Evaluating and managing postural tachycardia syndrome

ABSTRACT

Postural tachycardia syndrome (POTS) is a disorder of the autonomic nervous system with many possible causes, characterized by an unexplained increase in heartbeat without change in blood pressure upon standing. Associated cardiac and noncardiac symptoms can severely affect quality of life. Therapy, using a combined approach of diet and lifestyle changes, plus judicious use of medications if needed, can usually improve symptoms and function.

KEY POINTS

Several POTS subtypes have been recognized, including hypovolemic, neuropathic, and hyperadrenergic forms, overlapping with Ehlers-Danlos syndrome, mast cell activation, and autoimmune syndromes.

Treatment should take a graded approach, beginning with increasing salt and water intake, exercise, and compression stockings.

If needed, consider medications to expand blood volume, slow heart rate, or reduce central sympathetic tone.

Certain medications, including venodilators, diuretics, and serotonin-norepinephrine reuptake inhibitors, can exacerbate symptoms and should be avoided.

SOME PEOPLE, most of them relatively young women, experience lightheadedness, a racing heart, and other symptoms (but not hypotension) when they stand up, in a condition known as postural tachycardia syndrome (POTS). Although not known to shorten life, it can be physically and mentally debilitating. Therapy rarely cures it, but a multifaceted approach can substantially improve quality of life.

This review outlines the evaluation and diagnosis of POTS and provides guidance for a therapy regimen.

HOW IS POTS DEFINED?

POTS is a multifactorial syndrome rather than a specific disease. It is characterized by all of the following:\(^1\)\(^4\)-\(^6\):

- An increase in heart rate of \(\geq 30\) bpm, or \(\geq 40\) bpm for those under age 19, within 10 minutes of standing from a supine position
- Sustained tachycardia (\(> 30\) seconds)
- Absence of orthostatic hypotension (a fall in blood pressure of \(\geq 20/10\) mm Hg)
- Frequent and chronic duration (\(\geq 6\) months)

These features are critical to diagnosis. Hemodynamic criteria in isolation may describe postural tachycardia but are not sufficient to diagnose POTS.

The prevalence of POTS is estimated to be between 0.2% and 1.0%,\(^7\) affecting up to 3 million people in the United States. Most cases arise between ages 13 and 50, with a female-to-male ratio of 5:1.\(^8\)

MANY NAMES, SAME CONDITION

In 1871, Da Costa\(^9\) described a condition he called “irritable heart syndrome” that had characteristics similar to those of POTS, including...
POSTURAL TACHYCARDIA

extreme fatigue and exercise intolerance. Decades later, Lewis and Wood provided more detailed descriptions of the disorder, renaming it “soldier’s heart” or “Da Costa syndrome.” As other cases were documented, more terms arose, including “effort syndrome” and “mitral valve prolapse syndrome.”

In 1982, Rosen and Cryer were the first to use the term “postural tachycardia syndrome” for patients with disabling tachycardia upon standing without orthostatic hypotension. In 1986, Fouad et al described patients with postural tachycardia, orthostatic intolerance, and a small degree of hypotension as having “idiopathic hypovolemia.”

In 1993, Schondorf and Low established the current definition of POTS, leading to increased awareness and research efforts to understand its pathophysiology.

MULIFACTORIAL PATHOPHYSIOLOGY

During the last 2 decades, several often-overlapping forms of POTS have been recognized, all of which share a final common pathway of sustained orthostatic tachycardia. In addition, a number of common comorbidities were identified through review of large clinic populations of POTS.

Hypovolemic POTS

Up to 70% of patients with POTS have hypovolemia. The average plasma volume deficit is about 13%, which typically causes only insignificant changes in heart rate and norepinephrine levels while a patient is supine. However, blood pooling associated with upright posture further compromises cardiac output and consequently increases sympathetic nerve activity. Abnormalities in the renin-angiotensin-aldosterone volume regulation system are also suspected to impair sodium retention, contributing to hypovolemia.

Neuropathic POTS

About half of patients with POTS have partial sympathetic denervation (particularly in the lower limbs) and inadequate vasoconstriction upon standing, leading to reduced venous return and stroke volume. A compensatory increase in sympathetic tone results in tachycardia to maintain cardiac output and blood pressure.

Hyperadrenergic POTS

Up to 50% of patients with POTS have high norepinephrine levels (≥ 600 pg/mL) when upright. This subtype, hyperadrenergic POTS, is characterized by an increase in systolic blood pressure of at least 10 mm Hg within 10 minutes of standing, with concomitant tachycardia that can be similar to or greater than that seen in nonhyperadrenergic POTS. Patients with hyperadrenergic POTS tend to report more prominent symptoms of sympathetic activation, such as palpitations, anxiety, and tremulousness.

Norepinephrine transporter deficiency

The norepinephrine transporter (NET) is on the presynaptic cleft of sympathetic neurons and serves to clear synaptic norepinephrine. NET deficiency may be induced by common antidepressants (eg, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors) and attention-deficit disorder medications.

Mast cell activation syndrome

The relationship between mast cell activation syndrome and POTS is poorly understood. Mast cell activation syndrome has been described in a subset of patients with POTS who have sinus tachycardia accompanied by severe episodic flushing. Patients with this subtype have a hyperadrenergic response to postural change and elevated urine methylhistamine during flushing episodes. Patients with mast cell activation syndrome tend to have strong allergic symptoms and may also have severe gastrointestinal problems, food sensitivities, dermatographism, and neuropathy. Diagnosis can be difficult, as the condition is associated with numerous markers with varying sensitivity and specificity.

Autoimmune origin

A significant minority of patients report a viral-like illness before the onset of POTS symptoms, suggesting a possible autoimmune-mediated or inflammatory cause. Also, some autoimmune disorders (eg, Sjögren syndrome) can present with a POTS-like manifestation. Research into the role of autoantibodies in the pathophysiology of POTS offers the poten-
potential to develop novel therapeutic targets. Auto-
antibodies that have been reported in POTS include those against M1 to M3 muscarinic receptors (present in over 87% of patients with
POTS),
cardiac lipid raft-associated proteins,
adrenergic G-protein coupled receptors, alpha-
1-adrenergic receptors, and beta-1- and beta-
2-adrenergic receptors. Although commercial
enzyme-linked immunosorbent assays can assess
for these antibody fragments, it is not known
whether targeting the antibodies improves out-
comes. At this time, antibody testing for POTS
should be confined to the research setting.

■ LINKS TO OTHER SYNDROMES

POTS is often associated with other condi-
tions whose symptoms cannot be explained by
postural intolerance or tachycardia.

Ehlers-Danlos syndromes are a group of
inherited heterogeneous disorders involving
joint hypermobility, skin hyperextensibility,
and tissue fragility. The hypermobile subtype
is most commonly associated with POTS, with
patients often having symptoms of autonomic
dysregulation and autonomic test abnormali-
ties. Patients with POTS may have a his-

tory of joint subluxations, joint pain, cervical
instability, and spontaneous epidural leaks.
The reason for the overlap between the two
syndromes is not clear.

Chronic fatigue syndrome is characterized
by persistent fatigue that does not resolve with
rest and is not necessarily associated with or-
thostatic changes. More than 75% of patients
with POTS report general fatigue as a major
complaint, and up to 23% meet the full crite-
ria for chronic fatigue syndrome.

■ DIAGNOSTIC STRATEGY

A patient presenting with symptoms sugges-
tive of POTS should first undergo a detailed
history and physical examination. Other
causes of sinus tachycardia should be consid-
ered.

Detailed history, symptom review
The history should focus on determining
symptom burden, including tachycardia onset,
frequency, severity, and triggers; the presence
of syncope; and the impact of symptoms on
daily function and quality of life.

POTS-associated orthostatic intolerance
manifests with cardiac and noncardiac symp-
toms (Table 1).

Presyncope and its associated symptoms
occur in less than one-third of patients with
POTS, and syncope is not a principal feature. If
syncope is the predominant complaint, al-
ternative causes should be investigated. The
usual cause of syncope in the general popula-
tion is thought to be vasovagal.

In addition to orthostatic intolerance,
gastrointestinal disturbances are common in
POTS, presenting as abdominal pain, heart-
burn, irregular bowel movements, diarrhea, or
constipation. Symptoms of gastroparesis are
less common. Gastrointestinal symptoms tend
to be prolonged, lasting hours and occurring
multiple times a week. They tend not to im-
prove in the supine position.

POTS-associated symptoms may develop
insidiously, but patients often report onset af-

after an acute stressor such as pregnancy, major
surgery, or a presumed viral illness. Whether
these putative triggers are causative or coinci-
dental is unknown. Symptoms of orthostatic

<table>
<thead>
<tr>
<th>Noncardiac symptoms</th>
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<tbody>
<tr>
<td>Mental clouding (“brain fog”)</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Tremulousness</td>
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<tr>
<td>Blurred or tunnel vision</td>
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<tr>
<td>Sleep disturbances</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Presyncope</td>
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<tr>
<td>Gastrointestinal pain, heartburn, diarrhea, constipation</td>
</tr>
</tbody>
</table>

Hypovolemia occurs in up to 70% of patients.
intolerance tend to be exacerbated by dehydration, heat, alcohol, exercise, and menstruation.36,37 Consider the family history: 1 in 8 patients with POTS reports familial orthostatic intolerance,38 suggesting a genetic role in some patients. Inquire about symptoms or a previous diagnosis of Ehlers-Danlos syndrome and mast cell activation syndrome.

Other causes of orthostatic tachycardia are listed in Table 2.39-41 Most can be diagnosed with a careful history, physical examination, and laboratory tests. Two of the more challenging diagnoses are described below.

**Pheochromocytoma** causes hyperadrenergic symptoms (eg, palpitations, lightheadedness) like those in POTS, but patients with pheochromocytoma typically have these symptoms while supine. Pheochromocytoma is also characterized by plasma norepinephrine levels much higher than in POTS.4 Plasma metanephrine testing helps diagnose or rule out pheochromocytoma.5

**Inappropriate sinus tachycardia**, like pheochromocytoma, also has clinical features similar to those of POTS, as well as tachycardia present when supine. It involves higher sympathetic tone and lower parasympathetic tone compared with POTS; patients commonly have a daytime resting heart rate of at least 100 bpm or a 24-hour mean heart rate of at least 90 bpm.1,42 While the intrinsic heart rate is heightened in inappropriate sinus tachycardia, it is not different between POTS patients and healthy individuals.42,43 Distinguishing POTS from inappropriate sinus tachycardia is further complicated by the broad inclusion criteria of most studies of inappropriate sinus tachycardia, which failed to exclude patients with POTS.44 The Heart Rhythm Society recently adopted distinct definitions for the 2 conditions.1

**Physical examination: Focus on vital signs**
The most critical component of the physical examination is thorough measurement of orthostatic vital signs (Figure 1). Blood pressure and heart rate should be measured while the patient has been supine for at least 5 minutes, and again after being upright for 1, 3, 5, and 10 minutes. These measurements determine if orthostatic hypotension is present and whether the patient meets the heart rate criteria for POTS. Patients with POTS tend to experience greater orthostatic tachycardia in the morning, so evaluation early in the day optimizes diagnostic sensitivity.5 Dependent acrocyanosis—dark red-blue discoloration of the lower legs that is cold to the touch—occurs in about half of patients with POTS upon standing.5 Dependent acrocyanosis is associated with joint hypermobility and Ehlers-Danlos syndrome, so these conditions should also be considered if findings are positive.

**Laboratory testing for other causes**
Laboratory testing is used mainly to detect primary causes of sinus tachycardia. Tests should include:
- Complete blood cell count with hematocrit (for severe anemia)
- Thyroid-stimulating hormone level (for hyperthyroidism)
- Electrolyte panel (for significant electrolyte disturbances)

Evidence is insufficient to support routinely measuring the vitamin B12 level, iron indices, and serum markers for celiac disease, although these may be done if the history or..
physical examination suggests related problems.4 Sicca symptoms (severe dry eye or dry mouth) should trigger evaluation for Sjögren syndrome.

**Electrocardiography needed**

Electrocardiography should be performed to investigate for cardiac conduction abnormalities as well as for resting markers of a supraventricular tachyarrhythmia. Extended ambulatory (Holter) monitoring may be useful to evaluate for a transient reentrant tachyarrhythmia4; however, it does not record body position, so it can be difficult to determine if detected episodes of tachycardia are related to posture.

**Additional testing for select cases**

Further investigation is usually not needed to diagnose POTS but should be considered in some cases. Advanced tests are typically performed at a tertiary care referral center and include:

- Quantitative sensory testing to evaluate for small-fiber neuropathy (ie, Quantitative Sudomotor Axon Reflex Test, or QSART), which occurs in the neuropathic POTS subtype
- Formal autonomic function testing to characterize neurovascular responsiveness
- Supine and standing plasma norepinephrine levels (fractionated catecholamines) to characterize the net activation of the sympathetic nervous system
- Blood volume assessments to assess hypovolemia
- Formal exercise testing to objectively quantify exercise capacity.

**GRADED MANAGEMENT**

No single universal gold-standard therapy exists for POTS, and management should be individually determined with the primary goals of treating symptoms and restoring function. A graded approach should be used, starting with conservative nonpharmacologic therapies and adding medications as needed.

While the disease course varies substantially from patient to patient, proper management is strongly associated with eventual symptom improvement.1

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**Figure 1.** Results of head-up tilt-table (HUT) testing in a healthy person (top) and in a patient with postural tachycardia syndrome (POTS) (bottom). Upon passive head-up tilting, the heart rate increases in POTS by at least 30 bpm but remains largely stable in healthy individuals. Orthostatic hypotension (a fall in blood pressure of ≥ 20/10 mm Hg) does not occur in either patient.

**NONPHARMACOLOGIC STEPS FIRST**

A multipronged nonpharmacologic approach should be used for all patients before resorting to medications (Table 3). In an observational study, most patients reported that such interventions were more helpful than medications.45 The following elements are recommended:

**Education**

Patients should be informed of the nature of their condition and referred to appropriate healthcare personnel. POTS is a chronic illness requiring individualized coping strategies,
First try non-pharmacologic approaches

intensive physician interaction, and support of a multidisciplinary team. Patients and family members can be reassured that most symptoms improve over time with appropriate diagnosis and treatment.\(^1\) Patients should be advised to avoid aggravating triggers and activities.

Exercise
Exercise programs are encouraged but should be introduced gradually, as physical activity can exacerbate symptoms, especially at the outset. Several studies have reported benefits from a short-term (3-month) program, in which the patient gradually progresses from non-upright exercise (eg, rowing machine, recumbent cycle, swimming) to upright endurance exercises. At the end of these programs, significant cardiac remodeling, improved quality of life, and reduced heart rate responses to standing have been reported, and benefits have been reported to persist in patients who continued exercising after the 3-month study period.\(^{46,47}\)

Despite the benefits of exercise interventions, compliance is low.\(^{46,47}\) To prevent early discouragement, patients should be advised that it can take 4 to 6 weeks of continued exercise before benefits appear. Patients are encouraged to exercise every other day for 30 minutes or more. Regimens should primarily focus on aerobic conditioning, but resistance training, concentrating on thigh muscles, can also help. Exercise is a treatment and not a cure, and benefits can rapidly disappear if regular activity (at least 3 times per week) is stopped.\(^{48}\)

Compression stockings
Compression stockings help reduce peripheral venous pooling and enhance venous return to the heart. Waist-high stockings with compression of at least 30 to 40 mm Hg offer the best results.

Diet
Increased fluid and salt intake is advisable for patients with suspected hypovolemia. At least 2 to 3 L of water accompanied by 10 to 12 g of daily sodium intake is recommended.\(^1\) This can usually be accomplished with diet and salt added to food, but salt tablets can be used if the patient prefers. The resultant plasma volume expansion may help reduce the reflex tachycardia upon standing.\(^{49}\)

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**TABLE 3**

<table>
<thead>
<tr>
<th>Nonpharmacologic treatments for postural tachycardia syndrome</th>
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<tbody>
<tr>
<td><strong>Therapy</strong></td>
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<tr>
<td>Exercise</td>
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<tr>
<td>Dietary fluid</td>
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<tr>
<td>Dietary salt</td>
</tr>
<tr>
<td>Salt tablets</td>
</tr>
<tr>
<td>Acute intravenous normal saline</td>
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<tr>
<td>Chronic intravenous normal saline</td>
</tr>
</tbody>
</table>
Check medications
The clinician should review—and perhaps discontinue—medications the patient is already taking that may exacerbate tachycardia or related symptoms (Table 4). Venodilators decrease preload, thereby reducing cardiac output and blood pressure, which triggers compensatory tachycardia. Diuretics can reduce effective blood volume and lower preload, leading to worsened symptoms mediated by hypovolemia.

Rescue therapy with saline infusion
Intravenous saline infusion can augment blood volume in patients who are clinically decompensated and present with severe symptoms. Intermittent infusion of 1 L of normal saline has been found to significantly reduce orthostatic tachycardia and related symptoms in patients with POTS, contributing to improved quality of life.

Chronic saline infusions are not recommended for long-term care because of the risk of access complications and infection. Moak et al reported a high rate of bacteremia in a cohort of children with POTS with regular saline infusions, most of whom had a central line. On the other hand, Ruzieh et al reported significantly improved symptoms with regular saline infusions without a high rate of complications, but patients in this study received infusions for only a few months and through a peripheral intravenous catheter.

Drug therapy for POTS should be used only if nonpharmacologic interventions do not adequately relieve symptoms. Given the heterogeneity of POTS, treatment should be tailored to the patient’s underlying pathophysiology, key clinical features, and comorbidities. These considerations should guide the initial selection of medications, with adjustments as needed to alleviate adverse effects (Table 5).

No medications are approved by the US Food and Drug Administration (FDA) or Health Canada specifically for treating POTS, making all pharmacologic recommendations off-label. Although the drugs discussed below have been evaluated for POTS in controlled laboratory settings, they have yet to be tested in robust clinical trials.

### TABLE 4
Medications that can exacerbate postural tachycardia syndrome

<table>
<thead>
<tr>
<th>Medications</th>
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<tbody>
<tr>
<td>Antidepressants (serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants at higher doses)</td>
</tr>
<tr>
<td>Antipsychotic agents (phenothiazines)</td>
</tr>
<tr>
<td>Anxiolytic agents</td>
</tr>
<tr>
<td>Attention deficit medications</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Venodilators and vasodilators</td>
</tr>
<tr>
<td>Stimulants (including caffeine, nicotine)</td>
</tr>
</tbody>
</table>

Blood volume expansion
Several drugs expand blood volume, which may reduce orthostatic tachycardia.

**Fludrocortisone** is a synthetic aldosterone analogue that enhances sodium and water retention. Although one observational study found that it normalizes hemodynamic changes in response to orthostatic stress, no high-level evidence exists for its effectiveness for POTS.

It is generally well tolerated, although possible adverse effects include hyperkalemia, hypertension, fatigue, nausea, headache, and edema. Patients should be advised to use fludrocortisone no more than once a week for the acute improvement of symptoms. Intermittent monitoring of serum sodium levels is recommended for safety.

**Desmopressin** is a synthetic version of a natural antidiuretic hormone that increases kidney-mediated free-water reabsorption without sodium retention. It significantly reduces upright heart rate in patients with POTS and improves symptom burden. Although potential adverse effects include edema and headache, hyponatremia is the primary concern with daily use, especially with the increased water intake advised for POTS. Patients should be advised to use desmopressin no more than once a week for the acute improvement of symptoms. Intermittent monitoring of serum sodium levels is recommended for safety.

**Erythropoietin** replacement has been suggested for treating POTS to address the significant deficit in red blood cell volume. Although erythropoietin therapy has a direct vasoconstrictive effect and largely improves red blood cell volume in patients with POTS, it does not expand plasma volume, so ortho-
static tachycardia is not itself reduced. Nevertheless, it may significantly improve POTS symptoms refractory to more common methods of treatment, and it should be reserved for such cases. In addition to the lack of effect on orthostatic tachycardia, drawbacks to using erythropoietin include its high cost, the need for subcutaneous administration, and the risk of life-threatening complications such as myocardial infarction and stroke.58,59

### TABLE 5
Pharmacologic treatments for postural tachycardia syndrome

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosage</th>
<th>Pathologic mechanism addressed</th>
<th>Potential drawbacks</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood volume expanders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.05–0.1 mg twice daily</td>
<td>Hypovolemia</td>
<td>Hypokalemia, hypertension, fatigue, headache, fluid retention, edema</td>
<td>Only for occasional use; must monitor blood sodium</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>0.1–0.2 mg 3 times daily</td>
<td>Hypovolemia</td>
<td>Hyponatremia, headache, edema</td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>2,000–3,000 IU subcutaneously</td>
<td>Hypovolemia</td>
<td>High cost, requires injection, risk of vascular complications</td>
<td>Reserved for patients with symptoms refractory to more common treatments</td>
</tr>
<tr>
<td><strong>Heart rate-lowering agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>10–20 mg 3–4 times daily</td>
<td>All</td>
<td>Hypotension, fatigue, drowsiness, wheezing</td>
<td>Not well tolerated at higher dosages</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>5–7.5 mg twice daily</td>
<td>All</td>
<td>Palpitations, headache, dizziness, constipation</td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system sympatholytics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.05–0.2 mg twice daily</td>
<td>Hyperadrenergic</td>
<td>Mental clouding, fatigue, drowsiness, constipation</td>
<td>Can be associated with rebound hypertension and tachycardia</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>125 mg once or twice daily</td>
<td>Hyperadrenergic</td>
<td>Hypotension, fatigue, headache, drowsiness, constipation</td>
<td>Rare lupus-like syndrome reported</td>
</tr>
<tr>
<td><strong>Other drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midodrine</td>
<td>5–15 mg every 4 hours, 3 times daily only</td>
<td>Neuropathic</td>
<td>Hypertension, goose bumps, urinary retention</td>
<td>Not recommended for use within 4-5 hours of sleep</td>
</tr>
<tr>
<td>Pyrldostigmine</td>
<td>30–60 mg 3 times daily</td>
<td>All</td>
<td>Abdominal cramping, diarrhea, increased sweating</td>
<td>May increase gastrointestinal motility</td>
</tr>
<tr>
<td>Droxidopa</td>
<td>100–600 mg 3 times daily</td>
<td>All</td>
<td>Nausea, palpitations, urinary symptoms</td>
<td>May worsen tachycardia</td>
</tr>
<tr>
<td>Modafinil</td>
<td>100–200 mg twice daily</td>
<td>“Brain fog”</td>
<td>Headache, dizziness, anxiety, insomnia</td>
<td>May improve cognitive symptoms</td>
</tr>
</tbody>
</table>
Heart rate-lowering agents

Propranolol, a nonselective beta-adrenergic antagonist, can significantly reduce standing heart rate and improve symptoms at low dosages (10–20 mg). Higher dosages can further restrain orthostatic tachycardia but are not as well tolerated, mainly due to hypotension and worsening of existing symptoms such as fatigue. Regular-acting propranolol works for about 4 to 5 hours per dose, so full-day coverage often requires dosing 4 times per day.

Ivabradine is a selective blocker of the “funny” (If) channel that reduces the sinus node firing rate without affecting blood pressure, so it slows heart rate without causing supine hypertension or orthostatic hypotension.

A retrospective case series found that 60% of patients with POTS treated with ivabradine reported symptomatic improvement, and all patients experienced reduced tachycardia with continued use. Ivabradine has not been compared with placebo or propranolol in a randomized controlled trial, and it has not been well studied in pregnancy and so should be avoided because of potential teratogenic effects.

When prescribing ivabradine for women of childbearing age, a negative pregnancy test may be documented prior to initiation of therapy, and the use of highly effective methods of contraception is recommended. Ivabradine should be avoided in women contemplating pregnancy. Insurance coverage can limit access to ivabradine in the United States.

Central nervous system sympatholytics

Patients with prominent hyperadrenergic features may benefit from central sympatholytic agents. However, these drugs may not be well tolerated in patients with neuropathic POTS because of the effects of reduced systemic vascular resistance and the possible exacerbation of drowsiness, fatigue, and mental clouding. Patients can be extremely sensitive to these medications, so they should initially be prescribed at the lowest dose, then gradually increased as tolerated.

Clonidine, an alpha-2-adrenergic agonist, decreases central sympathetic tone. In hyperadrenergic patients, clonidine can stabilize heart rate and blood pressure, thereby reducing orthostatic symptoms.

Methyldopa has effects similar to those of clonidine but is easier to titrate owing to its longer half-life. Methyldopa is typically started at 125 mg at bedtime and increased to 125 mg twice daily, if tolerated.

Other agents

Midodrine is a prodrug. The active form, an alpha-1-adrenergic agonist, constricts peripheral veins and arteries to increase vascular resistance and venous return, thereby reducing orthostatic tachycardia. It is most useful in patients with impaired peripheral vasoconstriction (eg, neuropathic POTS) and may be less effective in those with hyperadrenergic POTS. Major limitations of midodrine include worsening supine hypertension and possible urinary retention.

Because of midodrine’s short half-life, frequent dosing is required during daytime hours (eg, 8 am, noon, and 4 pm), but it should not be taken within 4 to 5 hours of sleep because of the risk of supine hypertension. Midodrine is typically started at 2.5 to 5 mg per dose and can be titrated up to 15 mg per dose.

Midodrine is an FDA pregnancy category C drug (adverse effects in pregnancy seen in animal models, but evidence lacking in humans). While ideally it should be avoided, we have used it safely in pregnant women with disabling POTS symptoms.

Pyridostigmine, an acetylcholinesterase inhibitor, increases cardiovagal tone and possibly sympathetic tone. It has been reported to significantly reduce standing heart rate and improve symptom burden in patients with POTS. However, pyridostigmine increases gastrointestinal mobility, leading to severe adverse effects in over 20% of patients, including abdominal cramps, nausea, and diarrhea.

Droxidopa, a synthetic amino acid precursor of norepinephrine, improves dizziness and fatigue in POTS with minimal effects on blood pressure.

Modafinil, a psychostimulant, may improve POTS-associated cognitive symptoms. It also raises upright blood pressure without significantly worsening standing heart rate or acute orthostatic symptoms.
Ehlers-Danlos syndrome
Pharmacologic approaches to POTS should not be altered based on the presence of Ehlers-Danlos syndrome, but because many of these patients are prone to joint dislocation, exercise prescriptions may need adjusting.

A medical genetics consult is recommended for patients with Ehlers-Danlos syndrome. Although the hypermobile type (the form most commonly associated with POTS) is not associated with aortopathy, it can be confused with classical and vascular Ehlers-Danlos syndromes, which require serial aortic screening.30

Mast cell activation syndrome
Consultation with an allergist or immunologist may help patients with severe symptoms.

Autoantibodies and autoimmunity
Treatment of the underlying disorder is recommended and can result in significantly improved POTS symptoms.

SPECIALTY CARE REFERRAL
POTS can be challenging to manage. Given the range of physiologic, emotional, and functional distress patients experience, it often requires significant physician time and multidisciplinary care. Patients with continued severe or debilitating symptoms may benefit from referral to a tertiary-care center with experience in autonomic nervous system disorders.

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10. Lewis T. The tolerance of physical exertion, as shown by soldiers suffering from so-called “irritable heart.” Br Med J 1918; 1(2987):363–365. pmid:20768980


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