Bristol, North Somerset and South Gloucestershire Clinical Commissioning Group

Use of Beta-Blockers in Postural Tachycardia Syndrome (PoTS)

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Introduction

This briefing is a follow-up on another detailing a search on Postural Tachycardia Syndrome (PoTS) in Long COVID, which should be read in conjunction with this one. Please find the document embedded below.

PoTS is an abnormal increase in heart rate that occurs on sitting up or standing, and symptoms include dizziness, fainting, palpitations, chest pain and shortness of breath, among others (NHS, 2019). A search has been requested to identify evidence on beta-blocker use in the management of PoTS, as no medications are currently licensed for this purpose.

Beta-adrenoceptor blocking drugs (also known as beta-blockers) block the release of the stress hormones adrenaline and nor-adrenaline from beta-adrenoreceptors in the heart, peripheral vascular system, bronchi, pancreas, and liver (British National Formulary (BNF), 2022). Selective beta-blockers, such as atenolol and bisoprolol, selectively target cardiac beta-adrenoreceptors. Conversely, non-selective beta-blockers, such as propranolol, have a more systemic effect (British Heart Foundation (BHF), 2022).

The aim of this briefing is to provide an outline of key findings and recommendations of, as well as signposting to, appropriate literature, in addressing the following question:

1. What evidence is available regarding the use of beta-blockers in the pharmacological management of PoTS?

Points to note

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

Key Points

- Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance (Raj *et* al., 2020) is a key piece of grey literature on this topic
- Raj *et al*. (2020) recommends propranolol as a first-line treatment for PoTS, where the predominant symptom is tachycardia
- Raj *et al*. (2020) suggests a regimen of 10-20mg orally four times per day, or as needed
- Raj *et* al. (2009) found evidence to suggest that low-dose oral propranolol significantly attenuated tachycardia and improved symptoms in PoTS, whereas high-dose propranolol did not further improve, and may worsen, symptoms
- Raj *et al.* (2020) state that a non-selective beta-blocker is preferred over selective ones because there is more evidence supporting their use

Findings

The literature returned by the search outlined in the Method section have been summarised here, in reverse chronological order. 5 papers were included.

Raj *et al*. (2020)

Raj *et al*. (2020) wrote the *Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance* in which they sought to provide an updated overview of the evidence base and a series of recommendations for the evaluation and treatment of PoTS.

They highlight that:

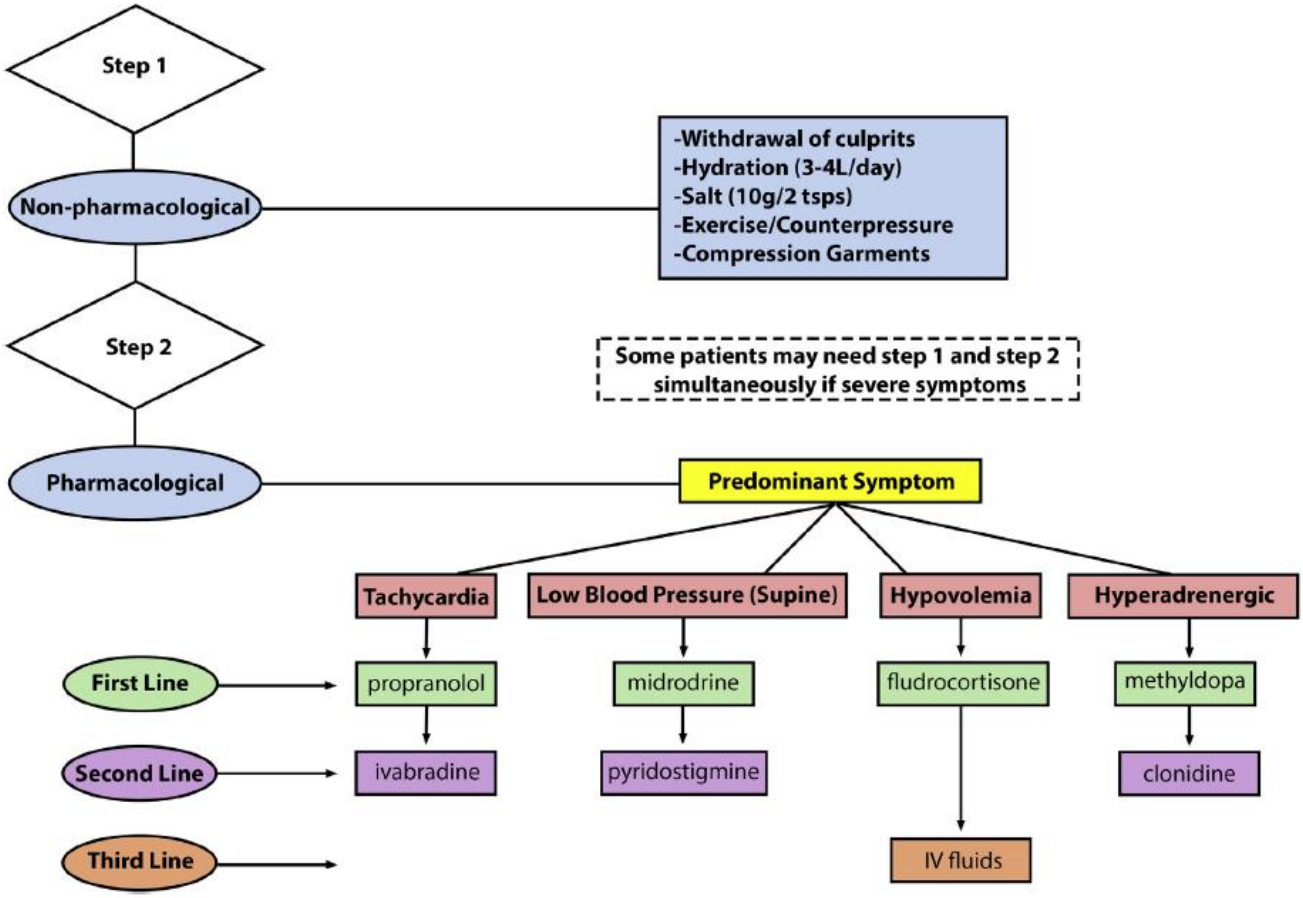
> "There have been no robust multicentre randomized controlled trials of treatment modalities and no single treatment has been shown to be effective in all patients" (Raj *et al*., 2020, p366).

Furthermore, as is the case in the UK, they note that, in Canada, no medication is currently licensed to be used in the management of PoTS.

They propose an approach to management, with first- and second-line therapeutics, which can be seen in the algorithm presented in Figure 1, overleaf. Propranolol is recommended as the first-line treatment, where the predominant symptom is tachycardia. This 'strong' recommendation was made based on moderate quality evidence, as assessed using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology[1]. They suggest a regimen of 10-20mg orally four times per day, or as needed. Additionally, they state that a non-selective is preferred over selective beta-blockers because there is more evidence supporting their use. Please see Table 1, overleaf for a summary of their treatment recommendations, and the strength of those recommendations. This recommendation was based on the findings of Fu *et al*. (2011) and Arnold *et al*. (2013) (both included below).

[1] For more information, please see What is GRADE? (Siemieniuk and Guyatt, no date)

Figure 1: Postural orthostatic tachycardia syndrome treatment algorithm: a suggested algorithm for patients with postural orthostatic tachycardia syndrome



(Raj *et al*., 2020, p366)

Table 1: Summary of treatment and management of POTS

Intervention	Strength of recommendation	Quality of evidence	Special dose range
Multidisciplinary Approach	Weak (suggest)	Low	
Nonpharmacological			
Withdraw exacerbating medications	Strong (recommend)	Low	
Salt and water PO	Strong (recommend)	Low-moderate	Water: 3 L/d; NaCl: 10 g/d
Lower body compression garments	Weak (suggest)	Low	Waist high; 20-30 mm Hg or 30-40 mm Hg compression
Exercise training	Strong (recommend)	Moderate	Every other day; ≥ 30-minute sessions; nonupright; focus on aerobic reconditioning
Pharmacologic (first-line)			
Midodrine	Strong (recommend)	Moderate	2.5-15 mg PO every 4 hours 2-3 times per day (eg, 8 AM, noon, 4 PM
Propranolol (nonselective β-blocker)	Strong (recommend)	Moderate	10-20 mg PO QID (PRN)
Pyridostigmine	Weak (suggest)	Low	30-60 mg PO TID
Fludrocortisone	Weak (suggest)	Low	0.1-0.3 mg PO daily
Ivabradine	Weak (suggest)	Low	2.5-7.5 mg PO BID
Methyldopa	Weak (suggest)	Low	125-250 mg QHS-BID
Clonidine	Weak (suggest)	Low	0.1-0.2 mg PO TID
I.V. NS bolus; occasional as rescue medication	Weak (suggest)	Low	1-2 L over 1-2 hours
I.V. NS; regular long-term use	Strong (against)	Low (harm)	
Devices			
Radiofrequency ablation of sinus node	Strong (against)	Very low (harm)	
Surgical decompression of Chiari malformation	Strong (against)	Very low (harm)	Unless there is another specific neurological indication
Balloon dilation of superior jugular vein	Strong (against)	Low (harm)	

BID, twice per day; I.V., intravenous; NS, normal saline; PO, orally; POTS, postural orthostatic tachycardia syndrome; PRN, as needed; QHS, every night at bedtime; QID, 4 times per day; TID, 3 times per day.

(Raj *et al*., 2020, p367)

Lei *et al*. (2019)

Lei *et al*. (2019) have written a review paper called *Evaluating and Managing Postural Tachycardia Syndrome* in which they provide an overview of PoTS, diagnosis, and treatment options. They note that pharmacological treatment should only be considered after a multi-pronged non-pharmacological approach has been attempted and failed to provide sufficient symptom control. Table 2, below, provides a summary of pharmacological treatments for PoTS

Table 2: Pharmacological Treatments for PoTS

Therapy	Dosage	Pathologic mechanism addressed	Potential drawbacks	Comments
Blood volume expanders				
Fludrocortisone	0.05–0.1 mg twice daily	Hypovolemia	Hypokalemia, hypertension, fatigue, headache, fluid retention, edema	
Desmopressin	0.1–0.2 mg 3 times daily	Hypovolemia	Hyponatremia, headache, edema	Only for occasional use; must monitor blood sodium
Erythropoietin	2,000–3,000 IU subcutaneously 1–3 times per week	Hypovolemia	High cost, requires injection, risk of vascular complications	Reserved for patients with symptoms refractory to more common treatments
Heart rate-lowering agents				
Propranolol	10–20 mg 3–4 times daily	All	Hypotension, fatigue, drowsiness, wheezing	Not well tolerated at higher dosages
Ivabradine	5–7.5 mg twice daily	All	Palpitations, headache, dizziness, constipation	
Central nervous system sympatholytics				
Clonidine	0.05–0.2 mg twice daily	Hyperadrenergic	Mental clouding, fatigue, drowsiness, constipation	Can be associated with rebound hypertension and tachycardia
Methyldopa	125 mg once or twice daily	Hyperadrenergic	Hypotension, fatigue, headache, drowsiness, constipation	Rare lupus-like syndrome reported
Other drugs				
Midodrine	5–15 mg every 4 hours, 3 times daily only	Neuropathic	Hypertension, goose bumps, urinary retention	Not recommended for use within 4-5 hours of sleep
Pyridostigmine	30–60 mg 3 times daily	All	Abdominal cramping, diarrhea, increased sweating	May increase gastrointestinal motility
Droxidopa	100–600 mg 3 times daily	All	Nausea, palpitations, urinary symptoms	May worsen tachycardia
Modafinil	100–200 mg twice daily	"Brain fog"	Headache, dizziness, anxiety, insomnia	May improve cognitive symptoms

(Lei *et al.* 2019, p340)

As can be seen from Table 2, propranolol, a non-selective betablocker, has been recommended as a heart rate lowering agent. Lei *et al*. (2019) state the following:

> "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" (p341)

This recommendation was based on the findings of Raj *et al*. (2009) (see below).

Arnold *et al*. (2013)

Arnold *et al*. (2013) report on a randomised controlled trial (RCT) on *Low-dose propranolol and exercise capacity in postural tachycardia syndrome*. They compared the effect of placebo versus a single 20mg propranolol dose on peak oxygen consumption (VO_2max) in patients with PoTS (n=11) and healthy participants (n=7). This trial was double-blinded. It was assessed as providing Class II evidence using the Classes of Evidence[2] system

Findings include:

- Maximal exercise capacity was similar between groups following placebo
- Low-dose propranolol improved VO_2max in patients with POTS (24.5 ± 0.7 placebo vs 27.6 ± 1.0 mL/min/kg propranolol; p= 0.024), but not healthy subjects
- The increase in VO2max in POTS was associated with attenuated peak heart rate responses (142 ± 8 propranolol vs 165 ± 4 bpm placebo; p= 0.005) and improved stroke volume (81 ± 4 propranolol vs 67 ± 3 mL placebo; p= 0.013)
- In a separate cohort of POTS patients, neither high-dose propranolol (80 mg) nor metoprolol (100 mg) improved VO2max, despite similar lowering of heart rate.

[2] For more information, please see Definition of Classes of Evidence (CoE) and Overall Strength of Evidence (SoE) (ESBJ, 2013)

They concluded:

> "These findings suggest that nonselective b-blockade with propranolol, when used at the low doses frequently used for treatment of POTS, may provide a modest beneficial effect to improve heart rate control and exercise capacity" (Arnold *et al*., 2013, p1927).

Limitations of this study include:

- Not examining sex differences, as PoTS mostly affects premenopausal women
- Small sample size
- Healthy volunteers were not placed on a controlled diet, which could influence exercise testing
- Lack of clarity about whether chronic propranolol would provide similar benefit for exercise capacity
- Since propranolol is permeable across the blood-brain barrier, this study could not differentiate whether there was a contribution of central vs peripheral actions for effects on exercise capacity.

Fu *et al*. (2011)

Fu *et al*. (2011) report on a study which examines Exercise Training versus Propranolol in the Treatment of the Postural Orthostatic Tachycardia Syndrome. They conducted a double-blind cross-over trial in which patients with PoTS (n=19 (female=18, male=1)) and an age-matched control group (n=15) were first treated with 80mg propranolol or placebo for four weeks, followed by three months of exercise training. A 2-hour standing test was performed before and after drug treatment and training. Haemodynamics, catecholamines, plasma renin activity, and aldosterone were measured supine and during 2-hour standing.

Findings include:

- Both propranolol and training significantly lowered standing heart rate
- Standing cardiac output was lowered after propranolol treatment (P=0.01), but was minimally changed after training

- The aldosterone-to-renin ratio during 2-hour standing remained unchanged after propranolol treatment [4.1±1.7 (SD) pre vs. 3.9±2.0 post, P=0.46), but modestly increased after training (5.2±2.9 vs. 6.5±3.0, P=0.05)
- Plasma catecholamines were not affected by propranolol or training
- Patient quality of life, assessed using the 36-item Short Form Health Survey, was improved after training (physical functioning score 33±10 pre vs. 50±9 post; social functioning score 37±9 vs. 48±6, both p<0.01) but not after propranolol treatment (34±10 vs. 36±11, P=0.63; 39±7 vs. 39±5, P=0.73).

They conclude:

> "These results suggest that for patients with POTS, exercise training is superior to propranolol at restoring upright haemodynamics, normalizing renal-adrenal responsiveness, and improving quality of life" (Fu *et al*., 2011, p167).

Raj *et al*. (2009)

Raj *et al*. (2009) wrote a paper entitled *Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more* in which they report on a cross-over RCT. This study sought to test the hypothesis that propranolol would reduce tachycardia and improve symptom control in patients with PoTS, dose response was also assessed. In this cross-over design, two protocols were employed. In Protocol 1, patients (n=54) with PoTS were given 20mg propranolol and placebo, on separate mornings. In Protocol 2, patients (n=18) with PoTS were given high-dose (80mg) and low-dose (20mg) propranolol, also on separate mornings. In both protocols blood pressure, heart rate, and symptoms were assessed whilst patients were seated and after standing for 10 minutes before and hourly after administration, for 4 hours.

Significant findings for Protocol 1 include:

- Supine (P<0.001) and standing (P<0.001) heart rates were significantly lower after propranolol compared with placebo
- The symptom burden improvement from baseline to 2 hours was greater with propranolol than placebo (median, -4.5 versus 0 arbitrary units; P=0.044).

Significant findings for Protocol 2 include:

- The high dose elicited a greater decrease than the low dose in standing heart rate (P<0.001) and orthostatic tachycardia (P<0.001)
- The improvement in symptoms at 2 hours was greater with low-dose propranolol (-6 versus -2 arbitrary units; P=0.041).

They concluded:

> "Low-dose oral propranolol significantly attenuated tachycardia and improved symptoms in PoTS. High-dose propranolol did not further improve, and may worsen, symptoms" (Raj *et al*., 2009, p725).

Limitations of this study include:

- It was single-blind and not double-blind as the research nurse was not blind to the intervention. However, the nurse in question was not involved in data collection and so it is unlikely that the findings are biased on this basis
- Protocol 2 had a very small sample (n=18). However, Raj *et al*. (2009) note that this sample size is comparable to other PoTS trials, indicating that the sample size for Protocol 1 was somewhat larger
- 4 hours of follow-up is very short and so the long-term efficacy of propranolol use in PoTS could not be determined.

Method

The following PICO search strategy was used:

Population: Adults experiencing PoTS

Intervention: Beta-blockers

Comparison:

Outcomes: Management of PoTS

Searches took place on 19/05/2022.

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

("postural orthostatic tachycardia syndrome" OR "postural tachycardia syndrome") AND “management” AND (medic* OR pharma*)

Exclusion criteria:

Outside of time limit 2019-2022, lack of relevance to PICO, non-research and non-guidance, duplicates, abstract not included, non-English language.

Databases and sources searched included:

Trip Medical Database: 169 results. List sorted by “relevance.” Top 10 citations subjected to abstract screen. Exclusion criteria applied. 2 articles subjected to full-text screen. 2 included.

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

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