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Adolescent Fatigue, POTS, and Recovery: A Guide for Clinicians

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Abstract

Many teenagers who struggle with chronic fatigue have symptoms suggestive of autonomic dysfunction that may include lightheadedness, headaches, palpitations, nausea, and abdominal pain. Inadequate sleep habits and psychological conditions can contribute to fatigue, as can concurrent medical conditions. One type of autonomic dysfunction, postural orthostatic tachycardia syndrome, is increasingly being identified in adolescents with its constellation of fatigue, orthostatic intolerance, and excessive postural tachycardia (more than 40 beats/min). A family-based approach to care with support from a multidisciplinary team can diagnose, treat, educate, and encourage patients. Full recovery is possible with multi-faceted treatment. The daily treatment plan should consist of increased fluid and salt intake, aerobic exercise, and regular sleep and meal schedules; some medications can be helpful. Psychological support is critical and often includes biobehavioral strategies and cognitive–behavioral therapy to help with symptom management. More intensive recovery plans can be implemented when necessary.

Introduction

Fatigue is common during adolescence, with 31% of American adolescents experiencing significant morning tiredness more than one day each week.[1] A significant number of affected individuals are unable to participate in some routine daily activities[2] or are debilitated with fatigue.[3] Wolbeek et al.[2] found that approximately 20% of adolescent Dutch girls and 6% of adolescent Dutch boys reported experiencing severe fatigue, with almost 50% of those girls and 35% of those boys reporting fatigue lasting greater than 3 months. Consequently, adolescent fatigue is a common presenting complaint in clinics around the world. In these tired patients, the diagnosis of chronic fatigue is evident based on the clinical course and examination findings that do not reveal any other worrisome fatigue-causing condition.

In our practices, we frequently encounter chronically fatigued patients who also report symptoms of dizziness, lightheadedness, nausea, vomiting, sleep disturbances, pain, altered mental quality (sometimes described as “brain fog”), or altered temperature sensations as well as changes in sweating and purplish skin discoloration in dependent extremities. Many of these symptoms are autonomic in nature and suggest some sort of autonomic dysfunction in this group of patients. There is increasing evidence that chronic fatigue is often

accompanied by significant dysfunction in the autonomic nervous system. It seems likely that chronic fatigue and autonomic dysfunction are often overlapping conditions.

Autonomic dysfunction is a broad umbrella term for conditions involving abnormally altered regulation of the involuntary nervous system. Postural orthostatic tachycardia syndrome, POTS, is a type of autonomic dysfunction characterized by chronic fatigue, orthostatic intolerance, and excessive postural tachycardia. Some other different and distinct types of autonomic dysfunction are neurocardiogenic syncope, pure autonomic failure, and orthostatic hypotension. In clinical practice, the terms “autonomic dysfunction” and “POTS” are sometimes used interchangeably. Nonetheless, some physicians do not yet recognize POTS as a legitimate physical diagnosis.

Each patient with debilitating fatigue or POTS is unique, but their stories often sound similar.[26] Parents and adolescent patients with POTS often describe the long and difficult process they experience from the moment they became ill to decreased school attendance with dropped extracurricular activities and poor academic performance to visiting a variety of doctors and, frequently, numerous medical centers in order to find answers about their child's illness. In this process, they often receive different diagnoses, try numerous medications, and sometimes even undergo surgical procedures. As a result, there are significant social and economic consequences related to undiagnosed POTS. Without accurate and timely diagnosis, education, and motivation to incorporate new healthy living practices into their lives to remediate their symptoms, affected adolescents are at heightened risk for academic decline, truancy, and delayed graduation from high school and college. This condition takes a financial toll on families due to personal costs related to multiple health care visits, out-of-pocket expenses for non-insurance-covered integrative alternative therapies, missed work, and travel expenses to multiple medical centers for care.

This article pulls together input from the world's medical and psychologic literature combined with the experiences of the 14 authors who represent general pediatrics and nine pediatric sub-specialties at five institutions on two continents. In so doing, we explore links between fatigue and autonomic dysfunction as well as relationships between fatigue and multisystem symptoms. We seek to provide a broad understanding of the underlying pathophysiology of chronic fatigue and autonomic dysfunction that will help readers understand multidisciplinary treatment modalities that offer affected adolescents good hope for full recovery.

Fatigue

Definitions, Incidence/Prevalence, and Factors Associated With Fatigue

Chronic fatigue (CF) is common in adolescents. The classification of chronic fatigue ranges from prolonged fatigue (>1-month duration) to chronic fatigue syndrome (CFS). CFS is characterized by 6 or more months of debilitating physical and mental fatigue for which an alternate medical and psychiatric explanation is lacking. The current case definition of CFS and the conceptual framework for its study was proposed by the International Chronic Fatigue Syndrome Study Group at the Centers for Disease Control and Prevention in 1994.[4] CFS is described as clinically evaluated, unexplained, persistent, or relapsing chronic fatigue

that is of new or definite onset [has not been lifelong]; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities. Additionally, it is accompanied by 4 or more of the following symptoms: self-reported short-term memory impairment, sore throat, tender cervical or axillary lymphadenopathy, musculoskeletal pain, non-restorative sleep, and post-exertion malaise.[4]

Fatigue is reported in about 20% of pediatric patients who seek care at tertiary medical centers, presumably often related to other medical conditions, and is often considered a post-infectious phenomenon.[5] According to the British Child and Adolescent Mental Health Survey 1999, CF was present in 0.57% and CFS in 0.19% of the 5–15-year-old children in a cross-sectional study.[6] National Jewish Medical and Research Center in 2004 reported the baseline weighted prevalence of CFS-like illness among adolescents to be 338 per 100,000.[5] Conversely, the estimated prevalence of CF and CFS among adults ranges from ~1.8% to 9% and ~0.075% to 0.42%, respectively.[7,8] Incidence rates for CF and CFS in adolescents are reported as 1.1% and 0.5%, respectively.[3]

Female gender, older age, physical inactivity, depression, and anxiety have been shown to be independent risk factors for CFS among adolescents.[3] Furthermore, increased nightlife activities and shorter sleep duration have also been identified as predictors of CFS.[9] In our experience, physical inactivity and subsequent deconditioning are the most frequent predisposing factors for CF. It is not uncommon to see adolescents entrapped in a vicious cycle of deconditioning and fatigue, usually following a period of prolonged bedrest due to an otherwise self-limited viral infection. One representative scenario would be a 16-year-old female who suffered from mononucleosis and 6 months later has lingering fatigue, which has caused her to be on homebound schooling. She has dropped out of volleyball and basketball and now has limited contact with her friends, but she does have phone contact with two friends. She tries to go to a friend's house about once a week, but she is usually too tired so her friend may come over to her house. She complains of a chronic daily headache, dizziness when she stands up, abdominal pain, pain in her legs, extreme fatigue, and inability to exercise. Her course is a downward spiral of deconditioning, fatigue, and social withdrawal.

Sleep and Fatigue

When evaluating a patient for fatigue, it is important to assess sleep, looking for sleep disorders and poor sleep hygiene since chronic fatigue can result from sleep that is either quantitatively or qualitatively inadequate. But, why do we sleep anyway? There are a number of theories proposed including memory consolidation and pruning, immune regulation, brain plasticity, and restorative theory.[10,11] If there is insufficient sleep or poor quality of sleep, a person does not feel well. One may feel tired and anergic or frankly sleepy with an increased propensity to doze during the daytime. Sleep deprivation has been associated with learning and behavioral difficulties, inattentiveness and impulsivity, mood disorders, weight problems, and increased risk-taking behaviors.[12,13]

The vast majority of at least American adolescents are sleep deprived with only 20% getting the recommended 9 ¼ h of sleep. Average sleep duration is 7–7 ½ h, yet 70% of parents

think teens are sleeping enough.[14] The reasons for insufficient sleep are multifactorial including a physiologic shift in circadian rhythms linked to Tanner stage. Adolescents transitioning through puberty have a physiologic delay in bedtime of about 2 h.[15] Unfortunately, school start times do not shift in the same fashion, and sleep needs do not change significantly across adolescence despite later bedtimes; hence, there is innate sleep deprivation.[16] Adolescents on average fall asleep around 10:00–10:30 p.m. and have to awaken on average at 6:30 a.m., so there is a sleep debt accumulated on a regular basis which can never truly be completely recovered.[14] Adolescents often try to sleep in on the weekends but this can compound the problem by decreasing the sleep drive on Sunday nights leading to a later bedtime and more sleep debt Monday morning.

To further compound matters, environmental and lifestyle factors can significantly affect sleep in adolescents.[17] There are increasing demands on adolescents to enhance their college applications with extracurricular activities including sports, clubs, and volunteer activities. Frequently, young people hold part-time jobs in addition to attending school, either out of choice or necessity. An overly full daily schedule often leads to restricted sleep hours. Increases in screen time (often for non-educational gaming and entertainment) and self-imposed demands for 24 h per day of availability (often for social media with frequent interruptions and obligations for multi-tasking) lead to reduced deep sleep. Excessive use of communication and entertainment technology contributes to the increased screen time, which is not only mind-activating but can also interfere with the production of the sleep stabilizing hormone melatonin.[14,18,19]

The two major determinants of when and how long we sleep are process S and process C.[20] Process S is essentially the sleep drive, meaning the longer a person is awake, the stronger the drive is to sleep. Process C is the circadian rhythm which is tied intrinsically to hormonal and temperature changes and extrinsically to light exposure. Young children have a strong process S whereas adolescents have a greater tendency to “override” this. A 7-year-old child would find it next to impossible to stay up until 1 a.m., but the teen would easily do this.

Young people with chronic fatigue and/or POTS are at risk of having dysregulation of both processes S and C. Typically they spend a lot of time resting and sleeping off and on during daytime hours in darkened rooms such that sleep drive at night is poor and circadian rhythms become disrupted. This results in significant complaints of both fatigue and sleepiness.

Psychological Correlates of Chronic Fatigue

When studying a school-based cohort of 3454 Dutch students, ter Wolbeek et al.[2,9,21] attempted to study the natural course of chronic fatigue. Higher levels of depression and anxiety were the best predictors of fatigue severity in both boys and girls. Other factors that correlated with the severity of fatigue were decreased participation in sports (boys and girls) and shorter nocturnal sleep on schooldays (girls only) and shorter nocturnal sleep on weekends (boys only). In a follow-up study of these patients 6 and 12 months later, the authors founds that teens who were persistently fatigued had higher levels of depression and anxiety at the beginning of the study as well as slept shorter lengths of time and participated in less physical activity.[9] Similarly, 4 years later, an increase in chronic fatigue-related symptoms was predicted by anxiety and decreased physical activity during adolescence.[21] In

a US population, Smith et al.[22] also found that adolescents meeting CDC criteria for chronic fatigue syndrome had higher anxiety and depression scores than healthy adolescents.

Although this group of studies does not answer the question of whether severe fatigue causes an increase in depression and anxiety or whether high levels of anxiety and depression predispose someone to fatigue, they do make clear that the symptoms of fatigue, anxiety, and depression cluster together. As such, it seems important to assess both anxiety and depression in teens being assessed for POTS or fatigue. Effective treatments for both anxiety and depression are available and may help improve the course of teens experiencing fatigue-related illnesses. Assessment and intervention related to sleep and physical activity also appear important in controlling the symptoms of chronic fatigue whether the patient is anxious or depressed or not. Further evidence for the role of psychological factors in patients with chronic fatigue comes from the fact that personal and web-based cognitive–behavioral therapy can be effective in treating chronic fatigue.[23]

Diagnostic Considerations and Evaluation of a Fatigued Adolescent

Thus, chronic fatigue is common and multifactorial in adolescents. Even with this backdrop of common lifestyle and psychological factors related to chronic fatigue, however, medical evaluation is important—at least to rule out hidden disease. Even sleep-deprived stressed teenagers can also have underlying serious illness.

The diagnostic evaluation of fatigued individuals includes a detailed assessment directed toward identification of an underlying condition that requires treatment, as well as to identifying sleep problems and active psychological illness. Thus, the diagnosis of CF or CFS requires a thorough history that covers medical and psychiatric symptoms as well as the psychosocial circumstances of the patient at the onset of their fatigue. A complete physical examination is essential to exclude alternative explanations of fatigue. Since there is no diagnostic test to confirm CF, the recommended laboratory tests are meant to confirm or exclude other etiologies. The International Chronic Fatigue Syndrome Study Group in 1994 recommended a minimum battery of laboratory screening tests including complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; thyroid-stimulating hormone; and urinalysis.[4] With increasing recognition of autonomic dysfunction, it seems likely that chronic fatigue syndrome and autonomic dysfunction are overlapping conditions so it is important to assess for POTS. Testing for POTS will be discussed in detail in a later section.

Additional laboratory or imaging studies have not been shown to be useful in making the diagnosis of CFS; however, they may be obtained if deemed necessary given the information obtained through history and physical examination.[24]

The diagnosis of unexplained chronic fatigue cannot be made if patient has an active medical condition that explains chronic fatigue such as hypothyroidism, primary sleep disorder, or a medication side effect. In addition, the presence of a previously diagnosed condition that may not have fully resolved such as malignancy or hepatitis B or C infection

precludes the diagnosis of CFS. Certain psychiatric conditions including major depressive disorder with psychotic or melancholic features, bipolar disorder, schizophrenia, delusional disorders, anorexia nervosa or bulimia as well as substance abuse exclude a patient from the diagnosis of CFS. Moreover, CFS cannot be diagnosed in patients with morbid obesity with a body mass index of more than 45.[4]

The diagnosis of CFS is not excluded by conditions such as fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or non-melancholic depression, neurasthenia, and multiple chemical sensitivity disorder. Similarly, adequately treated conditions such as hypothyroidism, Lyme disease, or syphilis do not exclude the diagnosis of CFS.[4]

POTS

Autonomic Abnormalities in “Chronic Fatigue” Patients

Our chronically tired patients often have findings suggestive of autonomic dysfunction, and others have reported similar observations. Dizziness, palpitations, diarrhea, and even nocturia have been reported as common symptoms experienced by patients with CFS.[25] In addition, patients with postural orthostatic tachycardia syndrome, a clinical manifestation of autonomic dysfunction, often report chronic fatigue.[26]

The association between chronic fatigue and autonomic abnormality was first recognized in 1932 when Sir Thomas Lewis described a young soldier with longstanding fatigue who developed syncope and relative bradycardia following venipuncture.[27] Large epidemiological studies in 1990s confirmed the association between hypotension and fatigue.[28,29] In 1995, neurally mediated hypotension was demonstrated in adolescents who fulfilled the CDC-defined diagnostic criteria of CFS, and their symptoms improved remarkably after initiation of atenolol for treatment of hypotension.[30]

In addition, patients with CFS have been shown to have higher resting heart rates and blood pressure values compared to controls.[31] They have also been shown to have elevated nocturnal blood pressures and heart rate on ambulatory blood pressure monitoring.[32] Patients with CFS demonstrate sympathetic overactivity when subjected to stress.[25,33] These patients have also been shown to have increased heart rate and decreased heart rate variability during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggesting a state of sympathetic predominance and neuroendocrine alterations.[34] Furthermore, patients with CFS have a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.[35] While further research in patients who qualify for a diagnosis of chronic fatigue syndrome is needed, these observations as a whole suggest that there is likely significant involvement of the autonomic system in the pathogenesis of CF.

History and Definition(s) of POTS

Adolescent fatigue is not new. For millennia, teenagers have experienced bothersome fatigue. Since at least the mid-1800s, fatigue (neurasthenia) was commonly diagnosed,[36] and old descriptions of this condition overlap significantly with what we now call either chronic fatigue syndrome or POTS. Fatigue in conjunction with orthostatic intolerance was reported

in adolescents who otherwise would have served in America's Civil War.[37] The diagnoses of “chronic fatigue” and “chronic fatigue syndrome” seemed to grow in popularity during the second half of the 20th century, and popular etiologic explanations varied from “chronic mononucleosis” to “depression” to “hypoglycemia.” The advent of an awareness of fatigue with orthostatic intolerance being linked to autonomic dysfunction came in 1993 when POTS was first described.[38] POTS was then reported in teenagers in 1999. This led to hope that there was a physiologic basis for fatigue and orthostatic intolerance in some chronically tired teenagers and offered the potential of improved recovery with targeted treatment regimens. Anecdotally, however, some physicians still doubt that POTS is a legitimate diagnosis.

So, what is POTS? Specific definitions vary but generally have the following two key components: (1) symptoms of orthostatic intolerance and (2) excessive postural tachycardia. In adults, the postural tachycardia “break point” of 30 beats/min seems to differentiate patients with fatigue and dizziness into those who have POTS and those who do not have POTS as the basis of their symptoms. This is usually based on standardized testing with an orthostatic challenge. There is a correlation, albeit imperfect, between active standing postural challenge and passive (tilted without weight-bearing) postural challenge[39]; nonetheless, tilted challenges seem most accurate for both research and clinical diagnosis. The individual should be relaxed and adapted to the supine position (adapting to supine rest for at least 10 min) before being gently tilted to about 701.[40] Heart rate changes are recorded, and the maximum sustained rate during tilting is usually compared to the baseline rested supine heart rate to determine the extent of postural tachycardia. A 10 min tilted challenge is usually adequate. Anxiety, dehydration, and deconditioning can sometimes yield “false-positive” tilt table results.

Recent studies suggest that whether standing[41] or tilted,[42] a heart rate change of up to 40 beats/min can be normal in teenagers. Thus, the criterion of a 40 beats/min postural tachycardia is now used for a diagnosis of POTS during adolescence; this replaces the previous habit of imposing the 30 beats/min criterion of adults on teenagers. However, in adolescents, the extent of symptoms does not always correlate very well with the degree of postural tachycardia; many tired dizzy teenagers have similar seeming symptoms whether they have excessive postural tachycardia or not. It could be that the degree of postural tachycardia would better be considered to be a marker of a particular phenotypic syndrome (chronic fatigue associated with orthostatic intolerance) rather than a feature distinguishing whether or not someone has a disease condition.

Some normal adolescents can have relative postural tachycardia even in a baseline state. A number of common health variations (dehydration, anxiety, and deconditioning, for instance) are also associated with postural tachycardia, Therefore, it is important that clinicians consider a diagnosis of POTS only when the postural tachycardia is associated with chronic symptoms that impede routine age-appropriate activities (school and sports, for example) and when symptoms are specifically related to discomfort (dizziness, nausea, peripheral extremity heaviness, or pain) with upright posture. Some adolescents have intermittent postural tachycardia associated with a predisposition toward fainting but do not have persistently bothersome symptoms impeding normal activities; they might have

orthostatic hypotension (which some would consider to be a form of autonomic dysfunction) but not POTS.

Thus, a definition of postural orthostatic tachycardia syndrome that is relevant to adolescents is “a chronic clinical condition characterized by chronic fatigue (and/or nausea and/or dizziness and/or pain) and intermittent intolerance of upright positions associated with postural tachycardia of greater than 40 beats per minute.” Considered in this fashion, POTS overlaps with but can also be distinct from “chronic fatigue syndrome” and “neurocardiogenic syncope” and “deconditioning.”

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Typical Presentations of POTS

Each patient with POTS is unique, but their stories often sound similar.[26] There is no quantitative system for scoring symptoms to diagnose POTS, but POTS can be considered as a diagnostic possibility when an adolescent has chronically bothersome fatigue associated with dizziness and, often, a constellation of other symptoms including nausea, pain, and a sense of altered mental clarity (sometimes described as “brain fog”).

Age—POTS can occur throughout adolescence, but the majority of affected individuals report symptoms beginning within a year or two of the beginning of puberty (growth spurt or, for girls, menarche). Similarly, symptoms often fade or resolve by the end of the process of the physical changes of puberty.

Genetics—Anecdotally, POTS is more common in Caucasians than in adolescents of other races. In addition, approximately 15% of affected adolescents have a close relative (parent or sibling) who had similar symptoms during adolescence or young adulthood. This suggests that there might be a genetic predisposition toward POTS in at least some individuals, but no differentiating gene has been identified. [In adults, one of several genes that was evaluated was linked to the degree of postural tachycardia in subjects with POTS, but no gene differed between POTS-affected and healthy subpopulations.[43] In addition, there are known genetic syndromes that manifest with findings including POTS, but these conditions (norepinephrine transporter deficiency[44] and dopamine beta-hydroxylase deficiency[45]) are found only in a small minority of adolescents with POTS.]

Physical Features—Many adolescents with POTS have hyperextensibility, and some are thought to have “benign joint hypermobility syndrome” or Ehlers–Danlos syndrome.[46] It is not clear whether the elastic soft tissues actually predispose to the development of POTS or if the lax tissues simply allow further increases in vasodilatation that make it more likely for hyperextensible individuals to report more venous pooling and dizziness when they get POTS.

Psychological Features—Most adolescents with POTS are characterized as being "high achievers." They typically get excellent grades and are successfully involved in multiple extracurricular activities. While no particular biochemical patterns have been consistently identified in patients with POTS (though a few are hyperadrenergic with elevated supine and/or standing norepinephrine levels), it could be postulated that the hyperstimulated nervous system of a high achiever may be more prone to develop neurotransmitter abnormalities leading to POTS.

Triggering Conditions—At least half of POTS patients initially become symptomatic following a significant febrile illness, often mononucleosis or influenza. Some become symptomatic following a period of injury-induced inactivity. A few seem to develop POTS after an otherwise minor traumatic brain injury such as a concussion.

Hormones—Of adults with POTS, 90% are female, and about two-thirds of adolescent POTS patients are female. This raises a question of hormonal triggers to POTS, but no specific endocrine abnormalities have been identified in POTS patients.

Thus, there are several typical features retrospectively identified in many POTS patients at presentation with symptoms including symptom onset during early puberty, Caucasian race, high achievers in school and athletics, joint hypermobility, and recent illness or injury. On top of this background, patients present with long-lasting fatigue and a variety of other symptoms. Dizziness, headache, nausea, and cloudy thinking ("brain fog") are commonly noted. Other patients have altered hot–cold sensation, abdominal discomfort, and other pains. Rarely, POTS patients have irregular stooling (frequent to infrequent) and, even less commonly, bladder control irregularities (mild retention or frequency).

Physical examination on presentation with POTS reveals postural tachycardia with symptoms of upright dizziness and/or nausea and/or heaviness of distal extremities. The patients usually look otherwise well but often have mottling, duskiness, and bluishness of the distal extremities when standing still. Blood pressures are usually normal, but they are often on the lower side of the normal range. Pupils are often more widely dilated than average.

Cardiovascular Pathophysiology of POTS

Upright posture (orthostasis) and exercise are two quotidian physical stressors. They "demand the full capabilities of our circulatory reflexes"[47] because of the gravitational redistribution of blood flow upon bipedal standing. If uncountered, upright stance produces central hypovolemia and hypotension in everyone.

Orthostatic intolerance (OI) is defined as the inability to remain upright because of signs and symptoms that are improved on recumbence.[48] Symptoms and signs partition between those related to defective cerebral autoregulation[49] such as lightheadedness, reduced neurocognitive function, mental fatigue, and perhaps headache and those related to sympathetic activation and parasympathetic withdrawal such as sweating, pallor, exercise intolerance, gastrointestinal abnormalities, and hypertension. POTS is sometimes defined as OI plus excessive upright tachycardia without hypotension.[38,50] POTS has common features

with hypovolemia,[51] and indeed, POTS may be simulated by dehydration or mild to moderate blood loss.[52]

Patients with POTS, especially when upright, lack normal responses to the influences of gravity. Usually, those responses include the skeletal and respiratory muscle pumps, intact cardiovascular structures, sufficient blood volume, and appropriate vascular regulation for effective oxygen delivery to tissues. Vascular regulation comprises rapidly acting mechanisms—the autonomic nervous system, the myogenic response, and flow mediated mechanisms—and slower responses that set a tonic milieu (baseline state of contraction of smooth muscle) to directly or indirectly modulate adrenergic vasoconstriction. Examples include perisynaptic angiotensin-II, nitric oxide, and circulating epinephrine. Genetic and epigenetic responses to orthostatic stress develop more gradually.[53]

The tachycardia of POTS results from four interacting etiologic factors: (1) sinoatrial node abnormalities, (2) hypovagal responses improved by ivabradine,[54] (3) hypersensitivity to norepinephrine, and (4) beta-receptor-sensitive “inappropriate sinus tachycardia.”[55]

POTS patients are sometimes regarded as falling into one of two subsets based on autonomic (serum norepinephrine levels) and circulatory (postural blood pressure changes) characteristics: “neuropathic POTS,” in which regional partial sympathetic denervation or adrenergic hypoactivity occurs, and “hyperadrenergic POTS,” in which upright adrenergic overactivity dominates.

Neuropathic POTS—As originally described, neuropathic POTS is caused by decreased sympathetic adrenergic vasoconstriction in the legs, associated with reduced norepinephrine spillover[56] and vasoconstriction.[57] There is often increased blood flow (“high flow”) in the legs even supine. Another neuropathic variant has normal leg hemodynamics (“normal flow”) but decreased splanchnic sympathetic adrenergic vasoconstriction.[58] Neuropathic POTS is rarely due to autoimmune autonomic neuropathy.[59] Tachycardia in neuropathic POTS is the result of excessive redistribution of blood causing reflex tachycardia and vasoconstriction. While treatment is mostly discussed later in this article, specific therapeutic measures can be emphasized when a classification of neuropathic POTS is linked to a specific patient. This would include support of circulation with physical counter-maneuvers and exercise. Pharmacotherapy focusing on improving vasoconstriction uses medications with widespread systemic effects. Midodrine, an alpha-1 adrenergic agonist, causes piloerection.[60] Droxidopa is in trials outside the USA. Mestinon (pyridostigmine),[61] an acetylcholinesterase inhibitor, alone or in combination with midodrine, can be very helpful through its potentiation of ganglionic nerve activity and through its muscarinic effects.

Hyperadrenergic POTS—The tachycardia of hyperadrenergic POTS is caused by pre- or post-synaptic adrenergic potentiation.

This could result from either central sympathetic activity or increased sympathetic nerve activity. While varying sympathetic nerve functions are reported,[50] most investigators find

normal supine muscle sympathetic nerve activity[62] and increased upright muscle sympathetic activity.

Central findings of marked sympathetic activation are also provoked by initial decreases of cerebral blood flow when upright resulting in hyperpnea, hypocapnia, extreme tachycardia, hypertension, and induced anxiety.[63] Exogenous carbon dioxide causes hyperpnea as tachycardia and blood pressure return to normal.

Another cause of hyperadrenergic POTS is increased synaptic norepinephrine as occurs in the rare autosomal recessive norepinephrine transporter (NET)-deficient heterozygote.[64] Less extensive, epigenetic NET deficiency has also been demonstrated and may have wider prevalence.[52]

Alternative mechanisms include modulation of the adrenergic synapse through enhanced norepinephrine synthesis and enhanced post-synaptic affinity modulated by the reciprocal actions of nitric oxide (NO)[65] and angiotensin-II. Nitrergic NO acts at pre-synaptic and post-synaptic sites to decrease adrenergic transduction into smooth muscle contraction.[66] Conversely, studies of sympathoexcitation show that angiotensin-II acts through angiotensin1 receptors to increase production of reactive oxygen and nitrogen species (ROS) within the brain at pre-synaptic sympathetic neurons[67] and acts peripherally to produce pre- and post-synaptic augmentation of sympathetic transduction and up-regulation of adrenergic receptors.[68] This depends critically on the formation of ROS,[69] decreasing NO,[70] and uncoupling nitric oxide synthase[71] and is associated with tachycardia, pallor, vasoconstriction (“low flow”) and absolute hypovolemia even while supine.[72] Plasma angiotensin-II is increased by a defect in ACE-2.[73]

Thus, various mechanisms are hypothesized and identified as bases of the pathophysiology of hyperadrenergic POTS. Whatever the mechanism for this form of POTS, beta blockers have been used for hyperadrenergic POTS with variable success.[74,75] Innovative treatments with angiotensin receptor blockers and droxidopa are under investigation. Exercise has always been a mainstay of rehabilitation in these patients.[74]

Bedrest Causes POTS—Another etiology of POTS is bedrest or “gravitational deconditioning.” Prolonged bedrest simulates the weightlessness experienced by astronauts in space and has deleterious effects[76] including OI,[77] profound reductions in blood volume and cardiac size, redistribution of blood, osteoporosis, skeletal muscle pump atrophy, and more.[78] Vasoconstriction is impaired.[79] Bedrest causes a self-perpetuating state of OI that can simulate or intensify POTS. It is paramount for POTS patients to leave bed and recondition using structured exercise protocols.

GI Physiology and Pathophysiology as Related to POTS

Postural tachycardia syndrome although defined based on increased heart rate in the upright position and associated orthostatic symptoms is usually associated with a myriad of other symptoms, ranging from headaches with migraine features to generalized body aches and pain, sleep complaints, fatigue, and gastrointestinal symptoms as well as other symptoms.[80] Many years ago, Sandroni et al.[81] reported that subjects with postural tachycardia syndrome

(POTS) not only complained of orthostatic symptoms like dizziness, lightheadedness, and lower extremity weakness but also reported many gastrointestinal symptoms like nausea, bloating, abdominal pain, and early satiety. The association of POTS and gastrointestinal symptoms, mainly in functional gastrointestinal disorders (FGID), was then further explored in adult and pediatric subjects. Camilleri and Fealey[82] described 8 adult subjects with FGID and found sympathetic denervation with or without parasympathetic dysfunction. Chelimsky et al.[83] studied 8 children with recurrent abdominal pain without any known non-autonomic organic cause and found that the majority of these children had orthostatic intolerance and some had an associated neuropathy. In 2005, Sullivan et al.[84] described a group of children with functional gastrointestinal symptoms, mainly abdominal pain, nausea, and vomiting, who also underwent tilt table testing and demonstrated either POTS or neutrally mediated hypotension alone or with POTS. Interestingly, some of these children had resolution of the gastrointestinal symptoms when treated with fludrocortisone (4/18), and 9 of 18 improved with either fludrocortisone (4), sertraline and fludrocortisone (4), or midodrine (1). The improvement of the gastrointestinal symptoms when treatment was aimed at the orthostatic intolerance suggests a strong association between the orthostatic changes and the pathogenesis of the gastrointestinal symptoms. Still, however, the pathophysiology of this association is unknown.

So, gastrointestinal function relates to autonomic regulation and to abdominal pain. In an attempt to better understand this association by measuring the nerve and electrical activity of the stomach, Safder et al. performed electrogastrography (EGG) in the supine position and during tilt in subjects with and without POTS.[85] Subjects with POTS showed significant decreases in the percent of normal gastric activity in the channels overlying the fundus and antrum of the stomach when upright as compared to their own baseline supine activity. These changes were not found (if anything there was an improvement) in the subjects without POTS, suggesting that perhaps these electric changes may play a role in the pathogenesis of nausea and upper gastrointestinal symptoms that subjects with POTS many times report; however, this study did not directly correlate EGG findings and gastrointestinal symptoms. Seligman et al.[86] performed EGG in POTS subjects with and without gastrointestinal symptoms and healthy controls. In Seligman's study, the EGG was done always pre-prandial, immediately post-prandial, and in the late post-prandial phase (but not in different positions). The authors found increased variability in the frequency of nerve activity in subjects with POTS. The subjects with POTS and gastrointestinal symptoms also had a higher variability of the nerve activity frequency post-prandially, perhaps explaining partially the pathogenesis of the gastrointestinal symptoms.[86] Interestingly, children with POTS do not show consistently delayed gastric emptying. Antiel et al.[87] retrospectively reviewed data on subjects who underwent autonomic testing and also had gastric emptying studies. They had 31 subjects that met the inclusion criteria, 21 with POTS and 10 without POTS. They did not find any significant difference in gastric emptying velocity between the two groups. Thus, nerve activity in the stomach varies depending on whether or not someone has POTS, but the actual emptying of stomach contents does not necessarily directly relate to having POTS or to the presence of nausea. Further studies will be needed to better elucidate the links between autonomic nerve activity, gastrointestinal function, and symptoms.

Thus, studies of gastrointestinal nerves do not yet make it completely clear why subjects with POTS have so many gastrointestinal symptoms. Vascular studies provide other clues. Stewart et al.[58] have studied the pooling of blood in the splanchnic vasculature in subjects with normal-flow POTS. They found that while supine, there is low resistance in the splanchnic vasculature, but the resistance does not increase as the subject is being tilted up. Therefore, in the upright position, the subjects with POTS show splanchnic hypervolemia with decreased splanchnic vascular resistance with increased splanchnic venous pooling. The clinical implication of this venous pooling is unclear, neither is it clear how this may contribute to the gastrointestinal symptoms.

Headaches and POTS

Headaches and POTS often occur concurrently in the same individual.[88,89] Approximately two-thirds of patients with chronic daily headache have dizziness, and two-thirds of patients with POTS have headaches. Sometimes it is difficult to differentiate what symptoms the headache disorder is causing, and what symptoms should be attributable to POTS.

The most common cause of headaches in teens and children is migraines, and some of the symptoms of migraines are very similar to POTS. During migraines, bright lights and loud noises are bothersome, people experience nausea and may vomit, and they often need to fall asleep in order to improve the severe headache. During migraines, it is typical to feel dizzy, lightheaded, and even as if the room is spinning (vertigo). Moreover, all of these symptoms of migraines are worse with exercise. Many patients with POTS describe worsening headache with standing or with exercise. Although some authors have described a “coat-hanger” headache (where the headache is in the neck and shoulders, similar to the appearance of a coat-hanger)[90,91] as part of POTS symptoms, our patients will notice many different headache types when their POTS symptoms are aggravated by standing (orthostasis). Often this POTS-related headache is relieved by rest.

There are also other types of headaches (headache syndromes) in which both the symptoms of POTS and headache seem to co-occur (and one does not necessarily cause the other), such as New Daily Persistent Headache (NDPH). Approximately 4% of women (2.4% of middle school girls) and 2% of men (0.8% of middle school boys) will have a chronic daily headache, a syndrome in which the patient has a headache more often than not for at least 3 months. In a quarter of the adolescents that we see with chronic daily headache, the headache comes on all of a sudden, and the child has no previous headache history. This is called NDPH and may be precipitated by a viral infection or some other type of physical stress. In many patients, POTS symptoms and symptoms of a severe daily headache start at the same time, and both sets of symptoms are quite troublesome. A similar co-occurrence of headaches and orthostatic intolerance can be seen in a post-concussive syndrome as well.

These observations underscore the complexity, and multiple symptoms, of many of our patients diagnosed with POTS. When one set of symptoms improves, it will often positively affect the other symptoms. However, we have also seen in some patients that these symptoms will improve at different rates.

Exercise Physiology, Deconditioning, and POTS

As already mentioned, bedrest, like space travel, can lead to POTS. To further explore the relationship between deconditioning and POTS, there are two key questions to be addressed. The first is how one defines deconditioning, and the second is whether deconditioning plays a primary role in the pathogenesis of POTS or whether it is a secondary phenomenon.

First, then, what is deconditioning? It is an ineffective or inefficient response to the physical demands of exercise. Normally, at the onset of exercise, the heart receives more venous return from the exercising limbs and responds by pumping more blood per beat, i.e., stroke volume (SV) rises, into a systemic circulation which now operates under higher pressure (as blood pressure rises). At the same time, there are concomitant changes in distribution of this higher cardiac output to other vascular beds geared to maintain central blood volume and perfusion of exercising muscles.

In order to truly identify deconditioning, one must obtain a maximal exercise test in order to measure peak oxygen uptake (peakVo_2). Classic cardiovascular deconditioning is defined as a deterioration of heart and skeletal muscle, related to a sedentary lifestyle, debilitating disease, or prolonged bedrest which leads to reduced peakVo_2, low stroke volume (SV) with consequent relative tachycardia, abnormal vasomotor control, and exercise intolerance.[92] Put simply, if a patient achieves a low peakVo_2 accompanied by rapid heart rate (HR), ergo low maximum oxygen pulse (peakVo_2/HR), then she/he fulfills criteria for cardiovascular deconditioning as understood above. Although there are still issues to be resolved in defining normal standards for peakVo_2 (particularly in adolescents), our own data suggest that approximately 70% of pediatric POTS patients are deconditioned,[93] whereas the prevalence approaches 90% in adults.[94] However, even as there are various etiologies and varying pathogenetic mechanisms underlying POTS, individual POTS patients display varied associations between their autonomic regulation and their degree of deconditioning. When the available volume of the peripheral vasculature changes (such as with positional change in POTS patients), heart rate or O_2 pulse alone will not yield reliable approximations of cardiac output. For example, we recently demonstrated that among patients who met the definition of POTS, more than one-third had evidence of a hyperdynamic circulation during exercise.[95] This means that a large minority of adolescents with POTS had not only an excessive HR during exercise but a normal and appropriate SV response as well. In other words, they did not appear to have the “small heart” seen with classical cardiovascular deconditioning. We speculate this group of patients has failure of normal regional vasoconstriction required during dynamic exercise and must greatly increase flow through an inappropriately dilated systemic circulation to maintain perfusion pressure. We were unable, however, to identify these patients by any parameter measured during our head-up tilt or autonomic reflex testing. Until we acquire a better understanding of circulatory dynamics, it would seem prudent to expect that peakVo_2 will indeed be low in the majority of adolescents with POTS but that some do not have deconditioning in the classical sense and in fact may not be “out of shape” at all.

The answer to the question of whether deconditioning is primary in or secondary to POTS should now be obvious—it depends! In non-neuropathic POTS, exercise training has been shown to ameliorate symptoms and orthostatic tachycardia, though not all patients

responded, nor was the response “complete” with resolution of symptoms.[96,97] Nonetheless, exercise must be considered a cornerstone of therapy in patients with POTS, as it will confer benefits in overall health and assists patients in coping with the chronic pain that often plagues them.[98] While exercise is beneficial, though, measurable cardiac effects (lower HR, higher SV) may not be so apparent in the subset of POTS patients with hyperdynamic circulation and excessive peripheral vascular dilatation. Those patients with hyperdynamic circulation appear not to have the small heart associated with classic deconditioning, so it follows that having them exercise more may not improve their symptoms although they would still derive other benefits of a training program. This group of patients with hyperdynamic circulation challenges our understanding of what regulates the circulation during exercise. Broadly speaking, any physiologic system is generally governed by mechanisms that dampen perturbations in order to maintain homeostasis or prevent harm to the organism. Is the primary error corrected by the autonomic nervous system during exercise a mismatch between blood flow and metabolism or a mismatch between vascular conductance and cardiac output, or is a blended correction of both perturbations essential for maintaining requisite blood pressure and flow during exercise in patients with POTS? Again, it depends! Further research about the links between POTS, deconditioning, and recovery is necessary.

Chronic Pain and POTS

Prevalence rates of pediatric chronic pain have increased during the past decade, with 20%–35% of children and adolescents affected worldwide. Chronic pain has loosely been defined as persistent and/or recurrent pain that lasts more than 3–6 months.[99] Patients who struggle with chronic pain often undergo multiple evaluations in search of a diagnosis and treatment that will alleviate their symptoms. For many adolescents, these evaluations demonstrate no underlying etiology for the pain, and this can be frustrating for patients.[100,101] Even more frustrating, chronic pain is often difficult to treat, with variable responses to pain relief medicines and procedures. Chronic pain is sometimes considered to result from a disruption of peripheral nerve activity but also often involves disturbance of the central nervous system, termed central sensitization.[102] Central sensitization involves “an amplification of neuronal signaling within the CNS that elicits pain hypersensitivity.”[26]

Many adolescents with POTS report symptoms of chronic pain with the most common complaints being headache, abdominal discomfort, chest pain, and nonspecific generalized pain.[102] Possibilities of why patients with autonomic dysfunction struggle with chronic pain are described above in the sections on headache and gastrointestinal problems. It is likely that sensitization also explains the co-occurrence of generalized pain and fatigue, as such comorbidities have been found in epidemiologic studies.[26]

Potential “Etiologies” of POTS

There appears to be no single mechanism that satisfactorily explains the clinical findings of POTS, rather a combination of possible processes that manifest with decreased blood return to the heart and with similar symptoms. In adults, POTS is seen secondary to other conditions such as chronic diabetes mellitus, chemotherapy, or lupus. However in adolescents, POTS is usually a primary disease process. Having discussed the

pathophysiology of POTS related to specific organ systems and physical processes, we now pull everything together to consider the overall (and underlying) etiologies of POTS.

There are a number of possible etiologic mechanisms that have been identified.

1. Partial dysautonomia/neural mechanism

   In some patients, patchy denervation of the sympathetic fibers to the blood vessels in the extremities appears to be the mechanism behind POTS. Findings consistent with this theory include skin biopsy results, sudomotor axon reflex testing, and hypersensitivity to infusions of norepinephrine into the foot veins despite high circulating levels of norepinephrine.[103,104] On standing, inadequate vascular tone results in diminished venous return to the heart, causing stroke volume to fall and reflex tachycardia as a compensatory response. Severe venous pooling in the feet is seen leading to characteristic purple discoloration of the feet on standing. This form of POTS often starts after an acute febrile illness; this has led researchers to conclude that there is an autoimmune process behind the denervation, and neurologic auto-antibodies may be found to be positive at this time.[105]

2. Hyperadrenergic form

   Less commonly, in some patients, excessive sympathetic discharge seems to be the primary underlying process. These patients manifest with hypertension on standing, tremor, and sweating. Often very high levels of circulating norepinephrine are seen. The symptoms may come on gradually. The reason for the abnormal sympathetic discharge is not clear. In a small number of patients, a specific genetic abnormality has been identified. A single point mutation in the norepinephrine transporter gene results in an inability to clear norepinephrine and in a constant state of excessive sympathetic activation.[64] Mast cell activation has also been associated with hyperadrenergic POTS.[106] It is not clear if the mast cell activation with release of vasoactive mediators is the primary cause of the sympathetic stimulation or the result of it.

3. Hypovolemia

   Many patients with POTS have been documented to have low blood volumes. Using labeled albumin, plasma volumes have been documented to be less in POTS patients than in controls.[72] In the low-volume patients, a paradox in the renin– aldosterone mechanism has been observed. Instead of the compensatory increase in renin and aldosterone to reverse the hypovolemic state, the opposite has been found. This finding remains unexplained, but as the sympathetic nervous system is a significant modulator of renin release, sympathetic failure may be part of the mechanism. The further finding of raised angiotensin-II in low-volume patients has also led to the theory that angiotensin-II may be responsible for increased circulating norepinephrine levels by direct action on sympathetic nerves. Some patients report clinical improvement when their blood volume is augmented using intravenous fluids or erythropoietin, providing

further support for the theory that hypovolemia is the underlying mechanism in this form of POTS.

Diagnostic Evaluation of Possible POTS

By definition POTS is excessive heart rate increment among symptomatic patients, when moving from supine to upright position.[38] The diagnosis of POTS is therefore based on a head-up tilt test that allows us to measure the heart rate increment with a change in position. In 1999, when the first case of POTS was described in adolescents, the adult criteria of a 30 beats/min increase in heart rate was utilized for diagnostic evaluations. However, in 2012, based on normative data, POTS in adolescents was redefined as a heart rate increment ≥40 beats/min or an absolute orthostatic heart rate ≥130 bpm for ages 13 years and younger and ≥120 bpm for ages 14 years and older, within 5 min of head-up tilt.[42] The diagnostic evaluation of POTS entails a detailed history covering the multisystem symptoms seen with this condition. The interviewer should specifically inquire about the presence of chronic pain, dizziness, fatigue, gastrointestinal symptoms such as abdominal pain, nausea and vomiting, altered temperature sensation, sleep disturbances, and extremity changes including purplish discoloration or peripheral edema. Postural characteristics of the symptoms should be elicited, such as improvement of dizziness with recumbency. Information should also be obtained about daily fluid and caffeine consumption as well as level of physical activity. A comprehensive physical examination should be performed. Physical assessment may show signs of altered autonomic activity such as cold and clammy extremities, edema, or purplish skin discoloration.[26]

Although the tilt table test is sufficient to document postural tachycardia, a detailed evaluation is performed to exclude alternate diagnoses that may either secondarily cause postural tachycardia or co-occur with POTS. The goal is to exclude primary cardiac causes of inappropriate tachycardia, identify treatable causes of autonomic neuropathy in patients with neuropathic POTS and exclude endocrine or other systemic causes of a hyperadrenergic state in patients.[107] Some additional secondary causes of orthostatism to be considered include diabetes mellitus, chemotherapy, heavy-metal poisoning, Sjögren's syndrome, systemic lupus erythematosus, paraneoplastic syndrome, and side effects of medications such as diuretics, anxiolytics, and vasodilators.[26]

The following screening tests are frequently performed for evaluation of POTS: Head-up tilt table testing to demonstrate postural tachycardia and impact of tilt on blood pressure, electrocardiogram to evaluate for primary cardiac pathology, cardiovagal and sudomotor function tests to detect autonomic neuropathy, and maximal exercise test with measurement of peak oxygen uptake to measure physical deconditioning. Additional tests to consider include a complete blood count (CBC), inflammatory markers, thyroid function tests, and morning cortisol levels. Plasma and urinary metanephrines in addition to serum tryptase and urinary methylhistamine may also be considered to exclude neuroendocrine causes such as pheochromocytoma and mast cell disorders.[107] Since low ferritin levels and hypovitaminosis D are common in adolescents with chronic fatigue and POTS, we routinely check for these.[108]

Further investigations are guided by the symptom profile, for instance, gastric motility evaluation may be undertaken in patients with prominent gastrointestinal symptoms such as nausea and vomiting.

Recovery

Organization of Care for Patients With POTS

Patient and family education is vital in the care of adolescents with POTS and must be incorporated into the multidisciplinary programs where POTS patients are evaluated and treated. This is especially important as the treatment plan for POTS needs to be multidisciplinary and no single medication or treatment is adequately effective. Patient education must be designed to improve the family's knowledge of POTS along with promoting teen health behavior change. Patients and their parents often express feelings of isolation and lack of social support. Thus, education must focus on self-management and fostering social support that will empower the family to initiate a recovery plan where the teen and family re-engage in normal life activities

We have tried individual POTS education that required a 2-h session for patients and families and also a group session for 1 h followed by an individual session that lasted about an hour. Sessions were conducted by a nurse or nurse practitioner. In our experience, group education followed by an individual session has been most beneficial for patients. Due to the extreme fatigue associated with POTS, patients can find it challenging to stay awake and pay attention during a 2-h individual session and may also repeatedly ask to have educational information restated. Additionally, the authors found that teen patients and their parents were asking clinic staff for names and contact information for other teens with POTS in order to seek out peer support. Parents also requested names of other parents who have teens with POTS so that they could connect for social support.

In the 1- h group session, information may be provided on the pathophysiology of POTS, natural history of the condition, and the treatment plan, and time is allowed for the adolescents and parents to interact with each other. The second component of the education program can be a 1-h individual education session to tailor the program to the specific needs of the patient and family and address barriers to implementation. The session focuses on “meeting them where they are at” in order to encourage a systematic, stepwise approach to the comprehensive lifestyle changes necessary for disease management. Motivation and readiness for change can be assessed. An individualized exercise prescription can be developed focusing on gradual progression toward the goal of 30 min of cardiovascular exercise 6 days a week that is recommended for these patients.

Management of POTS and Associated Conditions

Non-Pharmacologic Strategies—Regardless of the underlying mechanism causing POTS, there is decreased venous return to the heart. The management of POTS, therefore, is aimed primarily at improving the effective circulatory volume and enhancing venous return.

Patients are generally advised to avoid factors that are associated with exacerbation of symptoms such as sudden changes in posture, prolonged recumbency, high environmental

temperatures, large meals, and vasodilating or sympathomimetic drugs.[107] Most of these factors mediate their effect through vasodilation with consequent blood pooling and decreased effective circulatory volume.

Adequate water and sodium intake are essential to maintain the intravascular blood volume. Patients are usually instructed to consume 64–80 oz of fluids (preferably caffeine free) and as much salt as their taste buds can tolerate. Adequacy of fluid intake is generally judged by the regular production of clear, non-yellow urine. If quantification is needed, adequacy of salt intake is assessed by measuring 24-h urinary sodium excretion; an output if at least 170 mmol/day is desired. While some physicians use intravenous saline infusions in an effort to provide temporarily symptomatic relief, such treatment is costly and risks infection and blood clots, and is not advised. Oral intake of fluid and salt is preferred.

Compression stockings (15–30 mmHg pressure) can theoretically facilitate venous return from the lower extremities. Many adolescents, however, do not tolerate the use of these stockings.

Exercise is a vital component of treatment of POTS. Both aerobic exercise and resistance training have been shown to be beneficial. Exercise not only increases the effective circulatory volume by minimizing blood pooling but also improves stroke volume and conditioning. Since many patients with POTS initially report exercise intolerance, it is often helpful to incrementally increase the duration of daily exercise sessions (perhaps by 1–2 min every 4–7 days) from an initially tolerable duration up to a non-stop 30-min session (which is part of the total daily target of 60 min of physical activity).

Patients with POTS should resume regular physical and academic activities. Sometimes, this must be done in an incrementally increasing fashion over several weeks, but recovery from POTS hinges on avoidance of daytime recumbency and inactivity.

Medications for Blood Flow—The exact pathophysiology of altered blood flow in POTS is not clear. Thus, medication management is not well-proven, and the “evidence base” to guide customized medication choices is limited. We often begin treatment with non-pharmacologic therapies, but a majority of our patients end up needing to include some medication in their therapeutic regimen. We often continue medications until the patient has been symptom-free for several months.

Fludrocortisone is sometimes used to facilitate fluid and salt retention.[109] Doses vary from 0.05–0.1 mg once to twice daily. Electrolyte imbalances are an uncommon side effect. If the patient is able to comply with fluid and salt intake recommendations, the addition of fludrocortisone to the treatment regimen is not usually necessary.

Beta blockers are associated with symptomatic improvement.[110] Separate from cardiac effects, beta blockers seem to reduce pooling of blood peripherally to increase venous return to the heart. Propranolol is effectively used in adults, even at low doses,[75] but anecdotal evidence suggests that up to 10% of adolescents have paradoxical increases in fatigue with propranolol. Other beta blockers such as metoprolol and atenolol seem well-tolerated, perhaps due to varying transit across the blood–brain barrier. Anecdotally, the long-acting

succinate form of metoprolol is less effective than the regular metoprolol tartrate. The first daily dose (usually 25 mg but perhaps varying with patient size and medication effectiveness) may be given before rising in the morning, and a second dose may be given at mid-day.

Midodrine, as mentioned, is an effective vasoconstrictor that facilitates venous return. Side effects include piloerection (with a “creepy crawly” scalp sensation) and supine headaches. Thus, initial small doses are used to avoid side effects, and the dose is increased as needed to provide adequate effectiveness. Three daily doses are usually provided with the final dose being at least 4 h prior to bedtime (to avoid supine headaches). Teenagers usually start with 2.5 mg three times daily and increase to 5-mg (or higher) doses as tolerated and needed. Only rarely is more than 10 mg three times daily needed.

Selective serotonin reuptake inhibitors (SSRIs) such as citalopram and venlafaxine are also sometimes used as an adjunct to POTS treatment. SSRIs seem to favorably affect intestinal flow while also facilitating blood flow.

Anecdotally, stimulants such as methylphenidate have been used to help with “brain fog,” but it is not certain whether altered mentation results from altered cerebral blood flow or from other central nervous system imbalances. There are no real data to support the use of stimulants in POTS patients, and patients report variable value with therapeutic trials. Interestingly, attention-deficit hyperactivity seems much less common in POTS patients than in the general population, and it could be that an alteration of neurotransmitters in POTS runs counter to the risk of attention-deficit disorders (and the effectiveness of stimulant therapy).

Pyridostigmine has been effective in facilitating blood flow and relieving symptoms in some adults with POTS and could theoretically be most useful with “neuropathic” POTS; experience with this agent in adolescents is limited. Erythropoietin has been proposed in an effort to increase blood volume, but no real data exist to evaluate its effectiveness for POTS. Clonidine has been proposed, but experience is too limited to suggest its use.

Medications for Gastrointestinal Function—Biobehavioral strategies have proven effectiveness in treating nausea and abdominal pain. Currently, however, all the medications used in the treatment of the gastrointestinal symptoms in POTS are used off-label, and the data are very scarce. Based on the association of POTS and GI symptoms, often treatment is aimed at the treatment of the orthostatic intolerance. Sullivan et al.[84] have described that at least a subset of subjects have improvement of the gastrointestinal symptoms when utilizing fludrocortisone or midodrine, aimed at controlling the orthostatic intolerance.

We believe it is important to determine if the gastrointestinal symptoms are brought on or exacerbated by upright position. If so, this is more suggestive of orthostasis-induced symptoms. Therefore, we may initially suggest using salt, increased fluids, low-dose fludrocortisone, and physical activity. It is very difficult many times to determine the cause of nausea and epigastric discomfort. Many patients also complain of early satiety. We sometimes recommend performing a gastric emptying study, although in the vast majority of

subjects, gastric emptying is normal, as described by Antiel et al.[87] It is impossible to determine based on clinical symptoms if the subject has delayed gastric emptying.[111,112] If gastroparesis is present, low-dose erythromycin may be tried to improve gastric emptying.[113] Erythromycin is a macrolide and is a motilin receptor agonist. There is always a concern about the prolonged use of erythromycin and tachyphylaxis.[113] Erythromycin may also produce prolonged QT and therefore needs to be used with caution, mainly in association with other medications.[114]

Exercise is an important, if not critical, treatment strategy in POTS.

Although the data about POTS and abnormal antroduodenal motility are limited, if the patient has delayed gastric emptying and feeding intolerance, the patient may need antro-duodenal motility testing to better understand the extend of the motility disorder and determine if other treatments are needed. Octreotide improves small bowel motility by increasing the number of migrating motor complexes in the small intestine, but octreotide inhibits antral contractions, which can be overcame by pretreatment with erythromycin.[115,116] Octreotide has been shown in patients with POTS to decrease the standing heart rate.[117] Therefore, if the subject has POTS and poor foregut motility, octreotide with or without erythromycin should be considered.

Nausea can also represent a migraine equivalent. POTS is known to have associated migraine as well as other systemic symptoms including fatigue, sleep issues, aches, and pains.[80] Therefore a detailed history needs to be obtained looking for migraine headaches, photophobia or phonophobia associated with nausea, or a strong family history of migraines. In these cases, migraine treatment may improve the nausea. Amitriptyline has been used often in functional gastrointestinal disorders with mixed results.[118–120] Cyproheptadine should be considered when the upper gastrointestinal discomfort is thought to be related to poor gastric accommodation.[121] Cyproheptadine as well as amitriptyline is also used to treat migraines; therefore the benefit of these medications may be through multiple mechanisms.[122]

“Get Moving”—Exercise and Activity in the Management of POTS—The majority of individuals with POTS are deconditioned and have associated cardiac atrophy and reduced blood volume.[93,94,96,123] Exercise is known to increase cardiac size as well as plasma volume,[96,124] and exercise has been shown to result in a decrease in compensatory tachycardia when upright.[125] It would seem logical that exercise is an important, if not critical, treatment strategy in POTS.

Comparison has been made between deconditioning related to prolonged bedrest or space flight and POTS. In combination with oral fluid load, supine exercise training during 5 weeks of strict bedrest preserved orthostatic tolerance[126] and maintained cardiac mass and chamber compliance.[127] In the adult POTS population, studies demonstrate that short-term exercise training is associated with a decrease in upright heart rate such that a majority of patients with POTS no longer qualified for the diagnosis after training.[96,128] Another study compared the effect of propranolol to 3 months of conditioning exercise in a group of individuals with POTS. Although both propranolol and exercise training reduced standing heart rate, the exercise group experienced a better restoration of upright hemodynamics and

reported an improved quality of life.[74] In a study of military recruits with POTS, one group underwent 3 months of aerobic training, and a control group participated in no extra exercise training. The trained group significantly improved with respect to tilt table testing and symptoms of orthostatic intolerance.[97]

While there may be universal acceptance of the cardiovascular benefits of regular exercise and conditioning, a lesser known benefit is its effect on chronic pain[129] which also afflicts many adolescents with POTS. Exercise has been shown to be effective in treatment of fibromyalgia[130] and chronic fatigue,[131] two syndromes that share many phenotypic features with POTS. The pathophysiological basis for this phenomenon has been elucidated using various animal models. Exercise is thought to activate central inhibitory pathways resulting in an analgesic effect mediated by opioid receptors in the rostral ventromedial medulla.[132] Exercise results in release of metenkephalin in brainstem nuclei,[133] prompting the cliché "get the endorphins flowing."

Although it is widely accepted that exercise is a foundational treatment for POTS, there is limited consensus related to specific exercise recommendations. Exercise programs described in the literature for adult POTS patients contain varied exercise parameters (mode, duration, intensity, frequency, and progression) ranging from strengthening plus a variety of conditioning methods two to four times per week[96] to jogging for 50 min three times per week.[97]

On the other hand, widely accepted and scientifically supported general exercise recommendations do exist for healthy children and adolescents,[133–139] and these recommendations differ substantially from those for adults.[140]

In summary, even healthy youth should pursue 1 h or more of enjoyable, age-appropriate aerobic exercise every day in addition to three times per week strengthening activities. The aerobic activity should include a baseline of moderate- to vigorous-intensity exercise with at least 3 days per week exercise at the vigorous activity level. In addition, it is recommended that youth pursue activities that strengthen muscle and bone 3 days per week.[134,135,138,141,142] In fact, it may turn out that resistance training is even more beneficial than endurance (aerobic) training. This mode of conditioning results in improved systolic and diastolic BP as well as tolerance to orthostatic stress, compared with aerobic conditioning.[143] Benefits of this exercise regimen include improved cardiometabolic conditioning,[144–147] body composition,[134,148,149] bone health,[150,151] and psychosocial well-being and cognitive function.[152–158] Because evidence to support a specific type of exercise in adolescents with POTS is lacking, it is suggested that the generally accepted recommendations for youth should be applied to the POTS population as well, including both aerobic and strength exercises.

Most adolescents with POTS cannot begin their program at their exercise target of 1 or more hours of moderate to vigorous exercise daily. Strategies for those who are most severely affected might include starting with recumbent strengthening, cycling, rowing, or swimming. Gradual transition to upright posture for cycling, walking, sports, or other physical activities should be encouraged. Some clinicians recommend monitoring heart rate

during training and targeting 65–85% of maximal heart rate. We prefer to use a perceived exertion scale in order to reduce the medical focus (since upright posture alone can reach near “target” heart rate in some adolescents with POTS). We suggest that these patients start with a duration and intensity with which they are comfortable and establish a daily habit at that level. Time is gradually added toward the 1 h or more target, and then intensity is increased. In order to improve compliance, we suggest that individuals log their progress and participate in types of exercise that they enjoy and enable them to socially interact. Access to exercise equipment and family support is crucial. An occasional patient will require the assistance of a physical therapist or personal trainer to progress toward goal.

Biobehavioral Strategies for POTS—As described earlier, patients with autonomic dysfunction and POTS often report struggles with chronic pain.[26] Although some patients respond to typical medical treatments for pain, many continue to struggle with symptoms to the point they decrease their participation in regular daily activities such as school, social, and physical activity. Parents and adolescent patients with POTS often describe a long and difficult ordeal from the moment they became ill to the time they finally receive a helpful diagnosis, sometimes with lots of unhelpful medical intervention along the way. Initially patients and their parents are relieved to receive a diagnosis such as POTS and a treatment plan that oftentimes results in initial symptom decrease or resolution, but they then sometimes become frustrated if symptoms linger. During this process, parents take on responsibility to monitor symptoms to guide assessment and treatment, and many parents end up decreasing other activities in their lives such as work, caring for their other children, and spending time with their spouse, friend, and hobbies. Taking care of their child with chronic pain or POTS becomes a central part of their lives.

Through this process, many adolescents with chronic pain and POTS decrease participation in school as well as social and physical activities; as they do this, they become physically deconditioned and socially isolated. Subsequently, they feel sad about missing out on normal teenage activities and may struggle with self-esteem as they feel incompetent in many areas. Many patients also develop anxiety about engaging in any activities that might exacerbate their symptoms, which leads them to avoid many typical adolescent experiences such as going to the mall or spending the night at a friend’s house.

Multidisciplinary recommendations for POTS patients often include improvement in sleep hygiene, increase in exercise, and cognitive–behavioral therapy for pain and symptom management. If patients do not respond to these treatments to the extent that they are fully functional (e.g., attending school full time and participating in social activities), an intensive pain rehabilitation program is warranted.

Multidisciplinary recommendations for POTS patients often include improvement in sleep hygiene, increase in exercise, and cognitive–behavioral therapy for pain and symptom management.

Comprehensive pain rehabilitation programs have been shown to be effective at increasing pain management, quality of life, and functioning for adults with chronic pain.[159] There are also several comprehensive pediatric pain programs that report improvements in overall functioning, school attendance, sleep, medication usage, and emotional well-being post-

treatment.[160,161] We have treated approximately 500 children, adolescents, and young adults with chronic pain, and approximately 35% of them also struggled with autonomic dysfunction or POTS. Patients with POTS demonstrated similar improvements in depression, anxiety, and overall functioning from pre- to post-treatment. In addition, in a subsample of 15 patients, most reported experiencing fewer POTS symptoms such as dizziness, visual changes, fainting, rapid heart rate, nausea, vomiting, and weakness post-treatment, and 3-month follow-up data look promising.

The Mayo Clinic Pediatric Pain Rehabilitation Center (PPRC) consists of fifteen 8-h days of a group pediatric outpatient interdisciplinary chronic pain rehabilitation program. Groups typically consist of 10–15 patients. Adolescent patients and their parents (both separately and together) focus on goals related to restoring function and learning how to adaptively self-manage chronic pain and POTS symptoms. Collaborative treatments are delivered by multiple providers including a physician, psychologists, nurses, and physical, occupational, and recreational therapists. During each treatment day, patients participate in 1 h of biobehavioral relaxation, physical therapy, occupational therapy, recreational therapy, and family group and 3 h of cognitive–behavioral groups. Patients also participate in two biofeedback sessions each week. Parents participate in parent group 3 days each week for 2-h sessions in addition to daily family groups. Nurse case managers and psychologists meet with patients and families separate from the group in order to work on individual issues as needed. Cognitive–behavioral groups focus on pain management coping skills (e.g., distraction and positive self-talk), stress management, wellness instruction (e.g. sleep hygiene and healthy diet), chemical health education, and activity pacing. Operant learning strategies such as elimination of pain behaviors and parent behaviors that may serve as secondary reinforcement for pain behavior are employed throughout the program. Identification and treatment of co-morbid psychiatric illnesses (e.g. depression and anxiety disorders) is also an important aspect of the program. In addition, tapering from opioid, muscle relaxant, and benzodiazepine medications is included as a treatment goal if appropriate. Discontinuation of further medical workup and interventional procedures is strongly recommended.

A major focus of this 3-week program and one of the more difficult aspects of the program is taking one's focus off of physical symptoms and focusing one’s efforts toward increasing functioning. Many of the families that attend our program have been struggling with debilitating symptoms for 1–2 or more years. They have been working with the conceptualization that one must rest when not feeling well in order to recover from illness. Unfortunately, this plan does not work well for adolescents with chronic pain and/or POTS, and in fact, pulling away from activities seems to make matters worse. A substantial part of the recovery program is teaching patients that they can do everything else healthy adolescents do, but they need to practice healthy coping and pain/symptom management skills. Since this is a group program, adolescents are able to work on these skills together, and many patients report that the support and positive peer pressure from the group is invaluable to their recovery.

Although there is limited research on effective treatment for adolescent POTS, studies illustrate effective home-based treatments for many symptoms associated with POTS,

including pain, nausea, and dizziness. Studies suggest that over 80% of adolescents with POTS report chronic pain, and research evidence for the efficacy of biobehavioral treatments to reduce pain in children and adolescent is strong.[162,163] Evidence exists for both individual-based strategies as well as family strategies. Individual strategies often include pain management strategies but may also include techniques to reduce the pain indirectly through stress management, treatment of depression and anxiety, and sleep hygiene. Family-based strategies include teaching the family to reduce attention and secondary gain from the pain and promote independent use of positive coping skills.

Many treatments combine all of the above elements in a comprehensive cognitive–behavioral program that is delivered briefly, typically in six to ten 1-h sessions. Sessions may be delivered individually or in a group format. A recent meta-analytic study[163] including 25 randomized controlled trials with children experiencing headache, abdominal pain, and fibromyalgia found a large positive effect on pain reduction post-treatment (odds ratio = 5.92) and at 3 month follow-up (odds ratio = 9.88). Findings were similar for programs including multi-component CBT, relaxation, or biofeedback. Limited research is available for patients experiencing POTS and pain, but clinical impressions suggest findings would be similar.

Training in relaxation strategies is a core treatment element in many pain management programs. Multiple strategies can be used, including diaphragmatic breathing, progressive muscle relaxation, imagery, self-hypnosis, and biofeedback. The relaxation may directly affect the pain by promoting endorphins and enkephalins, but may also contribute to other body changes such as reducing muscle tension, and slowing the heart rate. Indirectly, use of relaxation strategies may also give children or teenagers increased confidence in their ability to manage their symptoms.

We have found that teenagers especially enjoy learning relaxation through the use of biofeedback. Biofeedback allows teenagers to receive immediate feedback regarding their level of relaxation including muscle tension, heart rate, breathing, and sweating. This immediate feedback combined with coaching often allows the teen to learn relaxation quickly and to readily gain a sense of accomplishment. The major downside of biofeedback is the lack of trained providers in rural locations. However, technology is making this treatment component more portable and less expensive. Simple biofeedback devices can be purchased for home computer use or even for mobile devices.

Most adolescents with POTS experience significant fatigue, and this fatigue is often a primary reason they think they are unable to attend school, sports, and extracurricular activities.[164] Many of these previously high-functioning teenagers enjoyed school in the past, but their fatigue, other symptoms, and concern about being able to achieve their previous level of functioning make return difficult. Prioritizing return to school appears to be an important treatment component with children with POTS. Often a gradual approach to school return along with strategies to reduce pain and nausea makes school return an acceptable goal and outcome.

Nausea is another symptom frequently cited by teenagers with POTS. Relaxation and biofeedback therapies have long been known to reduce anticipatory nausea in adolescents and adults undergoing chemotherapy. For children and adolescents experiencing nausea for other reasons, Silverman and Tarbell[165] cite clinical reports regarding the effectiveness of cognitive and behavioral treatments for nausea reduction. Treatment typically includes a focus on identifying stress and lowering arousal during stressful experiences through relaxation training and/or cognitive restructuring.

Many of these cognitive–behavior interventions also include a parent component. Although research is less robust on parent intervention strategies, there is some suggestion that adding parents may improve treatment efficacy for teens with chronic pain.[162] Solicitous responses from parents have been shown to increase the sick role and pain behaviors in children with recurrent abdominal pain.[166] Parents of teenagers with POTS also demonstrate solicitous behaviors, and these behaviors are associated with anxiety in their teens with POTS.[167] These solicitous behaviors are well-intentioned and may include attention to pain symptoms, reduced expectation for chores, schoolwork, or even reduced expectations for emotional control. Therefore, treatment includes teaching parents to pay increased attention to their child's well behavior and coping attempts. Parents and other family members are taught to minimize attention to pain behaviors such as describing their pain, groaning, and crying. Parents are also taught to effectively use behavior management strategies such as praise, rewards, and consequences to help motivate their child to utilize their pain management strategies and move toward wellness. Privileges (e.g., use of the car, phone, and computer and extracurricular activities) can become contingent on wellness activities (practicing pain management, and attending school). Parents usually grasp the concept of this system fairly easily, but they often need coaching and assistance from a behavior specialist to follow through with the plan.

> Effective management of POTS patients requires a “village” of support beginning with a knowledgeable physician.

“It Takes a Village”—Involving Families and Support Systems in POTS Care

Adolescents with chronic symptoms of fatigue, dizziness, presyncopal, and/or syncopal spells often experience severe disruptions in family function, school attendance, and peer relationships. The patient, the family, and the social community are all impacted.

Patients and families without a clear explanation for the patient's symptoms are often fearful and increasingly anxious that the symptoms represent an, as yet, undiagnosed life-threatening disease. The patient and family become hypervigilant to any symptoms, as well as to many bodily sensations that are normal.[107] With this severe somatic preoccupation, normal bodily symptoms often become interpreted as worrisome and in need of medical assistance, at times urgently.

In our structured rehabilitation program, we have treated patients who have had frequent 911 (emergency assistance) calls and ambulance rides to the emergency room for their symptoms, because parents view their symptoms as life-threatening. We recently treated a

17-year-old girl whose parents reported that they have seen no fewer than 75 specialists in their search for a diagnosis and cure for their daughter with autonomic dysfunction.

Effective management of POTS patients requires a “village” of support beginning with a knowledgeable physician. Families and patients need clear information regarding diagnosis and prognosis to reduce anxiety and hypervigilance. Patients need clear instructions regarding the need to return to school. Normalizing activity for these children is an essential part of effective management beginning with school.

We have seen children who have missed up to 6 years of school due to these symptoms. One patient was 21 years of age and had not completed a single day of high school. Despite her high level of intelligence, she had no high school credits and no plan as to how she might move into her future. She did not drive nor leave her home. Missing school for these patients results in poor social adjustment, poor social skills, isolation, lack of education and future employment opportunities, and can lead to a sense of despair.[80]

Unfortunately, often school personnel including school nurses, school counselors, teachers, and administrators may view the patient and their family as malingerers. We are seeing increased numbers of families with a child with these symptoms in which the school considers the absenteeism as truancy, not a medical issue. Courts are becoming involved and these anxious families are struggling to return their children to school without appropriate assistance. Families are being threatened with the removal of their child and placement in foster care. School personnel including tutors need to be a part of the solution. Adolescents with significant absences experience increased anxiety surrounding missed classes and missed credits, as well as disrupted social relationships, and concern about school authorities' view of their illness. Education of school personnel is a key to assisting patients and their families in successfully returning their children to school. When school personnel understand the fatigue and autonomic symptoms, support can be provided to the children and their families, making return to school possible.

Part of the “village” of support is the increasing number of formal and informal support groups available to these patients, many of which are on-line. Support groups can assist with the profound isolation that many of these patients feel due to their perceived inability to leave their homes. If support groups help patients set goals for increased functioning, that is a step toward rehabilitation. At times, however, so-called support groups are focused on the discouragement of the disease and can add to the patient’s sense of fear regarding their future.

When symptoms are severe or lead to significant disability, a structured rehabilitation program may be needed to improve functioning. Such a program would have improved functioning as the primary goal. Education and support for patients (and parents) in moving away from the sick role to full functioning is essential. Cognitive–behavioral skills that target distress, anxiety, and avoidance can be powerful self-management strategies in assisting patient's rehabilitation. In the 3-week Mayo Clinic Pediatric Pain Rehabilitation Center program for severely impaired adolescents, often referred to as the Mayo Clinic POTS and Pain Recovery Program, we have treated over 500 patients, many of whom have

diagnoses of autonomic dysfunction and POTS. We are likely the only rehabilitation center in the world that treats POTS. Our goal is to teach self-management skills that allow our adolescents to return to a full level of functioning that includes returning to school full time at the end of our 3-week program. Preliminary outcome data has shown significant improvement in depression, anxiety, and functioning over the course of the 3-week program that appears to be durable at 3-month follow-up.[168]

"Get Motivated"—Empowering Teens and Families for Recovery

POTS is a life-altering, debilitating condition that requires comprehensive lifestyle changes in order to promote chronic disease management. Most patients with POTS have undergone extensive diagnostic testing and numerous health care visits prior to obtaining a POTS diagnosis. Thus, visits with these patients and families are extremely intense because they are anxious to get answers about why the adolescent is sick and reassurance that the condition is not psychosomatic. These families are searching for effective treatment to restore the health and well-being of the adolescent. The following includes tips on how to motivate teens and empower them toward recovery.

Establish a diagnosis—Teens and families first need a diagnosis to hold onto in order to begin learning about how to recover. They can be assured that their problem is "real" and physical. But, they should be advised to use the diagnosis as a springboard from which to launch toward a full recovery of functional ability rather than as a burden to drag them down.

Be positive and optimistic about recovery and moving on with life.

Validate their symptoms and the idea that their symptoms are not psychosomatic.

Give them a specific plan to follow (increased salt and fluids, exercise, school attendance, and daily schedules). Focus on consistency, moderation, and a "just do it" approach. Discuss the importance of making baby steps toward all of their goals. Empower them and their "village" with knowledge about POTS.

When providing an exercise prescription, focus on gradually working the patient toward the exercise goal. For example, some teens start with 5 min of walking outside or on the treadmill and add 1–2 min every 2–4 days until they reaching the goal of 30 min of sustained aerobic exercise 6 days of the week (in addition to other less programmed physical activity).

Encourage Goal Setting—Allow adequate time for education, and recognize that getting a recovery plan is an emotional process for teens and parents.

Take the focus off of symptoms. Encourage them to go back to normal life (attending school and spending time with friends doing social activities, chores, and outings).

Encourage a team partnership and recommend primary care involvement. Provide contact information for specific POTS questions.

Remind them that lifestyle changes are a process and do not all have to be done all at once because the treatment plan frequently seems overwhelming. Give them examples of how to gradually start incorporating all the components of the recovery plan.

Encourage the teens and families to celebrate their success and accomplishments!

Provide the teens with a “Plan B” backup option in case they struggle with the treatment plan and the motivation to recover. Referral to a more intensive specialty program— such as the Mayo Clinic Pain Rehabilitation Program, described above—might be such a backup recovery plan.

With good education, motivational encouragement, and specific plans, adolescents with POTS can anticipate a full and complete recovery.

Conclusion

Thus, many adolescents are tired, even chronically fatigued. Sometimes, the fatigue is the consequence of a concurrent medical condition, inadequate sleep habits, or coexisting psychological challenges. Often, however, the fatigue persists in the absence of other identifiable medical conditions. Increasingly, however, autonomic dysfunction is identified in chronically tired teenagers with its constellation of orthostatic intolerance and excessive postural tachycardia. Even while research continues to explore the pathophysiology of this condition, helpful treatment is available. Affected adolescents and their families must move beyond a non-productive quest for medical diagnoses and press on toward recovery. Full recovery is anticipated, and this can be facilitated by multi-disciplinary care. Symptomatic management of headache, circulatory problems, and intestinal symptoms can be helpful. Fluid and salt intake should be increased. Aerobic exercise is a key to successful recovery. Care systems and care teams should work together to support and encourage patients along the way.

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