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Review

Pharmacotherapy for postural tachycardia syndrome

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ABSTRACT

Postural tachycardia syndrome (POTS) is a disorder characterized by the presence of orthostatic symptoms (including lightheadedness, palpitations, nausea, dyspnea, and tremulousness) as well as excessive upright tachycardia. POTS predominantly affects women of childbearing age. Treating POTS involves a multi-faceted approach using non-pharmacological and pharmacological interventions. There are no pharmacological treatments that are currently United States Food and Drug Administration (FDA) approved for POTS due to lack of randomized controlled trials. Yet, several medications can improve POTS symptoms and are supported by small prospective studies or retrospective case series. Drugs that are most commonly used for POTS target the following mechanisms 1) blood volume expansion, 2) reduction of heart rate, 3) peripheral vasoconstriction and 4) sympatholysis. Pharmacological approaches can also be used to target specific symptoms including "brain fog," fatigue, sleep, and depression. This review outlines pharmacological approaches for treating POTS and summarizes evidence supporting each treatment approach.

1. Introduction

Postural tachycardia syndrome (POTS) is form of chronic orthostatic intolerance that elicits daily symptoms including lightheadedness, palpitations, weakness, fatigue, and nausea. POTS is defined by the presence of these symptoms as well as an increase in heart rate (HR) of at least 30 beats/min (at least 40 beats/min in adolescents) within 10 min of standing from a supine position, or head-up tilt, in the absence of orthostatic hypotension (Sheldon et al., 2015). It is estimated that POTS affects 500,000–3 million Americans, predominantly young women of child-bearing age.

Treating POTS is not straightforward and often involves an individualized approach trying several therapies since no one therapy is universally effective. There is also no consensus on whether certain endophenotypes of POTS patients, discussed in another article in this issue (Arnold et al., 2018), respond differently to treatment or whether all POTS patients should be treated similarly.

There is no cure for POTS but there are many non-pharmacological and pharmacological approaches to relieving POTS symptoms. POTS itself does not lead to an increased mortality, so treatment is targeted at relieving symptoms and improving quality of life.

Non-pharmacological approaches to treating POTS should be employed as a foundation. When non-pharmacological approaches are insufficient at relieving POTS symptoms, pharmacological treatments for POTS are warranted to improve quality of life and prevent disability (Sheldon et al., 2015). While it may be reasonable to initially give a trial of non-pharmacological treatment alone, some patients will present with more severe symptoms that may require the initiation of pharmacological therapy (in addition to non-pharmacological therapy) even at the first visit. Treatment is aimed at relieving symptoms and not a specific hemodynamic target. The FDA has not approved any medications for the treatment of POTS; however, many drugs are used "off label" to relieve POTS symptoms. Most studies assessing treatments for POTS are retrospective analyses or acute single-center prospective studies. No pharmacological treatments for POTS have been tested in multi-center randomized control trials. This review will summarize pharmacologic approaches to treating POTS and the limited current evidence underlying these treatments.

2. Non-pharmacological treatment of POTS

The 2015 Heart Rhythm Society Expert Scientific Statement recommends that non-pharmacological approaches (including exercise training) should be attempted first for POTS (Sheldon et al., 2015) and these approaches are discussed in detail in another article in this issue on Exercise and Non-Pharmacological Approaches to POTS (Fu, 2017).

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Briefly, non-pharmacological management of POTS includes several lifestyle changes. It is recommended that all POTS patients increase intake of sodium to 10–12 g per day (Nwazue et al., 2013) and 2–3 L of water, in an effort to increase blood volume (Sheldon et al., 2015). Often POTS patients drink copious amounts of water which is ineffective without the addition of sodium to the diet. Another recommendation is to participate in a graded aerobic exercise program (Fu et al., 2010; Fu et al., 2011; George et al., 2016; Winker et al., 2005). The use of compression garments such as medical grade compression stockings, abdominal binders, and sports recovery suits may prevent blood pooling and lessen symptoms in some patients. Learning physical counter-measures such as squeezing the buttocks and crossing the legs while standing may alleviate pre-syncope. Since POTS patients have low sleep quality (Bagai et al., 2016), improving sleep hygiene may also be an important consideration that will be discussed more in detail in the chapter in this issue on Sleep Disorders in POTS (Miglis, 2018). While non-pharmacological approaches should be initiated early, some patients may also require the initiation of pharmacological therapies even at the first visit.

3. Pharmacotherapy options for POTS

3.1. Goals and approaches

The therapeutic target for treating POTS is symptomatic improvement. However, symptoms are very subjective and difficult to assess. Many studies investigate the effects of certain treatments on a hemodynamic target in POTS such as orthostatic BP or HR rather than symptoms. Yet, normalizing hemodynamics is not always associated with improved quality of life.

There are several different classes of drugs that are used to treat POTS symptoms which are summarized in Table 1. There is no specific formula to decide which treatment to use and treatment must be individualized to each patient. Many POTS patients are more sensitive to pharmacological treatments. Therefore, when initiating a therapy the lowest dose should be used first and titrated up to higher doses as needed for symptomatic improvement as long as the drug is tolerated. Often POTS patients require a lower doses of medications than what is recommended for other diseases and disorders.

3.2. Drugs that increase blood volume

Many POTS patients are hypovolemic and increasing fluid and blood volume is a useful target for ameliorating POTS symptoms (Fouad et al., 1986; Jacob et al., 1997; Raj et al., 2005). While blood volume is not often measured in POTS patients clinically, the plasma volume is lower than normal in most patients (Raj and Robertson, 2007). There are several ways to attempt to increase blood volume, although this can be a difficult task. The most common ways to do so in POTS are discussed below.

3.2.1. Salt supplementation

The Heart Rhythm Society Expert Consensus Statement recommends that POTS patients consume 10–12 g of sodium daily (Sheldon et al., 2015). For patients who have trouble increasing sodium through diet alone, salt supplements are available. Salt supplements can be added to reach the recommended amount, the dose should be varied based on how much sodium the patient consumes in food. Many NaCl supplements are available over the counter and marketed for athletes. Salt supplements should be taken in 250–1000 mg doses. Higher doses are often poorly tolerated and can cause GI discomfort. Taking this with food may minimize gastrointestinal upset. Buffered tablets or capsules may be better tolerated.

3.2.2. Fludrocortisone

Fludrocortisone is a synthetic form of aldosterone that is used to increase plasma volume in POTS. Some patients with POTS have been found to have low levels of aldosterone (Raj et al., 2005). Fludrocortisone is a glucocorticoid that has been modified to increase its affinity for the mineralocorticoid receptor compared to the glucocorticoid receptor. At low doses (up to 0.2 mg/day), it does not seem to cause suppression of the hypothalamic-pituitary axis. The main action

Table 1
Pharmacological treatments for postural tachycardia syndrome.

Drug	Dosing information	Side effects	Precautions
Blood volume expanders			
Salt supplementation	1 g orally 3 to 5 times daily with food.	Gastrointestinal upset, hypertension, edema	
Fludrocortisone	0.1 to 0.2 mg daily	Hypokalemia, edema, headache	Electrolytes should be monitored
Desmopressin (DDAVP)	0.1 to 0.2 mg as needed	Hyponatremia, edema	Electrolytes should be monitored if used chronically
Acute IV saline	2 L Intravenous over 2–3 h	Venous thrombosis, infection	
Chronic IV saline	2 L given intravenously once weekly	Infection risk of central venous catheters	Avoid long-term use and placement of central catheters
Erythropoietin	10,000 IU weekly	Increased risk of cardiovascular death	Hematocrit should be monitored
Heart rate inhibitors			
Propranolol	10–20 mg orally up to 4 times daily	Hypotension, bradycardia, bronchospasm	Can worsen asthma
Ivabradine	2.5–7.5 mg orally twice daily	Headaches, palpitations, hypertension, visual disturbances	
Pyridostigmine	30 - 60 mg orally up to 3 times daily	Increased gastric motility	Can worsen asthma
Vasoconstrictors			
Midodrine	2.5–15 mg orally 3 times daily	Headache, scalp tingling, supine hypertension	
Octreotide	Long-acting intramuscular injection 10–30 mg	Nausea, stomach cramps, diarrhea	
Methylphenidate	10 mg orally 2–3 times a day. Last dose should be avoided before bed.	Tachycardia, insomnia, nausea, headache, dizziness	
Droxidopa	100–600 mg 3 times daily	Headache, nausea, hypertension, and tachycardia	
Sympatholytic drugs			
Clonidine	0.1–0.2 mg orally 2–3 times daily or long acting patch	Hypotension, fatigue, brain fog	
Methyldopa	125–250 mg orally twice daily	Hypotension, fatigue, brain fog	
Other			
Modafinil	50–200 mg orally 1–2 times daily	Tachycardia	
Oral rehydration salts	1–2 L daily or less as needed	Hypernatremia, hyperkalemia, vomiting	

of fludrocortisone is on the Na^+/K^+ transporter in the kidney where it enhances reabsorption of sodium ions from the tubular fluid into the plasma, and increases the urinary excretion of potassium and hydrogen ions. This leads to increased sodium retention and increase in plasma volume. Fludrocortisone may also sensitize the alpha-adrenergic receptor, further helping to support blood pressure. One must be careful to watch for hypokalemia since fludrocortisone increases potassium excretion at the expense of sodium preservation. We recommend checking the serum potassium levels 1 week after any dose change (to allow the drug to reach steady-state) and every 3 to 4 months at a stable dose. If the potassium level is low, patients should be advised to increase intake of potassium-rich foods and to possibly take potassium supplements.

Since fludrocortisone promotes fluid retention, if it is effective, it should acutely cause a small weight gain (from the fluids) although some patients have significant weight gain while taking fludrocortisone. Fludrocortisone can worsen migraine headaches in some patients who are predisposed to migraines. It could also cause hirsutism and acne, although we have not often seen these adverse effects. Fludrocortisone is prescribed for POTS as 0.1 to 0.2 mg daily. The dose can be taken all at once or in divided doses. Given the long effective half-life of the medication, the dosing interval does not much matter (unlike most other medications used to treat POTS).

A small non-blinded study in pediatric patients with orthostatic intolerance found that fludrocortisone improved nausea in half of patients (Fortunato et al., 2011). Otherwise, it has not been studied properly in a POTS population. A placebo-controlled randomized trial of fludrocortisone in patients with neurally-mediated hypotension and chronic fatigue syndrome showed that fludrocortisone was ineffective at improving symptoms or orthostatic hemodynamics compared to placebo (Rowe et al., 2001). More recently, fludrocortisone was studied in patients with recurrent vasovagal syncope (but not POTS) in a double blind, placebo-controlled randomized trial. The primary intention to treat analysis did not quite achieve statistical significance, but analyses done with all patients after dose titration and of patients that reached the target dose of 0.2 mg/day (after a forced titration) did significantly benefit (Sheldon et al., 2016). Fludrocortisone was given a Class 2B recommendation for use in POTS in the Heart Rhythm Society 2015 Expert Consensus Statement that addressed POTS (Sheldon et al., 2015).

3.2.3. Desmopressin

The anti-diuretic desmopressin (DDAVP) is commonly used for diabetes insipidus and bedwetting in children. DDAVP is an antidiuretic hormone that limits the amount of water that is eliminated in the urine, and promotes free water retention. It binds to V2 receptors in the renal collecting duct, which signal for the translocation of aquaporin channels to the distal nephron increasing water reabsorption from the urine. DDAVP can also be used to increase fluid retention in POTS patients. One study found that an acute 0.2 mg dose of DDAVP compared to placebo attenuates orthostatic tachycardia and improves symptoms in POTS (Coffin et al., 2012). A retrospective analysis found that treatment with DDAVP for one year improved symptoms and decreased orthostatic tachycardia in half of the patients who tolerated the drug (Coffin et al., 2012). DDAVP can be used as a "special event drug" to help expand the blood volume before a specific event that the patient really wishes not to miss. Alternatively, it can be used at a low dose on a daily basis. DDAVP should be used with caution in POTS patients; since they are told to drink copious amounts of water, they are at increased risk for developing hyponatremia (Raj, 2013), which can be life threatening. In addition to hyponatremia, other side effects of DDAVP include edema and headache. DDAVP can be prescribed as 0.1 to 0.2 mg daily for POTS (Coffin et al., 2012). Electrolyte levels (especially the blood sodium levels) must be monitored to ensure patient safety. Patients taking DDAVP should also take salt supplements to decrease the risk of hyponatremia.

3.2.4. Intravenous saline - acute

Intravenous saline can increase blood volume in POTS. Several studies have shown that an acute infusion of intravenous saline decreases orthostatic symptoms in POTS acutely and for several hours to two days following infusion (Figueroa et al., 2014; Gordon et al., 2000; Jacob et al., 1997). We often recommend that this be used during an acute clinical decompensation. For example, when a patient feels poorly enough to go to the emergency department we advocate a trial infusion of 2 L of normal saline before making a decision about hospital admission. Often the saline can effect enough clinical improvement to allow the patient to be safely discharged home. These experiences further emphasize the important role of blood volume deficits in many patients with POTS.

3.2.5. Intravenous saline - chronic

The regular and chronic use of intravenous saline infusions for POTS is very controversial. Two retrospective case-series have recently reported that chronic administration of intravenous saline in POTS patient improves symptoms in patients whose POTS was refractory to several other treatments (Moak et al., 2016; Ruzieh et al., 2017). Moak et al. reported on a pediatric population. Their patients received 1–2 L of saline every 3 to 7 days (Moak et al., 2016). Of concern, there was a very high rate of upper extremity deep venous thrombosis, bacteremia and systemic infections, presumably as a result of the central venous catheter that was required. Ruzieh et al. reported their experience with an adult cohort who was treated with intravenous infusion of 1–2 L of saline every 1 to 4 weeks (Ruzieh et al., 2017). Of note, almost 75% of their patients received their saline ONLY through a peripheral intravenous catheter. Of the 50 (out of 57 patients) who weaned from the intravenous saline therapy, all had done so in < 6 months and 44% had weaned in < 3 months. These data suggest that short-term intravenous saline delivered through a peripheral intravenous catheter might be safe, as the majority of the risks relate the central line insertions and access. The challenge is to avoid the "slippery slope" leading to long-term saline infusions. Currently, the Heart Rhythm Society Expert Consensus Statement recommends occasional acute intravenous saline therapy to prevent hospitalization (Class 2B recommendation), but discourages the chronic use of intravenous fluids because this usually requires a central venous catheter, which carries the risk of infection and blood clots (Class 3 recommendation) (Sheldon et al., 2015). The pediatric writing group of the American Autonomic Society strongly discourages the chronic use of intravenous fluids in adolescents (Stewart et al., 2018).

3.2.6. Oral rehydration salts

Oral rehydration salts (ORS) is a therapy used to prevent and treat dehydration. ORS is a powder mixture of sodium, potassium, and glucose that is meant to be mixed with 1 L of water to create a low osmolality solution that optimizes sodium absorption by the small intestines. One pilot study found that ORS was similar to IV saline at increasing orthostatic tolerance in POTS (Medow et al., 2012). In this study, ingesting 1 L of ORS increased the time patients were able to tolerate lower-body negative pressure and improved blood pressure and cardiac output responses to this orthostatic stress (Medow et al., 2012). Since 1 L of ORS is equivalent to 1 L of IV saline, optimal dosing is 1–2 L of ORS daily or less on an as needed basis. The main side effects of ORS are hypernatremia, hyperkalemia, and vomiting. Some patients are deterred by the salty taste of ORS and should be reminded that the solution is a medication not a beverage.

3.2.7. Erythropoietin

Erythropoietin (EPO) therapy can be used to increase blood volume in POTS by increasing erythropoiesis. EPO has been given in POTS intravenously 10,000–20,000 IU per week and 50 IU/kg 2 to 3 times a week (Hoeldtke et al., 1995; Kanjwal et al., 2012). EPO can also be injected subcutaneously. It is important to realize that EPO has serious

side effects including increased risk of myocardial infarction, stroke, and venous thromboembolism. Hemoglobin and hematocrit levels should be monitored every 3–4 weeks to ensure that hematocrit remains < 50% (Kanjwal et al., 2012). There have been two studies that examined the effects of EPO in POTS. One small prospective study found that EPO did not improve orthostatic tachycardia but improved orthostatic symptoms in 3/8 subjects (Hoeldtke et al., 1995). The other was a retrospective analysis that showed improved orthostatic symptoms in the 24/39 patients who took EPO after other treatments failed (Kanjwal et al., 2012). There is a rationale for its use in POTS patients who are hypovolemic and refractory to other treatments. However, safety concerns and drug insurance coverage can limit its use.

3.3. Drugs to lower heart rate

One of the cardinal hemodynamic features of POTS is tachycardia, and this often drives symptoms such as palpitation, lightheadedness, and dyspnea. Therefore, the tachycardia can seem like an ideal treatment target. However, the tachycardia is often secondary to other hemodynamics problems, including a low cardiac stroke volume, with the tachycardia needed to maintain cardiac output. However, the "compensatory tachycardia" may sometimes be excessive, and contribute directly to the patient's symptoms. Therefore, many treatments do attempt to directly decrease HR in POTS. However, "normalizing" HR in POTS or excessively decreasing HR can worsen symptoms in patients with POTS. The goal is to "take the edge off" of the increased upright HR in POTS. This usually means treating POTS patients with smaller doses than are often used for other cardiovascular diseases.

3.3.1. β-Blockers

β-Blockers (or β adrenergic receptor antagonists) are commonly used to decrease the HR in patients with POTS. Most research on β-blockers in POTS have investigated the effects of the non-selective β adrenergic receptor antagonist propranolol (Arnold et al., 2013; Fu et al., 2011; Raj et al., 2009). These studies have found that low doses of propranolol (20 mg per dose) are better tolerated in POTS than higher doses are (Raj et al., 2009). Low dose oral propranolol improves tachycardia, symptoms, and exercise capacity in POTS (Arnold et al., 2013; Raj et al., 2009). β-Blockers may also improve headaches but that has not been extensively studied in POTS. Long-acting propranolol does not improve quality of life in POTS (Fu et al., 2011). Short-acting propranolol has a fairly short half-life, with each pill working for 4–5 h before the effects noticeably "wear-off", meaning that full day dosing requires taking this 4 times per day. The Heart Rhythm Society Expert Consensus made propranolol 10 to 20 mg (short acting) in patients with POTS as a Class 2B recommendation (Sheldon et al., 2015). β-Blockers should be used very cautiously in POTS patients with a history of asthma, since the β2-blockade can induce bronchoconstriction.

Propranolol is different than many other β-blockers. It is lipophilic and crosses the blood-brain barrier more than most other β-blockers, which may be important to its beneficial effects but also potential neurocognitive side effects. It is a non-selective β adrenergic receptor antagonist, with blockade of both β1- and β2-adrenergic receptors. β2-adrenergic receptor blockade leads to peripheral vasoconstriction, which might promote a "midodrine-like" effect, with a secondary reflex lowering of HR. Propranolol (often at higher doses) is also used as a migraine prophylaxis medication, so there is sometimes a "dual-benefit" from using propranolol.

Very few studies have investigated the effects of cardio-selective β1 blockers in POTS and no known studies have compared them to propranolol. One study found that 6-week treatment with bisoprolol 5 mg daily improved symptoms in a small sample of 11 POTS patients (Freitas et al., 2000). Another study found selective β1 blockade with intravenous esmolol did not affect supine or orthostatic hemodynamics in POTS (Stewart et al., 2002).

3.3.2. Ivabradine

Ivabradine reduces heart rate by blocking the I_f, or funny channel, which modulates the intrinsic pacemaker rate of the sinus node. While beta-blockers also modulate the sinus node firing rate, beta-blockers do many other things, including potentially worsening asthma, causing nightmares, and depressing cardiac function. In theory, ivabradine might control the heart rate in POTS patients with less fatigue than beta-blockers. However, this has not been shown in randomized or blinded studies. Ivabradine is increasing in popularity as a POTS therapy since its approval by the FDA in 2015 for the treatment of heart failure. It is also used off-label to treat inappropriate sinus tachycardia. Ivabradine is a theoretically desirable treatment for POTS because of its specific effects on lowering HR without affecting BP. Three studies have evaluated the effects of ivabradine in POTS (Delle Donne et al., 2018; McDonald et al., 2011; Ruzieh et al., 2017). In these studies, ivabradine was generally well tolerated and decreased resting and orthostatic HR in most POTS patients without altering blood pressure (Delle Donne et al., 2018; McDonald et al., 2011; Ruzieh et al., 2017). However, these studies were small and retrospective analyses. There is a small, randomized controlled trial of ivabradine in POTS currently in progress (https://clinicaltrials.gov/show/NCT03182725). Ivabradine has been shown to improve symptoms in patients with inappropriate sinus tachycardia (Cappato et al., 2012). Long-term studies of ivabradine in inappropriate sinus tachycardia suggest that ivabradine decreases HR and improves quality of life over time in these patients (Benezet-Mazuecos et al., 2013).

Ivabradine is dispensed in 2.5 to 7.5 mg pills and given orally twice daily. The typical starting dose is 5 mg twice daily. Side effects are relatively uncommon with ivabradine, but can include headaches, palpitations, hypertension, and visual disturbances. Ivabradine may be an option for POTS patients in which β-blockers are not well tolerated. Since there is a paucity of evidence to support use of this relatively new drug in POTS, there may be issues with drug insurance coverage at this time.

3.3.3. Pyridostigmine

Pyridostigmine is an acetylcholinesterase inhibitor that slows the breakdown of the neurotransmitter acetylcholine in the synaptic cleft. This increases the amount of acetylcholine that can bind to nicotinic receptors in the autonomic ganglia and muscarinic receptors in the heart to decrease HR (Raj et al., 2005). Pyridostigmine can also increase colonic motility, which typically limits tolerability in patients who are prone to diarrhea. However, in patients with early satiety, gastroparesis, or constipation this can be a desirable side effect and improve abdominal pain and nausea (Stewart et al., 2018). Pyridostigmine can also cause abdominal cramps, nausea, muscle twitching, headaches, and shortness of breath and should be used with caution in patients with asthma. Pyridostigmine is taken orally in 30 or 60 mg doses up to three times daily. Patients usually start with 30 mg TID, and increase to 60 mg TID, if tolerated and needed (Kanjwal et al., 2011). Pyridostigmine has been evaluated in POTS in a single dose randomized crossover study (Raj et al., 2005), and in one long-term retrospective study (Kanjwal et al., 2011). Both these studies found that pyridostigmine decreased orthostatic HR and improved symptoms in POTS (Kanjwal et al., 2011; Raj et al., 2005). The drug was generally well tolerated in both studies.

3.4. Vasoconstrictor drugs

3.4.1. Midodrine

Midodrine is a prodrug that is metabolized into a peripheral α-1 receptor agonist. Midodrine is a potent vasoconstrictor and venoconstrictor. Midodrine increases blood pressure but also increases venous return, cardiac preload, and stroke volume. Midodrine has a rapid onset and is short acting, working for about 4 h after each dose. The Heart Rhythm Society Expert Consensus states that the optimal dosing for

midodrine is 5 to 15 mg, every 4 h × 3 times daily (Sheldon et al., 2015). Nominal dosing times are 8 am, 12 pm, 4 pm; patients should be discouraged from lying down for 4–5 h after taking a dose to prevent supine hypertension (Sheldon et al., 2015). Treatment with midodrine should be initiated at a low dose (2.5–5 mg per dose) and increased in 2.5 or 5 mg increments up to 15 mg as needed for symptomatic improvement and as tolerated. Given the short half-life of the drug, the total daily dose is less important than the dose taken at each time. Midodrine is generally well tolerated but can commonly cause mild and transient side effects such as goose bumps, piloerection, and tingling of the scalp. Less commonly midodrine can cause worsening of headaches and hypertension. Studies have shown that midodrine increases orthostatic blood pressure and decreases orthostatic HR and venous pooling in POTS (Jacob et al., 1997; Ross et al., 2014). One study suggests that midodrine may be more efficacious in neuropathic POTS patients with poor venous constriction (Ross et al., 2014).

3.4.2. Octreotide

Octreotide is a peptide that mimics somatostatin and induces splanchnic vasoconstriction. Octreotide can be administered intravenously or as a subcutaneous or intramuscular injection. A small study with 9 POTS patients found that a single dose of octreotide (0.9 μg/kg subcutaneous injection) decreased orthostatic HR and increased standing time in POTS (Hoeldtke et al., 2006). Treatment with long-acting intramuscular injection 10–30 mg also decreased orthostatic HR, dizziness, and chronic fatigue in POTS (Hoeldtke et al., 2007). Neither of these studies were placebo controlled. A small, retrospective analysis of 5 patients with refractory orthostatic intolerance taking octreotide (50–100 μg 3 times daily) revealed that octreotide decreased orthostatic HR and improved symptoms in POTS patients (Kanjwal et al., 2012b). Octreotide has several potential side effects including pain at injection site, abdominal cramps, diarrhea, nausea, dizziness, bradycardia, shortness of breath, and depression. Given that it is a peptide that requires parenteral injections, it can be more difficult to use than many pills. Octreotide should be considered in patients who have suspected splanchnic pooling and do not respond to other vasopressors.

3.4.3. Droxidopa

Droxidopa is a prodrug that can be taken up by sympathetic neurons and converted to norepinephrine, which can then bind to α-1 adrenergic receptors and increase vasoconstriction and blood pressure (Ross and Stewart, 2015). However, droxidopa may increase tachycardia as well since it can be converted to epinephrine and activate β-adrenergic receptors. Droxidopa has been FDA approved for the treatment of neurogenic orthostatic hypotension due to Parkinson's, multiple system atrophy, pure autonomic failure or non-diabetic autonomic neuropathy. Droxidopa is taken orally 100–600 mg 3 times daily. Common side effects are headache, nausea, hypertension, and tachycardia. Droxidopa has been shown to improve symptoms in patients with neurogenic orthostatic hypotension in multi-center randomized controlled trials (Biaggioni et al., 2015; Kaufmann et al., 2014), but has not been tested as extensively in POTS. The one published clinical experience with droxidopa in POTS found that it did not significantly affect BP, HR, or quality of life but did improve orthostatic symptoms in some patients (Ruzieh et al., 2017). This study was open-label and retrospective. This drug might be useful, particularly in POTS patients with low to normal plasma norepinephrine levels or non-diabetic autonomic neuropathies. Droxidopa is currently being assessed in a small trial of patients with POTS (https://www.clinicaltrials.gov/NCT02558972).

3.4.4. Stimulants

Stimulant medications may be useful for treating POTS for their combined effects on blood pressure and cognition. While they are central nervous system stimulants, these drugs also increase sympathetic nerve traffic and synaptic norepinephrine. The result is that they are α1 adrenergic receptor agonists and have potent effects on peripheral vasoconstriction, and β1-adrenergic receptor agonists and promote sinus tachycardia. There are few studies that have evaluated these drugs in POTS. Randomized controlled trials have found many to be effective in treating chronic fatigue syndrome (Blockmans and Persoons, 2016; Olson et al., 2003; Young, 2013) and in preventing recurrent syncope (Grubb et al., 1996; Susmano et al., 1993). Methylphenidate (10 mg 3 times daily) has been shown to improve symptoms of fatigue and pre-syncope in (14/17) patients with refractory POTS (Kanjwal et al., 2012c). Other stimulant medications have not been studied in POTS. The increase in tachycardia with these medications may limit their tolerability in POTS. Although stimulants can increase tachycardia, a recent placebo-controlled trial found that modafinil increased orthostatic BP did not significantly worsen standing HR or acute orthostatic symptoms in POTS patients (Kpaeyeh Jr et al., 2014). A clinical trial is in progress to assess the effects of an acute dose of modafinil on cognitive function in POTS (https://clinicaltrials.gov/ct2/show/NCT01988883). Anecdotally, some patients have responded to favorably to modafinil 100–200 mg twice daily, although proper study data are still pending. Modafinil should be avoided in the evening or at bedtime to prevent insomnia. The use of these drugs long term especially in younger patients is controversial because of addictive properties.

3.5. Sympatholytic drugs

Central sympatholytic drugs can be useful in patients with increased sympathetic activity or hyperadrenergic POTS (Sheldon et al., 2015). Clonidine is an α-2 adrenergic receptor agonist that can decrease sympathetic nerve traffic centrally, and norepinephrine release from peripheral sympathetic neurons. The net effect is to decreasing sympathetic overactivity. Clonidine can be taken as 0.1 to 0.2 mg 2 to 3 times daily or as a long acting transdermal patch. One study found that long-term treatment with clonidine decreased catecholamine levels and symptoms in POTS patients who did not respond to β-blockers (Gaffney et al., 1983). The main challenge to clonidine is tolerability, as it is a central nervous system depressant. It can cause profound fatigue. The short-acting tablets can lead to on/off phenomenon with surges and then troughs in sympathetic nerve traffic, with matching symptoms.

Methyldopa likely has 2 synergistic mechanisms of action. First, it inhibits the enzyme DOPA decarboxylase to inhibit conversion of L-DOPA to dopamine, which is a precursor of norepinephrine and epinephrine. Second, methyldopa gets converted to alpha-methyl-norepinephrine, which can inhibit central alpha-2 receptors (like clonidine) and decrease central sympathetic nervous system traffic. The net effect of both actions is to blunt central sympathetic tone. One advantage of methyldopa over clonidine is that it has a longer half-life, and so does not have the peaks & troughs of actions that can be seen with clonidine. We start methyldopa at a dose of 125 mg just a bedtime. If it is tolerated, we will then increase it to 125 mg twice daily, and up to 250 mg twice daily. We have never gotten a POTS patient beyond this dose. Both clonidine and methyldopa can worsen fatigue and brain fog but may be useful in patients with particularly high sympathetic nervous system activity who have not responded well to other treatments.

3.6. Initial approach to pharmacological therapy

There is not a “correct” approach to initiating non-pharmacological therapy in patients with POTS. Patient presentations can vary tremendously, and the pharmacological approach to symptomatic improvement has to be individualized. Our approach to initial treatment is outlined below:

1. In the initial visit, we will institute a myriad of non-pharmacological approaches. Unless the patient's presentation is quite severe, we may

hold off on pharmacological approaches at this time to see the effects of the non-pharmacological approaches.
2. If the HR on standing is very high (> 130 bpm) and/or palpitation are a prominent symptom, we will prescribe propranolol 20 mg PO QID (or QID PRN) to take the edge off of the HR increases.
3. If there is a strong suspicion of a neuropathic pattern, then we will prescribe midodrine 5 mg PO Q4H ×3, with nominal dosing times of 8 am, noon, and 4 pm. This suspicion for inadequate vasoconstriction or venoconstriction can manifest in different ways. For example, during the head-up tilt test with continuous blood pressure monitoring, one can often get estimates of vascular resistance. If vascular resistance is quite low and seems to be driving the tachycardia, we will be more likely to use midodrine. If a patient reports that they are often relatively asymptomatic when walking, but get quite symptomatic when standing still, this suggests that enhancing venous return with midodrine-induced venoconstriction might be useful. Finally, if the HR is not high on standing (100–110 bpm), and prominent symptoms include lightheadedness but not palpitation, then we will preferentially use midodrine over propranolol.
4. If the patient does not report significant diarrhea, or if the patient has a tendency to constipation, then we will prescribe pyridostigmine at a starting dose of 30 mg PO TID.

Further augmentation of medication will often be necessary. These medications can often be used in combination with each other due to distinct pharmacological mechanisms of action. Treating more refractory cases of POTS does not have an algorithm but suggested treatment approach is displayed in Table 2. A suggest approach to treat POTS by targeting symptoms is shown in Fig. 1.

4. Targeting specific symptoms when treating POTS with pharmacotherapy

4.1. Treating brain fog and fatigue

"Brain fog" is defined by POTS patients as forgetfulness, difficulty thinking and focusing, and mental cloudiness or fatigue and is one of the most debilitating POTS symptoms (Ross et al., 2013). For a more detailed discussion cognitive issues in POTS, please refer to the article entitled "Cognitive and Psychological Issues in Postural Tachycardia Syndrome" in this special POTS Issue of *Autonomic Neuroscience* (Arnold, 2018). Often treating other POTS symptoms such as tachycardia and lightheadedness also improves brain fog. A few treatments can be used specifically to target brain fog. Intravenous saline is reported by patients to be a very successful treatment for brain fog (Ross et al., 2013). Other patient-reported successful treatments for brain fog include stimulant medications (amphetamine-based and modafinil), salt tablets, and vitamin B_{12} injections (Ross et al., 2013), although none have been studied specifically to see if they do improve cognitive function.

4.2. Treating depressed mood in POTS

Although POTS patients do not have a higher risk of major depression than the general population, some patients develop depressed mood secondary to having a chronic illness (Raj et al., 2009). Selective serotonin reuptake inhibitors (SSRIs) have a mild vasoconstrictor effect however, they are mostly used in POTS for the psychotropic effects. No studies to date have assessed the effectiveness in of SSRIs in POTS. Tricyclic antidepressants, such as amitriptyline and nortriptyline, should be used with caution in POTS since they can increase drowsiness and cognitive impairment.

Conversely, selective norepinephrine reuptake inhibitors (SNRIs) are not recommended for POTS. SNRIs have been suggested as a potential treatment for POTS because they can also increase blood pressure by increasing plasma levels of norepinephrine (the "N" in "SNRI"). Several SNRI drugs, such as duloxetine and venlafaxine, have been advocated for the treatment of neuropathic pain in related disorders such as fibromyalgia (Hauser et al., 2013). However, there have been very few trials of this drug in POTS. One randomized, placebo-controlled trial found that an acute 40 mg oral dose of the SNRI atomoxetine increased orthostatic tachycardia and worsened symptoms in POTS patients (Green et al., 2013). SNRIs also have numerous side effects including nausea, dry mouth, dizziness, headache, fatigue, and insomnia. The HRS Expert Consensus Statement made this a class 3 recommendation, meaning that in most case SNRIs should be avoided in POTS (Sheldon et al., 2015). The topic of depression in POTS is discussed more in detail in the article in this issue on "Cognitive and Psychological Issues in Postural Tachycardia Syndrome."(Arnold, 2018)

4.3. Treating sleep in POTS

POTS patients have low sleep quality which is associated with low quality of life (Bagai et al., 2011). POTS patients also have objective sleep deficits and lower heart rate variability during sleep suggesting lower parasympathetic tone and enhanced sympathetic tone (Mallien et al., 2014). The primary sleep problem seems to be insomnia – both sleep onset and sleep maintenance insomnia, and not other problems such as sleep apnea (Bagai et al., 2016; Miglis et al., 2016; Pengo et al., 2015).

No published studies have assessed the effects of pharmacological treatments on sleep in POTS. One study found that an acute oral dose of melatonin decreases HR while standing in POTS compared to placebo (Green et al., 2014) Melatonin also decreases the sympathetic response to orthostatic stress in healthy humans (Ray, 2003). Whether melatonin improves sleep or daytime symptoms in POTS remains unknown. However, melatonin supplementation may be particularly useful in POTS patients taking B-blockers since patients taking B-blockers can lower melatonin (Fares, 2011). Further work is needed to address the best methods (both non-pharmacological and pharmacological) to improve sleep quality in POTS patients.

4.4. Treating POTS patients with mast cell activation

A significant minority of patients with POTS may present with systemic flushing associated with their tachycardia or with allergic features (such as dermatographism) that are associated with their orthostatic symptoms, which may be a sign of mast cell disorders. Mast cell disorders are extremely difficult to diagnose. If these symptoms are present and limiting quality of life, then treatments such as anti-histamines, mast cell stabilizers, and non-steroidal anti-inflammatory drugs may help not only the allergic symptoms but also other POTS symptoms. When the flushing is associated with orthostatic hypertension in addition to tachycardia, central sympatholytic drugs may be helpful

Table 2
Suggested approach to pharmacological treatment for POTS.

	Blood volume expanders	Heart rate inhibitors	Vasoconstrictors	Sympatholytic drugs
Initial approach	Salt supplements, fludrocortisone	Low dose β-blockers, pyridostigmine	Midodrine	
Secondary approach	Acute IV saline, desmopressin, oral rehydration salts	Ivabradine	Stimulants, octreotide	Methyldopa, clonidine
Only use in refractory cases	Chronic IV saline, erythropoietin		Droxidopa	

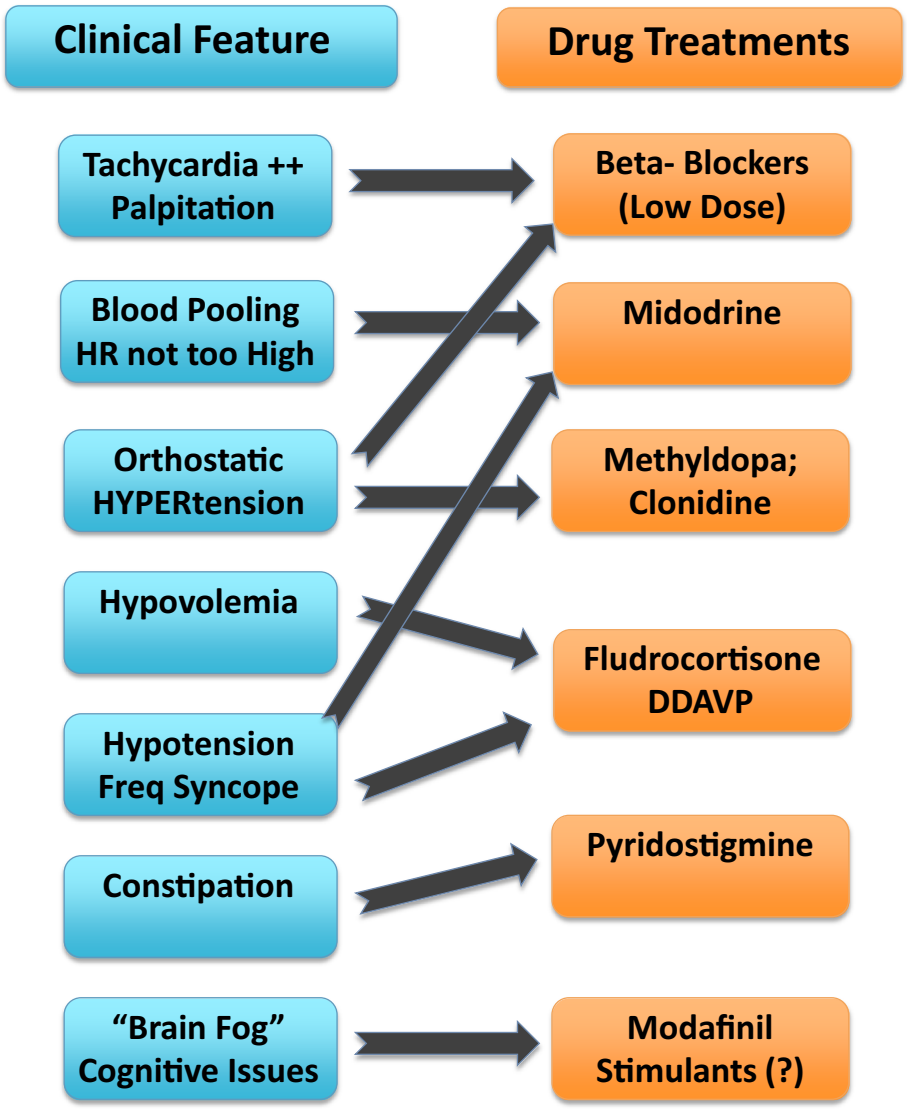

Fig. 1. A suggested approach to targeted POTS treatment. Individualizing POTS treatment by targeting clinical features or symptoms can help aid in symptomatic improvement and minimize side effects. For more information on treating specific symptoms including cognitive impairment, headache, chronic pain, and gastrointestinal issues please refer to other articles in this Special Issue on Postural Tachycardia Syndrome in *Autonomic Neurosciences.*

(Shibao et al., 2005). These issues are explored more thoroughly in the article entitled "Mast Cell Disorders and Postural Orthostatic Tachycardia Syndrome" elsewhere in this POTS Issue of *Autonomic Neuroscience* (Doherty and Mast, 2018).

4.5. Treating POTS patients with autoimmunity

Some refractory cases of POTS are due to underlying illness driving the symptoms. If these are not addressed than POTS symptoms may continue or worsen despite standard therapy. Some patients develop POTS secondary to an autoimmune disorder such Guillian Barré syndrome, Sjögren's syndrome, celiac disease, or systemic lupus erythematosus. While a detailed discussion of the investigation and treatment of these disorders is beyond the scope of this review, other articles in this special POTS Issue of *Autonomic Neurosciences* address the advanced evaluation of POTS (Goodman, 2018) and Autoimmunity in POTS (Vernino, 2018).

5. Future directions

5.1. Treating POTS as an autoimmune disorder

Growing evidence is emerging to suggest that in some patients, their POTS may have an autoimmune basis. Antibodies to the alpha-1, beta-1, and beta-2 adrenergic receptors have been detected in POTS which may explain insufficient vasoconstriction and tachycardia (Li et al., 2014). Antibodies to M1 and M2 muscarinic acetylcholine receptors are also present in a significant proportion of POTS patients tested and may contribute to tachycardia among other symptoms (Vernino et al., 2000). Similar antibodies have also been identified in patients with chronic fatigue syndrome which overlaps with the POTS patient population (Loebel et al., 2016). The origin of these antibodies still remains elusive. If POTS indeed has an autoimmune basis, this could significantly alter treatment strategies. Intravenous immunoglobulin (IVIG), plasmapheresis/plasma exchange and other immunotherapy drugs may become potential treatments to clear these antibodies. These treatments all carry severe risks including infection, aseptic meningitis, thrombosis, nausea, hypotension and death. There have been no prospective trials of these treatments in POTS to date. IVIG and

plasmapheresis are expensive, and are typically only covered by insurance for POTS patients who have a separately diagnosed autoimmune disorder.

5.2. Precision medicine in POTS

Given the increase in phenotyping POTS patients by antibodies, pathophysiology, and etiology of POTS there is an opportunity to assess treatments based on certain clinical characteristics of POTS patients. An overview of how to target POTS treatment based on phenotypes and symptoms is shown in Fig. 1. For example, it is possible that patients with antibodies to adrenergic receptors will have blunted responses to midodrine and β-blockers and patients with muscarinic receptor antibodies will have a more favorable response to pyridostigmine. It is also plausible that response to testing (such as norepinephrine levels or cholinergic sweat testing or leg blood flow assessments) will identify sub-groups of POTS patients who would respond differently to specific treatments. This is the holy grail of creating "POTS endophenotypes" within the larger clusters of patients diagnosed with POTS. To date, few trials have taken this approach.

5.3. Evidence-based medicine for POTS

Most treatments for POTS have been tested in single-center studies, and in small groups of patients. Some treatments have only been evaluated in retrospective case series or not at all. As the field of POTS management continues to evolve, there is a need for multi-center, blinded, placebo-controlled trials of pharmacotherapy options in POTS patients. This will allow for larger studies and potentially decrease the referral bias that is inherent to many of the current studies that buttress the evidence-base.

6. Conclusions

There are several pharmacological treatment approaches for POTS to improve symptoms. The most common treatments for POTS target increasing blood volume or vasoconstriction or decreasing heart rate or sympathetic tone. Each treatment approach has varying levels of evidence, side effects, and risks. There have been few multi-center, blinded, placebo-controlled trials in POTS and more are needed to evaluate common treatments more rigorously. Further research is needed to better elucidate the pathophysiology of POTS to identify new treatment targets and determine which patients will benefit most from each treatment.

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