Postural Orthostatic Tachycardia Syndrome (POTS): Assess, Diagnose, and Evaluate for POTS Treatment (ADEPT)

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Abstract

\textbf{Background/Aims:} Postural orthostatic tachycardia syndrome (POTS) is often identified as being clinically underdiagnosed and undertreated, resulting in unnecessary costs and poorer patient outcomes. \textbf{Method:} Through a literature search, the information has been synthesized, supporting the creation of a POTS diagnostic screening tool that can be implemented within the psychiatric outpatient clinic. \textbf{Results:} POTS patients are often referred to psychiatry for the treatment of chronic fatigue and anxiety disorders. Psychiatric professionals are in a position to prescreen for POTS in patients with orthostatic intolerance. \textbf{Conclusion:} A diagnostic prescreening tool helps to identify patients with POTS so they can be referred for proper treatment, improving their functionality and quality of life, and decreasing the healthcare burden.

Case Example

A 13-year-old male started having vague symptoms in middle school. That year, it all came to a head. As he was entering into his growth spurt, he became thin, pale with dark circles under his eyes, excessively fatigued, unmotivated, intolerant of standing and light exercise, and excessively thirsty with excessive urination. He also had a decrease in concentration and focus, palpitations, lightheadedness, dizziness, presyncope, and anxiousness at...
times, and suffered from abdominal discomfort, nausea, and a decreased appetite. Many social events were cut short because he would suddenly feel ill. After several appointments, specialist visits, and even a hospital stay, he was diagnosed with postural orthostatic tachycardia syndrome (POTS). Those days were haunting, since the school called numerous times to have him picked up (he missed 30 days that year). The physicians seemed to think it was constipation, abdominal migraines, and malingering, to name a few diagnoses. A pediatrician told him that if he did not have a fever of 100.4°F or more, he was going to school. The next day, he was driven to school—he pleaded to be taken home because he felt so miserable. As directed, he was told he had to get out of the car and go to school, as if he were being physically pushed out...

**Introduction**

POTS is a type of orthostatic intolerance that includes an elevation of heart rate in the upright position which is triggered by prolonged standing or even light exercise [1]. Orthostatic hypotension can occur concurrently; yet this is related to the autonomic nervous system (ANS) dysregulation of blood pressure drops (>20/10 mm Hg) and not to the heart rate [2]. Orthostatic hypotension can be secondary to other conditions such as multiple systems atrophy [3].

While POTS and inappropriate sinus tachycardia (IST) have similarities, it is important to differentiate POTS from IST, since the criteria for IST focus on a resting heart rate that is ≥90 beats per minute, while the tachycardia with POTS is the result of orthostatic change [4]. IST also involves an exaggerated response and increased heart rate with minimal activity, resulting in symptoms that are common with POTS [4]. In turn, POTS could be easily misdiagnosed as IST.

Information regarding the classification of POTS, as we know it today, dates back to 1993 [5]. POTS has an estimated prevalence of at least 170 out of 100,000 people, with an age range of 15–50 years, a mean age at onset of 30 years, and a female-to-male ratio of 5:1 [6]. A proper diagnosis can take nearly 8–10 years [7], or an average of 5 years and 11 months [8]. Approximately 45% of patients had their POTS symptom onset after 19 years of age [8]. It is believed that POTS can be found in any race, ethnicity, and geographic area, comprising a population of approximately 3 million persons in the USA and 11 million people globally [8].

There are unnecessary doctor’s visits, hospitalizations, medical tests, and costs to the school system in order to accommodate patients with POTS [9]. Delays can incur significant costs to the patient and family by impacting school and work time, and they contribute to unnecessary medical expenses [9] and medical disability [8]. Even when properly diagnosed, there is still confusion about who is best suited to managing this esoteric syndrome. Many physicians and clinicians advertise that they treat POTS; however, there are only a few autonomic specialists who treat POTS in the USA [5, 10]. Screening for POTS can be done by evaluating a symptomatic patient’s orthostatic vital signs [11]. Currently, the primary clinicians who manage patients with POTS are concentrated in cardiology and neurology practices that have an interest or specialize in disorders of the ANS.

**Implications for Current Practice**

The factors that contribute to the delay in the diagnosis and treatment of POTS can be related to the episodic and indiscriminate nature of the symptoms, which cause misunderstandings by both patients and professionals [5]. While many instances of POTS are thought
to be autoimmune related and follow an acute viral infection, other correlations include trauma, surgery, pregnancy, or the result of chronic medical illnesses [5]. In addition, persons with hypermobility or hyperflexibility can be at risk for POTS [11]. Oftentimes, patients are diagnosed and treated for psychiatric conditions, predominantly chronic fatigue syndrome [6, 12] and anxiety disorders [1, 5, 7].

While the prognosis of POTS can vary, 80% of teenagers improve within a few years with proper treatment [5, 13, 14]. Males tend to have a more favorable recovery [8]. Thus, it is important that the identification and treatment of POTS be expanded and made accessible to patients at risk. This can be accomplished by combining the literature with clinical and pragmatic concerns to improve the proper assessment, diagnosis, and treatment for patients with POTS.

**Clinical Diagnosis**

According to Raj [3], patients with POTS have a heart rate that is increased by ≥30 beats per minute (bpm) or an overall heart rate ≥120 bpm when standing for as little as 5 min, and they often have a low blood volume. Grubb and Karabin [15] indicate that the symptoms of POTS can result from the inability to maintain constriction of the blood vessels in the lower body while in an upright position. Grubb [1] further defines the symptoms as palpitations, fatigue, lightheadedness, exercise intolerance, diminished concentration, and presyncope, which greatly impact normal functioning.

**Identifying the Gap**

Too often, patient complaints of POTS symptoms are disregarded because the blood test results, scans, and X-rays are inconclusive, suggesting that the patient's symptoms are psychiatric in nature [5]. In fact, Carew et al. [2] summarized a case of a 21-year-old female who presented with an 18-month history of POTS symptoms, yet had a resting heart rate and ECG that were within normal limits. However, the patient's heart rate increased by 38 bpm in an upright position, and she had a syncopal episode with the tilt table test. In addition, Raj [3] found that the standing norepinephrine level was elevated in POTS participants (>600 pg/mL) due to the exaggerated neural sympathetic tone. Since POTS symptoms are episodic and exacerbated with upright posture and activity, they can be difficult to diagnose [9]. As a result of the delay in a proper diagnosis, patients feel misunderstood and do not feel validated, which could greatly impact their self-esteem and self-confidence [5]. Many POTS patients are treated with antidepressants and anxiolytics [7] and with cognitive behavioral therapy, which helps with the associated depression, anxiety, sleep and appetite disturbances, and chronic fatigue symptoms [5]. As such, POTS is being managed by psychiatric professionals without a clear understanding of this syndrome [7].

**ANS and POTS: Psychiatric Symptoms**

It is known that norepinephrine is both a neurotransmitter that facilitates communication between neurons in the central nervous system and brain [16], as well as a chemical released into the blood stream as a result of the stress response [17]. Norepinephrine in the circulatory system is also the result of excess in the vascular smooth muscle nerve synapse that gets released into the bloodstream unintentionally [18]. Norepinephrine binds to the α1
receptors, postsynaptically in the smooth muscle of the peripheral blood vessels, prompting muscle contractility and vascular constriction [19]. Norepinephrine also binds to the $\beta_1$ receptors postsynaptically in the heart, which stimulates an increased heart rate and contractility [20]. When there is increased activity in the sympathetic nervous system (SNS), there is an increase in norepinephrine in the bloodstream [18].

When studying the ANS with respect to stress, it is the SNS that is associated with an increased heart rate [21]. The function of the parasympathetic nervous system (PSNS) for recovery is recognized by looking at the sensitive beat-to-beat parameters of heart rate variability (HRV), particularly the high-frequency (HF) measures [21]. When the SNS’s fight-or-flight system is summoned, heart palpitations occur, blood pressure rises, and organs slow down to make blood, glucose, and other important nutrients available for the musculature [22]. The PSNS balances the function of the SNS on the heart, by controlling the heart rate through the vagus nerve and the thoracic spinal accessory nerve [22]. With POTS, there is reduced compensation for the veins to constrict, possible capillary leakage, dependent edema, and thus a lower blood return to the heart, leading to additional reflex tachycardia [23].

Low-frequency (LF) HRV (LF-HRV) is suggestive of activity from both the sympathetic and the parasympathetic branches [21], but caution should be taken if correlating LF-HRV with anxiety, since anxiety has not been found to negatively impact LF measures [24]. HF-HRV, also known as respiratory sinus arrhythmia, is the measure of heart rate increase with inspiration and decrease with expiration, and is predictive of the balancing effects of the PSNS on the heart [25]. Increased HF-HRV can be reflective of the recovery capability after a state of anxiety, allowing cognitive processing and reflective responses so that healthy reactions are chosen and unhealthy reactions are blocked [26]. A dysregulation between the SNS and the PSNS can be identified when there is a decreased HF-HRV [26].

Dysregulation of the ANS is seen in panic disorder, as well as in other psychiatric disorders, as the result of an exaggerated SNS response, withdrawing PSNS vagal tone to the heart and increasing the heart rate [20]. Patients with panic disorder have been found to have decreased HF-HRV with an increased heart rate, which impacts their ability to adapt emotionally and physically under stressful situations, putting them at risk for cardiac and other health problems [27]. With the introduction of stressors, it has been found that individuals with panic disorder get symptoms such as chest pain, heart palpitations, shortness of breath, sweating, and dizziness [27]. Additionally, a reduced HRV has been associated with attentional deficits and difficulty regulating emotions [27].

Conclusively, there is a large overlap between the ANS, psychiatric symptoms, and the cardiovascular system. This information about the ANS and psychiatric symptoms, which include palpitations, chest pain, sweating, dizziness, cognitive shortfalls, and emotional dysregulation (DSM-5), presents a similar picture to that seen in patients with POTS, since POTS is an ANS disorder [1]. Thus, the differentiation between psychiatric symptoms and POTS creates a diagnostic challenge for any clinician.

Literature Search

POTS is a relatively new diagnosis; therefore it is important to consider what it was historically known as, such as "soldier’s heart" [5, 11], "irritable heart," and "idiopathic orthostatic intolerance" [5], as well as "chronic orthostatic intolerance," "idiopathic hypovolemia," "mitral valve prolapse syndrome," "orthostatic tachycardia," and "positional tachycardia syndrome" [11]. Wilkinson et al. [28] refer to an 1871 study by Da Costa, suggesting that panic attacks were seen as irritable heart in soldiers at that time. This speaks to the commonalities involving the ANS in both panic and POTS, and the confusion in making a differential diag-
nosis. Because of this, there were no restrictions on publication dates, so the writer could gain a better understanding of the evolution of this syndrome.

The literature search led to the review of 105 articles, but not for all were full text versions available, and some were more supplementary to learning about the topic of POTS. The studies that were of most interest included the prevalence and incidence of POTS; the symptoms commonly assessed for; the misdiagnoses of chronic fatigue syndrome, anxiety, panic, and depression; the diagnostics used to identify the change in orthostatic heart rate; and the effectiveness of the head-up tilt table test (HUTT) and the active stand test (AST) for diagnosing POTS. In addition, the studies that addressed the role of the ANS with respect to POTS and psychiatric symptoms were highly useful. Other articles reflected expert opinion and advocacy information, which provided valuable information and qualitative feedback from patients with POTS.

### Synthesis of the Literature

#### Symptoms

POTS is a syndromic disorder with symptoms that are characteristic of the abnormal ANS response when assuming an upright position [5]. Many studies have defined indicators, including dizziness and lightheadedness [29, 30]; orthostatic intolerance, presyncope, and syncope [12–14, 31]; and palpitations [12–14, 30, 31]. In addition, fatigue is a common symptom in POTS patients [12–14, 29, 32]. Patients with POTS also report cognitive difficulties [12, 33]; visual blurring [12, 29]; chest pain [12, 30]; trembling, numbness or tingling, flushes or chills, and weakness [30]; and exercise intolerance [12]. In 2 of the studies, the Quantitative Sudomotor Axon Reflex Test (QSART) was used to assess alterations in sweating [13, 29]. Depending on the source of POTS, patients can have hypotension, hypertension, or no change in their blood pressure as a result of the positional changes [7, 13, 14, 31].

To summarize the psychiatric symptoms that have been associated with POTS, several studies have identified anxiety [12, 32–34] and panic [35], depression [35], attentional impairment [2, 34], and neurotic personality traits [35] that could equate to somatic hypervigilance. While these studies identified significant psychiatric symptoms, others did not find a correlation with panic [36] or anxiety and depression disorders [37] in patients with POTS. Raj et al. [37] did observe mild depressive symptoms and moderate symptoms of somatic anxiety in the participants in their study, but they were more indicative of the physical symptoms of POTS. While the accepted symptoms for the diagnosis of POTS are listed in the literature, we were unable to locate a structured diagnostic assessment tool to compile them for a succinct conclusion.

#### ANS and Psychiatric Disorders

The ANS is involved in psychiatric disorders, as seen in the meta-analysis by Alvares et al. [38]. Gold et al. [39] found that depression was correlated with elevations in cerebrospinal norepinephrine, as well as with basal and stress-related arterial norepinephrine levels ($p < 0.05$ and $p < 0.03$, respectively). This is interesting, since the inclusion criteria included hypervigilance and insomnia, which are commonly seen with anxiety disorders, while hypersomnia is seen with melancholic depression (DSM-5). Thus, it would be prudent to wonder if the participants had comorbid anxiety.

As a result of the activated ANS, a decreased HRV has been found in patients with many psychiatric disorders by measuring the heart rate, rhythm, and R-R interval [21, 27, 38, 40]. Many patients with panic disorder experience palpitations and a decreased HRV [21, 27, 40], which was more pronounced in patients with more severe symptoms [21]. While Silvia et al.
[25] did not find a correlation with HRV and positive emotionality, there are studies that found a significance regarding cognition and improved HRV [26, 28]. In addition, HRV has been found to improve (increase) with the introduction of antidepressants [40]. As such, psychiatry should be comfortable assessing for a differential diagnosis of POTS.

**Diagnostics**

While there are many symptoms identified in POTS patients, the diagnostics revolve around the key symptom, palpitations, which occur with an upright posture [7, 13, 15, 29–31, 41–43]. Much of the literature is focused on measuring the scale changes in heart rate and blood pressure, using the Valsalva maneuver [13, 29, 30] or HUTT [7, 13, 14, 29–31, 41–43]. When using the Valsalva maneuver or HUTT, the clinician should be looking for an increase in heart rate of ≥30 bpm, or an overall heart rate ≥120 bpm, since these are the criteria used for diagnosing POTS [7, 13, 14, 29–31, 41–43]. In addition, while Jones et al. [41] did not get analogous results with the AST and the HUTT, Kirbiš et al. [42] and Plash et al. [43] found that the AST is comparable to the HUTT when screening for POTS.

Although the measurement of increase in heart rate is the same, the terminology used to describe it differs between investigators. In the studies by Kimpinski et al. [13] and Pandian et al. [30], increment in heart rate was the maximum increase in heart rate with the tilt test, and in the study by Mayuga et al. [31], rise in heart rate was the dependent measurement with the tilt table test. Similarly, Ojha et al. [29] calculated heart rate variation with deep breathing in patients with POTS, and Sidhu et al. [14] indicated that the heart rate increased to 160 bpm in one participant when standing, and the heart rate went up to 140 bpm as measured by the HUTT in their second participant observed.

**Treatments**

The literature is reflective of the fragmentation of treatment, since it was not until recently that a treatment consensus statement became available [44], and there are many acceptable treatment options for POTS. Some studies cited the use of beta-blockers [6, 12–14, 30, 45], which can control the palpitations, and fludrocortisone, for plasma volume expansion and possible sensitization of the peripheral adrenergic receptors to catecholamines [6, 12, 13], as treatments of choice. Interestingly, low-dose propranolol was found to be more effective for the treatment of POTS symptoms [45, 46] than metoprolol and high-dose propranolol, which controlled the heart rate but unexpectedly worsened the POTS symptoms [46]. Because of the improvement in symptoms, low-dose propranolol was found to improve exercise capacity in patients with POTS [45].

Several studies indicated that selective serotonin reuptake inhibitors were used for effective treatment of POTS [12, 14, 27]. Pandian et al. [30] suggested the use of a combined serotonin-norepinephrine reuptake inhibitor (venlafaxine), but this requires close monitoring, since the peripheral increase in norepinephrine can be pronounced in some patients. This was evident with atomoxetine, a norepinephrine reuptake inhibitor, since it caused an increase in supine heart rate and blood pressure as a result of increased plasma norepinephrine levels [47]. Another pharmacological agent that showed efficacy was midodrine, an α-adrenoceptor agonist that did not have the side effects that beta-blockers had, such as fatigue and further aggravation of symptoms [6, 12–14].

Various conservative measures are also recognized for effective symptom relief in patients with POTS, such as the use of compression garments [6, 30]. While Figueroa et al. [48] did not find IV saline to be effective for improving exercise capacity in patients with POTS, many authors have recommended that treatment include volume expansion by increasing fluid and salt intake [6, 12, 13, 30]. The study by Mayuga et al. [31] supported the hypothesis that POTS patients should resume the supine position with their legs elevated to alleviate their symptoms,
since physical counter-maneuvers can offer quick recovery from symptoms. In addition, exercise retraining was found to be effective to improve functionality [6, 12, 45, 48, 49]. Finally, a number of studies included in the systematic review for chronic fatigue syndrome concluded that cognitive behavioral therapy reduces chronic fatigue severity, enhancing an overall sense of well-being [32]. Both cognitive behavioral therapy [50] and biofeedback [51, 26] have been shown to increase HF-HRV. As such, this information could be applied to suggest the usefulness of these measures in controlling the sympathetic symptoms of POTS.

Considerations

When reviewing the literature, some important considerations were identified that were significant. First of all, all of the studies included were conducted utilizing convenience samples. As a result, some caution should be taken with respect to the generalizability of their findings, which increases the importance of synthesizing the literature.

With respect to the treatment of POTS, an important consideration is the need to be familiar with the standard medications used and their possible side effects. For example, using a beta-blocker could cause additional fatigue and complications, so the treatment provider must be cognizant of an individualized treatment plan [14]. In addition, some serotonin reuptake inhibitors can be activating with respect to norepinephrine and dopamine at higher doses [52], yet they are not classified as such. This activation could aggravate the symptoms of POTS, which is why a slow titration process may be needed.

While the systematic review by Price et al. [32] does not address POTS patients, it takes an extensive look at the efficacy of cognitive behavioral therapy. Since many POTS patients are comorbid with chronic fatigue symptoms [6, 33, 53], the results could be generalized with some level of confidence, since it is a review of 15 randomized controlled trials (n = 1,043). All in all, the conclusions are valuable, because they help understand how fatigue, which is chronic in nature, can have physical, psychological, and social ramifications, further impacting the quality of life of patients if left untreated [31].

Conclusion

While exploring the information and literature on POTS, the area that was most interesting was the complex of the ANS. It was very fascinating to find a comparable role of norepinephrine in HRV for both anxiety and POTS. While both disciplines focus on the same neurotransmitter, which is a catecholamine, psychiatry speaks of norepinephrine as a neurotransmitter in the brain, as a part of the central nervous system [16], while cardiology speaks of norepinephrine as a circulating catecholamine that impacts the cardiovascular system, as part of the peripheral nervous system [18]. There is a dysregulation when the SNS and the PSNS do not work together, resulting in prolonged palpitations – whether they are the result of POTS, anxiety [12–14, 29–31], or panic disorder [21, 27, 38, 40]. This portrays a tremendous overlap between psychiatry and POTS by way of the sympathetic and parasympathetic branches of the ANS.

POTS is a complex syndrome that is misunderstood by many health professionals [1], causing perplexity in both patients and professionals. Because it does not follow a predictable illness pattern in a patient, the syndrome of POTS is often overlooked, constituting misdiagnoses [1]. If POTS patients are misdiagnosed, it jeopardizes the effectiveness of treatment, potentially leaving patients with a sense of helplessness, poorer psychosocial adjustment, and poorer healthcare outcomes. They may receive partial treatment for partial recovery. In turn, it is important that providers are knowledgeable so that they can assist patients to understand, cope with, and adapt to the diagnosis and treatment of POTS.
Many treatment providers, including cardiologists, do not specialize in autonomic disorders and do not assess for the full spectrum of POTS symptoms [5]. Many of the obvious symptoms reported are dismissed and are investigated no further by generalists and specialists alike, making the quest for help an arduous undertaking [9]. Some of the signature
signs of the syndrome that get overlooked include venous pooling, blanching, and acrocyanosis, as well as chronic fatigue and anxiety [14, 29–31].

Due to the underdiagnosis, comorbidity, and misdiagnosis of POTS, the ADEPT prescreening tool for identifying POTS symptoms was created (Fig. 1). If POTS is suspected, a referral should be made to a POTS specialist, an electrophysiologist, or a syncope clinic, which are a part of the neurology or cardiology departments of many hospitals [5]. If each
clinician becomes more adept in ruling out a diagnosis of POTS within their patient population suffering from chronic fatigue, anxiety, and orthostatic intolerance, fewer patients will struggle with the debilitating symptoms that impact their productivity and quality of life and tax our economic and healthcare systems.

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