Autonomic Neuroscience: Basic and Clinical 215 (2018) 62–69

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

Sleep disorders in patients with postural tachycardia syndrome: A review of the literature and guide for clinicians

Mitchell G. Miglis[a,b,*], Fiona Barwick[b]

[a] Department of Neurology and Neurological Sciences, Stanford University Medical Center, Palo Alto, CA, United States
[b] Department of Psychiatry and Behavioral Sciences, Stanford Center for Sleep Sciences and Medicine, Redwood City, CA, United States

ABSTRACT

Fatigue is common in POTS, and patients often report unrefreshing sleep. These symptoms are directly correlated with a reduced quality of life, however the treatment of sleep disorders in this population remains a challenge. This article will review the current literature on the prevalence of sleep disorders in POTS, their association with the underlying pathophysiology of POTS, and current treatment paradigms.

1. Introduction

While the term postural tachycardia syndrome (POTS) includes the features of this syndrome most easily identified by clinicians, most patients do not mention postural tachycardia or orthostatic intolerance as their most disabling symptom. In fact, the chief complaint for most patients with POTS is fatigue and unrefreshing sleep, and these symptoms are directly correlated with reduced quality of life (Bagai et al., 2011; Pengo et al., 2015). Some patients are also sleepy, and many if not all patients have some form of sleep disorder. This article will review the current literature on the prevalence of sleep disorders in POTS, their association with the underlying pathophysiology of POTS, and current treatment paradigms.

2. Clinical presentation

Almost every patient with POTS has fatigue. This symptom was reported by 73% of POTS patients in the Mayo cohort (Thieben et al., 2007), and by > 90% of patients in the Boston University cohort (Deb et al., 2015; Xu et al., 2016). When evaluating a patient with POTS, the clinician should attempt to distinguish symptoms of fatigue from those of sleepiness. Does the patient describe the overwhelming desire to sleep or nap? Do they find themselves dozing off in meetings or while driving? These are symptoms of sleepiness. Or do they describe a sensation of muscle "tiredness or body exhaustion?" These are symptoms of fatigue. Most patients will be able to make this distinction. This can aid in understanding what is driving the symptoms, and where to focus the workup and treatment. Many patients with POTS describe both sleepiness and fatigue.

The Epworth sleepiness scale (ESS) is used most frequently to quantify sleepiness (Johns, 1991). There are several scales that can be used to quantify fatigue, including the fatigue severity scale (FSS, Krupp et al., 1989) and the Chalder fatigue severity index (CFQ, Chalder et al., 1993). In our experience, patients with POTS tend to describe more fatigue than sleepiness, similar to patients with chronic fatigue syndrome (CFS) or fibromyalgia. In one study assessing fatigue and sleepiness in patients with CFS, a subgroup of POTS patients with CFS reported lower ESS scores than those with CFS only (Lewis et al., 2013). The majority of subjects in both groups scored the maximum possible fatigue score on the CFQ.

Many patients with POTS report difficulty either falling or staying asleep. In one survey study, more than half of patients reported trouble falling asleep at night (63.3%) and maintaining sleep through the night (62.1%, Xu et al., 2016). It is not clear if this difficulty falling or staying asleep is due to an etiology unique to POTS, or rather secondary to the combined effects of suboptimal sleep hygiene, circadian rhythm abnormalities, or other medical comorbidities. To date there has been no primary sleep disorder identified that is unique to POTS. While some patients describe cardiovascular symptoms such as palpitations and chest pain that prevent them from falling or staying asleep, many patients cannot identify a causative factor. One plausible explanation is that patients experience disrupted sleep from a combination of systemic factors, such as body fatigue, chronic pain, hyperactivity of arousal networks and, in some cases, sleep-state misperception. These theories are discussed in more detail in Section 3.

Patients with POTS also tend to have a delayed circadian phase. We assessed individual circadian phase preferences with the Horne and Ostberg morningness–eveningness questionnaire (MEQ) in our cohort, and found that most patients scored themselves as evening, or "owl," subtypes (Miglis et al., 2016). The reasons for this delayed sleep phase

* Corresponding author at: 213 Quarry Road, Palo Alto, CA 94304, United States.
E-mail address: mmiglis@stanford.edu (M.G. Miglis).

https://doi.org/10.1016/j.autneu.2018.05.002
Received 19 February 2018; Received in revised form 5 May 2018; Accepted 5 May 2018

are unclear, though there are several possible explanations. POTS typically affects younger patients, who tend to naturally have a delayed sleep phase. In addition, patients may report fatigue and other autonomic symptoms that limit their mobility, and as a result may nap or rest intermittently during daytime hours, thereby reinforcing this nocturnal chronotype. Some patients describe hyperadrenergic symptoms such as palpitations, racing thoughts, or excessive sweating that keep them up at night. Others state that they feel their best in the late evening, and as a result do not want to go to bed. Many may feel that even if they do sleep they never wake feeling refreshed, no matter how many hours they think they might have slept.

3. Sleep disorders in POTS

There have been several studies that have attempted to understand why nearly all patients with POTS report unrefreshing sleep. The literature addressing this topic is growing, and to date there have been several studies that have objectively evaluated sleep in patients with POTS. Taken in aggregate these studies have demonstrated that patients report more sleep complaints than controls (Bagai et al., 2011), have greater subjective symptoms than objective findings on polysomnography (PSG, Bagai et al., 2016; Mallien et al., 2014; Miglis et al., 2016), and demonstrate no consistent polysomnographic abnormalities that explain the severity of their symptoms. Patients in our cohort had mild obstructive sleep apnea (OSA), with a mean apnea-hypopnea index of 6.6 ($\geq$5 is normal, Miglis et al., 2016). A third of these patients were eventually diagnosed with Ehlers–Danlos hypermobility subtype (hEDS), which may predispose patients to upper airway collapse and thereby increase their risk of OSA (Guilleminault et al., 2013).

Bagai et al. at reported a greater subjective sleep-onset latency (SOL—the time from lights out to sleep onset) when compared to actigraphy SOL in their Vanderbilt cohort (56 vs 37 min, Bagai et al., 2013). Actigraphy measures body movement by means of a wrist accelerometer and can be used to approximate sleep duration and sleep timing. This led the authors of this study to propose a theory of sleep-state misperception, a model employed in the insomnia literature (Rezaie et al., 2018). Similarly, patients in our cohort reported greater subjective SOL when compared to PSG SOL (29.5 vs 17.25 min) but similar wake after sleep onset (WASO—the spent awake during the night excluding SOL), and similar sleep efficiency (SE—the percentage of time in bed spent asleep). A SOL and WASO value of > 30 min is considered abnormal, as is a SE of < 85%. Bagai et al. reported PSG findings on a subsequent cohort of their Vanderbilt patients several years later, and found no difference in any objective PSG parameter between patients and controls (Bagai et al., 2016). The authors did find a significant negative correlation between SE and the change in HR from supine to standing. While this finding may indicate a predisposition to a hyperadrenergic state which may disrupt sleep, the clinical significance of this isolated finding is uncertain.

Mallien et al. reported normal PSG SOL, SE, and total sleep time (TST) in their German POTS cohort (Mallien et al., 2014). REM latency was prolonged, as it was in our cohort. WASO was not reported. Sleep architecture, or the various percentages of each sleep stage during the night, was overall normal. These researchers also used spectral analysis of heart rate variability (HRV) to estimate the low-frequency (LF) and high-frequency (HF) components of various sleep stages. While they did report a reduction in LF/HF variability during sleep stage transitions in patients, there was no significant difference in stage-specific LF, HF or the LF/HF ratio when compared to controls. Based on these results, these researchers theorized that patients with POTS might have altered HRV during sleep, reflective of a hyperadrenergic state.

A study supporting this theory using 24-h blood pressure monitoring demonstrated a non-dipping pattern in 55% of POTS patients (Figueroa et al., 2014). “Non-dipping” refers to the absence of the normal 10–20% reduction in blood pressure that occurs during non-REM sleep, a state of parasympathetic dominance. A non-dipping pattern is suggestive of either increased sympathetic tone or decreased parasympathetic tone during sleep.

Pengo et al. analyzed PSG data on their London-based cohort and also found that these data were overall normal, with the exception of a slight reduction in the percentage of REM sleep and a reduction in SE (Pengo et al., 2015). They also found a prolonged REM latency, as in our cohort and the German cohort. The reasons for a prolonged REM latency seen across multiple studies is unclear, however there are several possibilities. Prolonged REM latency has been associated with a “first night effect” in the sleep laboratory, where an individual takes longer to fall asleep than at home and thus has a prolonged REM sleep latency, due to the unfamiliar environment. It is thought to be a normal phenomenon. Prolonged REM latency can also be secondary to certain medications such as tricyclic antidepressants and amphetamine stimulants, medications that are prescribed to POTS patients. It should be noted that medications such as antidepressants and stimulants were not controlled for in any of the PSG studies mentioned. As these medications can affect sleep architecture, this is a limitation of these studies.

A subset of patients in the study by Pengo et al. underwent additional quantification of excessive daytime sleepiness with multiple sleep latency testing (MSLT), whereby patients attempt to fall asleep during a series of four to five nap tests conducted during the day and performed at 2 h intervals. MSLT results in this subgroup of POTS patients were also normal, with a mean sleep latency of 14.4 min (range 11.8–17.5). A cutoff $\leq$ 8 min is indicative of sleepiness, and most patients with narcolepsy have a sleep latency of 2–3 min or less. When comparing patients with and without subjective daytime sleepiness, the authors found that the group that was not objectively sleepy had a lower HF component in HRV analysis. Based on this finding, the authors postulated that altered parasympathetic activity may precipitate sleepiness, though this has not been demonstrated systematically in other studies, and future research is necessary to support this statement.

Why then do POTS patients remain symptomatic while their objective data fail to demonstrate any consistent abnormalities? One initial explanation is the possibility of microarousals, which are not detected on routine PSG analysis but rather by frequency analysis or cyclic alternating pattern (CAP) analysis. While there have been no studies to our knowledge that have performed this analysis in POTS patients, there is some precedent in the CFS literature. Guilleminault and colleagues performed CAP analysis on a small cohort of patients with CFS and found that CAP rates were significantly higher values in subjects with CFS when compared to controls (50.9 vs. 27.0) (Guilleminault et al., 2006). In addition, there are some data in POTS patients that may indirectly support this theory. Lin et al. demonstrated that both morning and daytime salivary cortisol levels are significantly higher in children with POTS (mean age 12.0 $\pm$ 1.8, Lin et al., 2017), indicating a greater degree of sleep fragmentation. Cortisol generally increases during wake and stage 1 non-REM sleep and decreases in the deeper stage 3 non-REM sleep, thus sleep disruption or frequent arousals are associated with increases in plasma cortisol levels.

In line with this finding, POTS patients often describe a sensation of generalized hyperarousal that prevents them from falling asleep even in the setting of extreme exhaustion, a presentation referred to by sleep psychologists as “tired but wired.” This sensation is experienced by many patients with insomnia and is supported physiologically by several studies that have utilized functional imaging and EEG analysis. PET imaging in chronic insomnia patients during sleep has demonstrated increased activation and hypermetabolism in the arousal networks of the hypothalamus and brainstem, as well as their efferent projections in the medial prefrontal cortex and amygdala (Nofzinger et al., 2004). EEG frequency analysis has demonstrated that these patients have increased beta (14–35 Hz) and gamma (35–45 Hz) activity, frequencies associated with waking cortical activity (Spiegelhalder et al., 2012). Many patients with sleep-state misperception, or “paradoxical insomnia,” may in fact have increased beta and gamma frequencies during sleep. While these studies have not been performed in patients

with POTS, it would not be surprising if they too had evidence of hyperactive arousal networks, as Bagai et al. had suggested (Bagai et al., 2013). The hyperarousal model, with its focus on heightened hypothalamic–pituitary–adrenal tone, increased catecholamine secretion, and excessive cortical activity during wake and sleep, may provide a window into the understanding of the sleep disruption in patients with POTS.

Why do many patients with POTS exhibit symptoms of hyperarousal? One often overlooked possibility is that arousals from any source, if frequent enough, can result in increased sympathetic tone. This has been demonstrated in the literature on insomnia, obstructive sleep apnea, periodic limb movements and restless legs syndrome (RLS, Miglis, 2017). Prior to an electrocortical arousal, there is a typical cardiac response that occurs: initial tachycardia, which often precedes the arousal by several seconds, followed by bradycardia. With every arousal there is a small elevation in sympathetic tone. If the arousals become frequent enough, this elevation can persist after the patient has returned to sleep (Blasi et al., 2003), and even into the next day. In a large cohort of children and adolescents (ages 7–18), POTS was 6× more common in those who slept for < 8 h per day when compared to those in those who slept for ≥8 h per day (Lin et al., 2014). Whether this reflects cause or effect is unclear.

Some researchers have demonstrated that POTS patients exhibit "somatic hypervigilance" (i.e. a heightened ability to perceive internal sensations such as palpitations, gastrointestinal upset, or temperature intolerance) and have postulated that the degree of sensitivity to these sensations, or *interoception*, may enhance anxiety (Khurana, 2014; Owens et al., 2017). The degree to which a person is sensitive to interoceptive signals has been linked to emotional experience, and those who are more sensitive to fluctuations in their body's internal feedback system may be more prone to anxiety. This somatic hypervigilance and enhanced interception may actually disrupt sleep, as some patient report palpitations, chest pains, or gastrointestinal symptoms that keep them from falling asleep.

Many patients with POTS also describe problems with their circadian rhythm. While the subtleties of circadian rhythm disorders in these patients have not been systematically evaluated, there may be a connection between melatonin secretion and the autonomic system. Melatonin acts on two receptors, MT1 and MT2. MT1 receptors, when stimulated, lead to vasoconstriction of peripheral arterioles (Masana et al., 2002), and MT2 receptor stimulation leads to vasodilation (Jin et al., 2003). In addition, the stimulation of MT1 receptors in the suprachiasmatic nucleus may reduce central sympathetic output by stimulating GABA-ergic signaling to the paraventricular nucleus, which in turn inhibits adrenergic nuclei in the lateral medulla (Green et al., 2014). Many POTS patients are treated with nonselective β-blockers such as propranolol, which may impair melatonin secretion via blockade of pineal β-1-receptors (Stoschitzky et al., 1999), though these medications may also provide relief from nocturnal palpitations and are sometimes dosed at bedtime for this purpose. Interestingly, in one small study, 3 mg of melatonin dosed in the morning produced a moderate decrease in standing tachycardia in patients with POTS, although it did not improve symptoms of orthostatic intolerance (Green et al., 2014).

One final explanation for unrefreshing sleep in POTS is the association of comorbid psychiatric disorders in this patient population. Mood disorders in POTS is a controversial topic. Most autonomic clinicians agree that patients frequently describe symptoms of anxiety or depression, and the prevalence of suicidal ideation in this population is noteworthy (Pederson and Brook, 2017). However, many of the clinical symptoms of POTS overlap with those of anxiety, and studies have failed to establish causation. Raj et al. compared patients with POTS to controls with a diagnosis of attention deficit hyperactivity disorder (ADHD) and healthy controls, and found that POTS patients did not have an increased prevalence of major depression or anxiety disorders, although they did have higher scores on the Beck depression index and Beck anxiety inventory (Raj et al., 2009). A reduction in slow wave sleep, reduced REM onset latency, increased percentage of REM sleep, and decreased SE are common in depression (Kupfer et al., 1981). Some of these PSG findings have been noted in POTS, however there is not enough evidence to justify an underlying mood disorder as the cause of sleep-related complaints in patients.

In summary, based on the current literature, it is difficult to state that the sleep-related complaints of POTS patients are the result of a primary sleep disorder unique to POTS. A more plausible explanation is that these patients experience disrupted sleep from a combination of systemic factors, such as body fatigue, chronic pain, hyperactivity of arousal networks and, in some cases, sleep-state misperception. Like CFS, fibromyalgia, and hEDS, POTS is a multifactorial syndrome and a chronic illness with many possible etiologies, therefore there is unlikely to be one single associated sleep disorder or treatment algorithm that applies to all patients.

4. Approach to work-up and management

Just as there is no one size fits all algorithm for the treatment of autonomic symptoms in patients with POTS, there is no such algorithm for the treatment of sleep-related symptoms in patients with POTS. However, there are some universal principles that apply, summarized in Fig. 1. Reported symptoms and sleep complaints, along with the systemic factors underlying them, can be addressed explicitly using evidence-based cognitive-behavioral principles that have proven highly effective in treating insomnia (Morgenthaler et al., 2006; Qaseem et al., 2016; Schutte-Rodin et al., 2008).

The first step in managing sleep-related symptoms in patient with POTS is to take a careful sleep history. This includes asking questions about what time patients get into bed, what time they attempt to sleep ("lights out,"), how long it takes them to fall asleep, how often and how long they are awake during the night, what time they wake up in the morning, and what time they get out of bed. Questions that focus on assessing circadian rhythms apart from sleep-wake patterns can also be helpful, including the timing of meals, activities, and rest periods during the day. The amount and timing of stimulating compounds such as caffeine and nicotine should be assessed, though many patients with POTS tend to avoid these substances. The amount of screen time at night (including e-book readers, smartphones, computers and television) should also be assessed.

Patients should be queried for symptoms of all other primary sleep disorders, including OSA, RLS, periodic limb movement disorder (PLMD), and narcolepsy. Some symptoms and signs of OSA include snoring, pauses in breathing while sleeping, dry mouth or headaches upon awakening, and a narrow nasal or oropharyngeal airway. Periodic limb movements (PLMs) may manifest as frequent leg movements during sleep. These movements can wake patients and disrupt sleep and are often witnessed by bedpartners. It should be noted that none of the PSG studies reviewed in Section 3 found an elevated PLM index in POTS patients, however a careful sleep history should include questions about PLMs.

Symptoms of RLS should be addressed in any patient who reports difficulty falling or staying asleep. These symptoms occur while awake (as opposed to PLMs, which occur during sleep) and are characterized by an uncomfortable urge to move the legs that is relieved with movement and worse in the evening hours. While to our knowledge there are no studies addressing the prevalence of restless legs syndrome (RLS) in POTS patients, RLS is common enough that some patients with POTS also have RLS (prevalence 4–29% and 35–50% more common in women, Innes et al., 2011). All patients with symptoms of RLS that disrupt their sleep should have a serum ferritin test performed, and iron supplementation (325 mg daily with 200 mg of vitamin C) should be considered in patients with ferritin levels ≤75 μg/dL (Winkelman et al., 2016). Medications that exacerbate RLS include β-blockers (which many POTS patients are taking), antihistamines, neuroleptic agents, dopamine-blocking antiemetics, neuroleptics, lithium, and most

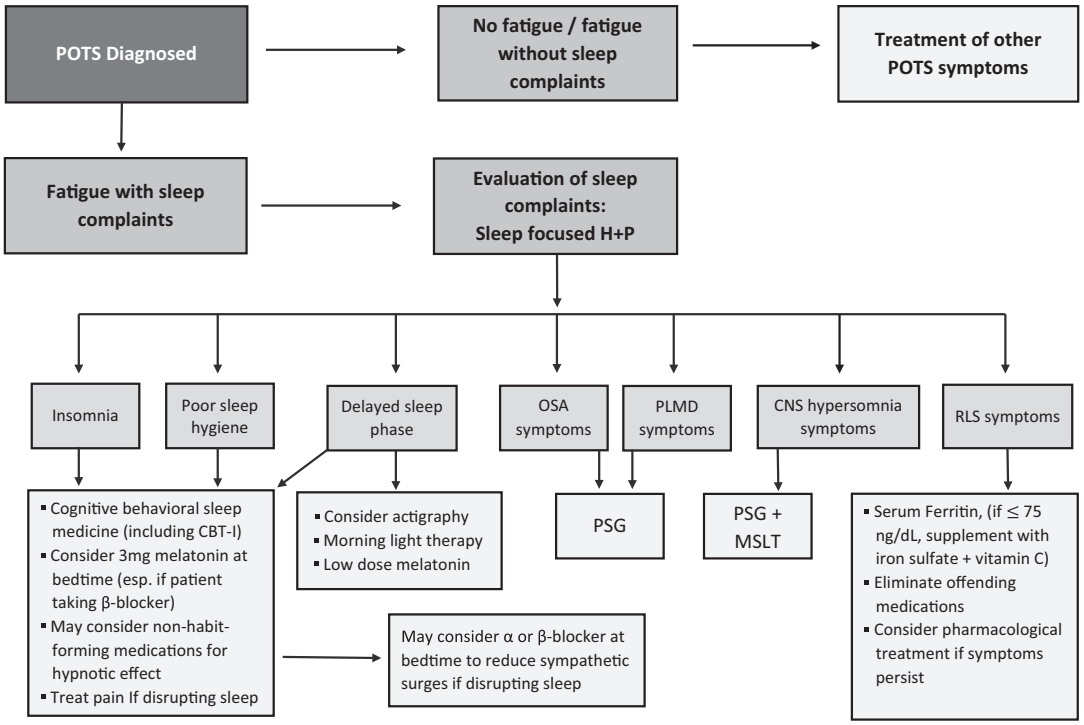

Fig. 1. Approach to workup and treatment of sleep disorders in patients with POTS. H + P = history and physical, CBT-I = cognitive behavioral therapy for insomnia, CNS = central nervous system, MSLT = multiple sleep latency testing, OSA = obstructive sleep apnea, PLMD = periodic limb movement disorder, PSG = polysomnogram, RLS = restless legs syndrome.

antidepressants. Pharmacological treatment with α2ϱ-ligands such as gabapentin or dopamine agonists such as pramipexole may be considered if non-pharmacological treatments are ineffective.

While rare, narcolepsy is a primary hypersomnia that also affects younger adults and should thus be considered in any patient with POTS and excessive daytime sleepiness. Patients with narcolepsy will describe more sleepiness than most POTS patients, and almost universally have elevated ESS scores (≥ 10). They will also describe some combination of sleep paralysis (waking up and being unable to move their body), hypnic hallucinations (dream-like images that occur shortly before falling asleep or after waking up), sleep attacks (falling asleep suddenly, sometimes in active situations), automatic behaviors, vivid dreams, or dream enactment (REM sleep behavior disorder). Cataplexy, the loss of skeletal muscle tone with preserved consciousness, triggered by positive emotions such as laughter, is present in patients with type-1 narcolepsy and absent in type-2 narcolepsy. Autonomic symptoms in patients with narcolepsy have been well described in the literature (Berteotti and Silvani, 2017), however there are no reports of an association between POTS and narcolepsy. We recently reported on a patient who developed both type-2 narcolepsy and POTS from a demyelinating lesion in the thalamus and amygdala, supporting the possibility of a connection between these two disorders, (Kim et al., 2018) though more systematic studies on this topic are needed.

Not all patients require a PSG. If they exhibit any signs or symptoms of OSA or PLMD, however, PSG may be warranted to evaluate for these physiologic sleep disorders. Heart rate during non-REM and REM sleep is typically normal (Bagai et al., 2016; Mallien et al., 2014; Miglis et al., 2016), and in most patients there is rarely additional clinical information to be gleaned from PSG. If a patient reports primarily symptoms of insomnia in the absence of symptoms of OSA or PLMD, a PSG will most often only confirm what is already suspected: that the patient does not sleep well. Actigraphy can help to quantify variability in sleep/wake patterns, although patients nowadays may simply report this data from Fitbit© and other wearable devices at their initial visit. Salivary cortisol and melatonin assays provide the most accurate markers of circadian phase but are not routinely employed in clinical practice.

Once an initial evaluation has been completed, treatment can focus on addressing the sleep problems most commonly reported by patients with POTS. These include insomnia (difficulty falling and staying asleep as well as non-restorative sleep), generalized hyperarousal (palpitations, racing thoughts), circadian dysregulation (irregular sleep schedule, delayed sleep phase), sleep state misperception (belief that one is awake when one is asleep), and daytime resting or napping due to fatigue. Guidelines for treating sleep complaints in patients with POTS are based on the successful use of cognitive-behavioral techniques for treating insomnia and circadian disruption in the general population, but are still theoretical given the minimal research to date with these patients.

5. Cognitive-behavioral techniques

5.1. Reduce time awake in bed

In our clinical experience, some patients with POTS spend too much time in bed, both at night and during the day. This may be due to orthostatic intolerance, pain, fatigue, or other symptoms. Although they may use their time in bed to rest (they typically do not fall asleep), patients also may engage in non-sleep activities such as reading, answering emails, or watching TV because they feel most comfortable in this setting.

Unfortunately, this learned behavior, or habit, is counter-productive and often leads to prolonged sleep latency or wakefulness during the night. Spending too much time in bed lowers the body's homeostatic drive for sleep, a drive that typically builds as one is awake and active and out of bed during the day (Borbély, 1982; Borbély et al., 2016). It also increases the risk of napping or dozing during the day, which further lowers sleep drive before bedtime. Additionally, doing activities in bed that are typically associated with wakefulness, including just "resting," weakens the association between bed and sleep, making it

hard for patients with POTS to take advantage of the powerful conditioned response to bed and bedtime that dates from childhood.

Patients with POTS, or anyone who is spending too much time in bed, can be encouraged to compress their time in bed, so that their sleep opportunity (time spent in bed) matches their sleep ability (average amount of sleep per night). This helps to increase sleep drive and possibly reduce the frequency of microarousals, even in patients with chronic conditions such as fibromyalgia (Edinger et al., 2005; Krystal and Edinger, 2010). Because patients spend more time awake, active, and out of bed during the day, sleep drive is higher when bedtime arrives, making it easier for patients to fall asleep and sleep more soundly throughout the night.

Patients can also be reminded of the powerful reinforcement provided by classical conditioning. If they are either asleep or sleepy every time they are in bed, eventually their brain will start to "salivate" for sleep when they see the bed, just as Pavlov's dogs salivated for meat powder when they heard a bell. If patients are reluctant to give up doing wakeful activities in bed, they can be encouraged to set up a "cozy nook" somewhere else – even a spare bedroom – which, with sufficient use and habit learning, will eventually become as comfortable a setting as their bed.

5.2. Decrease generalized hyperarousal

As noted above, POTS patients may exhibit a state of generalized hyperarousal during wake and sleep – including somatic hypervigilance, excessive cortical activity, and elevated sympathetic tone – that can be affected by emotional state and can make it difficult to fall asleep despite extreme exhaustion. Hyperarousal characterizes patients with insomnia more generally, which is why relaxation is one of the techniques emphasized in the cognitive-behavioral treatment of insomnia (Lichsteinet al., 2001; Morin et al., 2006).

Relaxation techniques, which reduce physiological hyperarousal, include diaphragmatic breathing, progressive muscle relaxation, visualization, meditation, and others, many of which can be practiced with the help of web-based, app-based, or in-person resources. It is important that patients try different techniques, as they will like some but not others, and they should practice one technique daily for at least two to four weeks before trying others. These techniques take time to learn, so patient, persistence and practice are key. With regular practice, these techniques can shift the sympathovagal balance to one of less stress and more relaxation (Pal et al., 2014). Relaxation techniques can also be incorporated into an hour-long "wind-down" period before bedtime, which helps to disengage and "de-stress" before trying to sleep.

In addition to relaxation techniques, patients can be taught to cultivate a mindful approach to the experience of being awake at night. This experience is often accompanied by anxiety and frustration, or emotional and cognitive hyperarousal. Mindfulness, an approach introduced by John Kabat-Zinn in the 1980s, emphasizes paying attention to and accepting present moment experience. This approach encourages letting go of any judgements about the experience ("This is terrible!") or any efforts to make the experience other than what it is ("I need to get back to sleep!"). The focus on here-and-now experience, and the willingness to accept the experience as it is, reduces the "suffering" and "catastrophizing" that can accompany wakefulness at night. Paradoxically, remaining calm and relaxed when awake at night makes it likelier that sleep will return (Hofmann et al., 2010; Ong et al., 2014).

Education about normal sleep can help patients to further reduce emotional and cognitive hyperarousal. Common "sleep myths" include believing that sleep should happen quickly and that waking up at night is abnormal, blaming sleep for all daytime fatigue and impairment, attributing any mental or physical health problem to poor sleep, and thinking that sleep should be the focal point of daily and nightly efforts. Helping patient to challenge and reframe their inaccurate and unhelpful beliefs about sleep can circumvent the vicious cycle of insomnia that ensues when unhelpful thoughts, negative emotions, and maladaptive behaviors exacerbate and perpetuate sleep disturbance. Even something as simple as not checking the time if awake at night can reduce the hyperarousal that prolongs wakefulness.

5.3. Establish regular circadian rhythms

As noted above, some patients with POTS may have an irregular sleep-wake schedule, going to bed and waking up at different times, and as a result may rest or nap during the day. Irregularities in sleep-wake schedule prevent the entrainment of a regular circadian rhythm. Encouraging patients to establish a consistent bedtime and rise time, and to refrain from napping or dozing during the day, is the first step toward re-establishing a healthy sleep-wake pattern. Ideally, this regular sleep schedule should reflect the patient's natural body clock, which is often delayed in patients with POTS. If patients are "night owls" and can go to bed and get up on a delayed schedule, then they should do just that.

However, if environmental, occupational, academic, and/or social demands require "night owls" to get up earlier, they can use light therapy in the morning and low dose melatonin in the evening to shift their circadian phase earlier. A typical "phase advance" would require 1.) at least 45 min of morning light exposure to sunlight or a light box (10,000 lx of broad spectrum blue-white light set about arm's length away); and/or 2.) melatonin < 1 mg (0.3–0.5 mg) taken 5 h before bedtime (timing might vary from 2 to 6 h before bedtime, although longer times are associated with larger advances (Zee et al., 2013).

As melatonin is not regulated by the FDA, patients should look for sublingual tablets with melatonin and minimal additional ingredients apart from filler (Erland and Saxena, 2017). Patients should also start closer to their natural circadian bedtime and, once their sleep window is stable, advance it by 30 min every 3–4 days. The regimen of melatonin and light must be maintained to keep an earlier window in place, however, as circadian biology tends to revert to its natural timing without these scaffolds. Patients with POTS who are taking β -blockers, which can suppress endogenous melatonin secretion, might also consider taking supplemental melatonin at bedtime to counter these effects (Scheer et al., 2012).

Patients should also try to avoid light at inappropriate times, especially during the hour or two before bedtime when melatonin levels start increasing in anticipation of nighttime sleep. The circadian system is powerfully affected by higher frequency light cues, especially blue-green light, which cues the circadian pacemaker to suppress melatonin and thus reduce sleepiness (or increase alertness). Unfortunately, all screens – phone, tablet, laptop, and television – emit blue light, although yellow filters and "night shift" settings can minimize blue light cues. Although research to date is inconsistent given the challenges of investigating this topic, patients should be encouraged to limit or eliminate screens at least 1 h before bedtime to avoid inadvertently reducing melatonin.

Finally, patients should be encouraged to align other circadian rhythms, such as rest-activity and feeding-fasting, with sleep-wake rhythms to strengthen and stabilize circadian patterns. For example, patients should be encouraged to eat something within 1 h of waking up and to finish eating three to 4 h before bedtime. If possible, they should incorporate physical activity shortly after they get up, which boosts core body temperature and thus alertness, but should ensure that vigorous activity is over at least 3 h before bedtime, so that core body temperature has time to come down. Creating clear differences between daytime and nighttime – being awake, active, out of bed, and exposed to light during the day while being sleepy, quiet, in bed, and in darkness at night – helps to establish and reinforce healthy, well-regulated circadian rhythms.

5.4. Maintain healthy sleep hygiene

Sleep hygiene comprises lifestyle and environmental factors that affect sleep. It is not an effective therapy by itself, but poor sleep hygiene can disrupt sleep. Patients with POTS should understand the importance of protecting their sleep environment – for example, having a comfortable mattress and keeping the bedroom as dark and quiet as possible. A protected sleep environment may be especially important for POTS patients, given the possibility of microarousals that disrupt their sleep and lead to more frequent nighttime awakenings.

As reports of heat intolerance are common, it may also be important for patients with POTS to keep their bedroom cool but allow for flexible temperature regulation. A fan or portable air conditioner helps if central heating and cooling are not available. Layers of blankets rather than a single quilt, pajamas made of wicking material, water kept on the nightstand, cool gel packs under the pillow, and even a cooling mattress pad can help to manage the temperature spikes and night sweats that patients sometimes experience.

Substances that disrupt sleep, such as caffeine and alcohol, should be consumed in moderation and limited to 3–4 h before bedtime. Patients may have to experiment with amount and timing, as individual sensitivity to caffeine and alcohol varies widely, and some patients may benefit from discontinuing use altogether. Although the legalization of cannabis for medicinal and recreational use in many US states has led people to experiment with it as a sleep aid, research to date is limited and shows minimal benefits for sleep, except possibly for cannabidiol. Given the paucity of rigorous research on cannabis and sleep, the risks of habituation and dependence, the fact that cannabis products are not regulated, and the lack of standardized training for those prescribing and selling it, patients with POTS are advised not to use cannabis as a sleep aid or to use caution if experimenting with it (Babson et al., 2017).

5.5. Identify sleep state misperception

As suggested above, patients with POTS may have hyperactive arousal networks at night, leading to sleep-state misperception, or the belief that they are awake when they are asleep. Although attended PSG can be useful to demonstrate this “paradoxical insomnia” to the patient – the fact that they sleep more than they think they do, as do most of us – it rarely changes management and often offends patients, who do not appreciate being told that it is “all in their head.” Indeed, it usually does not work to convince patients verbally that they might be getting more sleep than they realize.

Instead, patients can be encouraged to pay attention to how difficult it is to determine the amount of sleep they get. First, sleep is hard to perceive reliably because it is defined by an absence of memories. Second, sleep inertia – a normal transitional state between sleeping and waking that can last 30 min or more during which people feel tired and heavy-eyed – often leads people to mistakenly conclude that they did not sleep well. Third, our perceptions of sleep and wake are not always accurate, as witnessed by experiences of dozing off for what feels like minutes but turns out to be hours, or conversely feeling like we slept soundly for hours but finding out it was only minutes.

Indeed, our perception of time itself is elastic, as it can “fly” when we are having fun and “crawl” when we are bored, worried, or upset, especially if we are paying close attention to it rather than being engaged in what we are doing. Gently drawing attention to the difficulties and inconsistencies in their perception of sleeping and waking can help patients with POTS recognize and accept that their experience of being awake at night for hours may not be entirely accurate (Harvey and Talbot, 2006).

6. Pharmacological treatments for insomnia and circadian rhythm abnormalities

Cognitive behavioral techniques are the first line therapy for insomnia, delayed sleep phase syndrome, and poor sleep hygiene in the general population (Morgenthaler et al., 2006; Qaseem et al., 2016; Schutte-Rodin et al., 2008). Although there are no studies on use of these techniques for sleep-related symptoms in patients with POTS, they have proven effective in patients with similar conditions such as fibromyalgia (Edinger et al., 2005; Martinez et al., 2014). However, there are many cases in which adjunctive medical therapy is warranted. Incomplete treatment responses, lack of access to trained practitioners or insurance payor restrictions are all common limitations for many patients.

There is no FDA-approved medication for the treatment of POTS, and limited randomized controlled trials are available to guide therapeutic options. Thus, all medications are prescribed off-label, and thus choices are based on clinician experience and anecdotal experience. Traditional hypnotics such as benzodiazepines (e.g., triazolam) and benzodiazepine receptor agonists (e.g., zolpidem) should generally be avoided, as these medications will not completely eliminate the insomnia of POTS and will eventually lose efficacy with long-term use. In addition, women can be slower metabolizers of these medications and are prone to their side effects of sedation and non-REM parasomnias such as sleepwalking and sleep-eating. Melatonin is a safe and well-tolerated first-line option, and may have an added benefit of treating tachycardia (Green et al., 2014). When recommending melatonin for sleep initiation, a higher dose such as 3 mg at bedtime can be recommended. When recommending melatonin for circadian effect, for instance to help phase advance a patient with a delayed sleep phase, a much lower dose is used at a much earlier time, as described in Section 5.3.

If melatonin is not effective for sleep initiation, neuropathic agents can be considered for their hypnotic effect, especially if the patient also reports symptoms of chronic pain or headaches. Gabapentin at a low dose (200–300 mg, dosed 1 h before bedtime) is a well-tolerated medication that in our clinical experience often works well in patients with POTS. Nortriptyline, duloxetine, or mirtazapine are other medications that may work for both neuropathic pain, migraine, functional gastrointestinal disorders, and sleep, and may be a good fit for a particular patient, based on our experience. Trazadone is commonly prescribed however its benefit for those with POTS is variable, in our experience. Activating neuropathic agents or antidepressants should be avoided at bedtime as these medications may exacerbate the patient's insomnia. It is important to note that there are no randomized trials to guide these medication choices, and thus prescribing preferences are based on anecdotal clinical experience.

Sometimes a patient will report autonomic cardiovascular symptoms that disrupt their sleep, such as palpitations, excessive sweating, or a general sense of hyperarousal. In these patients, nighttime dosing of a β-blocker or sympatholytic such as clonidine or guanfacine may help to alleviate these symptoms and promote sleep. These medications can be combined with the non-traditional hypnotic mentioned if clinically indicated, however daytime sedation should be monitored. Other autonomic cardiovascular medications such as midodrine and fludrocortisone should be avoided at bedtime, due to the possibility of supine hypertension. There are no data that suggest that these medications or other cardiovascular medications prescribed for POTS, such as pyridostigmine or ivabradine, directly contribute to sleep disruption. The only exception to this are the β-blockers, which may impair melatonin secretion, as previously discussed.

The use of stimulant medications in POTS has not been systematically evaluated. In our experience, some patients on these medications note significant improvement in daytime fatigue and sleepiness, as well as improvement in cognitive impairment (referred to by patients as “brain fog”). However, it should be noted that most of these

medications exert their effects by increasing monoaminergic stimulating neurotransmitters such as dopamine and norepinephrine, which can exacerbate tachycardia and hyperadrenergic symptoms, thus promoting the patient's insomnia. Stimulant medications should therefore only be considered after all primary sleep disorders have been ruled out and the patient has been given an adequate trial of cognitive-behavioral therapy.

7. Conclusions

Fatigue is a nearly universal symptom in patients with POTS and results in significant disability and reduced quality of life. Subjective sleep complaints are common in patients, while objective polysomnographic parameters have failed to demonstrate any consistent abnormalities. This disconnect is intriguing, and comparable to the findings reported in the literature on patients with CFS and fibromyalgia. Possible explanations include an increased rate of microarousals not captured on the traditional PSG montage, increased electrocortical fast activity or cerebral blood flow during sleep, heightened interoception, excessive hypothalamic–pituitary–adrenal tone, comorbid mood disorders, and altered sympathovagal balance during sleep, though none of these theories have been proven in any study. Many patients exhibit symptoms of hyperarousal and present with insomnia and a delayed or irregular sleep phase. All patients should be evaluated for primary sleep disorders when clinically indicated, and treatment should include cognitive-behavioral therapy with a trained practitioner or online course. While there are no data on the use of cognitive-behavioral therapy specifically in patients with POTS, there is robust evidence to support its use in treating insomnia, delayed sleep phase syndrome, and poor sleep hygiene, all of which are common in patients with POTS. It has therefore become an integral part of our treatment paradigm and we have had good success in our patients. The chronic use of traditional hypnotics should be avoided, however non-traditional hypnotics such as neuropathic agents or antidepressants may be considered in the right patient. Similarly, stimulant medications may be considered, though in some patients these may medications may exacerbate other POTS symptoms. Ultimately, each treatment plan must be tailored to the individual patient's needs and source of the underlying sleep disruption, if such a source can be identified. Further studies are desperately needed in order to better characterize the nature of sleep complaints in this population and identify the most appropriate treatments, with specific focus on the cause and effect of autonomic dysfunction and sleep disruption in POTS.

References

Babson, K.A., Sottile, J., Morabito, D., 2017. Cannabis, cannabinoids, and sleep: a review of the literature. Curr. Psychiatry Rep. 19 (4), 23. http://dx.doi.org/10.1007/s11920-017-0775-9.

Bagai, K., Song, Y., Ling, J.F., Malow, B., Black, B.K., Biaggioni, I., Robertson, D., Raj, S.R., 2011. Sleep disturbances and diminished quality of life in postural tachycardia syndrome. J. Clin. Sleep Med. 7, 204–210.

Bagai, K., Wakwe, C.I., Malow, B., Black, B.K., Biaggioni, I., Paranjape, S.Y., Orozco, C., Raj, S.R., 2013. Estimation of sleep disturbances using wrist actigraphy in patients with postural tachycardia syndrome. Auton. Neurosci. 177, 260–265. http://dx.doi.org/10.1016/j.autneu.2013.02.021.

Bagai, K., Peltier, A.C., Malow, B.A., Diedrich, A., Shibao, C.A., Black, B.K., Paranjape, S.Y., Orozco, C., Biaggioni, I., Robertson, D., Raj, S.R., 2016. Objective sleep assessments in patients with postural tachycardia syndrome using overnight polysomnograms. J. Clin. Sleep Med. 12, 727–733. http://dx.doi.org/10.5664/jcsm.5806.

Berteotti, C., Silvani, A., 2017. The link between narcolepsy and autonomic cardiovascular dysfunction: a translational perspective. Clin. Auton. Res. http://dx.doi.org/10.1007/s10286-017-0473-z.

Blasi, A., Jo, J., Valladares, E., Morgan, B.J., Skatrud, J.B., Khoo, M.C.K., 2003. Cardiovascular variability after arousal from sleep: time-varying spectral analysis. J. Appl. Physiol. 95, 1394–1404. http://dx.doi.org/10.1152/japplphysiol.01095.2002.

Borbély, A.A., 1982. A two process model of sleep regulation. Hum. Neurobiol.

Borbély, A.A., Daan, S., Wirz-Justice, A., Deboer, T., 2016. The two-process model of sleep regulation: a reappraisal. J. Sleep Res. 25 (2), 131–143.

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., Wallace, E.P., 1993. Development of a fatigue scale. J. Psychosom. Res. 37, 147–153.

Deb, A., Morgenshtern, K., Culbertson, C.J., Wang, L.B., Hohler, A.D., 2015. A survey-based analysis of symptoms in patients with postural orthostatic tachycardia syndrome. Proc. (Baylor Univ. Med. Cent.) 28, 157–159.

Edinger, J.D., Wohlgemuth, W.K., Krystal, A.D., Rice, J.R., 2005. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch. Intern. Med. 165 (21), 2527–2535.

Erland, L.A.E., Saxena, P.K., 2017. Melatonin natural health products and supplements: presence of serotonin and significant variability of melatonin content. J. Clin. Sleep Med. 13, 275–281. http://dx.doi.org/10.5664/jcsm.6462.

Figueroa, J.J., Bott-Kitslaar, D.M., Mercado, J.A., Basford, J.R., Sandroni, P., Shen, W.-K., Sletten, D.M., Gehrking, T.L., Gehrking, J.A., Low, P.A., Singer, W., 2014. Decreased orthostatic adrenergic reactivity in non-dipping postural tachycardia syndrome. Auton. Neurosci. 185, 107–111. http://dx.doi.org/10.1016/j.autneu.2014.06.003.

Green, E.A., Black, B.K., Biaggioni, I., Paranjape, S.Y., Bagai, K., Shibao, C., Okoye, M.C., Dupont, W.D., Robertson, D., Raj, S.R., 2014. Melatonin reduces tachycardia in postural tachycardia syndrome: a randomized, crossover trial. Cardiovasc. Ther. 32, 105–112. http://dx.doi.org/10.1111/1755-5922.12067.

Guilleminault, C., Poyares, D., da Rosa, A., Kirisoglu, C., Almeida, T., Lopes, M.C., 2006. Chronic fatigue, unrefreshing sleep and nocturnal polysomnography. Sleep Med. 7, 513–520. http://dx.doi.org/10.1016/j.sleep.2006.03.016.

Guilleminault, C., Primeau, M., Chiu, H.-Y., Yuen, K.M., Leger, D., Metlaine, A., 2013. Sleep-disordered breathing in Ehlers-Danlos syndrome: a genetic model of OSA. Chest 144, 1503–1511. http://dx.doi.org/10.1378/chest.13-0174.

Harvey, A.G., Talbot, L., 2006. Intervention to Reduce Misperception. In: Perlis, M.L., Aloia, M.S., Kuhn, B. (Eds.), Behavioral Treatments for Sleep Disorders: A Comprehensive Primer of Behavioral Sleep Medicine Interventions. Academic Press, London.

Hofmann, S.G., Sawyer, A.T., Fang, A., 2010. The empirical status of the "new wave " of cognitive behavioral therapy. Child Adolesc. Psychiatr. Clin. N. Am. 33, 701–710. http://dx.doi.org/10.1016/j.psc.2010.04.006.

Innes, K.E., Selfe, T.K., Agarwal, P., 2011. Prevalence of restless legs syndrome in North American and Western European populations: a systematic review. Sleep Med. 12, 623–634. http://dx.doi.org/10.1016/j.sleep.2010.12.018.

Jin, X., von Gall, C., Pieschl, R.L., Gribkoff, V.K., Stehle, J.H., Reppert, S.M., Weaver, D.R., 2003. Targeted disruption of the mouse Mel(1b) melatonin receptor. Mol. Cell. Biol. 23, 1054–1060.

Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540–545.

Khurana, R.K., 2014. Visceral sensitization in postural tachycardia syndrome. Clin. Auton. Res. 24, 71–76. http://dx.doi.org/10.1007/s10286-014-0227-0.

Kim, P., During, E., Miglis, M., 2018. A Case of Narcolepsy Type 2 and Postural Tachycardia Syndrome Secondary to Lesions of the Thalamus and Amygdala. J. Clin. Sleep Med. 14 (3), 479–481 (Mar 15).

Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46, 1121–1123.

Kupfer, D.J., Spiker, D.G., Coble, P.A., Neil, J.F., Ulrich, R., Shaw, D.H., 1981. Sleep and treatment prediction in endogenous depression. Am. J. Psychiatry 138, 429–434. http://dx.doi.org/10.1176/ajp.138.4.429.

Krystal, A.D., Edinger, J.D., 2010. Sleep EEG Predictors and Correlates of the Response to Cognitive Behavioral Therapy for Insomnia. Sleep 33 (5), 669–677. http://dx.doi.org/10.1093/sleep/33.5.669.

Lewis, I., Pairman, J., Spickett, G., Newton, J.L., 2013. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. J. Intern. Med. 273, 501–510. http://dx.doi.org/10.1111/joim.12022.

Lin, J., Han, Z., Li, X., Ochs, T., Zhao, J., Zhang, X., Yang, J., Liu, P., Xiong, Z., Gai, Y., Tang, C., Du, J., Jin, H., 2014. Risk factors for postural tachycardia syndrome in children and adolescents. PLoS One 9, e113625. http://dx.doi.org/10.1371/journal.pone.0113625.

Lichstein, K.L., Riedel, B.W., Wilson, N.M., Lester, K.W., Aguillard, R.N., 2001. Relaxation and sleep compression for late-life insomnia: a placebo-controlled trial. J. Consult. Clin. Psychol. 69 (2), 227–239.

Lin, J., Zhao, H., Shen, J., Jiao, F., 2017. Salivary cortisol levels predict therapeutic response to a sleep-promoting method in children with postural tachycardia syndrome. J. Pediatr. 191http://dx.doi.org/10.1016/j.jpeds.2017.08.039. (91–95.e1).

Mallien, J., Isenmann, S., Mrazek, A., Haensch, C.-A., 2014. Sleep disturbances and autonomic dysfunction in patients with postural orthostatic tachycardia syndrome. Front. Neurol. 5, 118. http://dx.doi.org/10.3389/fneur.2014.00118.

Martinez, M.P., Miro, E., Sanchez, A.I., Diaz-Piedra, C., Caliz, R., Vlaeyen, J.W., Buela-Casal, G., 2014. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. J. Behav. Med. 37 (4), 683–697. http://dx.doi.org/10.1007/s10865-013-9520-y.

Masana, M.I., Doolen, S., Ersahin, C., Al-Ghoul, W.M., Duckles, S.P., Dubocovich, M.L., Krause, D.N., 2002. MT(2) melatonin receptors are present and functional in rat caudal artery. J. Pharmacol. Exp. Ther. 302, 1295–1302.

Miglis, M.G., 2017. Sleep and the autonomic nervous system. In: Sleep and Neurologic Disease, http://dx.doi.org/10.1016/B978-0-12-804074-4.00018-2.

Miglis, M.G., Muppidi, S., Feakins, C., Fong, L., Prieto, T., Jaradeh, S., 2016. Sleep disorders in patients with postural tachycardia syndrome. Clin. Auton. Res. 26, 67–73. http://dx.doi.org/10.1007/s10286-015-0331-9.

Morin, C.M., Bootzin, R.R., Buysse, D.J., Edinger, J.D., Espie, C.A., Lichstein, K.L., 2006. Psychological and behavioral treatment of insomnia:update of the recent evidence (1998-2004). Sleep 29 (11), 1398–1414.

Morgenthaler, T., Kramer, M., Alessi, C., Friedman, L., Boehlecke, B., Brown, T., Coleman, J., Kapur, V., Lee-Chiong, T., Owens, J., Pancer, J., Swick, T., American Academy of Sleep Medicine, 2006. Practice parameters for the psychological and behavioral

treatment of insomnia: an update. An american academy of sleep medicine report. Sleep 29, 1415–1419.
Nofzinger, E.A., Buysse, D.J., Germain, A., Price, J.C., Miewald, J.M., Kupfer, D.J., 2004. Functional neuroimaging evidence for hyperarousal in insomnia. Am. J. Psychiatry 161, 2126–2128. http://dx.doi.org/10.1176/appi.ajp.161.11.2126.
Ong, J.C., Manber, R., Segal, Z., Xia, Y., Shapiro, S., Wyatt, J.K., 2014. A randomized controlled trial of mindfulness meditation for chronic insomnia. Sleep 37, 1553–1563. http://dx.doi.org/10.5665/sleep.4010.
Owens, A.P., Low, D.A., Iodice, V., Critchley, H.D., Mathias, C.J., 2017. The genesis and presentation of anxiety in disorders of autonomic overexcitation. Auton. Neurosci. 203, 81–87. http://dx.doi.org/10.1016/j.autneu.2016.10.004.
Pal, G.K., Ganesh, V., Karthik, S., Nanda, N., Pal, P., 2014. The effects of short-term relaxation therapy on indices of heart rate variability and blood pressure in young adults. Am. J. Health Promot. 29 (1), 23–28.
Pederson, C.L., Brook, J.B., 2017. Health-related quality of life and suicide risk in postural tachycardia syndrome. Clin. Auton. Res. 27, 75–81. http://dx.doi.org/10.1007/s10286-017-0399-5.
Pengo, M.F., Higgins, S., Drakatos, P., Martin, K., Gall, N., Rossi, G.P., Leschziner, G., 2015. Characterisation of sleep disturbances in postural orthostatic tachycardia syndrome: a polysomnography-based study. Sleep Med. 16, 1457–1461. http://dx.doi.org/10.1016/j.sleep.2015.08.003.
Qaseem, A., Kansagara, D., Forciea, M.A., Cooke, M., Denberg, T.D., Clinical Guidelines Committee of the American College of Physicians, 2016. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann. Intern. Med. 165, 125. http://dx.doi.org/10.7326/M15-2175.
Raj, V., Haman, K.L., Raj, S.R., Byrne, D., Blakely, R.D., Biaggioni, I., Robertson, D., Shelton, R.C., 2009. Psychiatric profile and attention deficits in postural tachycardia syndrome. J. Neurol. Neurosurg. Psychiatry 80, 339–344. http://dx.doi.org/10.1136/jnnp.2008.144360.
Rezaie, L., Fobian, A.D., McCall, W.V., Khazaie, H., 2018. Paradoxical insomnia and subjective-objective sleep discrepancy: a review. Sleep Med. Rev. http://dx.doi.org/10.1016/j.smrv.2018.01.002.
Scheer, F.A., Morris, C.J., Garcia, J.I., Smales, C., Kelly, E.E., Marks, J., ... Shea, S.A., 2012. Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial. Sleep 35 (10), 1395–1402.
Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C., Sateia, M., 2008. Clinical guideline for the evaluation and management of chronic insomnia in adults. J. Clin. Sleep Med. 4, 487–504.
Spiegelhalder, K., Regen, W., Feige, B., Holz, J., Piosczyk, H., Baglioni, C., Riemann, D., Nissen, C., 2012. Increased EEG sigma and beta power during NREM sleep in primary insomnia. Biol. Psychol. 91, 329–333. http://dx.doi.org/10.1016/j.biopsycho.2012.08.009.
Stoschitzky, K., Sakotnik, A., Lercher, P., Zweiker, R., Maier, R., Liebmann, P., Lindner, W., 1999. Influence of beta-blockers on melatonin release. Eur. J. Clin. Pharmacol. 55, 111–115.
Thieben, M.J., Sandroni, P., Sletten, D.M., Benrud-Larson, L.M., Fealey, R.D., Vernino, S., Lennon, V.A., Shen, W.-K., Low, P.A., 2007. Postural orthostatic tachycardia syndrome: the Mayo clinic experience. Mayo Clin. Proc. 82, 308–313. http://dx.doi.org/10.4065/82.3.308.
Winkelman, J.W., Armstrong, M.J., Allen, R.P., Chaudhuri, Ray, K., Ondo, W., Trenkwalder, C., Zee, P.C., Gronseth, G.S., Gloss, D., Zesiewicz, T., 2016. Practice guideline: treatment of restless legs syndrome in adults. Neurology 87, 2585–2593. http://dx.doi.org/10.1212/wnl.0000000000003388.
Xu, X., Huang, H., Sethi, S., Zuzuárregui, J.R.P., Weinberg, J., Hohler, A.D., 2016. A survey based study on sleep disturbance in postural tachycardia syndrome. J. Neurol. Sci. 365, 199–202. http://dx.doi.org/10.1016/j.jns.2016.04.028.
Zee, P.C., Attarian, H., Videnovic, A., 2013. Circadian rhythm abnormalities. Continuum (Minneap. Minn). 19, 132–147. http://dx.doi.org/10.1212/01.CON.0000427209.21177.aa.