

# Diagnosis and management of postural orthostatic tachycardia syndrome

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**T**he main characteristic of postural orthostatic tachycardia syndrome (POTS) is tachycardia when standing, without a drop in blood pressure. Patients describe lightheadedness and palpitations when upright, particularly when standing, which sometimes leads to syncope. Patients may experience impaired quality of life and functional disability, which can be economically devastating.<sup>1-3</sup> The syndrome is more common in girls and young women and has been associated with other disorders, like migraine and Ehlers–Danlos syndrome.<sup>4</sup> We discuss the diagnosis of POTS, conditions to consider in the differential diagnosis, associated disorders and the pharmacologic and nonpharmacologic management of patients with POTS, based on original research, narrative reviews and consensus statements (Box 1).

## What is the definition of POTS?

Various professional societies in North America have published consensus criteria for the diagnosis of POTS, including the American Autonomic Society,<sup>6</sup> the Heart Rhythm Society,<sup>7</sup> the Canadian Cardiovascular Society<sup>5</sup> and, most recently, a POTS Working Group for the United States National Institutes of Health.<sup>8</sup> The consensus statements consistently require orthostatic tachycardia and symptomatic orthostatic intolerance to be chronic problems that coexist. The criteria for a diagnosis of POTS are listed in Box 2. Symptoms must occur after standing, with a marked increase in heart rate, but without a substantial drop in blood pressure. The presence of another condition that could explain the orthostatic tachycardia — such as anemia, anxiety, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, prolonged bed rest or the use of medications that can increase heart rate (including stimulants, diuretics and norepinephrine reuptake inhibitors)<sup>9</sup> — precludes the diagnosis of POTS.

The orthostatic tachycardia must occur in the absence of classical orthostatic hypotension, but transient initial orthostatic hypotension<sup>10</sup> does not preclude a diagnosis of POTS.<sup>5</sup> The patient's heart rate should rise by at least 30 beats/min (or  $\geq 40$  beats/min if patient is aged 12–19 yr) in at least 2 measurements taken at least 1 minute apart (Box 2). The Canadian Cardiovascular Society statement<sup>5</sup> set a minimum supine heart

## Key points

- Postural orthostatic tachycardia syndrome (POTS) is a chronic multisystem disorder; the cardinal feature is orthostatic tachycardia.
- Patients with POTS have symptoms of orthostatic intolerance that improve with recumbence.
- Girls and women are more commonly affected with POTS, beginning in puberty and through early adulthood.
- Postural orthostatic tachycardia syndrome can lead to marked functional disability, often limiting work or schooling.
- Treatments for POTS can improve symptoms and function, and can be initiated in primary care.

rate of 60 beats/min to prevent the diagnosis of POTS being made in a patient with a low resting heart rate that increases to a normal level on standing.

It is physiologically normal for orthostatic tachycardia to vary slightly from day to day and for diurnal variability to exist such that greater orthostatic tachycardia occurs in the morning than later in the day.<sup>11</sup> If a clinician has a high suspicion of POTS, but a patient does not meet the criterion for orthostatic tachycardia at their initial evaluation, reassessment at a later date is prudent, preferably in the morning.

## What is the epidemiology and natural history of POTS?

Postural orthostatic tachycardia syndrome is one of the most common disorders of the autonomic nervous system, with an estimated prevalence of 0.1%–1%.<sup>1,12,13</sup> It usually affects adolescent girls and young adult women,<sup>4</sup> and so the prevalence is higher in this population and lower in men and older people. Postural orthostatic tachycardia syndrome is a heterogeneous syndrome, with multiple causes that can produce a similar clinical phenotype. Although orthostatic symptoms are required for the diagnosis, other symptoms and clinical features differ among patients, and symptoms overlap with other clinically defined syndromes.<sup>8</sup>

Little evidence exists to inform the long-term natural history of POTS. Among children, orthostatic intolerance appears to

**Box 1: Evidence used in this review**

We reviewed recent position statements for the investigation and management of postural orthostatic tachycardia syndrome (POTS). These included the 2011 American Autonomic Society Consensus Statement, the 2015 Heart Rhythm Society Scientific Statement and the 2020 Canadian Cardiovascular Society Position Statement. For articles describing specific mechanisms and treatments, we searched MEDLINE to July 2021, using terms such as “POTS,” “postural tachycardia syndrome” and “postural orthostatic tachycardia syndrome.” We primarily considered original articles, but also review articles. We further searched the reference lists of relevant articles to find other articles of interest.

**Box 2: Diagnostic criteria for postural orthostatic tachycardia syndrome**

All of the following criteria must be met:

- Sustained heart rate increase of  $\geq 30$  beats/min (or  $\geq 40$  beats/min if patient is aged 12–19 yr) within 10 minutes of upright posture.
- Absence of significant orthostatic hypotension (magnitude of blood pressure drop  $\geq 20/10$  mm Hg).
- Very frequent symptoms of orthostatic intolerance that are worse while upright, with rapid improvement upon return to a supine position. Symptoms vary between individuals, but often include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision and fatigue.
- Symptom duration  $\geq 3$  months.
- Absence of other conditions that could explain sinus tachycardia (Box 3).

improve over time with treatment, although longer duration of symptoms before therapy has been associated with poorer long-term outcomes.<sup>14</sup> No data exist on the natural history in adults; clinical experience suggests that symptoms and function can improve with treatment, but many patients do not achieve permanent remission.<sup>3,15</sup>

**What other disorders can cause orthostatic intolerance?**

Several disorders can be misdiagnosed as POTS by clinicians or patients if they are focused solely on either the symptomatic orthostatic intolerance or the excessive orthostatic tachycardia. Patients with vasovagal syncope can have repeated episodes of lightheadedness while upright, in addition to intermittent fainting spells. These patients usually have normal orthostatic vital signs, but some also present with orthostatic sinus tachycardia.<sup>16</sup>

Patients with orthostatic hypotension of 20 mm Hg or greater may have symptoms of orthostatic intolerance and may also have orthostatic tachycardia, but the presence of orthostatic hypotension precludes a diagnosis of POTS.<sup>6</sup> Initial orthostatic hypotension is seen most commonly among adolescents and young adults and causes lightheadedness immediately on standing, but symptoms resolve within 45 seconds of quiet standing.

**Box 3: Other conditions that could explain sinus tachycardia on standing<sup>5</sup>**

- Acute hypovolemia (from dehydration or blood loss)
- Anemia
- Orthostatic hypotension
- Endocrinopathy
  - Adrenal insufficiency
  - Carcinoid tumour
  - Hyperthyroidism
  - Pheochromocytoma
- Adverse effects from medication
- Panic attacks and severe anxiety
- Prolonged or sustained bed rest
- Recreational drug effects

Some patients have symptoms of orthostatic intolerance in the absence of orthostatic tachycardia and hypotension, and a cause cannot be found. In the Canadian Cardiovascular Society statement, these patients are designated as having “postural symptoms without tachycardia.”<sup>5</sup>

Not all patients with orthostatic tachycardia have POTS. Most patients with POTS have a normal or high normal resting heart rate.<sup>17</sup> If patients have a consistently increased heart rate, without regard to body position, they may have inappropriate sinus tachycardia. Inappropriate sinus tachycardia requires a consistent resting heart rate of at least 100 beats/min or a 24-hour mean heart rate above 90 beats/min. Patients with inappropriate sinus tachycardia have distressing symptoms and no obvious underlying cause.<sup>7</sup> If the tachycardia is owing to another disorder known to cause sinus tachycardia, such as those mentioned in Box 3, the diagnosis is “postural tachycardia of other cause.”<sup>5</sup>

Finally, patients with POTS have sinus tachycardia, not another supraventricular tachyarrhythmia. Clinicians should consider paroxysmal supraventricular tachycardia, especially if the tachycardia is not always positional, if it has a sudden onset and offset (the heart rate usually increases more gradually in POTS), or if the tachycardia stops with a Valsalva manoeuvre.

**What other conditions commonly occur in patients with POTS?**

Patients with POTS may have other coexisting symptoms and diagnoses, and it is not clear if these define pathophysiological subsets of POTS. Headache and sleep disturbances are almost universal. Patients with POTS often have exercise intolerance, more than 90% have chronic fatigue and at least half meet criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).<sup>18</sup> A particularly disabling symptom is “brain fog” or perceived cognitive impairment,<sup>19</sup> which is often worse with upright posture.<sup>20</sup> Nausea, bloating and functional bowel symptoms are common. Another common sign is peripheral acrocyanosis in the lower extremities when upright. Common comorbid

conditions seen with POTS<sup>4,21</sup> include hypermobile Ehlers–Danlos syndrome, mast cell activation syndrome,<sup>22</sup> migraine and ME/CFS (Table 1).<sup>18</sup>

The estimated frequencies of these clinical associations vary, and the quality of the evidence about them is weak. Self-reported survey data<sup>4</sup> suggest that about 40% of patients with POTS have migraine, 20%–30% meet the diagnostic criteria for hypermobile Ehlers–Danlos syndrome or hypermobility spectrum disorder<sup>23</sup> and about 15% have a comorbid autoimmune disease. A review of studies that analyzed rates of POTS and other forms of orthostatic intolerance in patients with Ehlers–Danlos syndrome found that orthostatic intolerance and tachycardia occurred in 35%–50% of patients with hypermobility spectrum disorder.<sup>24</sup> Some patients with POTS have symptoms suggestive of abnormal mast cell activation. These patients report episodes of flushing, urticaria, dyspnea, headache and gastrointestinal symptoms, such as diarrhea, nausea and vomiting.<sup>25</sup> Hypermobility spectrum disorder may co-occur with mast cell activation disorder in some patients with POTS.

On initial presentation, patients with POTS are frequently misdiagnosed as having an anxiety disorder. In a large survey of patients with POTS, 77% of respondents reported being told that they had a psychiatric or psychological disorder before their diagnosis of POTS, but this decreased to 37% after their diagnosis.<sup>4</sup> These misdiagnoses likely occur because anxiety may be associated with tachycardia, palpitations and lightheadedness.

## What is the pathophysiology of POTS?

Some putative pathophysiological mechanisms for POTS are shown in Figure 1. Most patients with POTS have low cardiac stroke volume,<sup>26</sup> which may cause the sinus tachycardia. Features described in subgroups of patients include increased sympathetic nervous system tone (i.e., hyperadrenergic POTS),<sup>17</sup> partial peripheral sympathetic denervation leading to relative central hypovolemia (i.e., neuropathic POTS)<sup>27</sup> and low blood volume (i.e., absolute hypovolemia),<sup>28</sup> which may drive some of the other hemodynamic findings. Hyperadrenergic features can include tremulousness, anxiety, migraine and angina-like chest pain.<sup>22</sup> Some perturbations of the autonomic nervous system, particularly the sympathetic nervous system, may be primary (i.e., central hyperadrenergic POTS) or secondary to another physiologic abnormality (e.g., hypovolemia).

Postural orthostatic tachycardia syndrome may have an immunological cause. Many patients describe a postviral onset,<sup>29–32</sup> and 15%–20% of patients with POTS report a history of an autoimmune disorder such as Hashimoto thyroiditis, rheumatoid arthritis or Sjögren syndrome.<sup>4</sup> Recently, numerous cases of POTS<sup>33</sup> and other forms of sinus tachycardia (e.g., inappropriate sinus tachycardia)<sup>34</sup> after a SARS-CoV-2 infection have been reported. Good data on the frequency of POTS among patients with long-term complications from COVID-19 (“long COVID syndrome”) are lacking. Autoantibodies to cardiovascular G protein-coupled membrane receptors is a particular focus of research, but their role in the pathophysiology of POTS is still unclear.<sup>35</sup>

**Table 1: Comorbid conditions associated with postural orthostatic tachycardia syndrome\***

Comorbid condition	Common clinical features	Prevalence, %
Migraine headaches	<ul style="list-style-type: none"> <li>Frequent headache, often throbbing and unilateral</li> <li>May be associated with a prodrome</li> </ul>	40
Hypermobile Ehlers–Danlos syndrome and hypermobile spectrum disorder	<ul style="list-style-type: none"> <li>Hyperextensible joints with frequent subluxation</li> <li>Substantial peri-joint pain</li> </ul>	25
Myalgic encephalomyelitis/chronic fatigue syndrome	<ul style="list-style-type: none"> <li>Profound fatigue with regular activities</li> <li>Postexertional malaise</li> </ul>	21
Fibromyalgia	<ul style="list-style-type: none"> <li>Serious and diffuse myofascial pain</li> </ul>	20
Autoimmune disorders	<ul style="list-style-type: none"> <li>Often previously diagnosed</li> <li>Chronic dry eyes or mouth</li> </ul>	16
Mast cell activation disorder	<ul style="list-style-type: none"> <li>Strong allergic tendencies</li> <li>Dermatographism</li> <li>Frequent severe flushing</li> </ul>	9
Celiac disease	<ul style="list-style-type: none"> <li>Abdominal cramping and diarrhea</li> <li>Gluten sensitivity</li> </ul>	3

\*Data adapted from Shaw and colleagues<sup>4</sup> using Creative Commons Attribution (CC BY-NC-ND 4.0) licence.

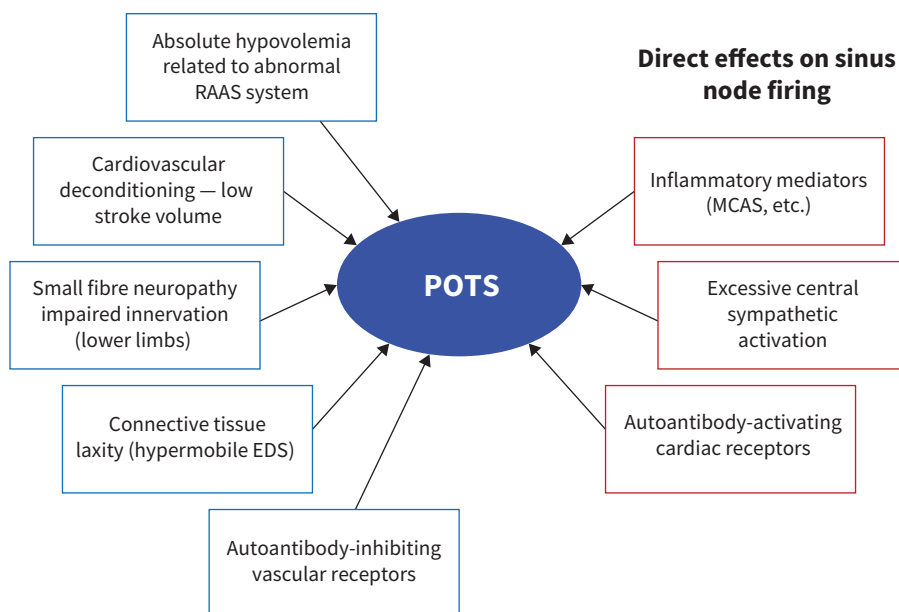
Clinical features of small fibre neuropathy have traditionally been used to diagnose a partial autonomic neuropathy. Some patients with POTS have phosphorylated  $\alpha$ -synuclein in skin biopsies,<sup>36</sup> suggesting a neuropathic mechanism that may be shared with Parkinson disease and pure autonomic failure.

The increased prevalence of POTS among family members suggests a genetic predisposition. With 1 notable exception of a particular mutation causing POTS in members of a single family,<sup>37</sup> no evidence supports a monogenic cause of POTS.

## How should patients be evaluated for POTS?

When POTS is suspected, clinicians should take a patient history, conduct a physical examination, including orthostatic vital signs at regular intervals after standing up (with recording of associated symptoms), and order 12-lead electrocardiography. A 24-hour Holter monitor can detect the presence of inappropriate sinus tachycardia. This minimal approach is usually sufficient to establish a diagnosis and initiate treatment. Most regions of Canada have a shortage of physicians with expertise in managing

### Decreased venous return leading to reflex orthostatic tachycardia



**Figure 1:** Proposed pathophysiological mechanisms for postural orthostatic tachycardia syndrome (POTS). The blue boxes indicate processes that may lead to reduced circulating blood volume, impaired venous return on standing and reflex orthostatic tachycardia. The red boxes indicate primary processes affecting sinus node response to orthostatic challenge and abnormal chronotropic response on standing. Different mechanisms may overlap. For example, autoantibodies that target cardiac receptors may produce an abnormal response during orthostasis, whereas those that target vascular receptors may lead to venous pooling, relative hypovolemia and reflex tachycardia on standing. Note: EDS = Ehlers–Danlos syndrome, MCAS = mast cell activation syndrome, RAAS = renin–angiotensin–aldosterone system.

POTS, but the initial evaluation can be performed by primary care physicians and pediatricians. If patients have a poor or inadequate response to initial treatment, a referral to an expert in POTS should be considered.

The medical history should focus on possible underlying causes and associated disorders, potential POTS triggers and precipitating events, severity of symptoms, factors that can improve or worsen symptoms, the patient's ability to exercise and how the symptoms affect the patient's quality of life. Clinicians should ask about symptoms that suggest possible signs of autonomic dysfunction, such as gastrointestinal or urinary dysfunction, abnormal sweating, acrocyanosis, dry mouth and unexplained fever. Most patients describe headaches, most commonly migraines. Patients also frequently report a combination of diarrhea and constipation. A substantial subset of patients will describe symptoms related to altered gastric motility, with nausea and vomiting that sometimes limit food and water intake. These patients may describe nausea that is worse with upright posture and that responds to treatment that targets the tachycardia. Some patients describe symptoms of bladder dysfunction with incontinence or urgency. Complaints of paresthesia and numbness in the limbs may suggest a small fibre neuropathy as autonomic nerves are small fibre. Heat and cold intolerance are commonly reported. Most patients complain of subjective cognitive dysfunction (“brain fog”) and pervasive fatigue. Clinicians should carefully review medications, as some may worsen symptoms, and ask about adequacy of salt and water intake.

Heart rate and blood pressure must be measured when the patient has been supine for 5–10 minutes to allow fluid equilibration, and then after standing for 1 minute, 3 minutes, 5 minutes, 8 minutes and 10 minutes.<sup>5</sup> To diagnose excessive orthostatic tachycardia (required for POTS), patients should have a sustained heart rate increase of at least 30 beats/min (for adults) or at least 40 beats/min (for patients aged 12–19 yr) on at least 2 of the readings taken when standing. The systolic blood pressure should not fall by more than 20 mm Hg.

Given the substantial diurnal variability, with greater upright heart rate and orthostatic tachycardia in the morning, morning assessments will likely be more sensitive.<sup>11</sup> Although not necessary, a head-up tilt table test (for at least 10 min), ideally with continuous beat-to-beat blood pressure monitoring,<sup>38</sup> can also be used to diagnose POTS. The tilt table test leads to a slightly greater increase in heart rate than the stand test,<sup>39</sup> which increases its diagnostic sensitivity. Head-up tilt table testing is often used in referral centres because it can be combined with advanced monitoring.

In addition to orthostatic vital signs, the physical examination should include an assessment of joint hypermobility if Ehlers–Danlos syndrome is suspected or if the patient reports hyperflexibility.<sup>23,40</sup> Cardiac auscultation might reveal signs that suggest the presence of mitral valve prolapse. Some patients with dependent acrocyanosis may present with a dusky red-blue discoloration of the feet and calves while standing with skin that is cool to the touch.

Core laboratory investigations<sup>5</sup> should screen for secondary causes of orthostatic tachycardia, including hemoglobin, electrolytes, renal function, ferritin, thyroid-stimulating hormone and morning cortisol. Aside from electrocardiography, cardiovascular or neurologic investigations are not recommended. Further investigations should be guided by the initial evaluation (for example, testing for Sjögren syndrome if the patient has suggestive symptoms or conducting echocardiography if the cardiovascular examination is abnormal). Testing for supine and upright fractionated plasma catecholamines and other hormones involved in regulation of blood pressure and blood volume is sometimes done as part of an advanced evaluation. Excessive increases in plasma norepinephrine on standing may point to an excessive sympathetic nervous system tone (“hyperadrenergic state”) that may be treatable with central sympatholytic medications.

## How is POTS treated?

Postural orthostatic tachycardia syndrome does not have a cure. Treatment goals include patient education, symptom suppression, improved physical conditioning and enhanced quality of life. Treatment usually involves both nonpharmacological and pharmacological approaches. An initial approach to treatment is shown in Box 4.

### Nonpharmacological treatments

We suggest that medications that might exacerbate orthostatic tachycardia be stopped. The findings of a small 2005 case-control intervention study suggest that advising patients to drink 3 L of water per day and to maximize their dietary salt intake can promote sodium retention and blood volume expansion.<sup>28</sup> A small 2021 case-control crossover study found that high sodium intake leads to expanded plasma volume, and reduced upright norepinephrine levels and heart rate in patients with POTS,<sup>41</sup> although long-term data about sustained benefit and late adverse effects are still needed. Compression garments for the lower body can mitigate the gravity-induced fluid shifts that occur on standing, and decrease orthostatic tachycardia and standing tachycardia as shown in a 2021 randomized crossover study of lower body compression during tilt table testing in patients with POTS.<sup>42</sup> Compression of the abdomen and the legs appeared to be more effective than compression of legs alone.<sup>42</sup> The findings of a 2010 case-control intervention study suggest that regular, nonupright exercise with a focus on aerobic reconditioning improves cardiovascular hemodynamics and symptoms in patients with POTS.<sup>26</sup> However, experts suggest that patients may initially feel worse and may not improve for a month.<sup>43</sup>

### Pharmacological treatments

Pharmacologic treatments should be considered if patients have severe symptoms at initial presentation or are still symptomatic after nonpharmacologic strategies have been tried. No robust, multicentre randomized controlled trials (RCTs) of drug treatments have been conducted, and no drugs have been approved specifically for the treatment of POTS in North America. Most

#### Box 4: Suggested initial approach to treatment of patient with postural orthostatic tachycardia syndrome

- Nonpharmacological treatments
  - All started at initial visit
    - Water 3 L/d
    - Salt 5 mL/d (2 tsp/d)
    - Waist-high compression garments
- Pharmacological treatments
  - May start at initial visit if symptoms are severe
    - If standing heart rate very high: propranolol 10–20 mg, 4 times per day
    - If standing heart rate very high and  $\beta$ -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)

Note: tsp = teaspoon.

medications that are used in patients with POTS target a reduction of upright sinus tachycardia or sympathetic tone, enhance vasoconstriction or venoconstriction, or augment blood volume (Table 2).

Propranolol blocks both  $\beta_1$ - and  $\beta_2$ -adrenergic receptors. A 2009 randomized crossover study found that low-dose oral propranolol improved tachycardia and symptoms on standing,<sup>45</sup> and a small, randomized, double-blind study in 2013 showed improved exercise capacity<sup>46</sup> in patients with POTS. Propranolol has a short half-life and requires dosing 4 times per day. The Canadian Cardiovascular Society gave propranolol (10–20 mg, 4 times a day) a “strong” recommendation.<sup>5</sup> Although most studies of  $\beta$ -blockers have used propranolol, bisoprolol may also be effective; better comparative data are needed.

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel ( $I_h$ ) blocker that lowers sinus node rate without  $\beta$ -blocker effects. A 2021 single-centre RCT found that ivabradine lowered the heart rate and improved symptoms in some patients with POTS.<sup>47</sup> Patients may have difficulty obtaining insurance coverage for ivabradine.

Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine. A 2005 study found that pyridostigmine (30–60 mg, given orally 3 times daily) can acutely decrease upright heart rate in patients with POTS;<sup>48</sup> it acts either by directly increasing vagal tone or by increasing sympathetic vasoconstriction. Although pyridostigmine is generally well tolerated, it can increase colonic motility. It should be avoided in patients prone to diarrhea but can be helpful in patients with constipation.<sup>49</sup>

Midodrine is a peripheral  $\alpha_1$ -adrenergic receptor agonist pro-drug that enhances venous return, cardiac preload and stroke volume. It may be most beneficial in patients with POTS accompanied by low blood pressure.<sup>50</sup> It is prescribed at 2.5–10 mg every 4 hours (avoiding a dose near bedtime), but it can also be used as needed for acute symptom management.



**Table 2: Pharmacological treatments for postural orthostatic tachycardia syndrome**

Drug	Dosing	Quality of evidence*	Adverse effects	Other considerations
<b>Heart rate inhibitors</b>				
Propranolol	10–20 mg orally up to 4 times daily	Moderate	Hypotension, bradycardia, bronchospasm	Can worsen asthma
Ivabradine	2.5–7.5 mg orally twice daily	Moderate	Visual disturbances, bradycardia	Expensive
Pyridostigmine	30–60 mg orally up to 3 times daily	Low	Increased gastric motility and cramping	
<b>Vasoconstrictors</b>				
Midodrine	2.5–15 mg orally 3 times daily	Moderate	Headache, scalp tingling, supine hypertension	Avoid within 4 hr of bedtime to avoid supine hypertension
<b>Sympatholytic drugs</b>				
Methyldopa	125–250 mg orally twice daily	Low	Hypotension, fatigue, brain fog	Start with a low dose
Clonidine	0.1–0.2 mg orally 2–3 times daily or long-acting patch	Low	Hypotension, fatigue, brain fog	Start with a low dose; withdrawal can lead to rebound tachycardia and hypertension
<b>Blood volume expanders</b>				
Fludrocortisone	0.1 to 0.2 mg orally per day	Low	Hypokalemia, edema, headache	Serum potassium should be monitored
Desmopressin	0.1 to 0.2 mg orally per day, as needed	Low	Hyponatremia, edema	Serum sodium should be monitored if used chronically

\*We critically appraised the literature using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.<sup>44</sup> We rated the quality of the evidence as high, moderate, low or very low based on the likelihood that further research would change confidence in the estimate of effect.

Central sympatholytic drugs can be useful in patients with increased sympathetic activity or hyperadrenergic features. Clonidine and methyldopa are both antihypertensive medications that can decrease central sympathetic nerve traffic and norepinephrine release from peripheral sympathetic neurons. Both medications have narrow therapeutic ranges, and it is important to start with lower doses.

Drugs that expand blood volume can be useful if nonpharmacologic approaches to blood volume expansion are not successful, or if low blood volume is objectively documented by an assessment of blood volume using nuclear medicine.<sup>51</sup> Fludrocortisone (0.1–0.2 mg daily) is a synthetic version of aldosterone that promotes renal sodium absorption and secondary blood volume expansion; hypokalemia is a potential adverse effect. Although data from a 2016 RCT suggest fludrocortisone suppresses vasovagal syncope,<sup>52</sup> the data for POTS are not as strong and controlled studies are lacking. Desmopressin is a synthetic vasopressin that promotes renal retention of free water. It has been shown to acutely reduce orthostatic tachycardia in patients with POTS,<sup>53</sup> but careful monitoring for hyponatremia is required.

### Procedural treatments

Radiofrequency ablation of the sinus node has been reported as a treatment for POTS.<sup>54,55</sup> Both the Heart Rhythm Society<sup>7</sup> and the Canadian Cardiovascular Society<sup>5</sup> currently recommend

against this approach, and any other procedural treatment for POTS, based on a lack of evidence for benefit and potential risks of serious harm.

### Management of comorbidities

It is beyond the scope of this article to offer an in-depth approach to manage the various comorbid conditions that can co-occur with POTS (Table 1). However, to improve patient quality of life and function, it is important that these comorbid conditions are properly addressed. This often requires referral to an appropriate specialist when the management of the individual problem moves beyond general management.

### Conclusion

Postural orthostatic tachycardia syndrome is a chronic, multi-system disorder involving the autonomic nervous system. The cardinal feature is symptomatic, exaggerated sinus tachycardia with upright posture. Girls and women are more commonly affected with POTS, starting around puberty and through early adulthood. Patients with POTS can experience functional disability, with a limited ability to work or go to school, and a decreased quality of life. Increased physician recognition and effective management has the potential to improve the lives of affected patients.

## References

- Arnold A, Ng J, Raj SR. Postural tachycardia syndrome: diagnosis, physiology, and prognosis. *Auton Neurosci* 2018;215:3-11.
- Bagai K, Song Y, Ling JF, et al. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. *J Clin Sleep Med* 2011;7:204-10.
- Bourne KM, Chew DS, Stiles LE, et al. Postural orthostatic tachycardia syndrome is associated with significant employment and economic loss. *J Intern Med* 2021;290:203-12.
- Shaw BH, Stiles LE, Bourne K, et al. The face of postural tachycardia syndrome: insights from a large cross-sectional online community-based survey. *J Intern Med* 2019;286:438-48.
- Raj SR, Guzman JC, Harvey P, et al. Canadian Cardiovascular Society position statement on postural orthostatic tachycardia syndrome (POTS) and related disorders of chronic orthostatic intolerance. *Can J Cardiol* 2020;36:357-72.
- Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011;21:69-72.
- Sheldon RS, Grubb BP II, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;12:e41-63.
- Vernino S, Bourne KM, Stiles LE, et al. Postural orthostatic tachycardia syndrome (POTS): state of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting — Part 1. *Auton Neurosci* 2021;235:102828.
- Green EA, Raj V, Shibus CA, et al. Effects of norepinephrine reuptake inhibition on postural tachycardia syndrome. *J Am Heart Assoc* 2013;2:e000395.
- Harms MPM, Finucane C, Pérez-Denia L, et al. Systemic and cerebral circulatory adjustment within the first 60 s after active standing: an integrative physiological view. *Auton Neurosci* 2021;231:102756.
- Brewster JA, Garland EM, Biaggioni I, et al. Diurnal variability in orthostatic tachycardia: implications for the postural tachycardia syndrome. *Clin Sci (Lond)* 2012;122:25-31.
- Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med* 2019;285:352-66.
- Raj SR, Robertson D. Moving from the present to the future of postural tachycardia syndrome: what we need. *Auton Neurosci* 2018;215:126-8.
- Tao C, Lu W, Lin J, et al. Long-term outcomes of children and adolescents with postural tachycardia syndrome after conventional treatment. *Front Pediatr* 2019;7:261.
- Bhatia R, Kizilbash SJ, Ahrens SP, et al. Outcomes of adolescent-onset postural orthostatic tachycardia syndrome. *J Pediatr* 2016;173:149-53.
- Medow MS, Merchant S, Suggs M, et al. Postural heart rate changes in young patients with vasovagal syncope. *Pediatrics* 2017;139:e20163189.
- Garland EM, Raj SR, Black BK, et al. The hemodynamic and neurohumoral phenotype of postural tachycardia syndrome. *Neurology* 2007;69:790-8.
- Okamoto LE, Raj SR, Peltier A, et al. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clin Sci (Lond)* 2012;122:183-92.
- Arnold AC, Haman K, Garland EM, et al. Cognitive dysfunction in postural tachycardia syndrome. *Clin Sci (Lond)* 2015;128:39-45.
- Miller AJ, Sheehan T, Bourne KM, et al. Attention and executive function are impaired during active standing in postural tachycardia syndrome. *Auton Neurosci* 2020;227:102692.
- McDonald C, Koshi S, Busner L, et al. Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young women: a UK perspective. *BMJ Open* 2014;4:e004127.
- Shibus CA, Arzubigi A, Roberts LJ II, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 2005;45:385-90.
- Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017;175:8-26.
- Roma M, Marden CL, De Wandele I, et al. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers–Danlos syndrome. *Auton Neurosci* 2018;215:89-96.
- Weinstock LB, Pace LA, Rezaie A, et al. Mast cell activation syndrome: a primer for the gastroenterologist. *Dig Dis Sci* 2021;66:965-82.
- Fu Q, Vangundy TB, Galbreath MM, et al. Cardiac origins of the postural orthostatic tachycardia syndrome. *J Am Coll Cardiol* 2010;55:2858-68.
- Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med* 2000;343:1008-14.
- Raj SR, Biaggioni I, Yamhure PC, et al. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. *Circulation* 2005;111:1574-82.
- Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology* 1993;43:132-7.
- Johansson M, Ståhlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep* 2021;3:573-80.
- Bisaccia G, Ricci F, Recce V, et al. Post-acute sequelae of COVID-19 and cardiovascular autonomic dysfunction: What do we know? *J Cardiovasc Dev Dis* 2021;8:156.
- Desai AD, Boursiquot BC, Moore CJ, et al. Autonomic dysfunction post-acute COVID-19 infection. *Heart Rhythm Case Rep* 2021 Nov. 27 [Epub ahead of print]. doi: 10.1016/j.hrcr.2021.11.019.
- Raj SR, Arnold AC, Barboi A, et al.; American Autonomic Society. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. *Clin Auton Res* 2021;31:365-8.
- Ståhlberg M, Reistam U, Fedorowski A, et al. Post-COVID-19 tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. *Am J Med* 2021;134:1451-6.
- Li H, Yu X, Liles C, et al. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc* 2014;3:e000755.
- Levine TD, Bellaire B, Gibbons C, et al. Cutaneous alpha-synuclein deposition in postural tachycardia patients. *Ann Clin Transl Neurol* 2021;8:908-17.
- Shannon JR, Flattem NL, Jordan J, et al. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N Engl J Med* 2000;342:541-9.
- Thijs RD, Brignole M, Falup-Pecurariu C, et al. Recommendations for tilt table testing and other provocative cardiovascular autonomic tests in conditions that may cause transient loss of consciousness: Consensus statement of the European Federation of Autonomic Societies (EFAS) endorsed by the American Autonomic Society (AAS) and the European Academy of Neurology (EAN). *Auton Neurosci* 2021;233:102792.
- Plash WB, Diedrich A, Biaggioni I, et al. Diagnosing postural tachycardia syndrome: comparison of tilt testing compared with standing haemodynamics. *Clin Sci (Lond)* 2013;124:109-14.
- Beighton score. *Physiopedia*. Available: [https://www.physio-pedia.com/Beighton\\_score](https://www.physio-pedia.com/Beighton_score) (accessed 2022 Jan. 8).
- Garland EM, Gamboa A, Nwazue VC, et al. Effect of high dietary sodium intake in patients with postural tachycardia syndrome. *J Am Coll Cardiol* 2021;77:2174-84.
- Bourne KM, Sheldon RS, Hall J, et al. Compression garment reduces orthostatic tachycardia and symptoms in patients with postural orthostatic tachycardia syndrome. *J Am Coll Cardiol* 2021;77:285-96.
- Raj SR. Row, row, row your way to treating postural tachycardia syndrome. *Heart Rhythm* 2016;13:951-2.
- McMurtry S, McGillion M, Oliver S, et al. Framework for application of GRADE in CCS guideline development. Ottawa: Canadian Cardiovascular Society; 2015, updated April 2020. Available: [https://ccs.ca/app/uploads/2021/07/CCS\\_GRADE\\_Framework\\_April2020.pdf](https://ccs.ca/app/uploads/2021/07/CCS_GRADE_Framework_April2020.pdf) (accessed 2022 Jan. 8).
- Raj SR, Black BK, Biaggioni I, et al. Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more. *Circulation* 2009;120:725-34.
- Arnold AC, Okamoto LE, Diedrich A, et al. Low-dose propranolol and exercise capacity in postural tachycardia syndrome: a randomized study. *Neurology* 2013;80:1927-33.
- Taub PR, Zadorian A, Lo HC, et al. Randomized trial of ivabradine in patients with hyperadrenergic postural orthostatic tachycardia syndrome. *J Am Coll Cardiol* 2021;77:861-71.
- Raj SR, Black BK, Biaggioni I, et al. Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome. *Circulation* 2005;111:2734-40.

49. Kanjwal K, Karabin B, Sheikh M, et al. Pyridostigmine in the treatment of postural orthostatic tachycardia: a single-center experience. *Pacing Clin Electrophysiol* 2011;34:750-5.
50. Brignole M, Rivasi G, Sutton R, et al. Low-blood pressure phenotype underpins the tendency to reflex syncope. *J Hypertens* 2021;39:1319-25.
51. Ertl AC, Diedrich A, Raj SR. Techniques used for the determination of blood volume. *Am J Med Sci* 2007;334:32-6.
52. Sheldon R, Raj SR, Rose MS, et al. Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. *J Am Coll Cardiol* 2016;68:1-9.
53. Coffin ST, Black BK, Biaggioni I, et al. Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome. *Heart Rhythm* 2012;9:1484-90.
54. Shen WK, Low PA, Jahangir A, et al. Is sinus node modification appropriate for inappropriate sinus tachycardia with features of postural orthostatic tachycardia syndrome? *Pacing Clin Electrophysiol* 2001;24:217-30.
55. de Asmundis C, Chierchia G-B, Sieira J, et al. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural orthostatic sinus tachycardia with new electrophysiological finding. *Am J Cardiol* 2019;124:224-32.

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