Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group

Postural Tachycardia Syndrome (PoTS) in Long COVID

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Introduction

Long COVID, or post-COVID-19 syndrome, refers to the longer lasting effects of the coronavirus infection COVID-19. Whilst many will make a full recovery within 12 weeks, for some these symptoms can last far longer (NHS, 2022). There is emerging evidence to suggest that some individuals with long COVID experience autonomic dysfunction (AD), also known as dysautonomia, with features of Postural Tachycardia Syndrome (PoTS) (Desai *et al*., 2021). PoTS is an abnormal increase in heart rate that occurs on sitting up or standing, and symptoms include dizziness, fainting, palpitations, chest pain and shortness of breath, among others (NHS, 2019).

An evidence search was requested to identify relevant literature and guidance on PoTS to support the work of the Long COVID Pathway in Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group (BNSSG CCG). The aim of this briefing is to provide an outline of key findings and recommendations of, as well as signposting to, appropriate literature, in addressing the following questions:

1. What diagnostic criteria are used for dysautonomia, and for the classification of mild/ severe dysautonomia)?

2. What guidance is available, or can be produced, that primary care and Long Covid Specialists can base recommendations on when providing non-pharmacological intervention for PoTS?
3. When non-pharmacological interventions are unsuccessful, when should a step up in management to pharmacological treatment be considered (and where/by who should this be instigated and managed)?

Points to note

This briefing presents the findings of a rapid, yet systematic, evidence search. As it is not intended to be a review but rather as a signposting document, the subsequent literature has not been appraised for quality, reliability, or replicability.

Key Points

Key points from this evidence search include:

- Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance (Raj *et* al., 2020) is a key piece of grey literature on this topic.
- Fedorowski (2019) is a regularly cited paper which presents an overview of the presentation, aetiology and management of PoTS, and provides clear references for practice discussed.
- Consensus over diagnostic criteria for PoTS has been largely achieved in the literature presented here. Appendix 1 (Fedorowski, 2019) provides a summary of those currently in use and their proponents.
- There is limited guidance available on the grading of condition severity. However, Fedorowski (2019) suggests that assessment using measures such as Orthostatic Hypotension Questionnaire (OHQ), and functional class 'pyramid' focusing on complaints associated with orthostatic intolerance, or Karnofsky Performance Status focusing on overall function limitation, can be used to determine how markedly the symptoms are being experienced.

- Pathophysiological subtyping of PoTS is not recommended by the Canadian Cardiovascular Society due to an insufficiency of tools available (Raj *et al*., 2020).
- Appendix 4 provides an overview of some the most widely used empirical, both non-pharmacological and pharmacological, therapeutic options for PoTS (Fedorowski, 2019).
- Non-pharmacological management recommendations include:
    - Increasing fluid intake
    - Increasing salt intake
    - Raising the head of bed
    - Exercise for the lower legs to improve muscle strength and pump action
    - Compression stockings
    - Changing eating patterns - for example, eating smaller meals more frequently
    - Avoiding of alcohol and other trigger factors (such as heat or sitting still for long periods of time)
    - Psychological support or cognitive behavioural therapy (CBT) may be required
- Pharmacological management should be considered if the symptoms are particularly pronounced and continue despite non-pharmacological intervention (Fedorowski, 2019).
- Currently, no medication is licensed for use in PoTS. Therefore, treatment should be instigated and prescribed by a specialist (Patient, 2021)
- PoTS UK (2021b) provides a list of specialists. Please find the link here.

Findings

The findings of this literature search will be presented, to coincide with the question being addressed, in tables under the following headings:

- Criteria for diagnosing dysautonomia and classifying severity
- Guidance on non-pharmacological management of PoTS
- Guidance on pharmacological management of PoTS

Please note, whilst this search was conducted to support the work for the Long COVID Pathway in BNSSG CCG, the findings presented here do not discuss dysautonomia and PoTS specifically in the context of long COVID.

Criteria for diagnosing dysautonomia and classifying severity

Author/ Date/ Document (See Reference List for Full Citation)	Condition	Summary	Literature Type	Link
Dysautonomia International (2019). *Postural Orthostatic Tachycardia Syndrome*	PoTS	"The current diagnostic criteria for POTS is a heart rate increase of 30 beats per minute (bpm) or more, or over 120 bpm, within the first 10 minutes of standing, in the absence of orthostatic hypotension"	Website	http://www.dysautonomiainternational.org/page.php?ID=30#:~:text=from%20Dysautonomia%20International&text=This%20opens%20in%20a%20new%20window.&text=The%20current%20diagnostic%20criteria%20for,the%20absence%20of%20ort

				hostatic%20hypotension.
Hakim and Grahame (2015) *Autonomic Dysfunction*	Cardiovascular autonomic dysfunction: • Orthostatic hypotension • Orthostatic intolerance • Postural orthostatic tachycardia	"There are three typical conditions described: orthostatic hypotension (OH), orthostatic intolerance (OI), and postural tachycardia syndrome (PoTS). These can be diagnosed in a clinic, without the need for complex tests, if the following are identified: • Orthostatic hypotension – a rapid drop in blood pressure by more than 20 systolic /10 diastolic mmHg from that when sitting that occurs within 3 minutes of standing. • Orthostatic intolerance – the same degree of blood pressure drop as above but over a more protracted period of time, e.g. 5–10 minutes, and symptoms relieved on lying down. • Postural orthostatic tachycardia – a greater than 30 beat-per-minute rise in the pulse on standing or a count greater than 120 beats per minute after 10 minutes with no other known cause" ***Please note: guidance intended to support the management of individuals experiencing PoTS secondary to Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders only***	Website	https://www.ehlers-danlos.org/information/autonomic-dysfunction/
Fedorowski (2019). *Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management*	PoTS	***Please see:*** • ***Appendix 1 for diagnostic criteria of postural orthostatic tachycardia syndrome*** • ***Appendix 2 for diagnostic modalities recommended in the workup of patient with suspected PoTS diagnosis***	Journal article	https://onlinelibrary.wiley.com/doi/10.1111/joim.12852

Grubb (2008) *Postural Tachycardia Syndrome*	PoTS	"POTS is currently defined as the presence of symptoms of orthostatic intolerance associated with a heart rate increase of 30 bpm (or rate that exceeds 120 bpm) that occurs within the first 10 minutes of standing or upright tilt, not associated with other chronic debilitating conditions such as prolonged bed rest or the use of medications known to diminish vascular or autonomic tone" (p2814) "Most authors feel that a patient should have been symptomatic for >3 months" (p2814) "Some investigators have noted that focusing on heart rate overlooks a number of other autonomic symptoms that may be present, such as disturbances in sweating, thermoregulation and bowel and bladder function" (p2814)	Journal article	https://www.ahajournals.org/doi/epub/10.1161/CIRCULATIONAHA.107.761643
Morgan *et al*. (2018). *Postural Orthostatic Tachycardia Syndrome during pregnancy: A systematic review of the literature*.	PoTS	"In adults, the current criteria for a POTS diagnoses is: the presence of excessive tachycardia and symptoms of orthostatic intolerance for more than six months, an increase of 30 beats per minute or heart rate > 120 beats per minute on Head Up Tilt test within 10 min of symptoms upon recumbence" (p106-7)	Journal article	https://www.autonomicneuroscience.com/action/showPdf?pii=S1566-0702%2818%2930019-5
Patient (2021). *Postural Orthostatic Tachycardia Syndrome: PoTS Syndrome*	PoTS	"The gold standard for PoTS diagnosis is head-up tilt test with non-invasive beat-to-beat haemodynamic monitoring • Sustained rise in heart rate of ≥30 beats per minute within 10 minutes of standing or on tilt test in the absence of orthostatic hypotension. (Increment of 40 beats per minute for those aged 12-19. Criteria may not be applicable for those with a low resting heart rate).	Website	https://patient.info/doctor/postural-tachycardia-syndrome-pots-pro

		• Standing heart rate is often >120 beats per minute. • As well as orthostatic tachycardia, there may be symptoms of cerebral hypoperfusion and autonomic overactivity which are relieved by lying down"		
PoTS UK (2021a). *About PoTS: Diagnosis*	PoTS	To be given a diagnosis of PoTS, a person needs to have: • PoTS symptoms mostly when upright over a period of at least 3 months. • A ***sustained*** increase in heart rate of greater than 30 beats per minute within 10 minutes of standing. • Those aged 12-19 years require an increase of at least 40 beats per minute. • These criteria may not apply to those with a low heart rate when resting. • There is usually no drop in blood pressure on standing.	Website	https://www.potsuk.org/about-pots/diagnosis/
PoTS UK (2021b) *GP Guide: PoTS on a Page*	PoTS	**"How to diagnose PoTS** **DIAGNOSTIC CRITERIA** – Sustained increase in heart rate of 30 beats per minute (40bpm in teenagers) from lying to standing associated with symptoms of PoTS **STAND TEST** – rest supine and record HR and BP. Then stand in a safe place and record BP and HR every 2 minutes to 10 minutes	Website	GP Guide: PoTS on a Page - PoTS UK

		INVESTIGATIONS – ECG. Exclude anaemia, hyperthyroidism, postural hypotension, phaeochromocytoma **MISDIAGNOSIS** – Mean time to diagnosis is 7 years. Meantime 50% of patients receive a psychiatric misdiagnosis e.g., anxiety, depression, hypochondriasis. Other misdiagnoses – CFS/ME **REFERRAL** – To a specialist with an interest in PoTS- there is a list on the PoTS UK website: https://www.potsuk.org/specialists"		
Raj *et al*. (2020). *Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance*	Chronic orthostatic intolerance syndromes including PoTS	"Current guidelines define POTS as a heterogeneous clinical syndrome that is characterized by sustained and excessive sinus tachycardia upon standing, in the absence of orthostatic hypotension and with chronic symptoms of orthostatic intolerance" (p360) "However, the term "POTS" is now commonly used to speak about a spectrum of disorders, some of which fit into the original definition1 of POTS, but much of which does not fit that original definition" (p360) ***Please see Appendix 3 for criteria*** "We recommend using specific hemodynamic and symptom criteria definitions for the diagnosis of POTS in adolescents and adults, to avoid misdiagnosis (Strong Recommendation, Low-Quality Evidence)" (p363) "We do not recommend pathophysiological subtyping during the initial screening and diagnosis of POTS because of the lack of tools to provide such characterization (Strong Recommendation, Low-Quality Evidence)" (p363)	Journal article	https://www.onlinecjc.ca/action/showPdf?pii=S0828-282X%2819%2931550-8

Guidance on non-pharmacological management of PoTS

Author/ Date/ Document (See Reference List for Full Citation)	Summary	Literature Type	Link
Dysautonomia International (2019). *Postural Orthostatic Tachycardia Syndrome*	"The most common treatments for POTS include increasing fluid intake to 2-3 litres per day; increasing salt consumption to 3,000 mg to 10,000 mg per day; wearing compression stockings; raising the head of the bed (to conserve blood volume); reclined exercises such as rowing, recumbent bicycling and swimming; a healthy diet; avoiding substances and situations that worsen orthostatic symptoms; and finally, the addition of medications meant to improve symptoms"	Website	Dysautonomia International: Postural Orthostatic Tachycardia Syndrome
Hakim and Grahame (2015) *Autonomic Dysfunction*	"The symptoms can often be successfully managed with the simple remedies of increasing water and salt intake, and support stockings. Exercise to improve muscle re-conditioning and heart condition is also important" ***Please note: guidance intended to support the management of individuals experiencing PoTS secondary to Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders only***	Website	Autonomic dysfunction – The Ehlers-Danlos Support UK
Fedorowski (2019). *Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management*	"The heterogeneity and wide spectrum of POTS-related symptoms create a great challenge for clinicians and affected patients" (p359) "The first step in the appropriate management of POTS is the correct diagnosis. Patients should be comprehensively informed about the syndrome both verbally, using dedicated printed material, brochures, etc. and appropriate Internet links, if available" (p360) "After the diagnosis has been established, patient should be thoroughly educated about non-pharmacological measures alleviating the symptoms, long-term prognosis and available therapeutic options adequate to patient's status" (p360) "If symptoms are pronounced, as evaluated by different symptom scores such as Orthostatic Hypotension Questionnaire (OHQ), and functional class 'pyramid' focusing on complaints associated with orthostatic intolerance, or Karnofsky Performance Status focusing on overall function limitation, the pharmacologic treatment should be considered" (p360)	Journal Article	Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management - Fedorowski - 2019 - Journal of Internal Medicine - Wiley Online Library

	Please see Appendix 4 for the most widely used empirical therapeutic options in postural orthostatic tachycardia syndrome		
Patient (2021). *Postural Orthostatic Tachycardia Syndrome: PoTS Syndrome*	"Because PoTS has a variety of causes, no single treatment is effective for everyone, and combinations of approaches are often needed" "Non-pharmacological therapy includes educating patients to avoid orthostatic intolerance triggers and increasing their understanding of the mechanisms of PoTS" "Increasing blood volume by adding extra salt to the diet and drinking more fluids, as well as reducing venous pooling by using compression garments, are recommended" **"Non-pharmacological management** • Increase fluid intake (2-2.5 litres per day). • Increase salt intake (3-5 g per day). (Not for the hyperadrenergic form.) • Raise the head of bed. • Exercises for the lower legs to improve muscle strength and pump action. Exercise programmes must be graduated. • Compression stockings. • Changing eating patterns - for example, eating smaller meals more frequently. • Avoidance of alcohol and other trigger factors (such as heat or sitting still for long periods of time). • Psychological support or cognitive behavioural therapy (CBT) may be required"	Website	Postural Orthostatic Tachycardia Syndrome (PoTS Syndrome) | Patient
PoTS UK (2021b) *GP Guide: PoTS on a Page*	**"How to manage PoTS** **AVOID TRIGGERS** – heat, large meals, alcohol, drugs that lower BP **FLUIDS** – at least 2 litres/day in adults **SALT** – Adults: +6g/day (unless contraindicated)	Website	GP Guide: PoTS on a Page - PoTS UK

	EXERCISE – initially supine, graduated regimen, can take 2 months to improve symptoms **POSTURAL MANOEUVRES** to avoid fainting – avoid prolonged standing, elevate legs, tense buttocks + thighs, fold arms, tiptoe **COMPRESSION** – class 2, waist-high tights **DRUGS** -include β blockers, calcium channel blockers, ivabradine, midodrine, fludrocortisone, clonidine, SSRI, desmopressin, pyridostigmine, octreotide **CBT** – to help adjust to chronic illness **IV FLUIDS** – in an emergency only”		

Guidance on pharmacological management of PoTS

Author/ Date/ Document (See Reference List for Full Citation)	Summary	Literature Type	Link
Dysautonomia International (2019). *Postural Orthostatic Tachycardia Syndrome*	"Many different medications are used to treat POTS, such as Fludrocortisone, Beta Blockers, Midodrine, Clonidine, Pyridostigmine, Benzodiazepines, SSRIs, SNRIs, Erythropoietin and Octreotide. If an underlying cause of the POTS symptoms can be identified, treating the underlying cause is very important as well"	Website	Dysautonomia International: Postural Orthostatic Tachycardia Syndrome
Hakim and Grahame (2015) *Autonomic Dysfunction*	"Different classes of drugs do different things to help the symptoms of OH and PoTS. These are best prescribed by an expert and after more detailed testing as to the cause of the autonomic dysfunction. They may have the effect of: • Increasing the blood flow / total amount of fluids in the circulation (e.g., fludrocortisone and clonidine) • Cause blood vessel constriction – reducing the capacity or space of the circulation giving an effect similar to increasing the fluid / blood volume (e.g., midodrine, Ritalin) • Blocking certain ANS chemicals (beta blockers, disopyramide, ACE-inhibitors)"	Website	Autonomic dysfunction – The Ehlers-Danlos Support UK
Fedorowski (2019). *Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management*	"If symptoms are pronounced, as evaluated by different symptom scores such as Orthostatic Hypotension Questionnaire (OHQ), and functional class 'pyramid' focusing on complaints associated with orthostatic intolerance, or Karnofsky Performance Status focusing on overall function limitation, the pharmacologic treatment should be considered" (p360) Please see Appendix 4 for the most widely used empirical therapeutic options in postural orthostatic tachycardia syndrome	Journal Article	Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management (wiley.com)

Patient (2021). *Postural Orthostatic Tachycardia Syndrome: PoTS Syndrome*	**"Pharmacological management** No medication is licensed for PoTS syndrome and pharmacological therapy should always be initiated by a specialist. • Options which have been used for PoTS syndrome include: • Fludrocortisone (causes salt and water retention and sensitises alpha-adrenergic receptors). • Selective serotonin reuptake inhibitor (SSRI) or a serotonin and noradrenaline (norepinephrine) reuptake inhibitor (SNRI) (stimulates the standing vasoconstriction reflex). • Pyridostigmine (improves neural transmission). • Erythropoietin (causes volume expansion and vasoconstriction. Use is dependent on haematocrit levels). • Sodium chloride infusions. • Vasoconstrictors such as octreotide, midodrine, ergotamine and methylphenidate. • Clonidine (reduces sympathetic nervous system tone - hyperadrenergic form only). • Ivabradine (sinus node blocker). • Methyldopa (false neurotransmitter). • Beta-blockers are occasionally helpful, although often make symptoms worse. Labetalol may be an option because it is a combined beta/alpha 1 blocker"	Website	Postural Orthostatic Tachycardia Syndrome (PoTS Syndrome) | Patient

Method

The following PICO search strategy was used:

Population: Adults experiencing dysautonomia and/or PoTS specifically

Intervention: TBC

Comparison:

Outcomes: Diagnostic criteria and management of dysautonomia and/or PoTS

Searches took place on 30/03/2022

Search strategy (including truncation (*) and index terms):

("dysautonomia" OR " autonomic dysfunction" OR "postural orthostatic tachycardia syndrome" OR "postural tachycardia syndrome") AND “management”

Exclusion criteria:

Outside of time limit 2017-2022, lack of relevance to PICO, non-research and non-guidance, duplicates, abstract not included, non-English language.

Databases and sources searched included:

PubMed: 7 results. List sorted by “best match.” Top 25 citations subjected to abstract screen. Exclusion criteria applied. 4 articles included.

NICE Evidence[1]: 269 results. List sorted by "Relevance." Top 25 citations subjected to abstract screen. Exclusion criteria applied. 4 articles included.

2 articles were identified via the process of 'snowballing' i.e., following up on reference lists of the documents returned using the search strategies outlined above.

References

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[1] Please note, *NICE Evidence* service was discontinued on 31/03/2022

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Patient (2021). *Postural Orthostatic Tachycardia Syndrome: PoTS Syndrome* [website]. Available from: https://patient.info/doctor/postural-tachycardia-syndrome-pots-pro [date accessed: 30/03/2022].

PoTS UK (2021a). *About PoTS: Diagnosis* [website]. Available from: https://www.potsuk.org/about-pots/diagnosis/ [date accessed: 30/03/2022].

PoTS UK (2021b). *GP Guide: PoTS on a Page* [website]. Available from: GP Guide: PoTS on a Page - PoTS UK [date accessed: 06/04/2022].

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Appendices

Appendix 1: Diagnostic criteria of postural orthostatic tachycardia syndrome

The diagnostic criteria	Endorsed by
Sustained heart rate increment of not less than 30 beats min^{-1} or above 120 beats min^{-1} within 10 min of active standing or head-up tilt	American Academy of Neurology
For individuals who are younger than 19 years the required increment is at least 40 beats min^{-1}	American Autonomic Society
Absence of orthostatic hypotension (i.e. sustained systolic blood pressure drop of not less than 20 mmHg)	American College of Cardiology
Reproduction of spontaneous symptoms such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision and fatigue. In some patients, tachycardia may evoke vasovagal syncope corresponding to spontaneous attacks from patient's history	American Heart Association
History of chronic orthostatic intolerance and other typical POTS-associated symptoms (for at least 6 months[a])	European Federation of Autonomic Societies
Absence of other conditions provoking sinus tachycardia such as anxiety disorders, hyperventilation, anaemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (sympathomimetics, anticholinergics)	European Heart Rhythm Association
	European Society of Cardiology
	Heart Rhythm Society

[a]This criterion may be controversial and is not unanimously accepted as patients may seek medical advice earlier due to increasing awareness of the syndrome. However, symptoms of shorter duration than 3 months should be re-evaluated to confirm the diagnosis.

Fedorowski *et al.,* (2019), p353

Appendix 2: Diagnostic modalities recommended in the workup of patient with suspected PoTS diagnosis

Diagnostic test	Diagnostic outcome	Comment
Head-up tilt test with non-invasive beat-to-beat monitoring (Fig. 2)	The characteristic orthostatic sinus tachycardia and reproduction of symptoms. The absence of orthostatic hypotension (Table 1)	'The golden standard' in POTS diagnostic [1, 4, 62, 63]
24 (48)-h ECG monitoring (Fig. 3)	Heart rate accelerations during daytime and in the morning after awakening. Normal heart rate night-time. Reduced heart rate variability	The test may be used to confirm the diagnosis and to discriminate POTS from inappropriate sinus tachycardia (elevated heart rate >90 bpm during 24 h and the absence of typical night-time dip) [3, 4]
External or implantable loop recorders (ILRs)	ECG record of spontaneous fainting spells. Brady- or tachyarrhythmia. Epilepsy. Psychogenic pseudosyncope Heart rate control	In very difficult diagnostic cases with multiple syncopal events, traumatic syncope, amnesia, therapy resistance, clinical suspicion of arrhythmia and epilepsy, this method might be recommended under restriction. Principally, it should be reserved for experts with good insights into the POTS and syncope pathophysiology. When implanted for other reasons, ILR might be used for heart rate monitoring during therapy
24-h ambulatory BP monitoring	Hypertensive or hypotensive tendency. Low-BP phenotype	The results of BP monitoring may be used for tailoring the therapy with cardiovascular drugs. The hypovolaemic type of POTS usually demonstrates hypotensive tendency and low-BP phenotype may be targeted by vasoactive and volume-expanding drugs [4]
Exercise ECG	The grade of overall physical performance compromise and abnormal haemodynamic responses during exercise	This method may be used for quantification of remaining physical capacity and may play role in tailoring the physical therapy. It may also be recommended if patient faints during exercise

Echocardiography	Structural cardiac changes	Echocardiography is recommended for exclusion of possible underlying cardiac changes if physical findings and basic cardiac workup suggests the presence of structural changes in the heart.
Valsalva manoeuvre	Exaggerated BP and heart rate overshoot in phase IV	It may be used as a confirmatory test; it also suggests the presence of 'hyperadrenergic' type of POTS [34, 62]
Active standing test	The same diagnostic criteria as for head-up tilt test (Table 1)	It may be used for initial screening and in clinics that lack access to fully equipped autonomic laboratory [5]. The chronotropic response may be blunted by patient using muscle pump [4, 5, 74]
Laboratory tests	Anaemia, electrolyte disorders, thyroid disease, adrenal hormone abnormalities, elevated catecholamines and their metabolites in blood and urine (especially plasma norepinephrine during tilt testing)	This test (except for catecholamines) should be considered in the basic workup [34]
Noncardiovascular autonomic function tests: gastrointestinal function tests, sudomotor function test, other autonomic tests, if available and appropriate	Autonomic neuropathy in different organs and body zones	These very specific tests should be performed by centres with sufficient expertise and access to appropriately equipped laboratories [34]. The positive results support the diagnosis of 'neuropathic' POTS subtype

Fedorowski *et al.,* (2019), p358-359

Appendix 3: Chronic orthostatic intolerance syndromes: diagnostic haemodynamic and symptom criteria

Condition	Hemodynamic criteria	Clinical criteria	Associated comorbidities	Duration of symptoms
POTS	Sustained increase in heart rate ≥ 30 bpm in adults (older than 19 years) or 40 bpm in children/adolescents (younger than 19 years), from supine position to upright within 10 minutes of standing, and absence of orthostatic hypotension (decrease in systolic blood pressure > 20 mm Hg or diastolic blood pressure > 10 mm Hg	Orthostatic intolerance symptoms: • Lightheadedness • Palpitation ("heart racing") • Tremulousness • Atypical chest discomfort Other symptoms not associated with changes in position: • Sleep disturbance • Headaches • Chronic fatigue • Exercise intolerance and deconditioning • Perceived cognitive impairment ("brain fog") • Peripheral acrocyanosis ("POTS feet") • Frequent nausea • Mild diarrhea, constipation, bloating, unspecific abdominal pain ("irritable bowel syndrome")	None	> 3 Months
POTS plus	Same as POTS	Same as POTS and 1 or more: • Gastric emptying problems • Intractable vomiting • Severe constipation • Neurogenic bladder • Severe chronic pain • Intractable headaches • Significant flushing anaphylaxis symptoms • Severe food intolerances	• Hypermobile Ehlers-Danlos syndrome • Hypermobile spectrum disorder • Mast cell activation disorder • Chronic fatigue syndrome/ME • Celiac disease • Autoimmune disorder • Chronic migraines • Cerebrospinal fluid leak • Mitochondrial mutations disorders • Multiple sclerosis	Same as POTS

PSWT	No evidence of orthostatic tachycardia and orthostatic hypotension	Orthostatic intolerance symptoms as with POTS and 1 or more: • Gastric emptying problems • Intractable vomiting • Severe constipation • Neurogenic bladder • Severe chronic pain • Intractable headaches • Significant flushing anaphylaxis symptoms • Severe food intolerances	None	Same as POTS
PSWT plus	No evidence of orthostatic tachycardia and orthostatic hypotension	Orthostatic intolerance symptoms as with POTS and 1 or more: • Gastric emptying problems • Intractable vomiting • Severe constipation • Neurogenic bladder • Severe chronic pain • Intractable headaches • Significant flushing anaphylaxis symptoms • Severe food intolerances	• Hypermobile Ehlers-Danlos syndrome • Hypermobile spectrum disorder • Mast cell activation disorder • Chronic fatigue syndrome/ME • Celiac disease • Autoimmune disorder • Chronic migraines • Cerebrospinal fluid leak • Mitochondrial mutations disorders • Multiple sclerosis	Same as POTS
PTOC	Same as POTS	Same as POTS	Secondary identifiable cause: • Acute hypovolemia • Endocrinopathy • Anemia • Anxiety and panic attacks • Medication side effects • Recreational drugs effects • Prolonged or sustained bed rest	Transient

bpm, beats per minute; ME, myalgic encephalomyelitis; POTS, postural orthostatic tachycardia syndrome; PSWT, postural symptoms without tachycardia; PTOC, postural tachycardia of other cause.

Raj *et al.,* (2020), p359

Appendix 4: The most widely used empirical therapeutic options in postural orthostatic tachycardia syndrome

Therapy	Comments
Non-pharmacological treatment	
Education of patient: • Understanding of orthostatic intolerance and POTS pathophysiology • Avoidance of immobilization, prolonged recumbency and physical deconditioning • Gradual rising from supine and sitting position, especially in the morning, after meals, and after urination/defecation • Small and frequent instead of large meals • Avoidance of prolonged standing, high ambient temperature and high humidity • Physical counter-manoeuvres (leg crossing, muscle tensing, squatting, etc.) during standing and prodromal symptoms [75–77]	This point is crucial and should form the fundament of treatment [3, 4]. It is rarely sufficient alone in pronounced symptoms. Patients and their families should understand the basics of orthostatic physiology and importance of non-pharmacological methods. Educational materials such as brochures, instruction films may be very helpful
Exercise training	There are different programmes available. A regular, structured, graduated, and supervised exercise programme featuring aerobic reconditioning with some resistance training for the thighs is preferable. Initial training should avoid upright position. Mild-to-moderate-intensity endurance training, progressing from semi-recumbent to upright position plus strength training is recommended. Rowing machines, recumbent bicycles and swimming may be applied. Class IIA recommendation [3, 67, 78–80]
Increased salt and fluid intake incl. peroral water bolus if needed	Volume expansion. A daily dietary intake of more than 10 g of sodium per day or salt tablets (e.g. 1 g TID) and a fluid intake of at least 2.5 litre per day is recommended. This method is especially effective in 'hypovolaemic' subtype. Class IIB recommendation [3, 4, 64]

Compression stockings/garments	Reduction of peripheral pooling in the lower limbs and splanchnic region. In general, Class 2 compression garments (>30 mmHg) are recommended [3, 63, 64, 81]. They might be considered in the 'hypovolaemic' subtype and low-BP phenotype. Especially, when venous pooling is observed or suspected
Pharmacological treatments	
Heart rate controlling agents	
Beta-blockers (propranolol, 10–40 mg TID; bisoprolol, 2.5–5 mg BID; metoprolol, 25–100 mg daily; atenolol, 12.5–50 mg daily)	Beta-blockers are especially recommended in 'hyperadrenergic' subtype associated with sinus tachycardia >120 bpm on standing. Beta-blockers may aggravate orthostatic intolerance in low-BP phenotype, asthma and paroxysmal chest pain. Class IIB recommendation [3, 64, 77, 82, 83]
Ivabradine (2.5–7.5 mg BID)	This drug is effective in low-BP phenotype or when beta-blockers are not well tolerated. It is usually seen as an alternative to beta-blockers. The evidence is based on small patient series [84–89]
Verapamil (40–80 mg BID/TID)	This calcium channel blocker with negative chronotropic effect can be tested in 'hyperadrenergic' type associated with higher BP, migraine, and chest pain [31]. The evidence and clinical experience are very limited
Vasoactive and volume-expanding agents	
Clonidine (0.2–0.6 mg BID)	Centrally acting α2-adrenoreceptor agonist with overall sympatholytic effect. It is generally recommended for 'hyperadrenergic' subtype and hypertensive tendency on standing. Class IIB recommendation [3, 64, 90]
Midodrine (2.5–10 mg TID)	Direct α1-adrenoreceptor agonist. One of the few pharmacological agents positively tested in placebo-controlled studies for orthostatic hypotension. It may be effective in 'hypovolaemic' subtype and low-BP phenotype with pronounced orthostatic intolerance. Class IIB recommendation [3, 4, 77, 82, 91–94]

Droxidopa (Northera, DOPS, 100–600 mg TID)	Peroral norepinephrine precursor. Drug has been empirically used off-label in severe POTS. Not included in the current guidelines [77, 95, 96]
Pyridostigmine (30–60 mg BID/TID)	Acetylcholinesterase inhibitor. It might be considered in POTS phenotype associated with suspected autonomic neuropathy, gastrointestinal dysfunction and non-specific muscle weakness. Effect on BP is small. Class IIB recommendation [3, 97–99]
Fludrocortisone (0.1–0.2 mg daily)	Mineralocorticoid. Volume expander. Increases sodium reabsorption and enhances sensitivity of α-adrenoreceptors. May worsen supine hypertension and hypokalaemia. It is recommended in 'hypovolaemic' subtype and low-BP phenotype. Class IIB recommendation [3, 100, 101]
Ephedrine and pseudoephedrine (25/30–50/60 mg TID)	Direct and indirect α1-adrenoreceptor agonist. Efficacy controversial [77]
Desmopressin (0.1–0.4 mg BID)	Vasopressin analogue. Volume expander. Increases water reabsorption and reduces nycturia. Sparse evidence exists. Efficacy uncertain [102]
In-hospital acute 1–2 L physiological saline infusion (during consecutive 3–5 days)	In acute decompensated POTS, this method should be considered to alleviate the short-term symptoms. Class IIA recommendation [3, 103–105]

BP, blood pressure.

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