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Reducing the Rate of Misdiagnosis of Postural Orthostatic Tachycardia Syndrome

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REDUCING THE RATE OF MISDIAGNOSIS OF POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

by

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Abstract

Postural orthostatic tachycardia syndrome (POTS) is a common yet frequently misdiagnosed dysautonomia characterized by a significant increase in heart rate upon standing. POTS patients experience severe fatigue, dizziness, pre-syncope, and a diminished quality of life. The intent of this thesis is to investigate factors contributing to POTS misdiagnosis and develop a proposal for improving diagnostic procedures. The first part of this thesis presents an overview of other frequently misdiagnosed conditions, providing an understanding of the basis for the diagnostic problems in POTS and methods to combat such difficulties. The second part of this thesis details a meta-analysis performed on POTS clinical studies since its classification in 1993, in an attempt to synthesize current knowledge and potential deficits in research. Results show the misdiagnosis rates for POTS are understandably high, as POTS shares many characteristics with other misdiagnosed conditions. Analysis of these conditions demonstrates the need for easier in-clinic diagnostic tests for POTS. The meta-analysis results demonstrate misunderstanding about POTS remains within the scientific community. The final recommendations to reduce POTS misdiagnosis include using a blood pressure/heart rate screening test to identify patients sooner and shifting research efforts from etiology and treatment to prevalence and diagnostic procedures.

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Table of Contents

Chapter One: Introduction 1

An Overview of Postural Orthostatic Tachycardia Syndrome 1

Diagnosis and Misdiagnosis 2

Chapter Two: Literature Review 5

Symptoms 5

Pathophysiology 6

Psychological Component 11

Treatment and Intervention 13

Chapter Three: Objectives 15

Identification of Problem 15

Proposed Research 16

Chapter Four: Examination of Other Frequently Misdiagnosed Conditions 18

Overview 18

Literature Review 18

Common Themes 28

Chapter Five: Meta-Analysis on POTS 31

Methodology 31

Results 32

Discussion 38

Chapter Six: Future Research 43

Chapter Seven: Conclusion 45

Appendix A: Meta-Analysis 49

Appendix B: Future Research 57

References 59

List of Figures

Figure 1: PubMed Review: References to POTS by Year..... 33

Figure 2: PubMed Meta-Analysis: POTS Clinical Studies by Year 34

Figure 3: Terminology Used for POTS 35

List of Tables

Table 1: POTS Symptoms 5

Table 2: CARE Method 20

Table 3: Summary of Examination of Misdiagnosed Conditions 30

Table 4: Meta-Analysis Impact Factors 36

Table 5: Categories of Clinical Studies 37

Table 6: Categories of Non-Pharmacologic Treatment 37

Table 7: Categories of Pharmacologic Treatment 38

Table 8: Meta-Analysis Summary 50

Chapter One: Introduction

An Overview of Postural Orthostatic Tachycardia Syndrome

Postural orthostatic tachycardia syndrome (POTS) is a defect of the autonomic nervous system in which patients present with rapid heart rate upon standing, and a subsequent inability to tolerate orthostatic posture for long periods.[56] Physiologically, the condition is characterized as a form of autonomic neuropathy leading to insufficient peripheral vasculature constriction when adopting an upright (orthostatic) posture; the associated tachycardia is assumed to be a mechanism for maintaining appropriate blood pressure and organ perfusion when in such a position.[64] As POTS is a nervous system deficit, its associated symptoms are diverse, manifesting as cardiology, gastrointestinal, and pulmonary complications.[19] Though often initially misdiagnosed as a psychological problem, symptoms in POTS patients have been proven to be physiological rather than psychological.[4]

Although misunderstood and under-recognized, POTS is actually a fairly prevalent disorder,[19] currently impacting 500,000 individuals in the United States; due to the low rates of diagnosis, however, some estimate as many as 3 million may actually be afflicted nationally.[4, 29, 65, 71] POTS is known to affect females at a rate five times higher than that of males; among these impacted women, the vast majority are of childbearing age (approximately 15-40 years of age).[19, 67] Interestingly, many report that the onset of their

POTS symptoms began after a specific event, such as a viral infection, pregnancy, surgery, or trauma. Although the mechanism behind this correlation is not confirmed, it has been postulated that significant blood loss is to blame in these situations, exacerbating already existing hypovolemia (decreased blood volume).[67] Most patients and physicians report a significant diminishment in health-related quality of life after the onset of POTS, with many in the medical community characterizing the condition as debilitating.[65] Some patients are unable to attend work or school due to the severity of their symptoms; estimates suggest up to 25% of POTS patients are functionally disabled.[8] Daily life tasks such as chores and bathing often lead to incapacitating fatigue, leading to a quality of life comparable to those with congestive heart failure.[67]

Diagnosis and Misdiagnosis

POTS is diagnosed following evidence of an increase in heart rate of 30 bpm in adults or 40 bpm in teenagers after transitioning from a supine to standing position, without indications of orthostatic hypotension (decrease in blood pressure on standing).[19, 68] The use of the tilt table test is encouraged when diagnosing POTS, as the patient's heart rate, blood pressure, and EKG recordings can be completed while the patient is closely monitored and raised from a supine to upright position.[65] Additionally, the use of a table and restraints prevents the patient from utilizing somatic movements of the limbs to increase venous return and distort vital signs.[53] The use of blood work and a detailed

history in conjunction with the tilt table test can help ensure that the patient's symptoms are not a result of other medical conditions, such as neurogenic orthostatic hypotension, autonomically mediated syncope, hyperthyroidism, dehydration, or anemia, or due to medications such as oral contraceptives, anti-depressants, vasodilators, or diuretics.[65] Such conditions and medications can cause an inability to tolerate orthostatic posture; however, tilt-table testing will not demonstrate an increase of heart rate of 30 bpm without a change in blood pressure when upright in these patients.

Unfortunately, POTS diagnoses are rarely this simple. In general, 83% of those with a form of dysautonomia are initially misdiagnosed with anxiety or panic disorders, a trend seen with POTS patients as well; some have even been diagnosed with conditions as unrelated as pneumonia.[65, 67] An overall lack of physician awareness is predominantly to blame, further complicated by its recent characterization. POTS was only clinically described in 1993, thus health care providers trained prior to the nineties are unlikely to have been exposed to the syndrome. Most believe, however, that early references to heart conditions such as irritable heart syndrome, soldier's heart, Da Costa syndrome, effort syndrome, and idiopathic tachycardia syndrome throughout the last century were indicative of early misdiagnosed POTS patients.[65] Even today, some references to POTS utilize the phrases "postural tachycardia" or "chronic orthostatic intolerance." Such naming discrepancies have likely contributed to misdiagnoses and clinical confusion as well.[29] As such, the average time from onset of symptoms to a POTS diagnosis is six years.[65] Reaching this diagnosis, however, is critical for the patient's health and symptom management; one Mayo study found that after accurate diagnosis and appropriate treatment, 80% of POTS

patients improved, with as many as 60% reaching a near-normal quality of life.[76] Thus, studying ways to reduce the high rate of misdiagnosis of POTS is critical; patients can usually manage symptoms successfully once a correct diagnosis has been made.

Chapter Two: Literature Review

Symptoms

The most commonly identified symptoms in POTS patients include:[19, 67]

Table 1: POTS Symptoms

Excessive fatigue	Lightheadedness	Difficulty standing still
Nausea	"Brain Fog"	Heart palpitations
Dyspnea	Numbness of extremities	"Pins and needles"
Headache	Exercise intolerance	Heat intolerance
Abnormal sweating	GI problems	Cyanosis in feet
Weakness	Tremulousness	Unrefreshing sleep

The most frequently reported symptom is a debilitating level of fatigue, shown to be three times higher in POTS patients than healthy members of society. A lack of deep sleep and high prevalence of sleep disorders in POTS patients likely contributes to this fatigue, resulting in a high level of daytime exhaustion.[4] Research shows sleep in POTS may be as impaired as that seen in chronic fatigue syndrome. Physical signs of orthostatic intolerance, including dizziness and lightheadedness, are also commonly reported; transitioning to a supine position moderately reduces symptoms by relieving this orthostatic stress.[56] Additionally, patients may develop subconscious mechanisms when standing to further compensate for decreased venous return.[53] While almost all POTS patients experience feelings of pre-syncope due to this orthostatic intolerance, not all experience true syncope, and fainting is certainly not a necessity for a POTS diagnosis.[81] Finally, about 50% of POTS

patients report acrocyanosis, reddish-blue coloring seen in lower limbs upon standing, though the reasoning behind this has yet to be determined.[65, 67]

POTS is often seen with autoimmune or connective tissue disorders, and patients may be double-jointed, indicative of Ehlers-Danlos syndrome.[19] Other conditions commonly comorbid with POTS include amyloidosis, celiac disease, chronic fatigue syndrome, diabetes, fibromyalgia, migraines, mitochondrial disease, and multiple sclerosis.[65]

Pathophysiology

Identifying the underlying cause for POTS has proven to be a challenge for both researchers and physicians. In all cases, the true pathology seems to lie in a defect of the autonomic nervous system; however, the manner in which this deficit manifests itself and impacts the individual varies. This variety in clinical manifestation likely contributes to a high rate of POTS misdiagnosis, though all causes are essentially interconnected along a continuum of ANS-mediated dysfunctions.[65]

The physiological basis for many of the symptoms presenting in POTS patients have been elucidated, however. For example, diminished blood flow to the cerebral cortex as a result of both hypovolemia and venous pooling leads to the "mental cloudiness" or "brain fog" symptom.[1] Sleep disorders have been shown to be associated with dysfunction of the

autonomic nervous system, suggesting an explanation for the chronic fatigue and lack of refreshing sleep in POTS.[4] Additionally, the tachycardia seen upon standing has been proven to originate from the sinoatrial node; if a patient's tachycardia does not meet this requirement, POTS can be ruled out.[67]

Below, the main physiological origins discussed for POTS in the literature are outlined. In addition to these, autoimmune dysfunction, mast cell activation, and deconditioning have been proposed.[18] Research shows low iron storage capabilities leading to mild anemia is common in POTS patients as well; whether or not this anemic state is a cause or result of the illness has yet to be elucidated.[44] As aforementioned, however, current literature tends to agree all "causes" are essentially manifestations of an underlying ANS defect, and are not truly distinct; denervation that impacts specific muscle and organ systems is nearly always to blame.[65]

Hypovolemic POTS

Most POTS patients present with some degree of hypovolemia. When compared to healthy individuals, POTS patients' plasma volume was an average of 13% less than ideal for their stature; in extreme cases, a deficit as high as 27% was seen.[65, 67, 68] This hypovolemia leads to POTS symptoms through what some researchers have called the renin-aldosterone paradox.[67] In a normal patient, hypovolemia would signal an increase in renin, and subsequently angiotensin I, angiotensin II, and aldosterone, in an attempt to

increase blood volume.[68] This mechanism would stimulate the reabsorption of sodium and water in the nephron, thus improving hypovolemia and subsequent hypotension. However, POTS patients have significantly lower serum aldosterone and inappropriately low renin activity despite their degree of hypovolemia.[65, 68] This deficit leads to an inability to retain sodium and water in an attempt to raise blood volume and blood pressure; as a result, a corresponding decrease in cardiac stroke volume means an increased heart rate is the only mechanism capable of maintaining cardiac output, resulting in tachycardia. Finally, while research shows 50% of POTS patients state a viral infection preceded the onset of their symptoms, most believe such traumas simply exacerbate already existing hypovolemic conditions.[76]

Neuropathic POTS

Studies have indicated 50% of POTS patients have partial sympathetic denervation, or a partial dysautonomia, in the lower limbs.[65, 68] Upon standing, blood typically shifts to the lower limbs and pools under the influence of gravity; however, in a healthy patient, the body can quickly correct this imbalance with peripheral smooth muscle contraction to return blood to the heart and major organ systems. In POTS, however, this lower limb denervation leads to venous pooling in the legs; venous return to the heart decreases, and the body responds with an increase in heart rate to maintain cardiac output.[65] This POTS pathology is the most likely reasoning behind the "difficulty standing still" phenomenon.

Internal physiological discomfort as a result of venous pooling and resultant tachycardia may lead to the fidgeting, leg tensing, and other unconscious maneuvers that POTS patients sometimes demonstrate. These counter maneuvers are meant to increase venous return to the heart through contraction of skeletal muscles, which aids in venous return.

Hyperadrenergic POTS

POTS patients also show levels of norepinephrine twice as high as controls after assuming a standing position.[65, 68] This increase in norepinephrine is thought to be a mechanism to compensate for the aforementioned hypovolemia and peripheral denervation.[65] These hyper adrenergic levels lead to tachycardia, tremulousness, anxiety, and heart palpitations, as seen in POTS. Although rare, it seems that in some patients this increase may be due to a genetic deficiency in norepinephrine reuptake. A single point mutation in the SLC6A2 norepinephrine transport protein leads to a decreased ability in clearing the hormone from synaptic clefts, and has been identified in some POTS patients.[64]

Deconditioned POTS

A slightly controversial study by Fu et al claims POTS is not due to an ANS disorder as commonly cited, but solely due to hypovolemia and cardiac atrophy. Findings of

decreased heart mass in sufferers of chronic fatigue syndrome and reported overlaps between this disorder and POTS prompted their research, which found reduced left ventricular mass in POTS patients when compared to controls. Based on a hypothesis that this atrophy was due to deconditioning, an exercise regimen featuring low-orthostatic stress routines (recumbent biking, rowing, and swimming) was implemented, which successfully increased heart size, mass, and volume. By the end of the program, participants could reportedly walk and jog without stress. Due to the potential pathological effects of this decreased heart size, Fu et al propose renaming of POTS to "The Grinch Syndrome."[4]

Genetics

Research shows genetic inheritance may play a role in the development of POTS, with up to 20% of patients showing indications of a family history of the condition.[64] Studies show many children with POTS demonstrate variations of the GNB3 gene C825T, which leads to changes in the G protein B3 subunit that serves as a component of the autonomic nervous system.[60] These polymorphisms lead to an increase in heart rate upon standing, and could represent a definitive cause for the dysautonomia behind POTS. Additionally, as mentioned, a defect in the SLC6A2 norepinephrine transport protein has also been indicated, leading to a hyperadrenergic state.[64] Finally, POTS patients are more likely to have genetic polymorphisms in the nitric oxide synthetase gene NOS3, which could

explain changes to blood flow in the condition.[35] While a number of possible genetic causes have been identified, further research is needed to determine which variations are most significant in the onset of POTS.

Psychological Component

As discussed, POTS patients are frequently misdiagnosed with psychological illnesses such as anxiety or panic disorder prior to their POTS treatment, likely due to symptoms such as heart palpitations, shortness of breath, and faintness.[64, 67] Studies based on criteria presented in the Diagnostic and Statistical Manual of Mental Disorders, however, show POTS patients do not have higher prevalence of depressive, anxiety, or substance abuse disorders than the general population. While some have reported high anxiety levels in POTS patients through the use of the Beck Anxiety Inventory scale, this index utilizes somatic as well as psychological indicators of anxiety, and thus over-predicts the prevalence of anxiety in POTS patients whose hyper-adrenergic states likely alter test results. When assessed with solely psychological measures, such as the Anxiety Sensitivity Index, anxiety levels were not higher than the general population.[71] In fact, studies have found that mental health was the only health indicator in which POTS patients did not score worse than controls from the general public.[5]

Although POTS is defined as a physiological disorder, stress can be a trigger that exacerbates symptoms.[18] As such, some still claim psychological factors are important to

consider when treating POTS patients, with adolescents in particular being at risk for increased stress and mental health disorders. Since life with POTS can mirror disabilities such as chronic pain and diabetes, researchers such as McTate et al have begun to explore the effectiveness of pain rehabilitation based treatment programs and claim moderate success.[56]

Prevalence in Women

As mentioned, POTS is far more prevalent in women than in men, with an incidence rate five times higher in females.[19] Such epidemiological differences have led to research aimed at investigating why most POTS sufferers are female. It is theorized that estrogen and progesterone, which play a role in RAAS regulation and maintenance of blood volume, could be related to the higher female prevalence.[66, 88] Although many POTS patients report worsening of symptoms during their menstrual periods, research has not shown any change or dysfunction in the activity of the sympathetic nervous system in menstruating female POTS patients.[88] Instead, natural changes in blood pressure may be involved in increased orthostatic intolerance during menstruation.[88] Healthy women also report lightheadedness during menses, suggesting menstruation may not play a significant role in POTS.[66] Although hypovolemia does seem to impact women to a greater extent than men, with studies demonstrating increased susceptibility to hypovolemic stress in females, no definitive link between sex-related hypovolemia and POTS has been confirmed.[49]

Treatment and Intervention

For many patients, pharmacological intervention represents an important step in symptom management. Treatments like salt supplementation and fludrocortisone target hypovolemia by increasing water and sodium retention and enhancing venous return, while midodrine acts as a norepinephrine agonist to induce vasoconstriction.[65, 67] Research has shown that such plasma volume expanders can lead to long-term improvement.[68] Frequently, however, patients are unable to tolerate the side effects of these drugs.[4] Additionally, while drugs are designed to mitigate symptoms, they are unable to treat the underlying sympathetic denervation assumed to the primary cause of POTS. When pharmacological intervention fails, patients can learn to manage their symptoms through simple strategies and avoidance behaviors. As mentioned, an increase in dietary salt intake is recommended, as well as the use of compression stockings to aid in venous return and frequent hydration to combat hypovolemia. Large meals should be avoided, as an increased volume of blood will be drawn to the intestines during digestion; instead, smaller meals and snacks should be eaten throughout the day. Other exacerbating conditions, such as heat, alcohol, and dehydration, should be avoided as well.[65]

Exercise training is highly recommended due to its ability to increase blood volume and train muscles to improve venous return.[29, 67] Unfortunately, even mild exercise worsens symptoms; patients can feel debilitating weakness and fatigue for days after physiological stress.[8, 67] As a compromise, low-intensity exercise that does not exacerbate orthostatic intolerance symptoms should be used, such as swimming, rowing, and

recumbent biking. Yoga and Pilates are frequently advised as well, and often met with success.[29, 65]

Chapter Three: Objectives

Identification of Problem

A review of the medical literature surrounding POTS suggests that a focus on improving clinician awareness and diagnostic procedures should be the primary approach to combat this disorder. Various teams have attempted to determine the physiological basis of this syndrome, but a correct understanding of the origin of POTS has limited practicality if existing rates of misdiagnosis are not improved. In most cases, the cause of a patient's POTS is unknown, and the physician will proceed with a similar set of standardized treatments rather than attempt to determine the pathology surrounding their condition anyway; furthermore, even when a cause is suspected, targeted drug therapy is often intolerable. It seems that for most cases, treatment of POTS is reduced to symptom management; thus, the critical step in any patient's recovery is simply an accurate POTS diagnosis, enabling them to understand techniques to alleviate symptoms and avoid exacerbating their condition.

As discussed, POTS is diagnosed after evidence of an increase in heart rate of at least 30 bpm after transitioning from a supine to standing position, and the tilt table test represents the best technique to observe this phenomenon. Patients can be closely monitored, and the fixed positioning of the patient to the table prevents unconscious compensatory movements developed to increase venous return and alleviate discomfort,

such as contraction of lower limb muscles to supplement the mechanism of the skeletal muscle pump. A variety of difficulties unfortunately prevent this procedure from being widely implemented. The tilt table test can cost patients upwards of $6000, with no guarantee of insurance coverage even when patient presentation indicates POTS. Additionally, primary care physicians likely lack access to such equipment, requiring a referral to a hospital or specialized clinic. Finally, the tilt table test is considered inherently hazardous for the patient, as it provokes cardiovascular symptoms and brings the patient near syncope.[14] Such problems with the tilt table test, combined with overall lack of physician awareness and understanding, potentially contribute to the slow rates of diagnosis.

Due to the aforementioned complications, reduction in the misdiagnoses of POTS patients is doubtful without medical education on the condition and widespread implementation of an easier method to identify POTS candidates. The goal of this thesis is to synthesize information from existing literature in order to develop a proposal for reducing the misdiagnosis rate based on these assumptions.

Proposed Research

The goal of this thesis is to develop a proposal for reducing both the high rate of misdiagnosis for POTS and the time it takes for patients to receive accurate diagnosis. As mentioned above, a critical part of such an endeavor is the identification of an easier way to

identify POTS patients. Research on how this can be accomplished will continue with a two-part project, as described below.

Part One: Examine methods used with other frequently misdiagnosed conditions

Part Two: Examine current research trends on POTS through a meta-analysis

Again, as described, implementation of a simple way to identify POTS patients is ideal, but cannot happen without first increasing clinician awareness. For this reason, an extended literature review on other frequently misdiagnosed conditions (Part One) will be performed to gain insight on methods successfully used to increase physician understanding and facilitate accurate diagnoses. Disorders planned to study include thyroid dysfunction, fibromyalgia, Lyme disease and Lupus. Next, a meta-analysis on current research being performed on POTS will be performed. This analysis serves two functions. First, the meta-analysis will provide an understanding of where the scientific community currently is in terms of awareness and diagnosis of POTS in the clinical environment. Second, the meta-analysis will enable a summarization of current advice from researchers that will be useful for the final proposal on reducing POTS misdiagnosis rates. Ideas from Part One and Part Two will be synthesized into a final recommendation for POTS education and diagnostic procedures. Such a two-pronged approach in reducing the misdiagnosis rate for POTS is recommended based on evidence that suggests there is not one "magic bullet" in approaching diagnostic error; thus, a multifaceted approach is required not only in the clinic, but in this thesis as well.[79]

Chapter Four: Examination of Other Frequently Misdiagnosed Conditions

Overview

The following chapter examines other frequently misdiagnosed conditions in an attempt to learn how physicians approach and combat high rates of diagnostic error. Information gained from an understanding of these maladies can then be applied to reducing the rate of misdiagnosis for POTS. The following conditions were selected due to their high rates of misdiagnosis and their assorted similarities to POTS. Before investigating individual diseases and syndromes, approaches to reduce diagnostic rates in general are discussed.

Literature Review

General Approaches to Reducing Diagnostic Error

Diagnostic errors are common not only for patients with POTS and the other conditions discussed below, but in everyday medical practice. The World Health Organization currently considers diagnostic error a high priority problem, and research on the subject seems to support this claim.[79] Rush et al. cite diagnostic errors as the "most

common, costly, and dangerous of all medical mistakes."[73] A survey of over six thousand doctors found at least 47% report diagnostic error occurring in their practice weekly; of these, 40% of mistakes were due to flawed or inaccurate history taking.[73] While one could argue some diagnostic error is expected in the demanding and complicated field of medicine, 96% of the surveyed physicians believed the diagnostic error they had reported could have been prevented.[73]

Various approaches have been recommended for reducing overall rates of diagnostic error. Singh et al. propose a lack of feedback contributes to the problem, as doctors rarely learn they have provided a misdiagnosis. This communication breakdown leads to inflated confidence in physicians' diagnostic accuracy and denies doctors the chance to learn from their mistakes.[79] While an actual feedback mechanism to provide doctors with performance results needs to be established, in the meantime, POTS patients or their new physicians can reach out to previous doctors that have supplied inaccurate diagnoses. No change in diagnostic error can be expected if the physicians diagnosing POTS patients with psychiatric conditions, viral or bacterial infections, and/or other neurological or cardiovascular disorders are alerted to their prior errors.

As mentioned previously, history-taking is a critical aspect of the diagnostic process, and one wherein diagnostic error is likely to occur. One reason for this could be communication difficulties – studies show patients are only able to speak to a physician for an average of 18 seconds before being interrupted.[73] Both doctors and POTS patients must work together to ensure all aspects of a history are being communicated fully and clearly.

Rush et al. propose the use of the pneumonic CARE to reduce the likelihood of diagnostic errors:

Table 2: CARE Method

Communicate with your team and patient
Assess for Biased Reasoning
Reconsider Differential Diagnosis
Enact a Plan

When assessing for biased reasoning, Rush suggests considering questions such as whether a colleague or patient first suggested the diagnosis, whether or not the patient is being stereotyped, whether causes other than the obvious have been considered, and whether the patient is perceived as having a "difficult" or "VIP" status. When reconsidering differential diagnosis, Rush suggests a "time out" be taken to examine medical findings inconsistent with the proposed diagnosis and ponder other possibilities.[73]

Hypothyroidism

Hypothyroidism, characterized by a decreased output of thyroid hormone (TH) or decreased ability to utilize TH in the body, is a common but often misdiagnosed condition. Reductions in thyroid function of as little as 15% can lead to symptoms of hypothyroidism,

impacting as many as 33% of adults by current estimates, though not all cases are severe enough to require treatment.[23] Complicating matters further, the severity of symptoms may not correlate appropriately with the severity thyroid dysfunction.[90] As TH has implications for almost every organ system symptoms are widespread and varied.[90] This diversity in clinical presentation likely contributes to poor rates of diagnosis: weight gain, headache, fatigue, temperature sensitivity, depression, hair loss, vertigo, and constipation are all indicative of low TH.[23] Similar to POTS, hypothyroidism is more often seen in female patients; the thyroid is five times more likely to be dysfunctional in women.[23]

Another symptom of hypothyroidism, decreased body temperature as a result of decreased metabolic rate, provides the basis for a useful diagnostic procedure.[23] Daily axillary temperature recordings represent an easy and inexpensive test that has been "ignored and derided by authorities" according to Durrant.[23] Durrant et al. argue 90% of hypothyroidism cases are missed due to an overreliance on serum lab results and underappreciation of clearly presented symptoms. Lab results for T3, T4, and TSH fall into broad ranges and are easily misconstrued by blood volume and renal clearance rate; additionally, they fail to demonstrate receptor defects.[23] These factors contribute to Durrant's argument that hypothyroidism misdiagnosis is exacerbated by poor clinical evaluation of history and symptoms and a dependency on lab tests that are often flawed. Most noticeable in this discussion of hypothyroidism diagnosis is the fear that simple yet effective tests have been ignored, representing a potential similarity to POTS. The future research portion of thesis will examine whether or not a heart rate/blood pressure screening test could be such an overlooked option for POTS.

In the elderly, symptoms of hypothyroidism such as muscle weakness, bradycardia, temperature intolerance, and decreased renal function may be overlooked or dismissed as normal signs of aging.[55] Due to these subtle symptoms, Maselli et al. propose routine TSH testing in older adults could be justified. The masking of hypothyroidism in elderly patients could be similar to the masking of POTS in older teen/young adult patients. Symptoms such as fatigue, "brain fog," and not feeling refreshed after sleep may be misinterpreted as signs of depression, a more common disorder impacting patients of this age.

Congenital hypothyroidism is common as well, but less frequently misdiagnosed. Neonatal screening catches most cases of congenital hypothyroidism, and stricter screening methods following a lowering of the TSH threshold required for a diagnosis has led to even the mildest cases being discovered.[90] This screening is essential, as areas lacking such measures are yet characterized by high rates of congenital hypothyroidism-caused intellectual disability.[90] Such examples demonstrate the importance of screening methods for frequently misdiagnosed conditions, supporting the argument of a heart rate/blood pressure screening method for POTS. The improvements seen after adjusting TSH threshold levels calls into question whether other frequently misdiagnosed conditions could benefit from reevaluations of threshold levels; for example, the 30 bpm increase in heart rate considered to be indicative of POTS.

Fibromyalgia

Fibromyalgia (FM) is a rheumatic condition characterized by widespread pain and sensitivity to pressure points. Although an understood and fairly common rheumatic condition, second in prevalence only to osteoarthritis, misdiagnosis and an extended period of time before accurate diagnosis is frequently seen in FM patients.[22] Similarities to other conditions complicate diagnosis; FM is often misdiagnosed as arthritis, connective tissue disease, and spondyloarthropathies.[22] Diagnosis can also be confused with myofascial pain syndrome, chronic fatigue syndrome, and depression; furthermore, FM was found to be the true disease state in many patients first diagnosed with Lyme disease.[57] An understanding of the incidence of FM has changed over time – once thought to be a rare condition, current studies estimate 2-3% or even as high as 5% of the population are affected.[22, 57] Increased physician awareness led to more frequent and more accurate diagnosis, calling into question whether other frequently misdiagnosed conditions, such as POTS, will have a higher incidence once better understood. Ming et al. propose physicians should continue to become more knowledgeable about FM and keep the condition in mind when examining patients whose history seems indicative of FM, a suggestion that could benefit POTS patients as well.[57]

FM was selected for study due to various similarities to POTS in addition to the high rates of misdiagnosis. FM is diagnosed ten times more often in women,[26] meaning over 90% of FM patients are female.[22] This parallels the higher incidence of POTS seen in women. Additionally, as in POTS, FM is a chronic and multi-systemic condition, leading to

varied symptoms.[22] Fatigue, Raynaud's, sleep disturbances, irritable bowel syndrome, depression, and anxiety are all considered FM symptoms.[22] The most common symptom, widespread pain, is considered vague and non-specific,[22] mirroring the generalized feeling of malaise seen in POTS and likely contributing to diagnostic error in both conditions.

Another similarity to POTS is the availability of clearly defined diagnostic criteria that is ignored by clinicians. Just as POTS should be diagnosed based on increase in HR of 30 pm upon standing, FM should be diagnosed in patients with widespread pain and tenderness at 11 out of 18 specific tender points (TP), as decided by the American College of Rheumatology.[22, 57] Ming et al. propose physicians learn to be comfortable making a diagnosis of FM based only on a history and TP criteria, as other clinical measures are flawed and contribute to high rates of diagnostic error.[57]

Work being done to combat the high rates of misdiagnosis in FM includes that of Fitzcharles et al., who have identified a clear deficiency in understanding of FM diagnosis among physicians. After following a rheumatology clinic over a period of six months, they determined only 34% of patients referred to the clinic for FM were indeed FM patients; additionally, 17% of those referred to the clinic for conditions other than FM turned out to be actual FM patients.[26] Such findings have been replicated; Calabozo et al. following a rheumatology clinic over the course of a year and found 10% of those referred under other syndromes were actually FM sufferers.[10] These statistics demonstrate a general deficit in physician understanding and ability to differentiate FM from other rheumatic conditions. To combat this, Fitzcharles et al. utilized their research to identify characteristics that should have been indicative of FM in these misdiagnosed patients, citing more fatigue, less

early morning stiffness, and reduction in spinal mobility deficits as tools for selecting FM over other rheumatic diagnoses.[26] Related to this problem is the work of DiFranco et al., who argue one problem for FM diagnosis is the absence of a "gold standard;" no laboratory tests are considered hallmarks for the condition, yet various non-specific lab results seemed to deter physicians from diagnosing FM.[22] Again, as Ming et al. cited, clinicians seem to ignore the easily available TP screening.[57] The work of Fitzcharles et al. demonstrated the potential for such a tool, as their study identified those with FM to have an average of 12.5 TPs, while those without FM averaged only 4 TPs.[26] DiFranco et al. agree, suggesting physicians begin to utilize the TP assessment and consider FM when patient symptoms appear vague and diverse.[22]

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, usually transmitted by the deer tick *Ixodes scapularis*. The infectious disease is characterized by fever, chills, malaise, fatigue, generalized achiness, and head and neck pain.[3, 58] Advanced cases can progress to include carditis, arthritis, and central nervous system deficits.[58] Overall, the symptoms of Lyme disease collectively yield a clinical presentation similar to that of many non-specific viral illnesses, complicating diagnosis, as will be discussed.[3] Thus, similar to POTS, the condition features generalized and diffuse symptoms. Successful antimicrobial therapy exists for those diagnosed with Lyme disease, meaning for many patients,

continued problematic symptoms are more likely to be due to misdiagnosis than failure of treatment.[58]

Despite its commonality in the US – Lyme disease is the most common vector-borne illness – the condition has continued to be frequently misdiagnosed.[3, 58] Estimates suggest the disease could be as much as 12 times more prevalent than is reported.[3] Complicating diagnosis is the potential for overlap between peak tick season and viral outbreaks.[3] Misunderstanding about the presentation of Lyme disease also exists among physicians. The commonly expected "bulls-eye" appearance of the hallmark erythema migrans rash is only present in a minority of patients. Most often, a rash will appear uniform; additionally, in up to 16% of patients, a rash will be entirely absent.[3, 58]

Interestingly, physicians also demonstrate a tendency to over-diagnose Lyme disease, again based on misunderstanding about the condition.[6, 58] Physicians readily perform serological testing in patients with only a few symptoms – malaise, fatigue, etc. – that could be indicative of a number of disorders.[6, 58] Such testing could lead to misdiagnosis and/or over-diagnosis, as both false positives and false negatives are frequent occurrences.[3] Serological testing currently involves a two-step procedure in which a positive ELISA is followed by a Western blot. However, research shows such tests are unable to distinguish between a previous infection and an active infection, and thus have limited utility.[6]

Recommendations for combatting misdiagnosis include considering the isolated geographic origins of the disease when examining patients – most cases occur in northeastern states, meaning those who live in or travel to these areas are far more likely

to have Lyme disease.[3] Physicians should also be aware of biases that could be priming their decision-making processes; for example, media coverage of viral outbreaks.[3] No gold standard exists for Lyme disease diagnostic testing, and automatic Western blotting may not be recommended even in the case of a positive ELISA.[6] Instead, all researchers stress the importance of thorough history and physical exams in the accurate diagnosis of Lyme disease.[3, 6, 58]

Lupus

Lupus (systemic lupus erythematosus, SLE) is a chronic autoimmune disease causing widespread inflammation affecting multiple organ systems.[45] The skin, joints, kidneys, blood, and nervous system are primarily affected.[24] Symptoms include pain, swelling, stiff joints, and fatigue, fever, and rash.[24, 45] Lupus affects mostly women; current estimates suggest 10-12 times more females than males are afflicted.[24, 45] The condition is also observed more frequently in black women than white women.[24] Thus, as in hypothyroidism, fibromyalgia, and POTS, women are predominantly affected.

Additionally, as seen in POTS and a number of the other conditions analyzed, the generalized nature of the symptoms contributes to difficulty in diagnosing the disease.[45, 89] Over 70% of lupus patients are initially misdiagnosed, causing most patients to wait years for an accurate diagnosis. [45, 89] A survey conducted among lupus patients and caretakers revealed lupus patients visited a median three physicians over the course of a median ten

appointments before receiving a correct lupus diagnosis.[45] Rheumatoid arthritis represented the most common incorrect diagnosis; like POTS, many lupus patients were also initially misdiagnosed with a mental health disorder such as depression.[45] Research shows this misdiagnosis is not only physically dangerous, but psychologically and economically burdensome.[89]

Recommendations to reduce the high rate of misdiagnosis seen in lupus highlight increasing awareness and education among medical providers.[24, 45, 89] The triad of fever, rash, and joint pain should be considered particularly indicative of lupus.[24] Proper history taking and physicals are also emphasized.[24] Additionally, surveys suggest physicians may dismiss non-specific and seemingly minor symptoms that, when considered as a whole, significantly affect patient wellbeing. Oversights such as these contribute to high rates of misdiagnoses and diminished patient quality of life.[89]

Common Themes

The major conclusions from the examinations of other frequently misdiagnosed conditions are outlined below; overall, analysis suggests the underlying cause(s) for misdiagnosis are similar across conditions. Diffuse, varied, and multisystemic symptoms (POTS, hypothyroidism, fibromyalgia, Lyme disease, lupus) was a characteristic of all analyzed pathologies, and likely represents the most significant source of diagnostic error. Additionally, a higher prevalence in females was a common trait (POTS, hypothyroidism,

fibromyalgia, lupus). Many arguments from the literature demonstrate a belief that physicians should be able to discern these frequently misdiagnosed conditions from clinical examinations and histories (hypothyroidism, fibromyalgia, Lyme disease, lupus); reliance on more extensive and expensive laboratory testing is problematic. In both hypothyroidism and fibromyalgia, physicians distrust what should be hallmark features of the condition in favor of lab tests (temperature recordings in hypothyroidism and tender points in fibromyalgia syndrome). The idea that a heart rate increase based on an in-clinic screening should be used as such a hallmark feature in POTS is the basis for research presented as future implications later on.

Table 3: Summary of Examination of Misdiagnosed Conditions

Misdiagnosed Condition	Similarities to POTS	Clinical Suggestions
General diagnostic error	(Not applicable)	• Take a thorough history • Improve feedback • Utilize CARE • Consider bias • Consider alternatives
Hypothyroidism	• Multisystemic symptoms • More common in females • Age may skew interpretation • Easy tests are ignored	• Employ routine screening • Consider easy/cheap tests • Adjust screening thresholds
Fibromyalgia	• Multisystemic symptoms • More common in females • Easy tests are ignored	• Prevalence may be higher • Define hallmark features • Increase clinician awareness
Lyme Disease	• Multisystemic symptoms • Blood tests are misleading • Diagnostic tests are lacking • Misunderstanding exists	• Focus on history, physical • Consider patient population • Avoid bias
Lupus	• Multisystemic symptoms • More common in females • Misunderstanding exists	• Focus on history, physical • Increase physician awareness • Define hallmark features

Chapter Five: Meta-Analysis on POTS

Methodology

The following meta-analysis on recent research done on POTS was conducted through a systematic review of available literature on PubMed. Studies were isolated through a search for articles containing both the phrases "postural orthostatic tachycardia syndrome" and "clinical study." This search produced 58 results. While additional focused selection criteria may be necessary for other meta-analyses, the relatively small number of current studies performed on POTS permits a review of all the literature. One study was removed due to language barriers, as the study was written in Chinese. Four other studies were removed after it was determined they did not perform primary research on POTS: one as the research focused on vasovagal syncope patients mimicking POTS, not POTS itself; one for its focus on orthostatic hypotension rather than POTS; and two wherein POTS became a side effect experienced by those in the study rather than the investigated condition. Thus, a total of 53 studies were selected to be reviewed.

As will be discussed below, analysis of the selected articles led to the conclusion that most research on POTS refers to the syndrome as "postural tachycardia syndrome" rather than "postural orthostatic tachycardia syndrome." In order to ensure a significant number of studies on POTS were not missed, the process described above was repeated with the search terms "postural tachycardia syndrome" and "clinical study." This search produced

50 results, 5 of which were articles not selected by the previous method. One of these studies was removed for its focus on postmenopausal symptoms rather than POTS. The remaining four were included in the meta-analysis leading to a total of 57 studies.

Finally, the selection of articles on PubMed was double-checked through the use of the site's filters. A search for "postural orthostatic tachycardia syndrome" yields 507 results; after selecting the article-type filter "clinical trial" the results are narrowed to 45, all of which were selected with the previously described methodology. A search for the variation "postural tachycardia syndrome" yields 370 results; after selecting the filter "clinical trial" the results are narrowed to 50, all of which were selected with the previously described methodology.

Results

See appendix for a table detailing each study. Studies are listed by article title, and described underneath by the topic or objective of the study, sample size, and conclusion. Studies are listed in the order they were reviewed, i.e. by PubMed's judgement of their relevance.

Preliminary Data

A number of ideas can be extracted from the meta-analysis before even addressing the individual research studies. The figures below demonstrate the number of publications referencing POTS (through a search of "postural orthostatic tachycardia syndrome" OR "postural tachycardia syndrome") by year (see Figure 1), as well as the number of clinical studies performed on POTS by year (i.e. those analyzed in the meta-analysis) (see Figure 2).

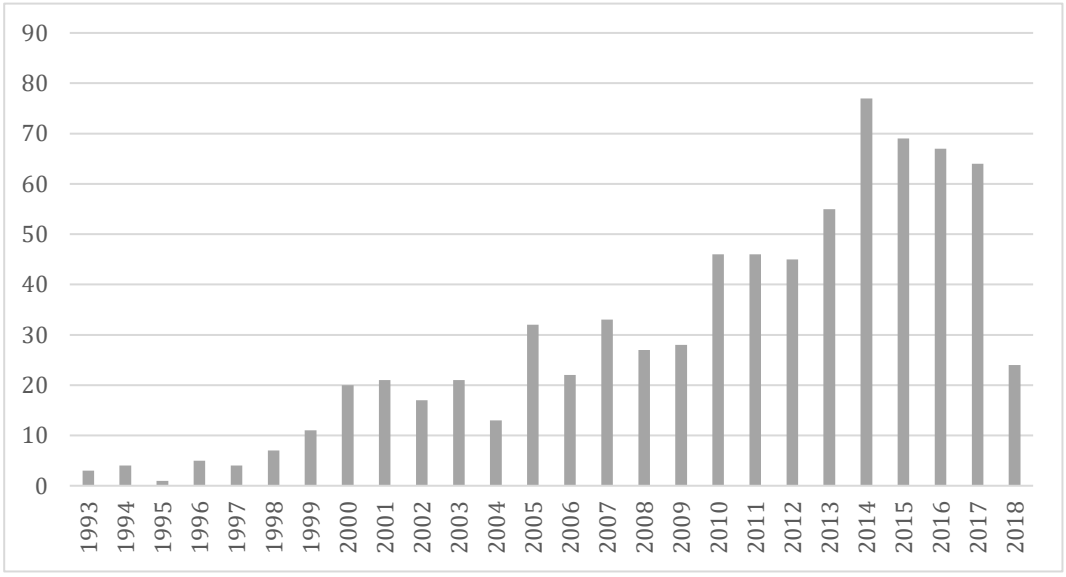

Figure 1: PubMed Review: References to POTS by Year

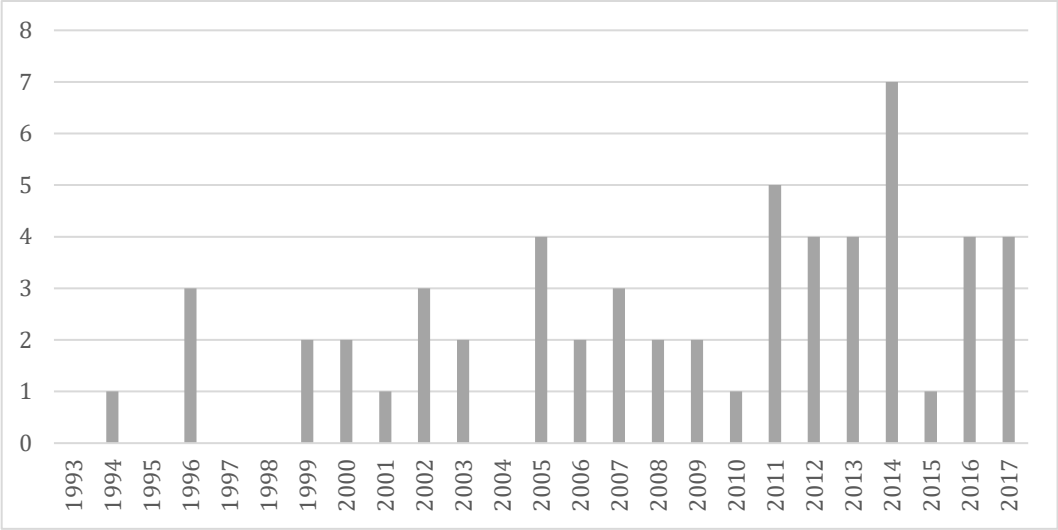

Figure 2: PubMed Meta-Analysis: POTS Clinical Studies by Year

Additionally, analyzing the titles and abstracts of the studies selected for meta-analysis shows there are variations in the terminology researchers use to describe POTS. As depicted in the diagram below (see Figure 3), most studies refer to POTS as "postural tachycardia syndrome" (37 out of 57 studies). Some studies refer to POTS as "postural orthostatic tachycardia syndrome" (17 out of 57 studies). One study refers to POTS as "orthostatic tachycardia syndrome" (1 out of 57 studies). Despite these variations, all of the above studies utilized the acronym "POTS." Two studies, however, differed in their use of "PoTS" rather than "POTS" (2 out of 57 studies).

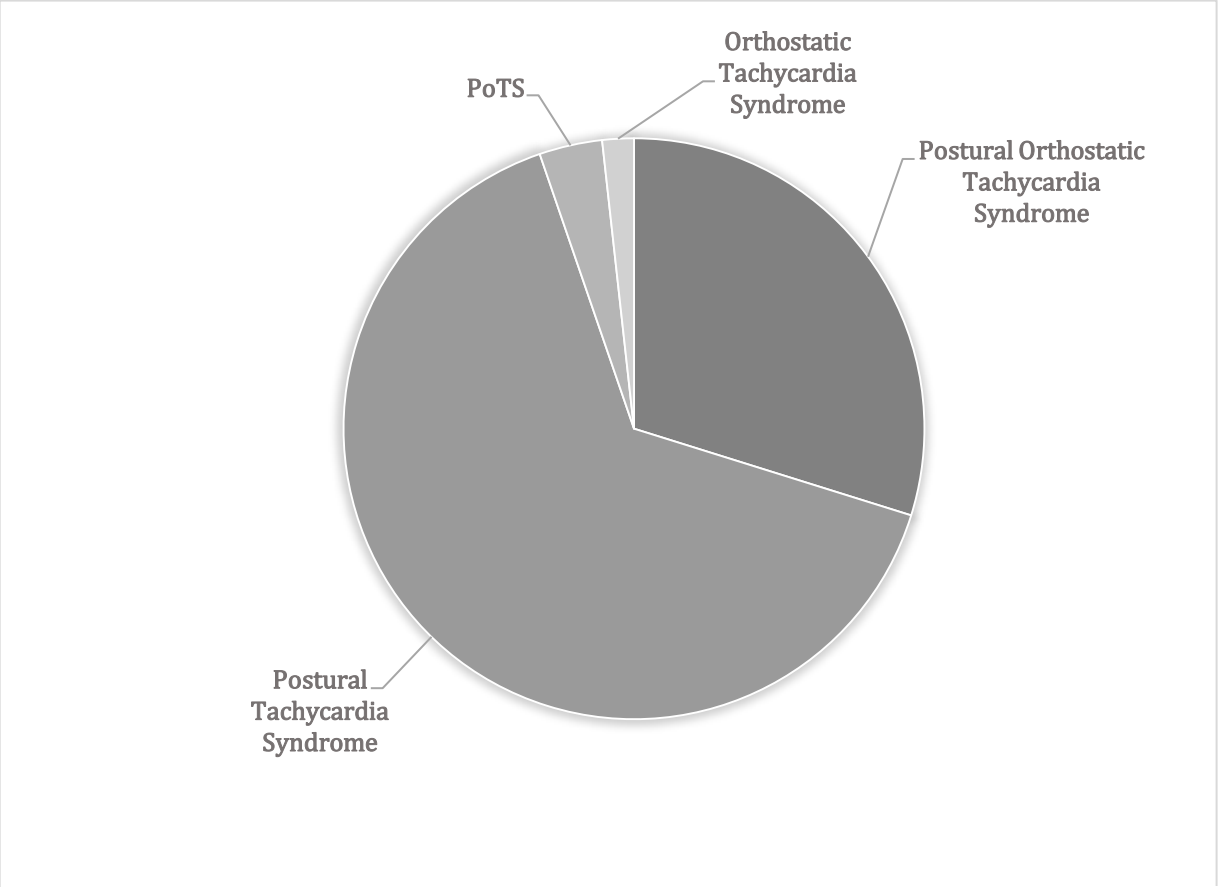

Figure 3: Terminology Used for POTS

Finally, analyzing the impact factors of the journals in which the analyzed studies were published can provide an understanding of how successful clinical studies on POTS have been at disseminating their conclusions (see Table 4). The range of impact factors was 0.190 – 19.896, with an average impact factor of 5.13 and a median impact factor of 3.243.

Table 4: Meta-Analysis Impact Factors

Journal	Number	Impact Factor
AJP Heart and Circulatory Physiology	3	3.348
AJP Regulatory, Integrative & Comparative Physiology	1	2.982
Annals of Pharmacotherapy	1	2.059
Cardiology in the Young	1	0.905
Cardiovascular Therapeutics	1	2.478
The Central European Journal of Medicine	1	0.974
Chinese Journal of Pediatrics	3	0.190
Circulation	6	19.309
Circulation: Arrhythmia and Electrophysiology	2	6.462
Circulation Journal	1	4.124
Clinical Autonomic Research	6	1.276
Clinical and Experimental Pharmacology and Physiology	1	2.010
Clinical Science (London)	1	4.936
European Journal of Neurology	1	3.956
European Neurology	1	1.697
Experimental Brain Research	1	2.395
Frontiers in Neuroscience	2	3.566
Heart Rhythm	2	5.076
Hypertension	2	6.857
Journal of Applied Physiology	2	3.056
Journal of the American College of Cardiology	1	19.896
Journal of the American Heart Association	1	5.117
Journal of the Autonomic Nervous System	3	3.240
Journal of Clinical Psychopharmacology	1	3.243
Journal of Interventional Cardiac Electrophysiology	1	1.826
Journal of the Kentucky Medical Association	1	0.290
Journal of Pediatrics	1	3.890
Journal of Physiology	1	4.739
Journal of Psychopharmacology	1	3.593
Medical Science Monitor	1	1.433
Medicine (Baltimore)	1	1.630
Neurogastroenterology & Motility	1	3.617
Neurology	2	8.320
Pacing and Clinical Electrophysiology	1	1.486
PLoS One	1	2.806

Meta-Analysis

Below, a breakdown of the different types of research identified through the meta-analysis is shown (see Table 5). Research was subdivided into five categories: research on the prevalence of POTS, the etiology and/or characteristics of the condition, diagnostic procedures used to identify POTS, case reports on POTS patients, and treatment. Treatment can be subdivided into non-pharmacological and pharmacological intervention (see Tables 6 and 7).

Table 5: Categories of Clinical Studies

Type of Research	Number of Clinical Studies
Prevalence of POTS	2
Etiology/Characterization of POTS	18
Diagnostic Procedures	2
Case Reports	3
Treatment	35

Table 6: Categories of Non-Pharmacologic Treatment

Type of Non-Pharmacologic Treatment	Number of Clinical Studies
Acute Fluid Ingestion	1
Exercise Training	3
HIRREM	1
Inspiratory Resistance	1
Saline Injections	1
Sleep Treatment	1

Table 7: Categories of Pharmacologic Treatment

Type of Pharmacologic Treatment	Number of Clinical Studies
Ang II Receptor Blocker	1
Ascorbate	1
Beta-Blockers	1
Bisoprolol	1
Desmopressin	1
Esmolol	1
Fludrocortisone	1
Melatonin	1
Metoprolol	3
Midodrine Hydrochloride	7
Modafinil	1
NRI	1
Octreotide	1
Phenylepinephrine	1
Propranolol	3
Pyridostigmine	2
SSRI	1

Discussion

Discussion of Preliminary Data

A look at the increase in the number of studies referencing POTS over time (Figure 1) shows a strong positive trend since its official clinical description in 1993, suggesting the medical field is on the right track in terms of increasing awareness of the condition.

Comparing this pattern to that of the increase in clinical studies on POTS over time (Figure 2) unfortunately seems to suggest the rate of current research on POTS is not keeping up with the apparent surge in awareness of the condition. Very few clinical studies on POTS are produced every year, and many of those that are published originate from the same research group. Finally, as will be discussed later, the studies that are available are failing to address the most important issues.

The variation in terminology used to describe POTS is also problematic. Despite the fact that the acronym POTS definitively stands for "postural orthostatic tachycardia syndrome," only about 30% of studies refer to it as such. The most common phrase, "postural tachycardia syndrome," was used in 65% of studies. While only differing by one word, the removal of the term "orthostatic" could drastically alter understanding of the condition, especially considering an *orthostatic* heart rate/blood pressure test defines the syndrome and could represent a potential screening method for patients. Other terms used, such as "orthostatic tachycardia syndrome" and "PoTS" (implying the acronym stands for only postural tachycardia syndrome, again leaving out the important *orthostatic*), further complicate the literature. Such differences in phrasing could be unimportant for a more familiar condition, but may be significant in this instance. Considering POTS is already an under-recognized syndrome that many physicians may lack experience with, frequent changes in the terminology will only serve to exacerbate confusion in the medical field.

The typical impact factors of the journals publishing clinical studies on POTS are average; rankings above 3 are considered to be in the top 20% of journals according to the Journal Citations Report, meaning 34 of the 57 studies analyzed are in such top-tier

journals. While publishing in more frequently cited journals would not be detrimental, the quality of the journals disseminating information on POTS is likely not the most significant problem facing POTS education.

Discussion of Meta-Analysis

Examining the number of clinical studies published in each of the identified categories (prevalence, etiology/characteristics, diagnostic procedures, case reports, and treatment) shows most current research on POTS is aimed at isolating a cause for POTS and testing pharmacologic intervention, themes that are questionable in terms of their ability to actually change the way POTS is handled in the medical field. As demonstrated by the initial literature review, many causes for POTS have already been identified and characterized. However, it seems most physicians proceed with a similar set of therapies regardless of a patient's underlying etiology. Additionally, the side effects from these treatments can be difficult for the patient to tolerate, leading to the use of over-the counter therapies such as salt tablets, oral rehydration, compression stockings, and exercise training. Thus, characterizing the etiology for POTS (as 32% of studies did) and analyzing treatment options (as 61% of studies did) has limited utility.

Instead, as it seems the most important aspect to recovering from POTS is simply receiving a POTS diagnosis, thus, the types of clinical studies that could have the greatest impact on the rate of misdiagnosis for POTS would be those aimed at developing a more

accurate understanding of the prevalence of the condition (as only 3.5% of studies did) and rethinking diagnostic procedures (again, as only 3.5% of studies did). Most researchers believe the incidence of POTS is greatly underestimated, meaning more comprehensive studies designed to identify POTS patients could lead to higher estimates of its prevalence. A more accurate knowledge of the incidence of POTS could then lead to increased physician awareness, more research studies, and overall reduced rates of misdiagnosis for patients. Similarly, rethinking the diagnostic process to identify patients sooner reduce such rates.

The four studies that did approach prevalence and/or diagnostic procedures show promise that future work in this area could yield positive results. For example, one trial found 9.5% of patients with multiple sclerosis (MS) to have POTS; if the study can be assumed to apply to the population at large, such a statistic could mean tens of thousands of MS patients in the United States have undiagnosed POTS. Another found 32.2% of child syncope cases in China to be due to POTS, again suggesting prevalence could be much higher than initial studies suggest. Studies on diagnostic procedures suggest a history of syncope associated with heart palpitations, dizziness, and headaches is more important for making a POTS diagnosis than a tilt table test, and that that Schellong test could replace the tilt table test with up to 61% specificity.

Finally, although this thesis is targeted at reducing the rate of misdiagnosis for POTS rather than recommending a course of treatment for POTS, a brief look at the performed clinical studies (see Table 5) demonstrates a clear need for a comprehensive study aimed at determining the most effective routes for therapy. With six types of non-pharmacologic and seventeen types of pharmacologic therapy – not to mention the fact that some

therapies could be utilized simultaneously – there are simply too many possibilities for a physician to consider. Even when the analyzed studies compared therapies, only two or three of the twenty-three avenues for treatment were used. A more definitive and standardized method to treat POTS would benefit patients and help physicians not feel overwhelmed by an already confusing condition. Perhaps a flow chart mapping out therapy options could be developed.

Within the aforementioned therapies, five were studied by more than one research group, leading to the need for a meta-analysis of their conclusions. Three studies analyzed the efficacy of exercise training in the treatment of POTS; all found exercise training to be beneficial in reducing symptoms and improving cardiovascular function. Three studies analyzed the use of metoprolol in treating POTS; all found metoprolol reduced symptoms, though one study found it was not as effective at mitigating symptoms as midodrine hydrochloride. Seven studies analyzed the use of midodrine hydrochloride in treating POTS, which seems to be the most common therapy utilized; all found midodrine hydrochloride to be a beneficial therapy, except in the specific case of hyperadrenergic POTS. Midodrine was found to be more effective than metoprolol, salt therapy, and octreotide, but less effective than beta-blockers. Midodrine plus salt therapy was the most effective therapy. Three studies analyzed the use of propranolol in treating POTS; all found propranolol to be beneficial, but only at low doses; additionally, exercise therapy was found to be superior. Two studies analyzed the use of pyridostigmine in treating POTS; one found pyridostigmine to reduce tachycardia, while the other did not. Further research on the utility of pyridostigmine could be useful.

Chapter Six: Future Research

As has been alluded to throughout this thesis, reduction in misdiagnoses of POTS patients is doubtful without widespread implementation of an easier method to identify POTS candidates. While not ideal, the use of a simple supine to standing heart rate and blood pressure screening at the primary care level is the most apparent solution. A report of extended excessive fatigue not alleviated by rest, in addition to lightheadedness and pre-syncope symptoms, should be considered indicators for a potential POTS diagnosis in females of childbearing age. A history of syncope, palpitations, dyspnea, numbness, and/or exercise and heat intolerance should indicate that a mechanism other than anxiety or depression is to blame. Once a health care provider has ruled out ailments such as bacterial and viral infections, a simple ten-minute screening mimicking a tilt table test should be used to consider POTS in such patients. This can be accomplished by asking patients to lie in a supine position for five to ten minutes while monitoring heart and blood pressure, and comparing vital signs after transitioning to a standing position. An increase in heart rate of at least 30 bpm in adults or 40 bpm in teenagers indicates POTS should be considered.

Future research should implement a study of this method on able volunteers in the general population to determine the usefulness of this technique. Demonstrating that the vast majority of non-POTS individuals fail to show a 30 bpm increase in heart rate upon standing would indicate that implementation of this procedure on a wider scale would not unnecessarily identify large numbers of patients for unneeded further testing, and instead flag only those in whom POTS is a real concern. Such a screening would proceed as follows:

Materials: Blood pressure cuff, timer, mat

1. Identify able and willing volunteer
2. Ask volunteer to fill out anonymous form identifying age, gender, and presence of POTS related symptoms
3. Ask volunteer to lie on mat in a supine position in a quiet environment; take heart rate/blood pressure after 5 minutes
4. Ask volunteer to stand; take heart rate/blood pressure immediately and after 2 minutes of standing
5. Record heart rate/blood pressure on aforementioned form

Volunteers who do demonstrate an increase in heart rate of 30 bpm upon standing would be assured that this test does not represent an accurate medical diagnosis. Information about POTS will be available for those interested. See Appendix B for an example of the form to be utilized. Such a research project could be completed in either a clinical or non-clinical environment.

Chapter Seven: Conclusion

An examination of POTS shows that changes can be made in the medical community to reduce the high rates of misdiagnosis surrounding the condition. Although a "gold standard" for POTS diagnosis exists in the form of the tilt-table-test, its expense diminishes its utility in identifying many patients. Thus, changes to clinical practice that can be implemented with minimal time and cost are more likely to reduce misdiagnosis rates and identify POTS patients sooner. Research on other frequently misdiagnosed conditions and a meta-analysis on current POTS research has led to the following proposals for improving POTS diagnosis.

Analysis demonstrates the aspects of POTS that most likely contribute to its misdiagnosis are its generalized symptoms, prevalence in young women, lack of appropriate diagnostic procedures, and the confusion about the condition within the medical community. Obviously, its presentation and epidemiology cannot be changed; however, diagnostic procedures and misunderstanding among medical professionals can be addressed.

History taking represents a critical part of the diagnosis of POTS and other commonly misdiagnosed conditions. Physicians should ensure POTS is considered in a differential diagnosis for patients presenting with fatigue, weakness, dizziness, pre-syncope, and other POTS symptoms. While discussing patient history with such individuals, doctors should ask questions such as "Are your symptoms worse upon standing?" and "When you felt faint (or fainted), what were you doing?" to isolate the underlying cause of

syncope. Orthostatic dizziness or fainting should indicate POTS is a possible diagnosis. Doctors should refrain from frequently interrupting patients during a history, and patients should ensure all aspects of symptoms or syncopal episodes are discussed. Physicians can utilize the aforementioned "CARE" method when working with patients whose diagnoses are not immediately apparent, making sure biased reasoning is not impacting decision-making – for example, assuming a teenaged patient is depressed or accepting the recommendation of another physician. The fact that many misdiagnosed conditions are most often seen in women suggests possible gender biases should be considered and adjusted as well. Finally, the medical community at large must consider the potential benefits in implementing feedback systems that allow doctors to learn from their mistakes.

Analysis of other frequently misdiagnosed conditions demonstrates many such ailments are characterized by easy in-clinic assessments that could be used to diagnose patients; however, physicians seem to distrust such measures, and instead rely on often inaccurate laboratory testing. POTS should be considered one of the conditions wherein this flawed system is at work. The clinical definition of POTS - an increase in heart rate of 30 bpm or more upon standing - represents what could be an overlooked, inexpensive, and easy method to identify POTS patients in clinics. Patients who present as likely POTS candidates based on age, gender, and symptomology should be asked to complete a simple heart rate/blood pressure test while seated and while standing in order to rule out POTS.

A standardized screening utilizing such a heart rate/blood pressure test could easily identify POTS patients with minimal time and effort in the appropriate settings; family medicine, cardiovascular, and neurological clinics should consider implementing a standing

heart rate/blood pressure test in addition to a seated assessment. Such a screening would not represent an extra cost to physicians or hospitals, and could be completed while patients await the doctor during an appointment. The heart rate/blood pressure screening test would not only identify POTS patients, but also those with orthostatic hypotension and other forms of dysautonomia. Future research should determine the utility of such a screening test in the clinical setting.

Current research on POTS unfortunately fails to address the aspects of the condition that contribute to misdiagnosis. Meta-analysis shows most current research on POTS focuses on the etiology of the condition (32%) or pharmacological therapy (47%). A holistic review of POTS, however, shows these efforts are misguided. Although research on the etiology of the disease has helped to characterize the condition, such information does not play a role in patient diagnosis and patient quality of life, as it is highly unlikely that patients outside of a hospitalized clinical study will undergo testing to determine which subtype of POTS (hypovolemic, neuropathic, hyperadrenergic, etc.) best explains their symptoms. Thus, focused research on pharmacological therapy targeted to such subtypes will likely not impact many patients – administration of medication seems to more usually follow a trial-and-error process. Few POTS researchers are approaching the condition with an interest in diagnostic procedures (3.5%). This deficit must be corrected, as simply reaching an accurate POTS diagnosis is often the turning point for dysautonomia patients – studies show accurate diagnosis and subsequent therapy leads to improvement in 80% of patients, with 60% reaching a near-normal quality of life.[76] Most therapies that mitigate POTS symptoms are over-the-counter or non-pharmacological (salt tablets, supplements,

fluid ingestion, exercise therapy). For those patients that do try pharmacological therapy, many treatment options are available and have been well characterized. Thus, the most difficult, yet arguably most significant, aspect of treating a POTS patient is simply identifying the correct condition (POTS) and providing patient education.

Before physicians can provide patient education, however, misunderstandings about POTS within the medical community must be addressed. The general increase in both POTS clinical studies and articles referencing POTS since its clinical description in 1993 suggests awareness is increasing; however, when compared to other conditions, the amount of research being performed on POTS is still minimal. Additionally, misunderstanding may increase while awareness increases due to the variation in terminology used to refer to POTS. Only 30% of studies utilize the term "postural orthostatic tachycardia syndrome," instead referring to the syndrome as "postural tachycardia syndrome" or "orthostatic tachycardia syndrome." Finally, the fact that POTS was not defined until 1993 presents the possibility for generations of practicing physicians unaware of the condition at all.

In conclusion, despite the difficulties surrounding POTS diagnosis, slight changes to clinical practice could dramatically reduce the high rates of misdiagnosis. Quicker detection and accurate diagnosis would improve the health-related quality of life of many POTS patients unaware of their condition. Physicians should consider the aforementioned recommendations on history-taking and heart rate/blood pressure screenings, while researchers studying POTS should focus on streamlining diagnostic procedures.

Appendix A: Meta-Analysis

Table 8: Meta-Analysis Summary

	Study Title		
Source Number	**Topic**	**Sample Size**	**Conclusions**
62	*Understanding the placebo effect in clinical trials for postural orthostatic tachycardia syndrome*		
	Placebo on tachycardia	21	Decrease in tachycardia over time is due to physiological changes, not a placebo
39	*Melatonin reduces tachycardia in postural tachycardia syndrome (POTS): a randomized, crossover trial*		
	Melatonin on tachycardia	78	Oral melatonin reduced orthostatic tachycardia more so than placebo
33	*Inspiratory resistance improves postural tachycardia: a randomized study*		
	Inspiratory resistance on orthostatic tolerance	26	Negative intrathoracic pressure improves heart rate control
2	*Low-dose propranolol and exercise capacity in postural tachycardia syndrome: a randomized study*		
	Propranolol on exercise tolerance	18	Propranolol may benefit POTS patients during exercise by improving SV and HR
37	*Structural and functional small fiber abnormalities in the neuropathic postural tachycardia syndrome*		
	Identify neuropathic from non-neuropathic POTS patients	34	Nerve fiber density, quantitative sensory testing, and autonomic testing can distinguish neuropathic from non-neuropathic POTS
94	*Midregional pro-adrenomedullin as a predictor for therapeutic response to midodrine hydrochloride in children with postural orthostatic tachycardia syndrome*		
	MR-proADM on predicting midodrine hydrochloride reponse	77	MR-proADM can be used to predict efficacy of midodrine hydrochloride
14	*A clinical manifestation-based prediction of hemodynamic patterns of orthostatic intolerance in children: a multi-center study*		
	Necessity of tilt table test in diagnosis	629	History of syncope associated with palpitation, dizziness, headache was most important for diagnosis

30	*Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome*		
	Exercise vs. propranolol in treating POTS	34	Exercise training is more effective at mitigating symptoms than propranolol
47	*Hemodynamic profiles and tolerability of modafinil in the treatment of postural tachycardia syndrome: a randomized, placebo-controlled trial*		
	Modafinil on cognitive, tachycardia symptoms	54	Modafinil does not worsen tachycardia and thus could treat cognitive symptoms
15	*Midodrine hydrochloride is effective in the treatment of children with postural orthostatic tachycardia syndrome*		
	Midodrine vs. metoprolol for POTS	53	Midodrine is more effective than metoprolol and/or conventional therapy
40	*Effects of norepinephrine reuptake inhibition on postural tachycardia syndrome*		
	NRI on POTS symptoms	27	NRI drugs increase HR and worsen symptoms in POTS
54	*Acute hemodynamic effects of a selective serotonin reuptake inhibitor in postural tachycardia syndrome: a randomized, crossover trial*		
	SSRI on mitigating POTS symptoms	39	SSRIs are not associated with reduced HR or improved symptoms in POTS
59	*Altered systemic hemodynamic and baroreflex response to angiotensin II in postural tachycardia syndrome*		
	Response to Ang II infusion	28	POTS patients have impaired Ang II response and baroreflex function
17	*Desmopressin acutely decreases tachycardia and improves symptoms in the postural tachycardia syndrome*		
	Desmopressin on treating POTS	30	Desmopressin reduces tachycardia and other symptoms by increasing blood volume
48	*Outcomes in adolescents with postural orthostatic tachycardia syndrome treated with midodrine and beta-blockers*		
	Midodrine vs. beta-blockers for POTS	47	Midodrine and beta-blockers both improved symptoms, but beta-blockers are more associated with improvement
85	*Ascorbate improves circulation in postural tachycardia syndrome*		
	Ascorbate on low-flow POTS patients	20	Ascorbate could mitigate POTS symptoms but is excreted too rapidly

27	*Use of an allostatic neurotechnology by adolescents with postural orthostatic tachycardia syndrome (POTS) is associated with improvements in heart rate variability and changes in temporal lobe electrical activity*		
	Use of HIRREM for brain oscillations	7	Reduced autonomic symptoms are seen after use of HIRREM neurotechnology
41	*Postural orthostatic tachycardia syndrome is associated with platelet storage pool deficiency*		
	Etiology of POTS; platelet pool deficiency	181	Platelet pool deficiency is a frequent comorbidity seen in POTS
70	*Propranolol decreases tachycardia and improves symptoms in the postural tachycardia syndrome: less is more*		
	Propranolol on tachycardia	54	Low dose propranolol mitigates tachycardia and improves symptoms; high dose may worsen symptoms
78	*Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome*		
	Circulatory control and exercise conditioning	19	Short-term exercise training improves cardiovascular response during exercise
93	*Therapies for postural tachycardia syndrome in children*		
	Oral rehydration salts, metoprolol, midodrine hydrochloride	118	All therapies improve symptoms; most effective is salts plus midodrine
72	*A double-blind placebo-controlled cross-over study of the vascular effects of midodrine in neuropathic compared with hyperadrenergic postural tachycardia syndrome*		
	Neuropathic vs. Hyperadrenergic POTS	20	Midodrine is effective in neuropathic, but not hyperadrenergic, POTS
32	*Nitric oxide and regulation of heart rate in patients with postural tachycardia syndrome and healthy subjects*		
	NO on cardiovascular regulation	13	No evidence for NO dysfunction in POTS
63	*The utility of Valsalva maneuver in the diagnosis of orthostatic disorders*		
	Hemodynamic responses in OI	66	Valsalva maneuver response can differentiate types of OI
92	*Acute fluid ingestion in the treatment of orthostatic intolerance – important implications for daily practice*		
	Water intake and OI	14	Water and clear soup improve POTS OI

9	*Vascular responses to orthostatic stress in patients with postural tachycardia syndrome (POTS), in patients with low orthostatic tolerance, and asymptomatic controls*		
	Cardiac response in POTS vs. low OI	49	POTS may be associated with peripheral neuropathy; problems are due to tachycardia, not hypotension
11	*Case reports and review of postural orthostatic tachycardia syndrome*		
	Case reports	2	POTS likely more common than we know; important to make correct diagnosis
28	*Clinical improvement in patients with orthostatic intolerance after treatment with bisoprolol and fludrocortisone*		
	Bisoprolol and fludrocortisone on symptoms	22	POTS may be due to hyperadrenergic or hypovolemic response; bisoprolol and fludrocortisone mitigate symptoms
12	*Effect of selective alpha 1 receptor agonist in the treatment of children with postural orthostatic tachycardia syndrome*		
	Midodrine on symptoms	55	Use of midodrine hydrochloride is significantly more effective than salt alone
31	*Pyridostigmine in the treatment of orthostatic intolerance*		
	Pyridostigmine and HR	106	Pyridostigmine bromide reduces standing HR, but not more than placebo
36	*The international POTS registry: Evaluating the efficacy of an exercise training intervention in a community setting*		
	Exercise therapy	103	Training is effective in treating POTS; more research is needed long-term
83	*Splanchnic hyperemia and hypervolemia during Valsalva maneuver in postural tachycardia syndrome*		
	Splanchnic blood flow POTS vs. control	27	POTS blood flow changes may be related to increase in splanchnic blood flow
52	*Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure*		
	Venous pooling	37	Arterial function is intact but venomotor function impaired
87	*Reflex vascular defects in the orthostatic tachycardia syndrome of adolescents*		
	Venous pressure and blood low	35	Subsets of POTS seem to exist: high Pv/low flow, and low Pv/high flow

84	*Clinical and physiological effects of an acute alpha 1 adrenergic agonist and a beta 1 adrenergic antagonist in chronic orthostatic intolerance*		
	Phenylephrine and esmolol	14	Phenylephrine (alpha 1 agonist) improves OI; esmolol (beta 1 antagonist) does not
86	*Angiotensin II type I receptor blockade corrects cutaneous nitric oxide deficit in postural tachycardia syndrome*		
	Losartan on NO-dept. vasodilation	27	Ang II type 1 receptor blockade via losartan corrects NO-dept. vasodilation
69	*Acetylcholinesterase inhibition improves tachycardia in postural tachycardia syndrome*		
	Pyridostigmine on tachycardia	17	Pyridostigmine significantly reduces tachycardia and relieves symptoms
77	*Cerebral autoregulation is preserved in postural tachycardia syndrome*		
	Cerebral autoregulation POTS vs. control	44	Cerebral perfusion is not altered in most POTS patients
16	*Underlying diseases in syncope of children in China*		
	Syncope etiology	888	Of 888 children suffering from syncope in China, 32.2% were found to have POTS
75	*Certain cardiovascular indices predict syncope in the postural tachycardia syndrome*		
	Syncope predictors	43	While increased HR is universal, TPR response to TTT varies
46	*Experimental induction of panic-like symptoms in patients with postural tachycardia syndrome*		
	Relationship POTS and panic disorder	22	POTS symptoms are different and distinguishable from panic disorder
21	*Cerebrovascular mechanisms in neurocardiogenic syncope with and without postural tachycardia syndrome*		
	Syncope etiology in TTT	16	Cerebral autoregulation is not affected
43	*Treatment of postural tachycardia syndrome: a comparison of octreotide and midodrine*		
	Octreotide and midodrine on OI	15	Both octreotide and midodrine mitigate tachycardia on standing; both is not better
50	*Self-reported post-exertional fatigue in Gulf War veterans: roles of autonomic testing*		
	Autonomic dysfunction in veterans	28	One veteran complaining of fatigue was found to have POTS

91	*Schellong test in orthostatic dysregulation: a comparison with tilt-table testing*		
	Schellong test vs. TTT	67	Schellong test specificity only 61% that of TTT, but can be first step to diagnosis
7	*Diagnosis of tachycardia syndromes associated with orthostatic symptoms*		
	POTS HR	18	POTS HR is not affected during Valsalva maneuver or deep breathing
61	*Postural tachycardia syndrome: time frequency mapping*		
	Neuropathic POTS	40	Impaired Valsalva maneuver and distal sudomotor dysfunction indicates neuropathic POTS
38	*Cardiac sympathetic dysautonomia in chronic orthostatic intolerance syndromes*		
	Norepinephrine levels	99	POTS patients have increased norepinephrine release
82	*Pooling in chronic orthostatic intolerance: arterial vasoconstrictive but not venous compliance defects*		
	Venous pooling	26	Venous pooling is due to arterial defects, not increased venous compliance
25	*Mechanisms underlying reflux symptoms and dysphagia in patients with joint hypermobility syndrome, with and without postural tachycardia syndrome*		
	GI problems	30	Reflux problems in JHS are more likely when comorbid with POTS
42	*Postural orthostatic tachycardia predicts early conversion to multiple sclerosis after clinically isolated syndrome*		
	POTS and MS	84	POTS identified in 9.5% if MS patients; could be useful for diagnosis
74	*Effects of intermittent intravenous saline infusions in patients with medication-refractory postural tachycardia syndrome*		
	Saline injections	57	IV saline significantly reduces symptoms and improves quality of life
51	*Salivary cortisol levels predict therapeutic response to a sleep-promoting method in children with postural tachycardia syndrome*		
	Sleep treatment predicted by cortisol	60	Salivary cortisol levels at waking may predict sleep-treatment utility

20	*Possible relationship between chronic fatigue and postural tachycardia syndrome*		
	POTS in CFS	5	All five CFS patients analyzed were found to have POTS
34	*The hemodynamic and neurohumoral phenotype of postural tachycardia syndrome*		
	Characterizing POTS	231	Evidence is provided for increased epinephrine & NE and impaired RAAS
80	*Microvascular filtration is increased in postural tachycardia syndrome*		
	Peripheral vasoconstriction	25	Peripheral edema in POTS is due to increased microvascular filtration
13	*A multicenter study on treatment of autonomous nerve-mediated syncope in children with beta-receptor blocker*		
	Treatment with beta receptor blocker	54	Metoprolol reduced symptoms in 68.75% of POTS patients

Appendix B: Future Research

Reducing Rates of Misdiagnosis for Postural Orthostatic Tachycardia Syndrome Health Questionnaire

Participation in this study is completely voluntary. If you choose to participate, identifying information will not be collected. Vital signs (heart rate and blood pressure) will be used for research purposes only. Thank you for your time.

Sex: ☐Female ☐Male **Age:** ☐18-29 ☐30-39 ☐40-49

Have you experienced any of the following symptoms for longer than six consecutive months? (Check all that apply)

☐Excessive fatigue	☐Lightheadedness	☐Shortness of breath	☐Difficulty standing still
☐Nausea/GI discomfort	☐Reddish-blue limbs	☐"Brain Fog"	☐Heart palpitations
☐Numbness	☐Headache	☐Inability to tolerate heat	☐Inability to tolerate exercise
☐Passing out	☐Feeling faint	☐Weakness	☐Feeling shaky
☐Need to drink excessive water		☐Do not feel refreshed after sleep	

_____ **The below section is for researcher use only** _____

Supine (5 minutes)	Standing (immediate)	Standing (2 minutes)
Heart Rate: _____ bpm	Heart Rate: _____ bpm	Heart Rate: _____ bpm
Blood Pressure: _____	Blood Pressure: _____	Blood Pressure: _____

Final Heart Rate Increase: _____
Significant BP decrease? ☐Yes ☐No
Potential POTS Candidate? ☐Yes ☐No

An increase in heart rate of 30 bpm or more without a large drop in blood pressure indicates an individual is at risk for having POTS.

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