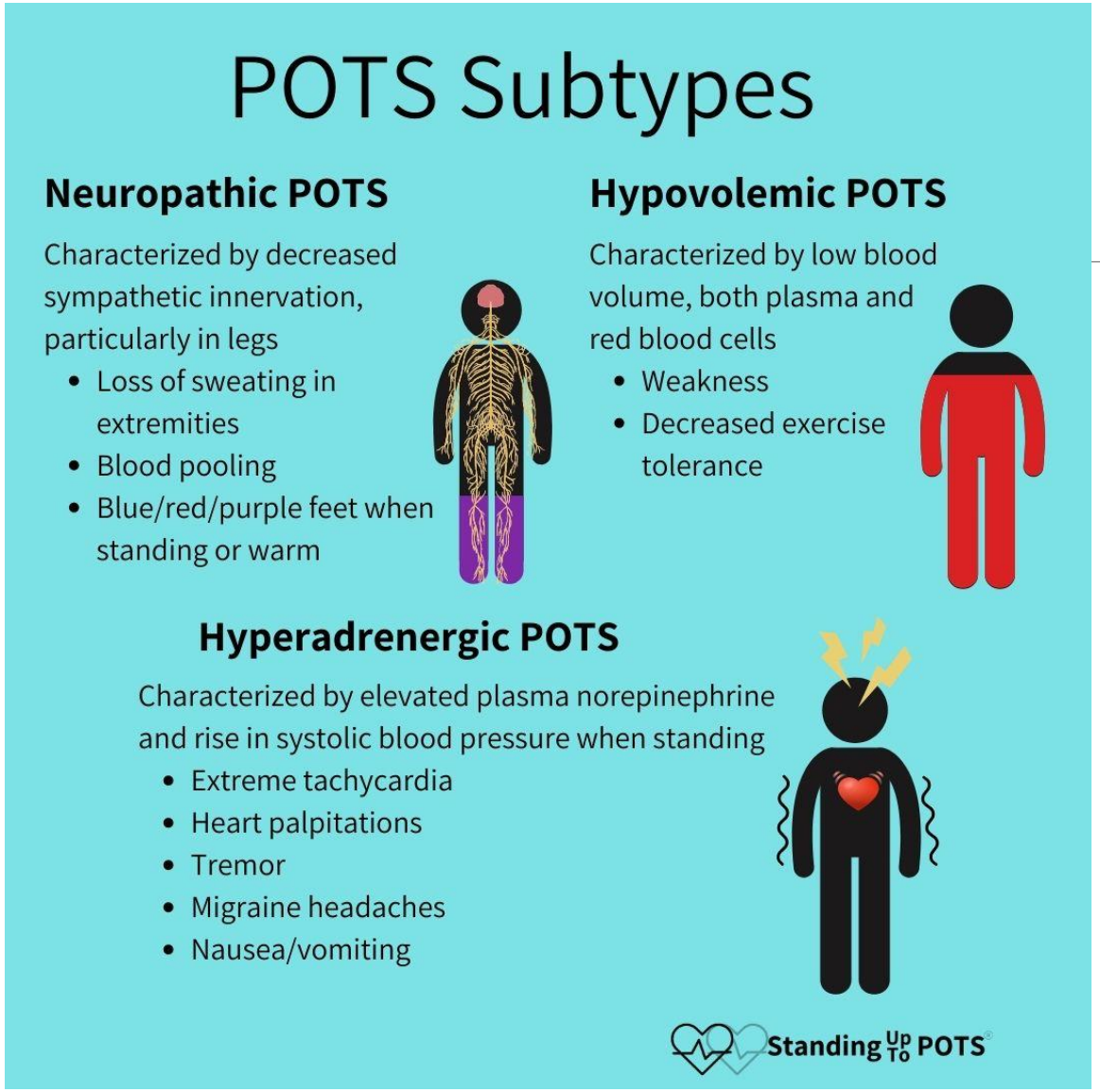
7. Ehlers-Danlos Syndrome (hEDS):

https://www.cmaj.ca/content/194/10/E378#ref-26

Where does POTS fit in a case?

- POTS has an impact on the circulatory system in both blood volume and inflammation.
- If a patient has POTS and say, any other condition, the POTS mechanically impacts the successful treatment of any thing else.
- You need blood to deliver your protocol and this condition stops effective blood flow

Fix the POTS first in a case



https://www.standinguptopots.org/POTSsubtypes

3 Types of POTS….but look at 5….

1) Hypovolemia
2) Hyperadrenergic
3) Neurogenic

4) Mast Cell Activation
5) EDS

Suggested initial approach to treatment of patient with POTS

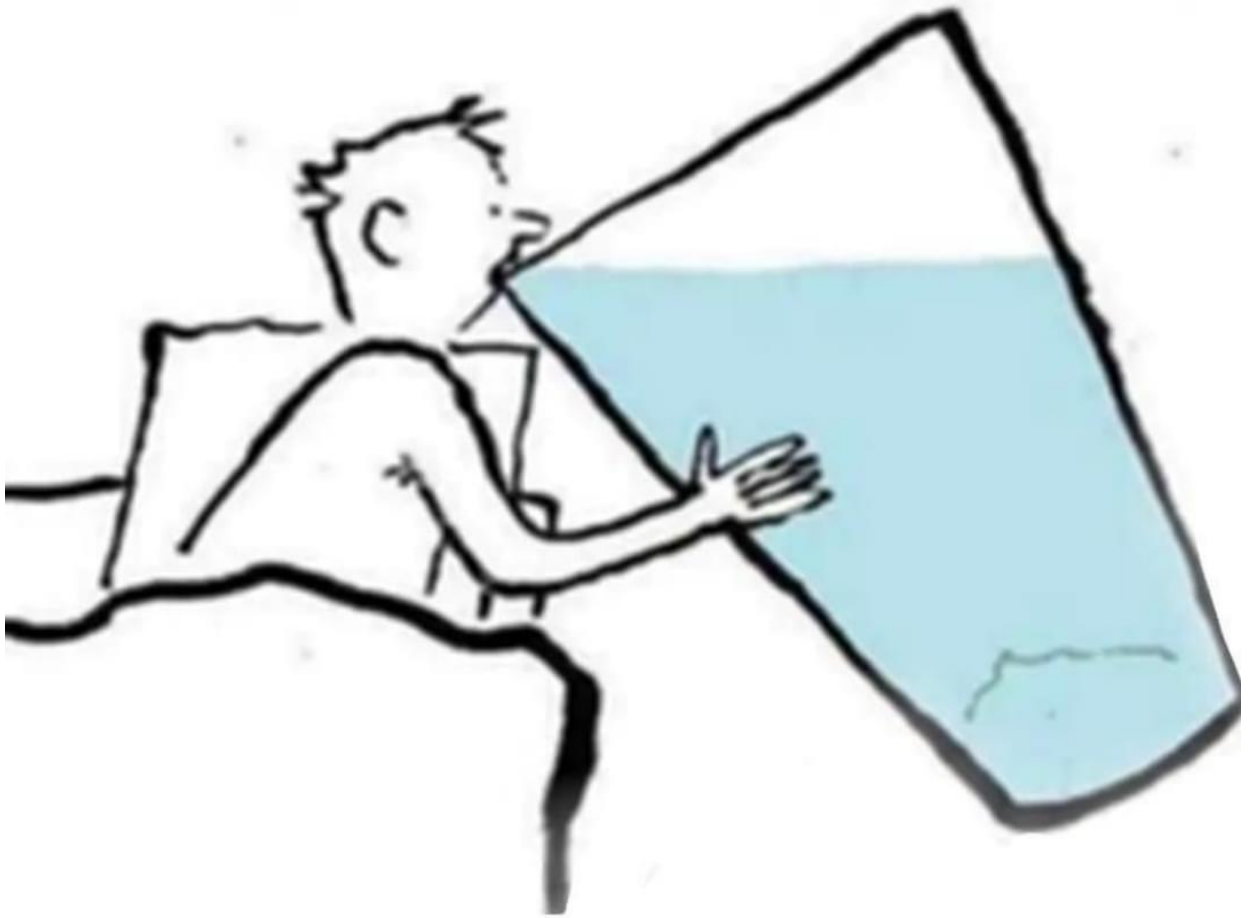
Nonpharmacological treatments

- Water 3 L/d
- Salt 5 mL/d (2 tsp/d)
- Waist-high compression garments

Pharmacological treatments

- If standing heart rate very high: propranolol 10–20 mg, 4 times per day
- If standing heart rate very high and β-blocker is contraindicated: ivabradine 5 mg 2 times per day
- If standing heart rate is not too high and blood pressure is low: midodrine 5 mg orally every 4 hours, 3 times per day (8 am, noon, 4 pm)

https://www.jacc.org/doi/abs/10.1016/j.jacc.2021.03.005
https://www.cmaj.ca/content/194/10/E378#ref-41



Treat POTS

How low can you go…Blood Volume

When a person with POTS stands up, about 500–700 mL of blood pools in the abdomen and legs due to gravity.

This leads to a ~30% drop in thoracic blood volume, reducing:

- Venous return to the heart
- Stroke volume
- Cardiac output (CO)

Though POTS has varied causes, its effects resemble hypovolemia (low blood volume).

Treatment must include efforts to restore blood volume

https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltext
https://www.sciencedirect.com/science/article/pii/S1566070222000108

Treat POTS

Salt, Salt and more Salt by IV

- More direct methods have been used to mitigate the effects of orthostasis, including the administration of intravenous (IV) saline solution, which can improve all forms of orthostatic intolerance by increasing central blood volume and venous return.

- Thus, saline may prevent syncope and improve orthostatic intolerance and HR changes in patients with POTS

https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltext

Saline IV

- Intermittent IV infusions of saline dramatically reduce symptoms and improve quality of life in patients suffering from POTS. Further work should explore its efficacy as a bridge study for patients of high symptomatic severity.
- The average number of medications trialed before referral for IV hydration was 3.6 ± 1.7 medications.
- Saline infusions occurred with mean frequency of 11.3 ± 8.5 days and at a mean volume of 1.5 ± 0.6 litre per infusion

https://pubmed.ncbi.nlm.nih.gov/28185102/

But what is better? IV or oral?

- IV saline is expensive, there is a repeated need for infusions, and unacceptable risks (eg, bruising, infection) of chronic central venous catheterization.
- Alternatives to IV saline, such as oral salt and water, have been recommended to reduce orthostatic intolerance symptoms
- One study at 2000mg salt found that oral rehydration solution (salt with water and glucose or ORS) is a convenient, safe, and effective therapy for short- term relief of orthostatic intolerance.

https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltext
https://www.sciencedirect.com/science/article/pii/S1566070222000108

Salt? But how much? ALOT!

- Patients are encouraged to consume electrolyte beverages to increase osmotic pressure and keep the fluids in the intravascular space.
- The rationale is expansion of intravascular volume to compensate for intravascular hypovolemia and orthostatic pooling.
- Consensus-based guidelines have recommended, in addition to drinking 2 to 3 L of water daily, sodium chloride, 8 g/d to 12 g/d (350–520 mmol/d sodium)

https://www.sciencedirect.com/science/article/pii/S1566070222000108

Hypovolemic POTS

Hypovolemic POTS is characterized by abnormally low blood levels, including both red blood cells and plasma.

plasma deficit in POTS is approximately 13% and may be related to low levels of circulating renin and aldosterone which typically help to increase blood volume and blood pressure.

Low blood volume leads to less blood return to the heart, which causes an increased heart rate and force of contraction in an attempt to keep blood circulation at normal levels.

What symptoms are typically associated with hypovolemic POTS?

- Weakness
- Decreased tolerance for exercise

https://www.standinguptopots.org/POTSsubtypes
https://www.ahajournals.org/doi/full/10.1161/01.CIR.0000160356.97313.5D

Hyper-adrenergic POTS

Hyperadrenergic POTS is characterized by elevated levels of plasma norepinephrine levels (neurotransmitter of the sympathetic NS) >600 pg/mL and >10 mmHg rise in systolic blood pressure while standing for 10 minutes

In hyperadrenergic POTS, the sympathetic nervous system is overactivated.

- Increased blood pressure
- Tachycardia that may be more extreme than other subtypes
- Heart palpitations
- Anxiety, tremor, cold, sweaty extremities while upright
- Migraine headaches
- Increased urinary output after being upright
- Nausea/vomiting

https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1540-8167.2008.01407.x
https://pubmed.ncbi.nlm.nih.gov/33980338/

Effects of Adrenaline on Circulation

- Increasing peripheral resistance through α_1 receptor-mediated vasoconstriction
- Boosting cardiac output via β_1 receptor stimulation

Purpose

- To raise coronary and cerebral perfusion pressures
- Improves oxygen delivery to tissues

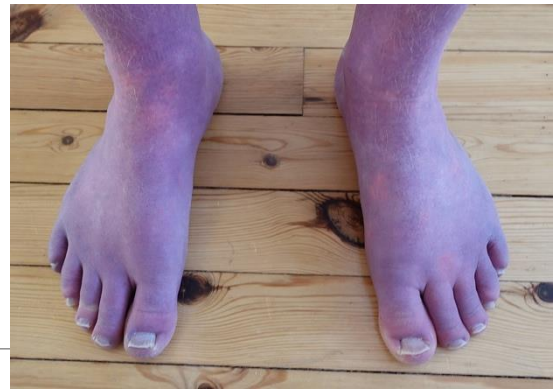
Trade-Offs

While it increases pressure in major arteries (aortic, cerebral, carotid), it can:

- Reduce carotid blood flow
- Lower end-tidal CO_2 ($ETCO_2$) — indicating less effective gas exchange
- Impair capillary perfusion, affecting microcirculation, where oxygen exchange happens

https://en.m.wikipedia.org/wiki/Capnography

Neuropathic POTS



Neuropathic POTS is characterized by a decrease in sympathetic innervation, particularly in the legs and is often associated with small fiber neuropathy.

Normally, these small fiber nerves regulate constriction of the blood vessels in the limbs and abdomen. Because these nerves are damaged in neuropathic POTS, however, activation of the sympathetic nervous system leads to less release of norepinephrine from these small fibers.

Because norepinephrine is a vasoconstrictor, neuropathic POTS is often associated with excessive blood pooling in the hands and feet. This decreases blood circulation and causes less blood to return to the heart (low venous return) which causes the heart rate to increase in order to compensate.

- The most prominent symptoms of neuropathic POTS include:
- Loss of sweating in extremities
- Blood pooling
- Cyanosis in the feet (turning a bluish color when standing/warm)

https://www.annualreviews.org/doi/full/10.1146/annurev-med-041818-011630
https://www.standinguptopots.org/POTSsubtypes
https://www.ahajournals.org/doi/full/10.1161/JAHA.113.000755

Hyper-adrenergic POTS: Epinephrine and Norepinephrine

Key co-factors needed for epinephrine and norepinephrine: Magnesium, B vitamins, methyl donors, and inositol and larger doses. COMT people can have B12 and often need it.

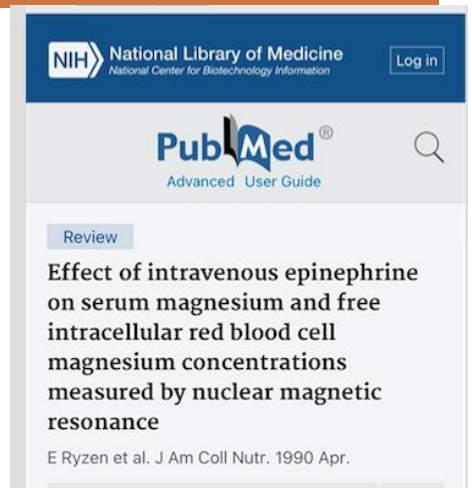

Journal of Cellular Physiology / Volume 153, Issue 2 / p. 234-243

Article

Norepinephrine stimulates the direct breakdown of phosphatidyl inositol in rat tail artery

Edward F. Labelle, Hong Gu, Snezana Trajkovic

First published: November 1992
https://doi.org/10.1002/jcp.1041530203
Citations: 6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Review

Effect of intravenous epinephrine on serum magnesium and free intracellular red blood cell magnesium concentrations measured by nuclear magnetic resonance

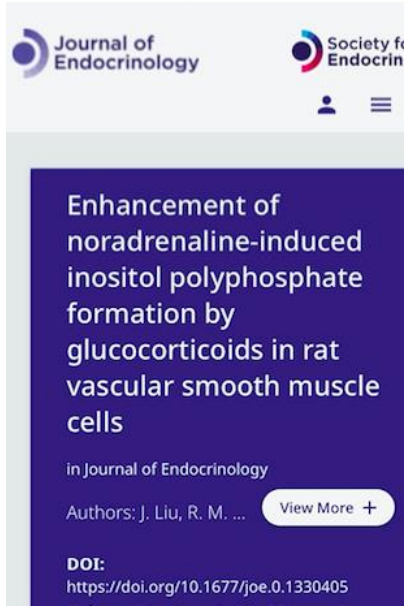
E Ryzen et al. J Am Coll Nutr. 1990 Apr.


Hypothesis

Does vitamin C deficiency result in impaired brain development in infants?

Pernille Tveden-Nyborg, Jens Lykkesfeldt

Section of Biomedicine, Department of Disease Biology, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark


Journal of Endocrinology

Society f Endocrin

Enhancement of noradrenaline-induced inositol polyphosphate formation by glucocorticoids in rat vascular smooth muscle cells

in Journal of Endocrinology

Authors: J. Liu, R. M. ...

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https://doi.org/10.1677/joe.0.1330405


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Vitamin B6 deficiency hyperactivates the noradrenergic system, leading to social deficits and cognitive impairment

Kazuya Toriumi et al. Transl Psychiatry. 2021.

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Full text links | Cite | ...

Abstract

We have reported that a subpopulation of patients with schizophrenia have lower levels of vitamin B_6 (VB6) in peripheral blood than do healthy controls. In a previous study, we found that VB6 level was inversely proportional to the patient's positive and negative symptom scale (PANSS) score for measuring symptom severity, suggesting that the

*See Further References

Hyper-adrenergic POTS: Valerian

- Valerian is antiadrenergic, is anxiolytic, induces GABA, regulates blood sugar, stabilizes SOD, anti-arrhythmia, enhances microcirculation, decreases levels of xanthine oxidase (XOD), decreasing levels of malondialdehyde (MDA), and tumor necrosis factor-alpha.
- Valerian can significantly inhibit the migration of vascular smooth muscle cells thereby lowering blood pressure.

Review

A Review Focused on Molecular Mechanisms of Anxiolytic Effect of Valerina officinalis L. in Connection with Its Phytochemistry through in vitro/in vivo Studies

Ilkay E Orhan. Curr Pharm Des. 2021.

Valerenic Acid Protects Against Physical and Psychological Stress by Reducing the Turnover of Serotonin and Norepinephrine in Mouse Hippocampus-Amygdala Region

Hyo Young Jung et al. J Med Food. 2015 Dec.

*See Further References

Test for Neurotransmitters: In blood

Catecholamine blood test

This test measures the levels of catecholamines in the blood. Catecholamines are hormones made by the adrenal glands. The three catecholamines are epinephrine (adrenaline), norepinephrine, and dopamine.

Catecholamines are more often measured with a urine test than with a blood test.

How the Test is Performed

A blood sample is needed.

Normal Results

The normal range for epinephrine is 0 to 140 pg/mL (0 to 764.3 pmol/L).

The normal range for norepinephrine is 70 to 1700 pg/mL (413.8 to 10048.7 pmol/L).

The normal range for dopamine is 0 to 30 pg/mL (0 to 195.8 pmol/L).

Note: Normal value ranges may vary slightly among different labs. Some labs use different measurements or test different samples. Talk to your provider about the meaning of your specific test results.

Test for Neurotransmitters: In urine

24.	Formiminoglutamic Acid	0.6	0.0 - 5.1	ug/mgCR	

Cell Regulation Markers

NEUROTRANSMITTER METABOLISM

(Tyrosine, Tryptophan, B6, Antioxidants)

25.	Homovanillic Acid (HVA)	6.36	2.39 - 14.92	ug/mgCR	
26.	Vanillylmandelic Acid (VMA)	2.66	1.40 - 5.09	ug/mgCR	
27.	5-Hydroxyindoleacetic Acid (5HIAA)	0.39	0.34 - 3.98	ug/mgCR	
28.	Kynurenic Acid.	*1.93 *H*	0.00 - 1.51	ug/mgCR	
29.	Quinolinic Acid (OA)	1.95	0.00 - 9.74	ug/mgCR	
30.	Picolinic Acid	0.1	0.0 - 1.5	ug/mgCR	
31.	Cortisol (OA)	25.7	5.0 - 65.0	ng/mL	

Oxidative Damage/AntiOxidant Markers

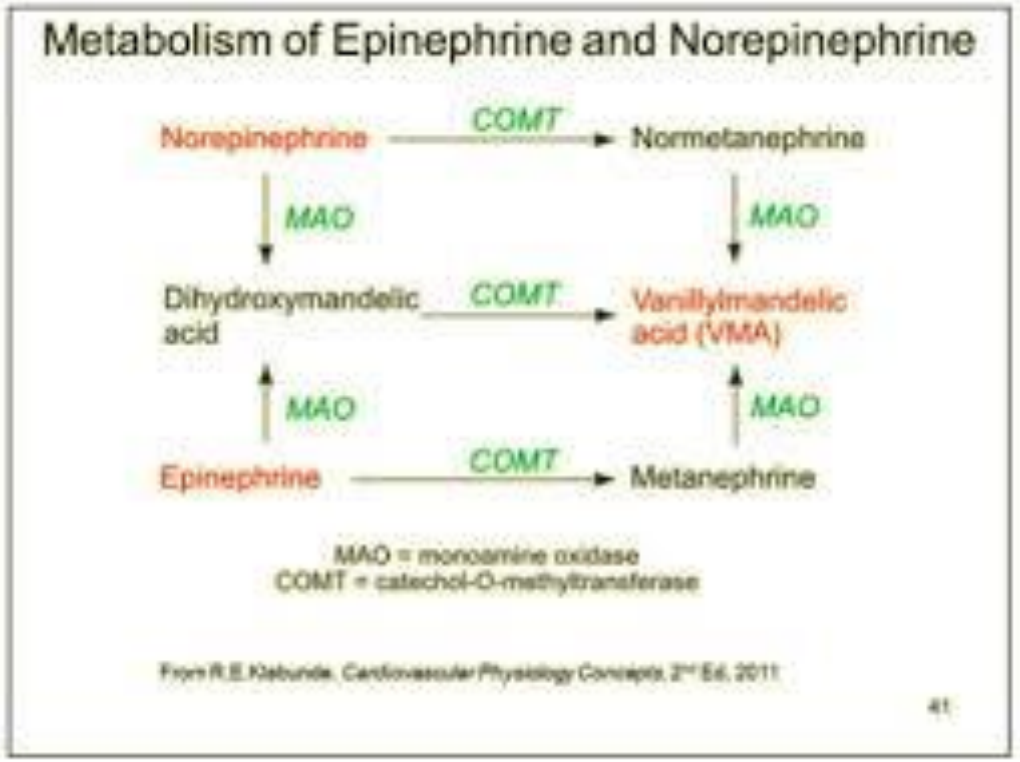
(Vitamin C and Other Antioxidants)

32.	ParaHydroxyphenyllactate	0.23	0.00 - 1.47	ug/mgCR	

COMT: Catechol-O-methyltransferase

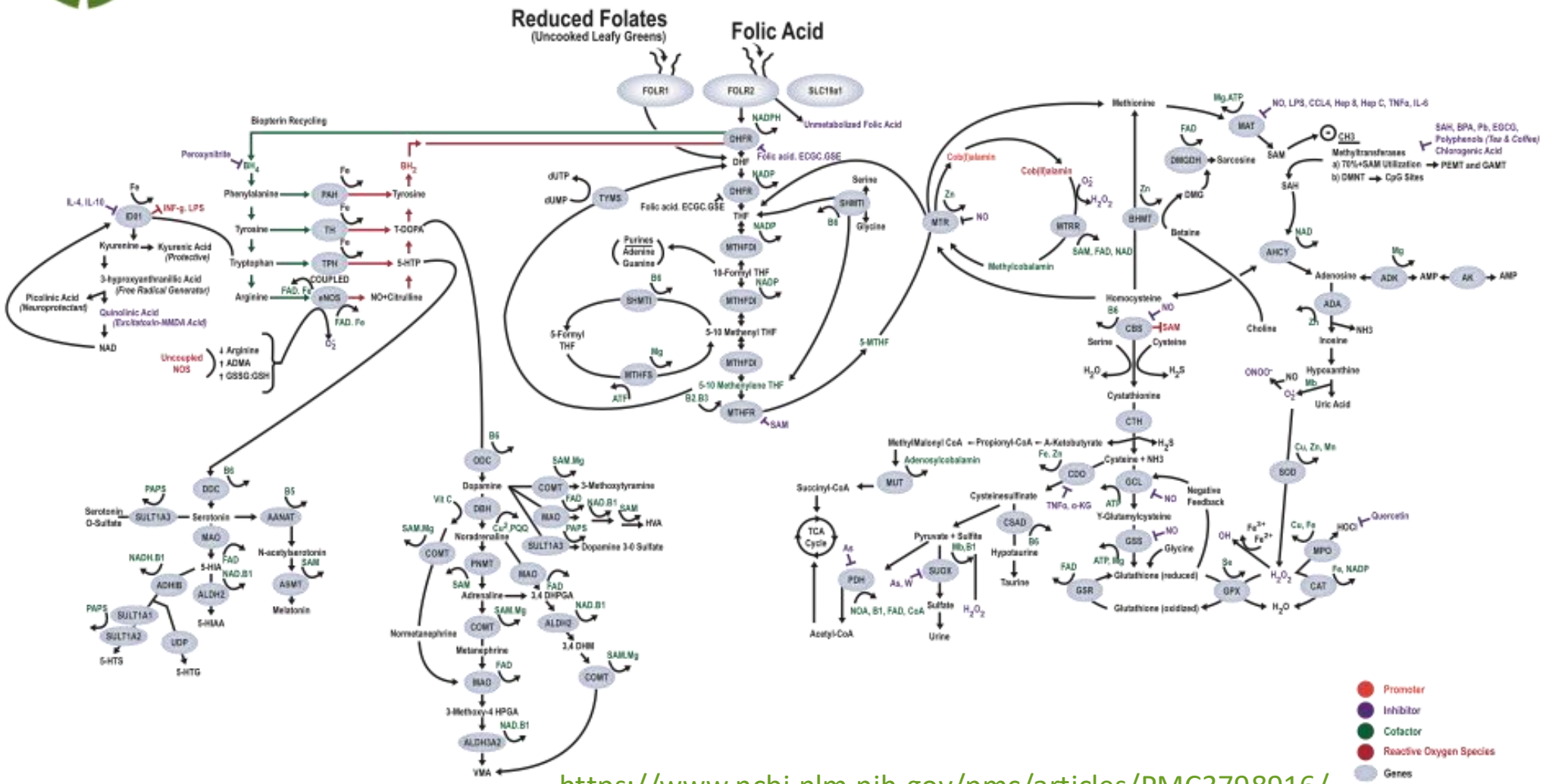
- COMT is one of several enzymes that degrade or inactivate catecholamines (such as dopamine, epinephrine, and norepinephrine), and catecholestrogen.
- The enzyme introduces a methyl group to the catecholamine, which is donated by methyl groups
- The methyl group can directly be delivered by dietary methyl donors, including methionine, folate, methylcobalamin, betaine, and choline

https://cvpharmacology.com/norepinephrine



NATURAL CARE CLINIC

Pathway Planner



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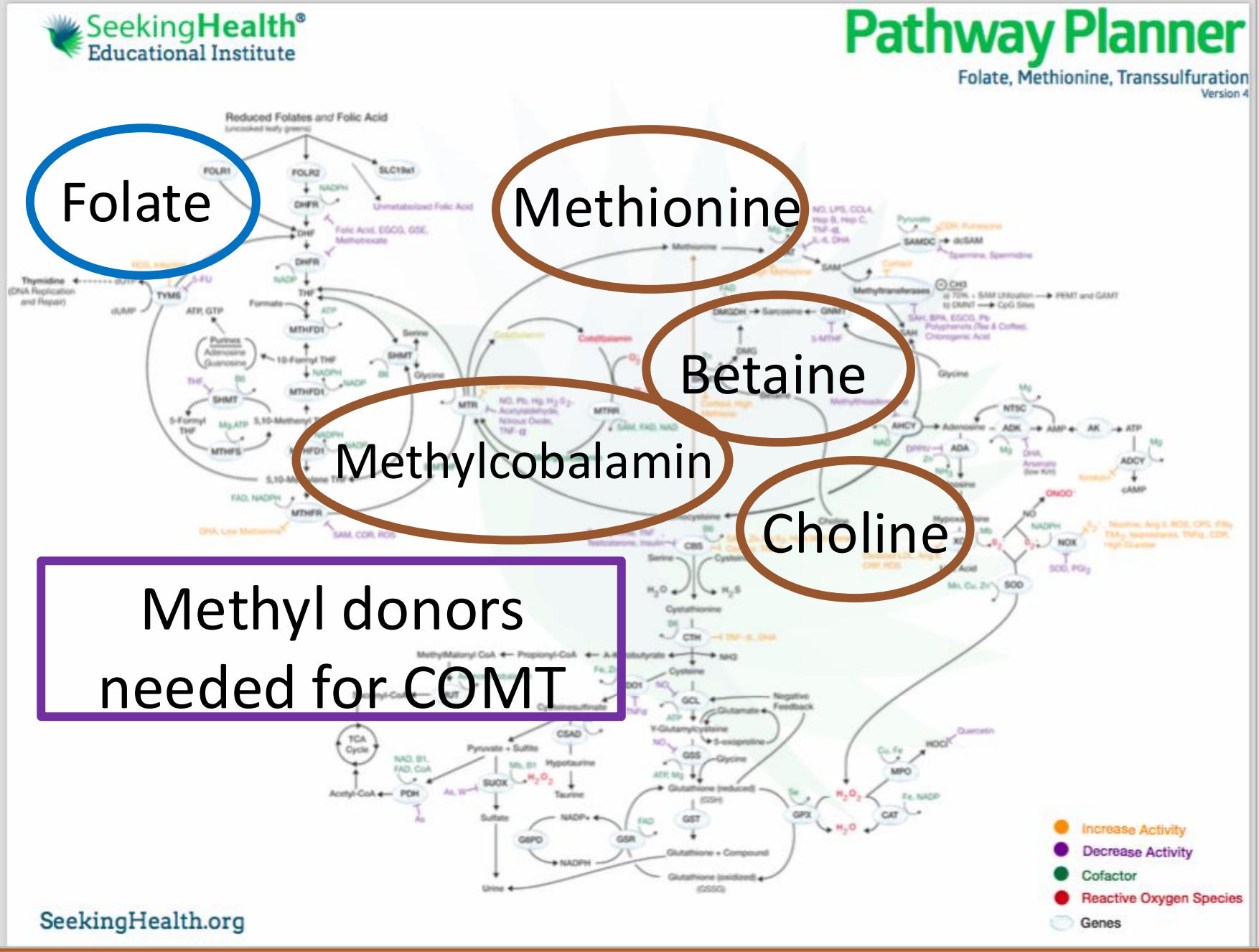

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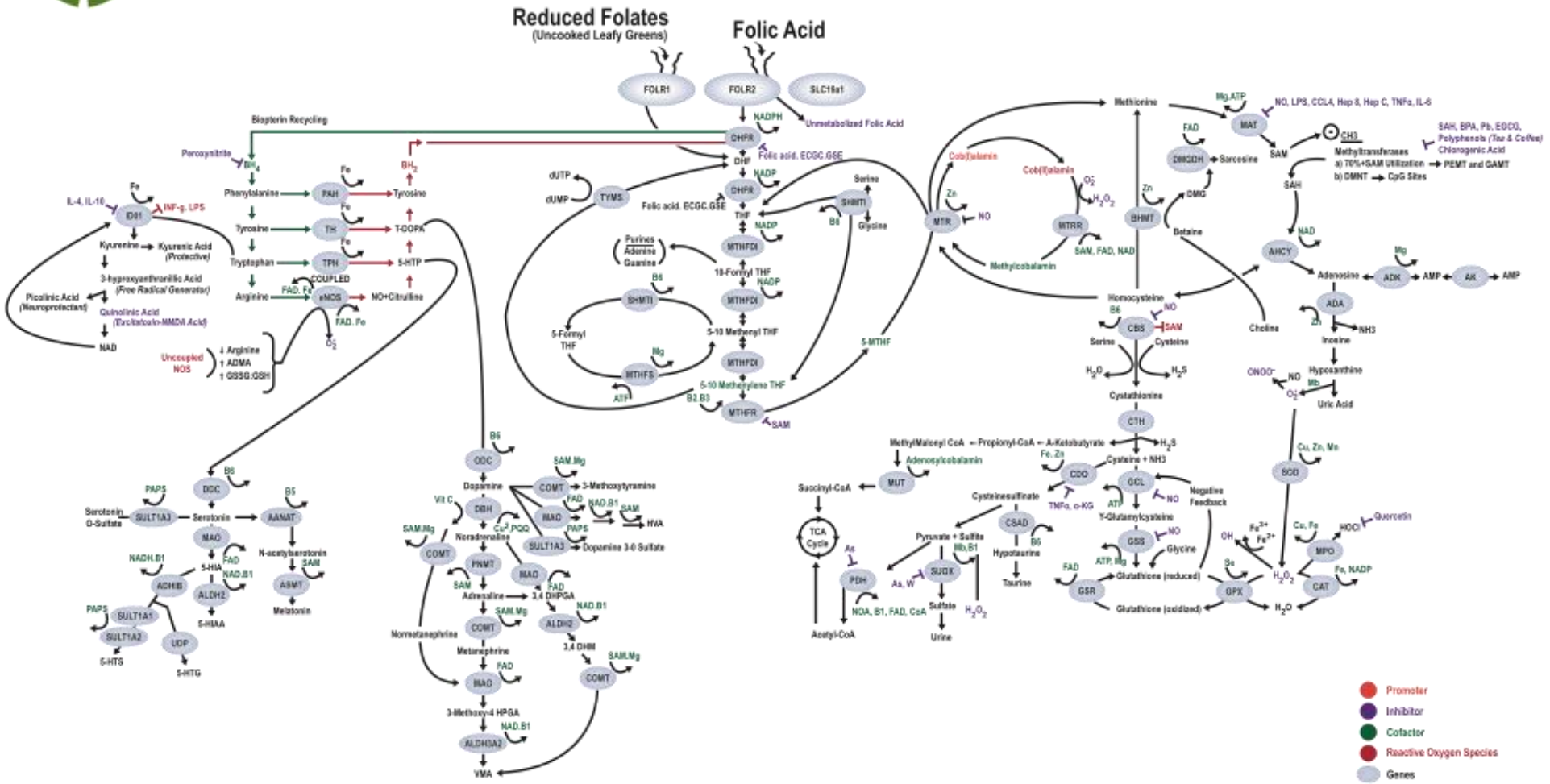

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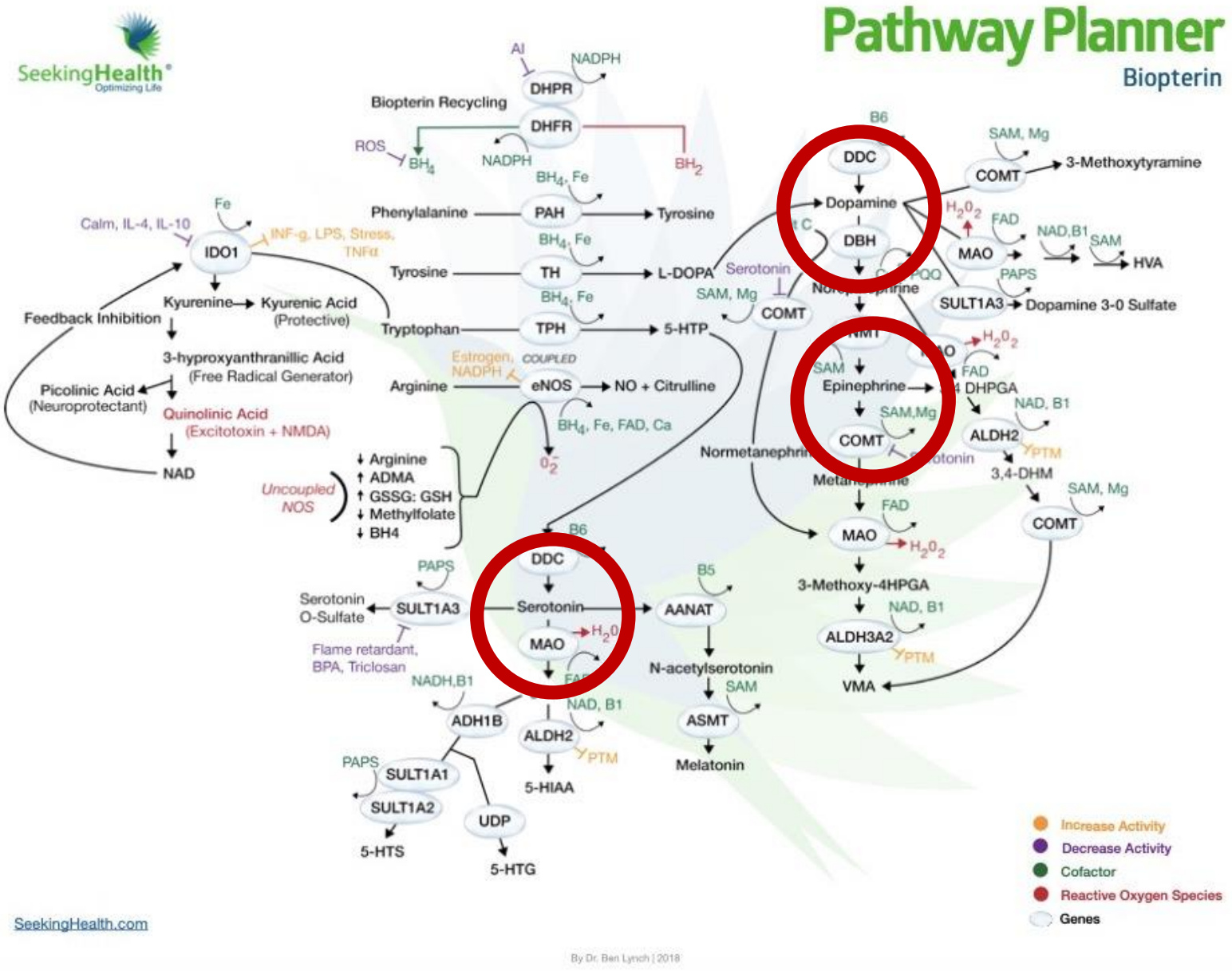
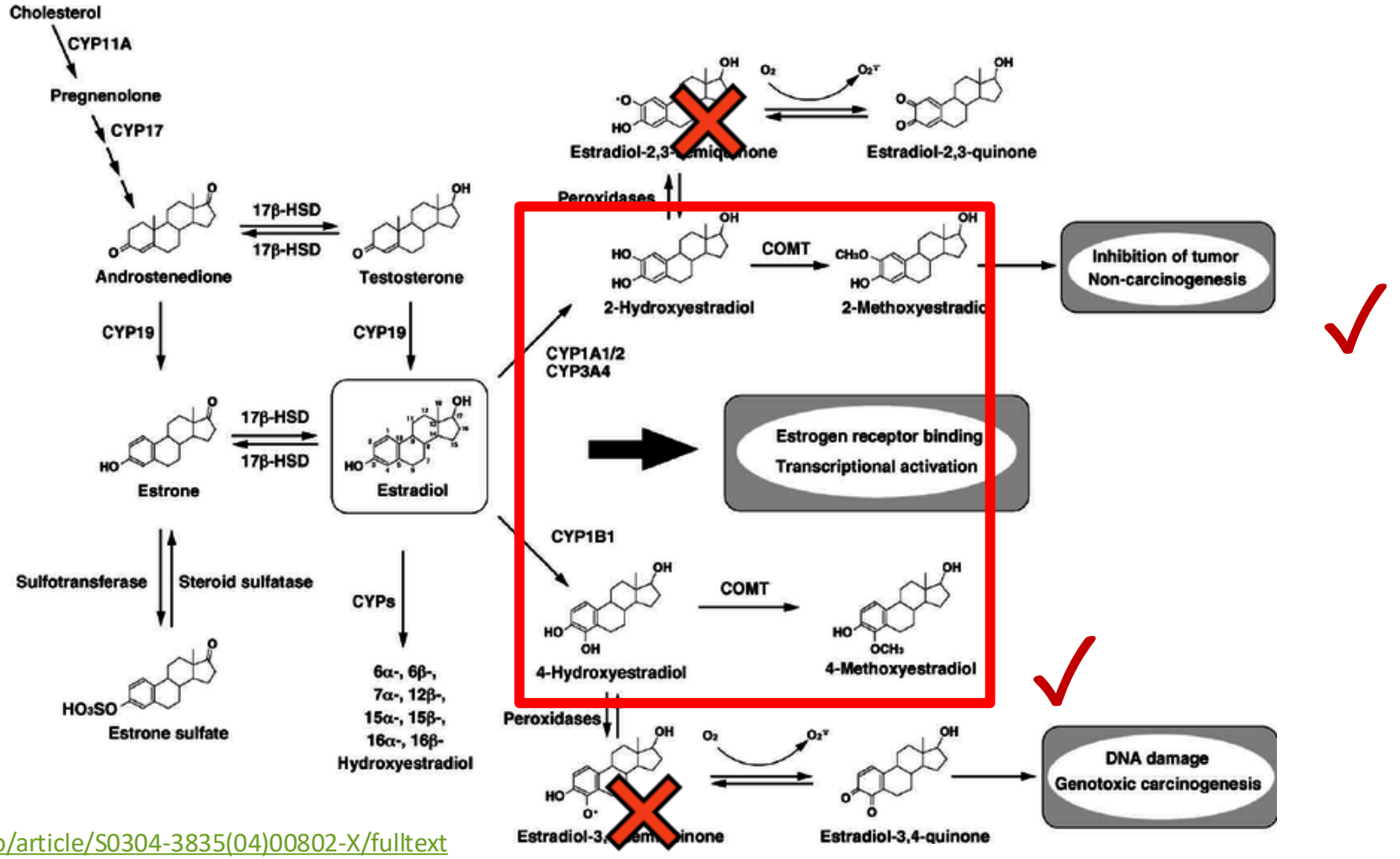
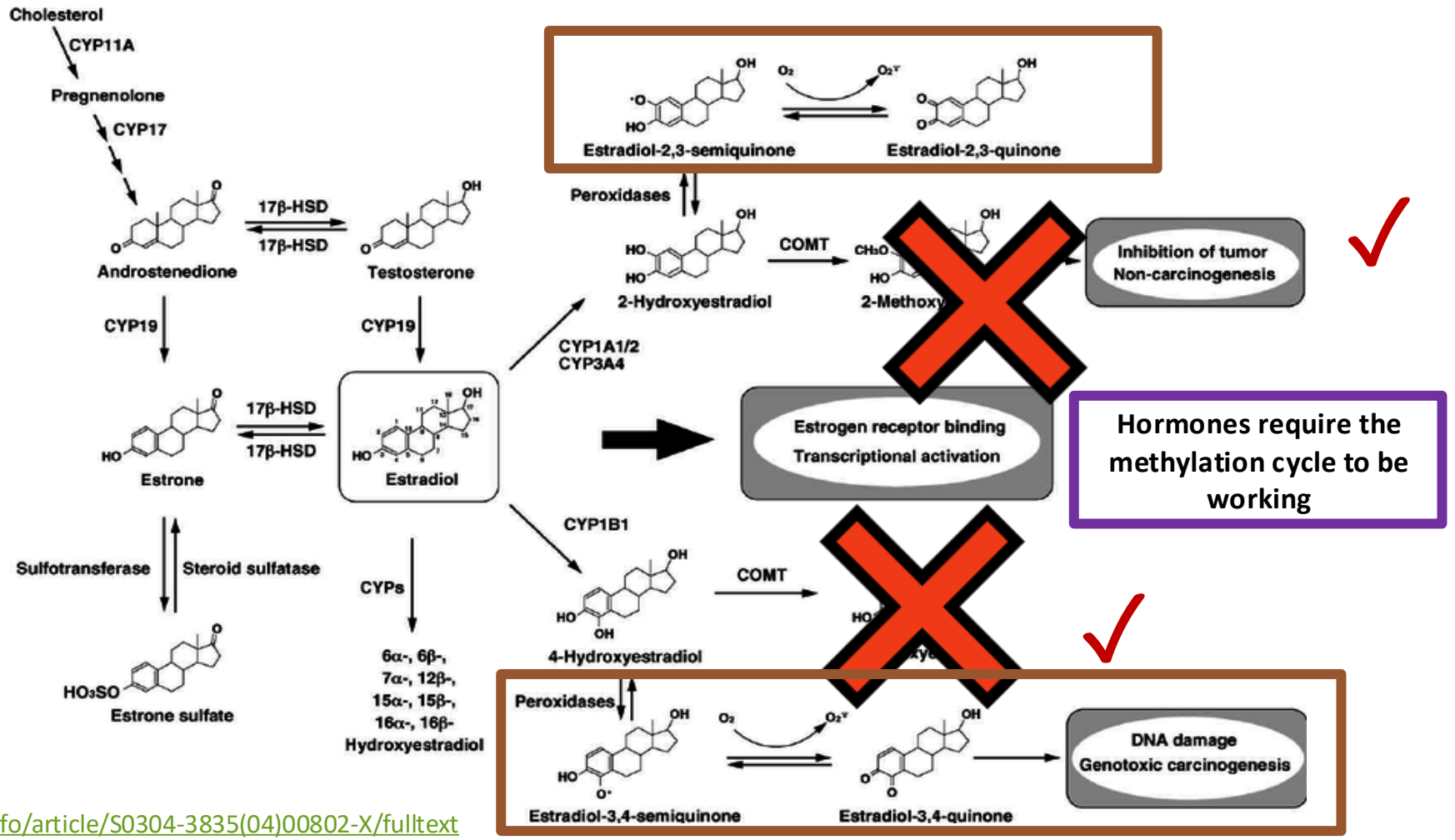


COMT: Catechol-*O*-methyltransferase



http://www.cancerletters.info/article/S0304-3835(04)00802-X/fulltext

Estrogen Dominance? When hormones don't get detoxified



http://www.cancerletters.info/article/S0304-3835(04)00802-X/fulltext

Case report

Improvement of hyperadrenergic postural orthostatic tachycardia syndrome (POTS) with methylated B vitamins in the setting of a heterozygous COMT Val158Met polymorphism

Nikita Mittal,[1] Ariel Portera,[2] Pam Taub [1]

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[2]Division of Family Medicine, Department of Medicine, University of California San Diego, La Jolla, California, USA

SUMMARY

A middle-aged woman was diagnosed with postural orthostatic tachycardia syndrome based on her clinical symptoms, elevated norepinephrine levels and positive tilt-table test. The patient was refractory to conventional treatment and improved only after she was treated with methylated B vitamins for her heterozygous catechol-O-methyltransferase Val158Met polymorphism.

symptoms such as tachycardia on standing, palpitations and anxiety. Patients also often experience lightheadedness, dyspnoea, headaches, fatigue and near syncope.[1] Due to the heterogeneity of symptoms, the diagnosis of POTS is usually delayed and patients are often dismissed as having psychiatric illnesses such as anxiety and depression.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8586883/pdf/bcr-2021-245012.pdf

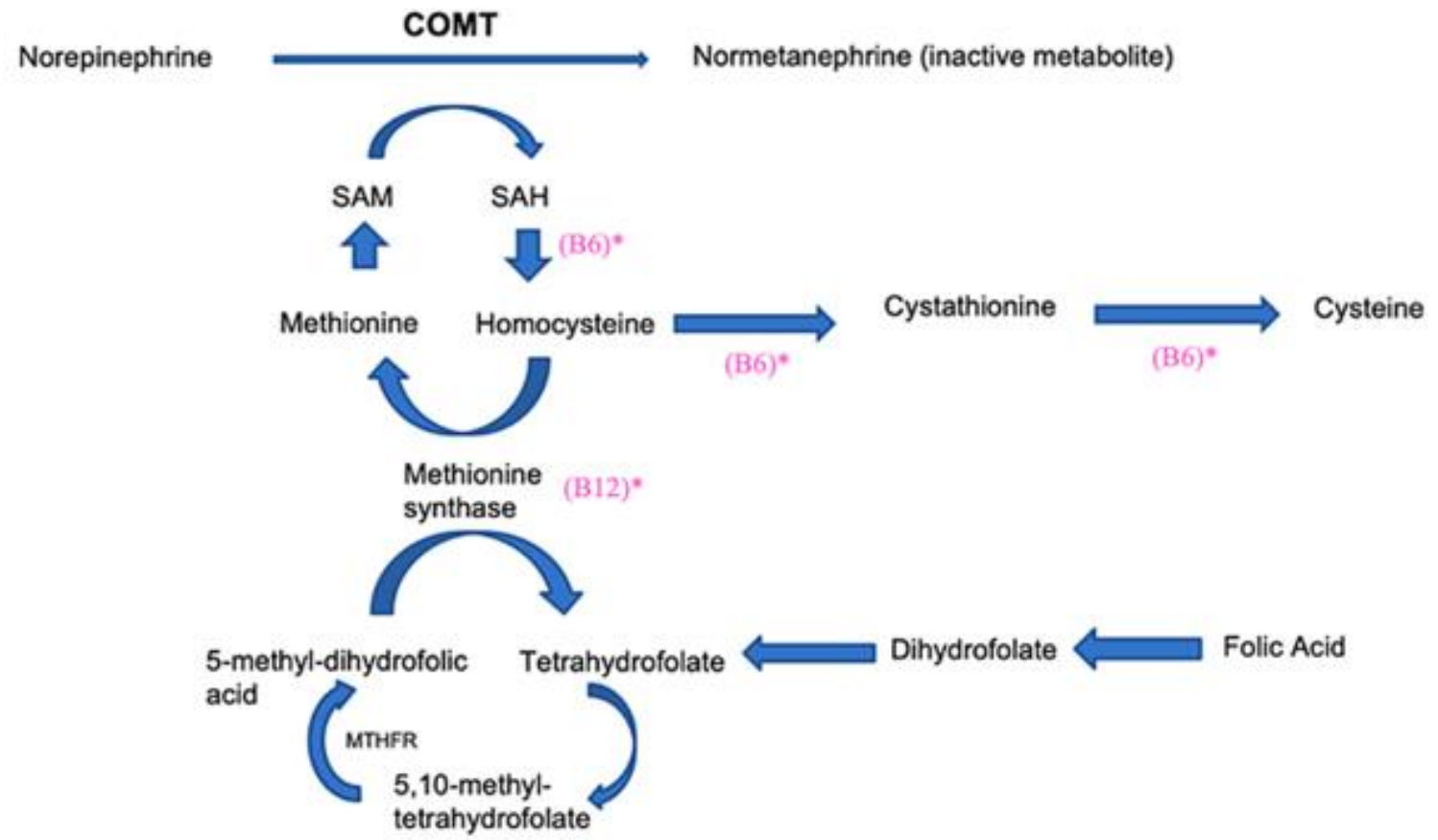
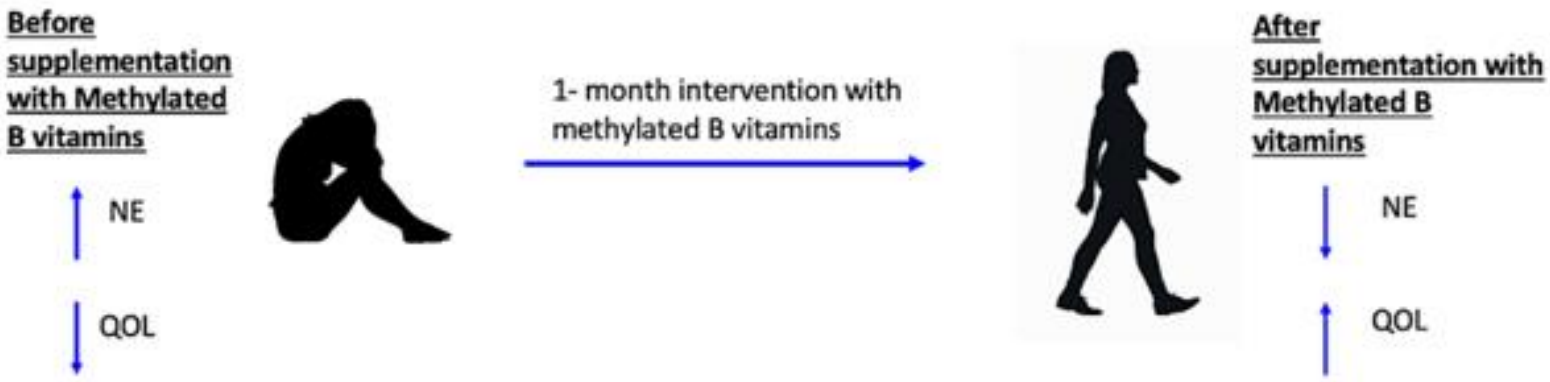


Figure 1 The role of the catechol-O-methyltransferase (COMT) enzyme in norepinephrine inactivation. Based on this pathway, we suggest that impaired function of the COMT enzyme can lead to increased levels of norepinephrine. This pathway is further dependent on adequate levels of cofactors including vitamins B6, B9 and B12. *Low levels of product. SAM, S-adenosyl-L-methionine; SAH, S-adenosyl-L-homocysteine.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8586883/pdf/bcr-2021-245012.pdf
https://pmc.ncbi.nlm.nih.gov/articles/PMC8586883/pdf/bcr-2021-245012.pdf



Norepinephrine (NE)	Clinical symptoms/Quality of life (QOL)
Methylated B vitamins decreased NE levels compared to baseline.	Compared to baseline, methylated B vitamins improved patient's symptoms to the point where she was able to return to full-time employment.

Figure 2 In our patient, who is a heterozygote for COMTVal158Met polymorphism, she was found to have low levels of vitamin B6, B9 and B12. Post supplementation of these methylated vitamins, her NE levels and quality of life improved.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8586883/pdf/bcr-2021-245012.pdf

Table 1 Analysis of methylated B vitamins on patient lab values in POTS

	Before methylated B vitamins	After methylated B vitamins (7 months post supplementation)
Norepinephrine (80–520 pg/mL)	Supine: 901 pg/mL Standing: 1676 pg/mL	Supine: 384 pg/mL Standing: 824 pg/mL
Vitamin B6 (20–125 nm/L)	26 nm/L	124 nm/mL
Vitamin B12 (211–946 pg/mL)	677 pg/mL	1207 pg/mL

https://pmc.ncbi.nlm.nih.gov/articles/PMC8586883/pdf/bcr-2021-245012.pdf

Hyper-adrenergic POTS: Epinephrine and Norepinephrine

Key co-factors needed for epinephrine and norepinephrine: Magnesium, B vitamins, methyl donors, and inositol and larger doses. COMT people can have B12 and often need it.


Hypothesis

Does vitamin C deficiency result in impaired brain development in infants?

Pernille Tveden-Nyborg, Jens Lykkesfeldt

Section of Biomedicine, Department of Disease Biology, Faculty of Life Sciences, University of Copenhagen, Copenhagen, Denmark

Journal of Cellular Physiology / Volume 153, Issue 2 / p. 234-243

Article

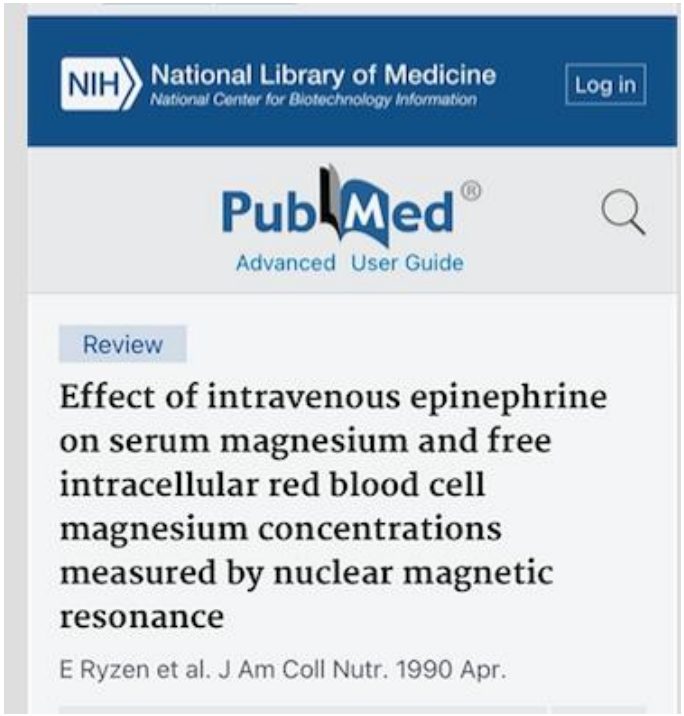
Norepinephrine stimulates the direct breakdown of phosphatidyl inositol in rat tail artery

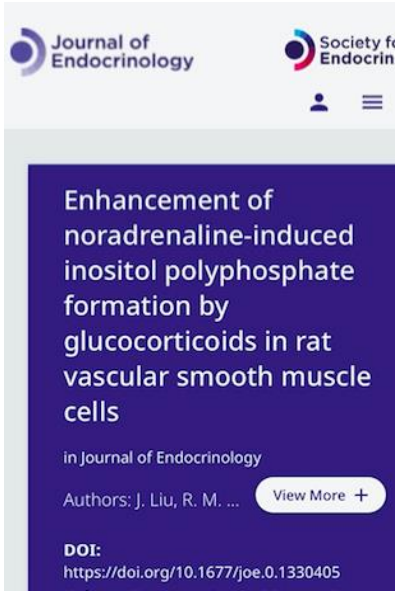
Edward F. Labelle, Hong Gu, Snezana Trajkovic

First published: November 1992

https://doi.org/10.1002/jcp.1041530203

Citations: 6





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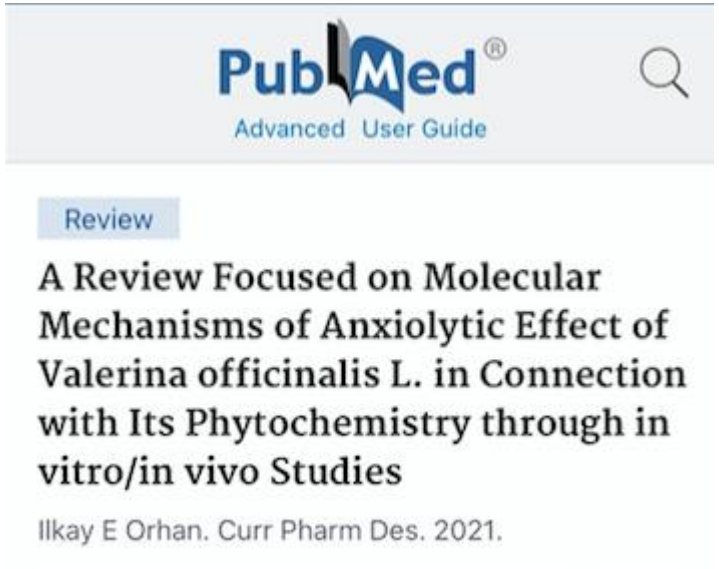
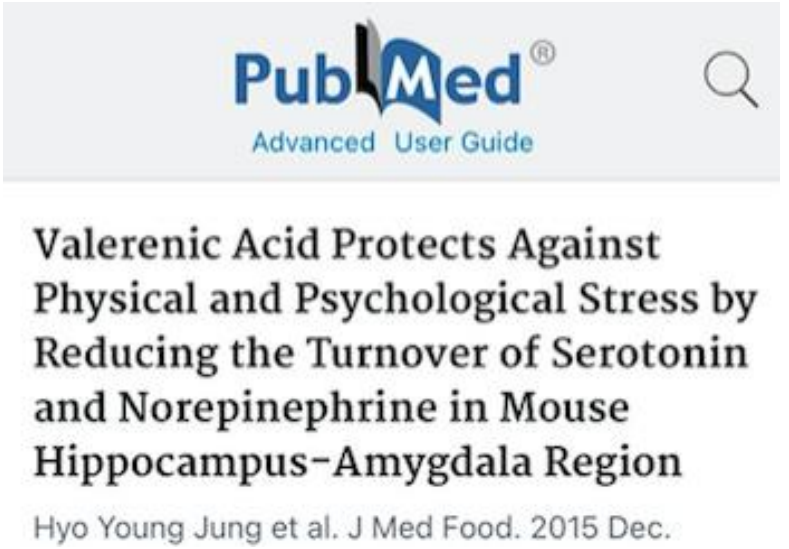




*See Further References

Hyper-adrenergic POTS: Valerian

3.1. Reduction in Blood Pressure Level and Heart Rate

PMC PubMed Central®

3.2. Antimyocardial Ischemia Reperfusion Injury

PMC PubMed Central®

3.3. Antiarrhythmia

PMC PubMed Central®

3.4. Regulation of Blood Lipid Levels

*See Further References

suppresses physical stress by electric shock and psychological stress by nociceptive stimulation-evoked responses by decreasing the ratio of monoamine neurotransmitters to their metabolites

Hyo Young Jung, Dae Young Yoo, Woos

Feedback

Valeriana officinalis root extracts have potent anxiolytic effects in laboratory rats

Neuropathic POTS

Neuropathic POTS involves damage to the small nerve fibers (peripheral neuropathy) that control blood vessel constriction, particularly in the legs and abdomen

Damaged nerves release less norepinephrine, a key vasoconstrictor.

Blood vessels in the limbs fail to constrict properly, leading to:

- Blood pooling in hands and feet
- Low venous return to the heart
- Compensatory increase in heart rate

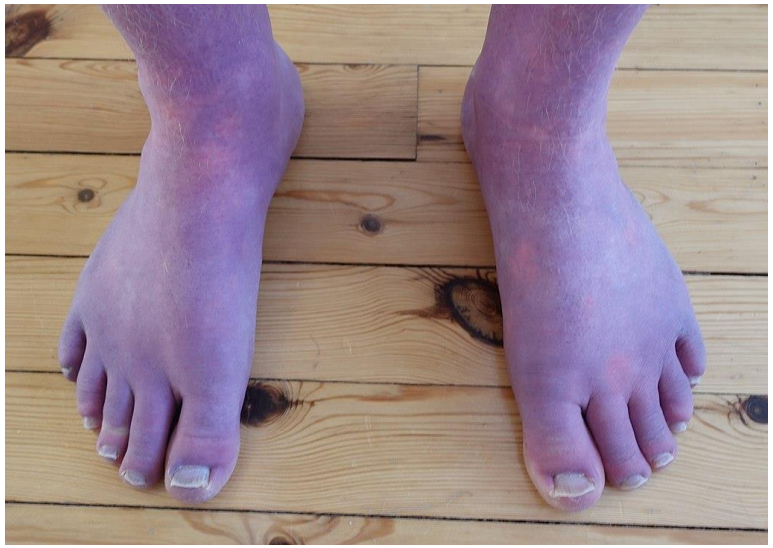
Key Symptoms

Blood pooling in extremities

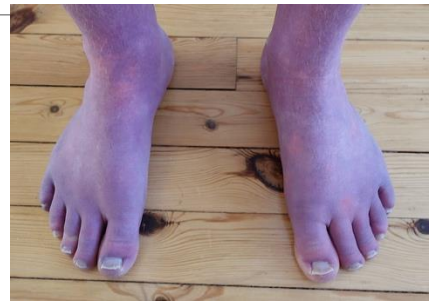
Cyanosis in feet when standing (bluish discoloration)

Loss of sweating in affected limbs

*See Further References



Neuropathic POTS



Healing small nerve neuropathy:

B12, B6, Alpha Lipoic Acid, Acety-l-carnitine

Neuropathy:

B1, sulfate, coenzyme Q10, St. John's wort, magnesium, glutathione, Cod Liver Oil. BHRT, Paleo, SCD, Keto, elimination diets

Microcirculation:

vitamin E and coenzyme Q10, herbs such as ginko, grape fruit seed extract, hawthorn, carnitine, bilberry, glutathione

Clotting factors:

Vitamin E, carnitine, nattokinase, serrapeptidase, fish oil, especially cod liver.

Venous return:

Hydrotherapy, venous herbs

Possible Mechanism for Long COVID

- Although the symptoms of Long COVID are multifarious, some researchers argue that Long COVID causes fibrin amyloid micro-clots (fibrinaloids) to block up capillaries,
- and thus to limit the passage of red blood cells and hence O_2 exchange, can actually underpin the majority of these symptoms of Long COVID.

https://portlandpress.com/biochemj/article/479/4/537/230829/A-central-role-for-amyloid-fibrin-microclots-in
https://pubmed.ncbi.nlm.nih.gov/34425843/
https://pubmed.ncbi.nlm.nih.gov/34896917/

Vitamin E

Vitamin E, comprising eight vitamers (four tocopherols (TFs) and four tocotrienols (TTs)), is the most abundant liposoluble antioxidant compound in the human body, and its modulatory effects regarding signal transduction, cellular pathways (e.g., NF-κB signaling), and gene expression (e.g., pro-inflammatory cytokines) have recently gained notoriety

Vitamin E has to be methylated to be active in the body

Vitamin E has known anti-clotting properties, elastin degradation, immunomodulation, and managing vascular health.

- https://pubmed.ncbi.nlm.nih.gov/19623831/
- https://cardiab.biomedcentral.com/articles/10.1186/s12933-021-01359-7

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Inhibition of plasmin-mediated fibrinolysis by vitamin E

BIOLOGICAL effects attributed to vitamin E i
maintenance of cell membrane integrity, inh
enzyme-dependent lipid peroxidation, partici
oxidative phosphorylation, and a general, non
antioxidant effect[1]. In spite of these observa
physiological function of the vitamin remains
Natural deficiency in man has been invoked in
genesis of several disorders, with convincing evider
to a specific type of haemolytic anaemia[2]. Thera
vitamin E has its advocates in treatment of
vascular and thromboembolic disease, although d
tion for its efficacy is meagre[3]. Although it is
non-toxic[4], little is known about adverse effects of
dietary vitamin E.

Plasminogen is the plasma proenzyme which,
version to its active form, plasmin, is considered re
for lysis of fibrin deposits resulting from physiol

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC41118/?page=1

Vitamin E high dosing needs vitamin K

- As vitamin E is a fat-soluble vitamin, there is a safe upper limit of 100-300mg/kg
- Vitamin E has slight blood thinning properties and may cause easy bruising and bleeding.
- Once a formula with the proper vitamin E/vitamin K ratio is used, there may be nose bleeds or telangiectasia if there is carnitine deficiency or a fat absorption issue. That may have to be addressed first.

POTS: Cases

Long COVID Case 1, Visit 1: KS 43 yoa F

- Heath care professional, healthy, runs daily, up at 5:30am, busy life w kids and work
- Got COVID in March 2020, woke w HA, went for a run and could barely get home, legs tired and heavy, fever, sore neck, joint pain, lost taste and smell, terrible diarrhea, no appetite
- Symptoms that are constant that have stayed for past 5 months post COVID include: fatigue but can work, can't run, too tired, daily headache, diarrhea, tight chest when walk up stairs, and started to wheeze when deep breathing and triggers cough.
- Developed purple toes (summer), body cold
- has plugged sinus and postnasal drip

Long COVID Case 1, Visit 2: KS 43 yo F

- Energy is better, can work, but can't run and can barely do a normal day of work and be a mom
- No shortness of breath. Headaches not constant anymore but still present several times a week, severity decreased but still persistent
- Sinus pain is gone and nose stuffiness is gone
- Still is cold and has purple, swollen toes
- Labs all within normal limits

Long COVID Case 1, Visit 1: KS 43 yo F (cont'd)

- Nasal Spray (saline, 2% EDTA, 10% Xylitol, 1% Lugols Iodine, 1% grape fruit seed extract, 15% muco- adhesive polymer gel and the rest saline - 2 sprays 3 times a day .
- Glutathione 450mg – 1 dose a day
- Vitamin A 10,000IU/drop: 10 drops a day for 10 days
- Vitamin C 1000mg - 6 capsules, 3 times a day
- Quercetin 500mg - 2 capsules, twice a day
- Zinc 100mg - 1 capsule, once a day, 30 days

Long COVID Case 1, Visit 2: KS 43 yo F (cont'd)

- Got COVID again, was OK, but low energy and HA before COVID, now HA back daily, energy is even lower but can still work. Dizziness, nausea, insomnia, nystagmus and eyes are sore.....can see fine, huge bags under eyes, and this cycle terrible menstrual pain, not typical

Methylcobalamin Syringe (2500 mcg/0.1 mL) 20 unit(s):
Dose: 5000mcg subcutaneous injection. 3 x week

Supplements

- **Ubiquinol 60 gelcaps 100 milligrams** 2 capsules/day
- **Vitamin E gelcaps 400IU All 8 vitamin E** 2 capsules/day
- **Benfotiamine 80mg 3/day**
- **Acetyl-L-Carnitine 500mg 3/day**

Methylcobalamin / B12 injections

James Neubrander Protocol:

- Concentration: 2500mcg/0.1ml or 25000mcg/1ml
- 65mcg/kg every 3 days (usually 0.05ml)
- Suggested syringes are BD Ultra fine 3/10th CC
- 30-31 Gauge subcutaneous*

*Ontario ND's cannot inject vitamin B12 subcutaneously

Long COVID Case 1, Visit 3: KS 43 yo F (cont'd)

- Feeling a little better, sleeping better, but when started the protocol, got a cold and then got another cold 1 week after. Feels like always about the catch a cold
- Is feeling better, symptoms have calmed down

Supplements

B Complex SAP 3 capsules/day
Methyl Folate 1mg x 5/day
Cod Liver OIL 500 milliliter liquid 2 tablespoon/day
Eggs 2-6 /day
Salt 1000mg salt, 200mg potassium, 60mg magnesium citrate. powder 1 packet/day. If feel better, 2-4 packets a day

POTS: Cases

CASE – 12 year old male

Medical history

- Parents called an ambulance when he was 9 yo because he woke up in the middle night, distressed saying he couldn't breath
- Oxygen saturation was in the 80's, paramedics immediately supplied oxygen and patient was admitted
- Diagnosed with asthma after a 4 day hospitalization

CASE – 12 year old male (cont'd)

Medical history

- No pre-existing typical or atypical asthma symptoms were reported before the episode leading to hospitalization
- Follow up visit after discharge with pediatrician identified 70% lung function after FEV evaluation
- Rx – Flovent and Ventolin were prescribed
- Follow up visit with pediatrician 1 month later – no improvements
- Referral to allergist

CASE – 12 year old male (cont'd)

Medical history

- Allergist appointment 4 weeks later (new allergist joined the practice)
- Scheduled for allergy testing – no allergens found
- Referred for methacholine test and sweat test to rule out atypical Cystic Fibrosis which were negative
- Patient developed cold symptoms during the SARS-CoV2 pandemic and was hospitalized again for 4 days with very low oxygen that wouldn't stabilize

CASE – 12 year old male (cont'd)

- Parents sought an evaluation by a Naturopathic Doctor who evaluated oxygen and heart rate values, seated, lying down and standing. Heart rate rose over 40 points when standing. Positive for POTS. Postural orthostatic tachycardia syndrome.
- Naturopathic treatment basics for POTS include B12, coenzyme Q10, carnitine, and oral salt rehydration for suspected hypovolemia.
- Patient now has stable oxygen unless sick or prolonged exertion in which case more a double prescription is needed on that day
- No hospital visits in 2 years

Comorbidity	Number (%) (of 3933 respondents)
Migraine headaches	1557 (40%)
Irritable bowel syndrome	1192 (30%)
Ehlers–Danlos syndrome	994 (25%)
Chronic fatigue syndrome	809 (21%)
Asthma	798 (20%)
Fibromyalgia	786 (20%)
Raynaud's phenomena	610 (16%)
Iron deficiency anaemia	628 (16%)
Gastroparesis	548 (14%)
Vasovagal syncope	499 (13%)
Inappropriate sinus tachycardia	448 (11%)
Mast cell activation disorder	353 (9%)
Autoimmune disease	616 (16%)
Hashimoto's thyroiditis	228 (6%)
Coeliac disease	133 (3%)
Sjögren's syndrome	112 (3%)
Rheumatoid arthritis	93 (2%)
Lupus	81 (2%)
Other	160 (4%)

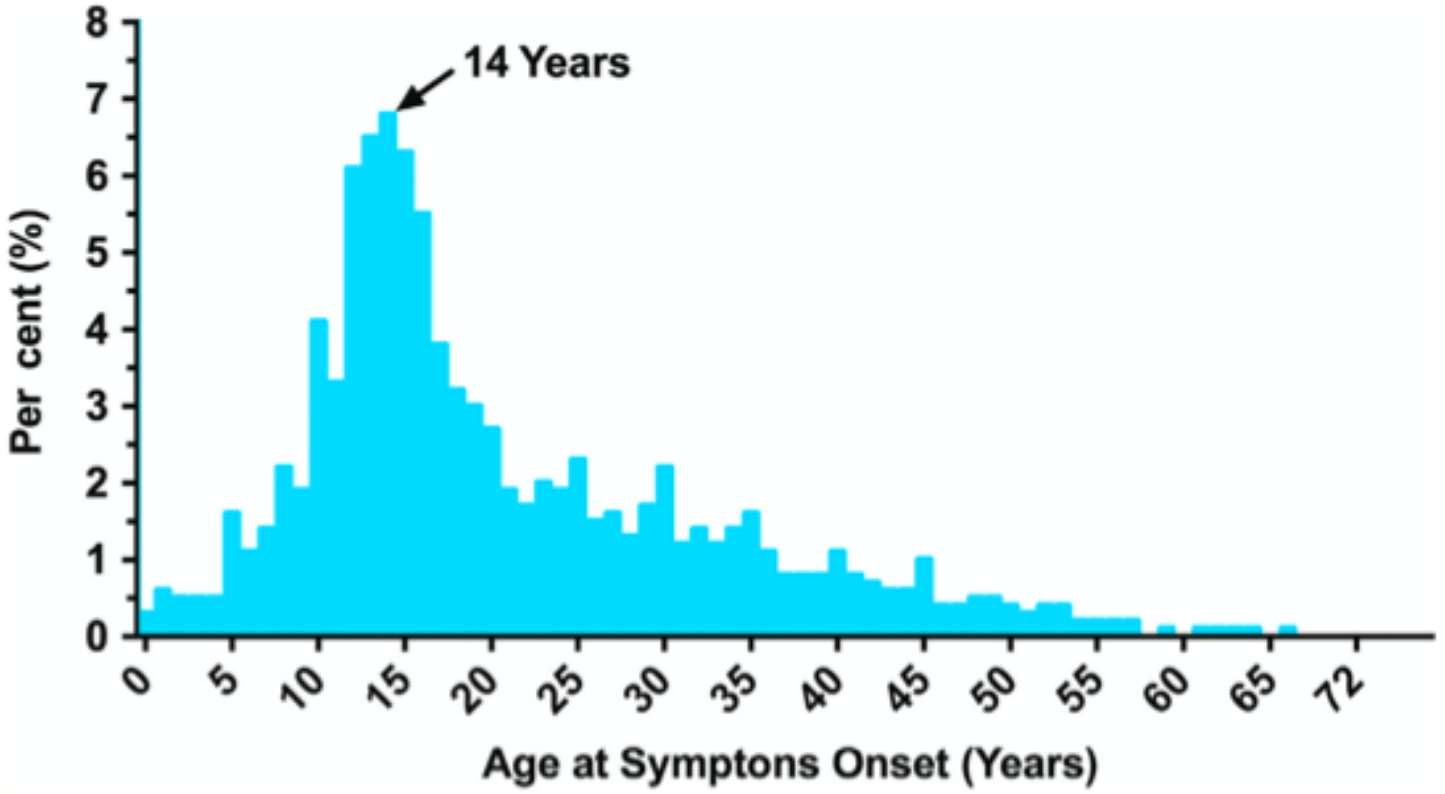


Fig. 2 *Age of symptom onset. Distribution of reported symptom onset age amongst survey participants.*

POTS: Cases

CASE – 83 year old female

- Presented to the clinic after multiple comprehensive cardiovascular work-ups, 5 trips to ER and countless visits with her GP and her cardiologist due to chest pain, hypertensive episodes and tachycardia. Both ER and GP maintain heart is fine. EEG's normal. Holter monitor normal
- Diagnosed with idiopathic tachycardia.
- Patient presented during an episode. Experienced heart palpitations and anxiety. Heart rate was 170 beats per minute, Blood pressure was 210/120. Patient was advised to go to ER but refused.
- Patient given 1 tablespoon beet crystals which vasodilate blood vessels and provide nitric oxide through the vessels. B12 15mg, and lavender and carnitine. Within 10 minutes, blood pressure 140/90, heart rate 70 beats per minute.

POTS strategies

1. Low blood volume or hypovolemic….SALT, electrolytes, beet crystals, licorice
2. Adrenaline or hyper adrenergic…inositol combo, valerian, B12, magnesium, melatonin, B Complex
3. Neurogenic ...B1, sulfate, salt, B12, CoQ10, carnitine, St. John's wort, magnesium, glutathione
4. Microcirculation….vitamin E and coenzyme Q10, herbs such as ginko, grape fruit seed extract, hawthorn, carnitine, bilberry, glutathione
5. Inflammation in the blood vessels. Immunophore (zinc and quercetin) antihistamines…like raynauds in the blood vessels, vitamin E, cod liver oil, glutathione
6. Autoimmunty
7. Mast cell activation...B6, vitamin C, methyl donor
8. EDS strategies , don't forget vitamin C

https://tahomaclinic.com/Private/Articles4/PosturalTachycardia/Oner%202014%20-%20Postural%20orthostatic%20tachycardia%20syndrome%20(POTS)%20and%20vitamin%20B12%20deficiency%20in%20adolescents.pdf

Postural Tachycardia Syndrome (POTS)

Dr. Carissa Doherty ND

POTS Definition

- (POTS) is a chronic multisystem disorder.
- POTS) is a condition characterized by an abnormally large increase in heart rate upon sitting up or standing.

Table 3 *Diagnostic journey in POTS patients*

	Number (%) or mean (SD)
Misdiagnosed prior to POTS diagnosis	3421 (75%)
POTS diagnosis suggested by patient	1557 (34%)
Number of physicians seen prior to diagnosis	7 (11)
Number of ED visits prior to diagnosis	9 (16)
Specialty of physician who made diagnosis	
Cardiologist	1973 (41%)
Cardiac electrophysiologist	696 (15%)
Neurologist	889 (19%)
Family physician	392 (8%)
Emergency room physician	79 (2%)
Rheumatologist	74 (2%)
Other	711 (15%)

Emergency department, ED. The total number of respondents to this question was 4760. Additional physicians who made the diagnosis under the category 'other' included nephrologists, gynaecologists, otolaryngologists and unsure/not specified.

https://onlinelibrary.wiley.com/doi/10.1111/joim.12895

POTS Symptoms

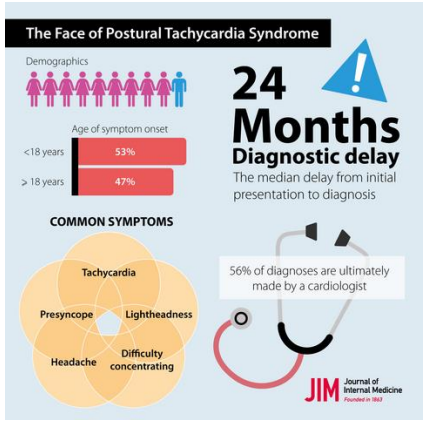
Table 1: Commonly Reported Symptoms of Postural Orthostatic Tachycardia Syndrome

System	Complaint
Cardiovascular	Palpitations, syncope, pre-syncope, tremor, diaphoresis, chest pain, limb edema, venous pooling, Raynaud's phenomenon
Respiratory	Shortness of breath
Gastrointestinal	Nausea, vomiting, diarrhea, bloating, abdominal pain, constipation, gastroparesis
Genitourinary	Increased urinary frequency, nocturia, bladder dysfunction
Musculoskeletal	Muscle weakness, muscle pain, joint pain, joint dislocation/ hypermobility
Neurological	Lightheadedness, dizziness, vertigo, headache, weakness, visual blurring, brain fog/cognitive disturbance, fatigue, sleep disturbance
Endocrine	Heat intolerance, menorrhagia, PCOS
Psychiatric	Anxiety, ADHD

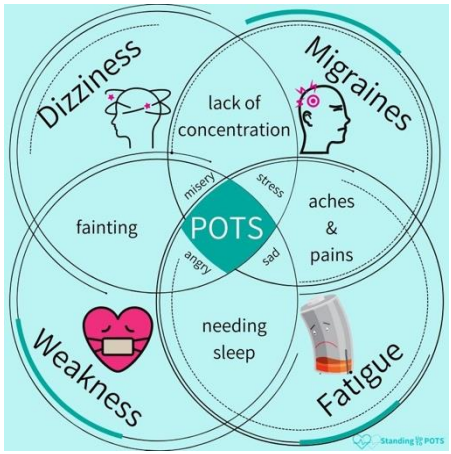
ADHD = attention deficit/hyperactivity disorder; PCOS = polycystic ovary syndrome.

https://assets.radcliffecardiology.com/s3fs-public/article/2023-09/e13_table_1.jpg

POTS Quality of Life

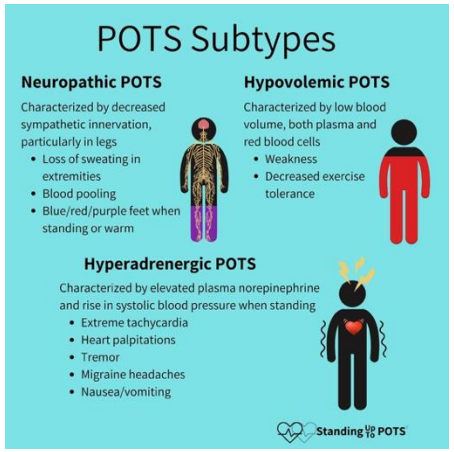


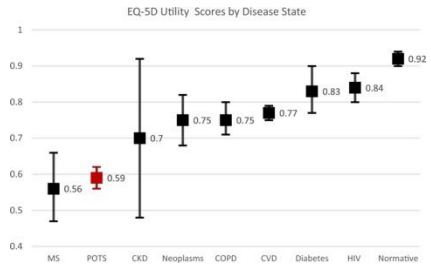
https://onlinelibrary.wiley.com/doi/10.1111/joim.12895



https://www.standinguptopots.org/resources/resources

POTS Subtypes

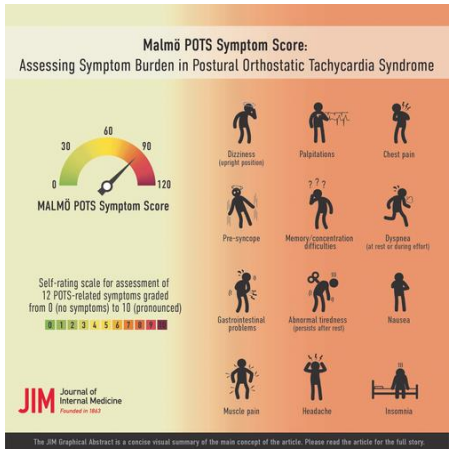


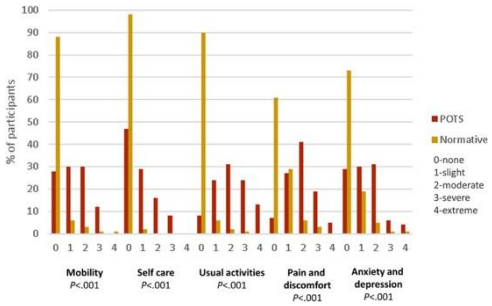


EQ-5D-5L is a standardized, health-related quality of life (HRQoL) questionnaire used tool for assessing health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10439037/

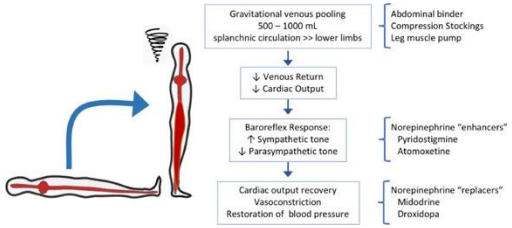
POTS Tests





https://pmc.ncbi.nlm.nih.gov/articles/PMC10439037/

POTS: Cerebral Blood Flow



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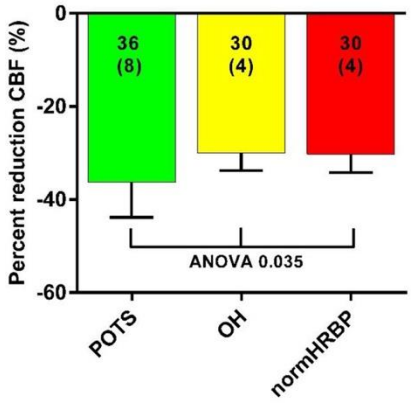
Cerebral blood flow reduction



https://www.mdpi.com/2227-9032/10/10/2105

Questions?

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