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Review

Management of headache and chronic pain in POTS☆

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ABSTRACT

Primary headache syndromes and chronic pain syndromes are common in patients with postural tachycardia syndrome (POTS). There is overlap in potential mechanisms for migraine, chronic pain, and POTS symptomatology. Management of chronic pain and headaches in POTS requires a judicious use of pharmacotherapies that takes into account patient comorbidities and co-existing symptoms. Patient-centric, non-pharmacologic modalities include physical exercise, cognitive behavioral therapies, and treatment of sleep disorders.

1. Introduction

Chronic pain and headache are prevalent conditions in the general population and a frequent cause for seeking medical care in both primary and specialty care settings. About 1 in 5 adults in the United States reports daily pain (Nahin, 2015) and about 10% of adults have neuropathic pain (Yawn et al., 2009). Migraine, responsible for the majority of disability and medical cost related to headache (Younger, 2016), occurs in 18% of people across their lifetime and at a rate of 13% of all people in any given year (Abu-Arafeh et al., 2010).

There are no studies of pharmacologic or non-pharmacologic management of headache or chronic pain specific to POTS. Therefore, the clinician must consider other symptoms and comorbidities of POTS patients when selecting treatment approaches. Mechanisms of action and common side effects of treatments must be weighed against other symptoms the patient with POTS may have.

2. Headache epidemiology

Data regarding the prevalence of pain and headache disorders in persons with postural tachycardia syndrome (POTS) are limited. Deb et al. (2015) reported on a cohort of 39 patients diagnosed in their center with POTS. Eighty-seven percent of these patients reported headaches. Ojha et al. (2011) reported a headache rate of 46% in adolescents and 61% in adults with POTS. Khurana and Eisenberg (2011) reported that 96% of their cohort of 24 POTS patients met criteria for migraine or probable migraine. In a survey of 3030 patients diagnosed by a physician with POTS, Raj et al. (2016) reported migraines in 41% of people with POTS.

2.1. Headache classification and pathogenesis

Headaches are classified in a hierarchical fashion according to criteria delineated in the International Classification of Headache Disorders (ICHD), now in its third version (*Cephalalgia*, 2013). As noted above, migraines and other primary headaches are highly prevalent in POTS populations. Key diagnostic features of common primary headache disorders are summarized in Table 1.

Auras may occur in the absence of headache (*Cephalalgia*, 2013). Typical aura without headache (previously referred to as acephalgic migraine) and other migraine equivalents, including chronic persistent perceptual dizziness (Holle et al., 2015; Baker et al., 2013), may contribute to the symptomatology in POTS (Heyer et al., 2013).

Migraine is more common in women than in men, with prevalence of 17.3–20.2% in females compared to 5.7–9.4% in males (Buse et al., 2013; Burch et al., 2015). Fluctuations in estrogen levels are largely, but not solely, responsible for this gender difference (Lay and Broner, 2009). As the population of patients with POTS is predominantly

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Table 1
Key diagnostic features of common and selected primary headache disorders (*Cephalalgia*, 2013).

Primary headache classification	Headache type	Description and comments
Migraine	Migraine without aura	Headache has at least two of the following four characteristics: • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity And at least one of the following: • Nausea and/or vomiting • Photophobia and phonophobia
	Migraine with typical aura	Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms At least two of the following four characteristics: • At least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession • Each individual aura symptom lasts 5–60 min • At least one aura symptom is unilateral • The aura is accompanied or followed within 60 min by headache Aura may occur without headache
	Migraine with brainstem aura	As with migraine with typical aura, but with at least two of the following brainstem symptoms: • Dysarthria • Vertigo • Tinnitus • Hypoacusis • Diplopia • Ataxia • Decreased level of consciousness
	Hemiplegic migraine	Similar to migraine with typical aura, but aura consisting of both of the following: • Fully reversible motor weakness • Fully reversible visual, sensory and/or speech/language symptoms May be sporadic or familial
	Chronic migraine	Headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache
Tension-type headache		Headache is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present. May be classified as infrequent episodic, frequent episodic, or chronic. May be associated with pericranial tenderness.
Trigeminal autonomic cephalalgias (TACs)	Hemicrania continua, cluster headache, paroxysmal hemicranias, and short-lasting neuralgiform headache attacks	The TACs exist along a spectrum (Newman, 2015) and are associated with symptoms of craniofacial autonomic alterations ipsilateral to the pain, such as lacrimation, ptosis, pupillary changes, tear production, conjunctival injection, rhinorrhea, or sweating. Magnetic resonance imaging and pituitary testing should be performed to exclude pituitary tumors, which can rarely cause TAC-like pain. Hemicrania continua and paroxysmal hemicrania are typically responsive to indomethacin
Other	Primary stabbing headache	Transient and localized stabs of pain in the head that occur spontaneously in the absence of organic disease of underlying structures or of the cranial nerves. No accompanying cranial autonomic symptoms
Other migraine	Episodic and other syndromes that may be associated with migraine	Recurrent gastrointestinal disturbance (cyclical vomiting syndrome and abdominal migraine) Benign paroxysmal vertigo/chronic persistent perceptual dizziness

female, this accounts for some of the higher rate of migraine in the POTS population generally. However, the 46% to 96% prevalence in POTS patients (cited above) is much greater than that seen in the female population generally.

Migraine involves the release of neuropeptides near sensory fibers innervating the meninges and meningeal arteries. These peptides lead to both pain and vasodilation (Shevel, 2011). Migraine can be associated with vestibular and autonomic symptoms, possibly originating in the brainstem. Whether the vascular, vestibular, and autonomic phenomena of migraine and POTS share similar mechanisms is still undetermined.

While migraine is seen most commonly, patients with POTS can present with varied headache types, and a single patient may have more than one type of headache.

2.2. Approaches to the treatment of primary headache syndromes

Two specific considerations must be made in the POTS patient with headaches: First, headache types or mechanisms that occur at increased rates in the POTS population. Second, symptoms and comorbidities common in POTS patients may affect the usefulness of specific treatments.

2.2.1. Behavioral headache management

Non-pharmacologic treatment of primary headache syndromes requires proper attention to headache triggers, physical exercise,

cognitive behavioral therapies, and sufficient sleep.

Patients should be asked about potential migraine triggers. Emotional stress, changes in weather, menstruation, visual stimuli, nitrates, wine, fasting, sleep disturbances, and aspartame may trigger migraines in susceptible individuals (Martin and Behbehani, 2001). Once identified, such triggers may be avoided.

Sleep disturbance can exacerbate migraine (Kelman, 2007; Walters et al., 2014) and tension-type headache (Rains et al., 2015). Sleep disorders are common in people with migraine (Yang and Wang, 2017), and should be screened for in all patients with POTS and migraine. Headaches occurring upon waking may be secondary to sleep apnea, and polysomnography should be considered for individuals with prominent waking headaches. Insomnia should be treated with sleep hygiene, stimulus control, and relaxation therapies. Cognitive behavioral therapies are effective for treating insomnia (Trauer et al., 2015). Pharmacologic treatment of insomnia may be appropriate in some patients, and has been reviewed elsewhere (Sateia et al., 2017). Both pharmacologic and non-pharmacologic approaches to treating sleep disturbance prevent chronification of migraine and reduce headache frequency (Yang and Wang, 2017; Ruff et al., 2009; Johnson et al., 2013; Bruni et al., 1999; Guidetti et al., 2014).

Aerobic exercise appears to be particularly beneficial for the prevention of migraine in the general population (Daenen et al., 2015). Exercise for patients with POTS is addressed elsewhere in this issue (Fu and Levine, 2018).

Biofeedback training, relaxation training, and cognitive behavioral therapies have all shown high levels of evidence for their benefit in treating migraine and tension-type headaches (Pistoia et al., 2013; Holroyd and Drew, 2006). The delivery methods and formats of these treatments have been reviewed in detail by Holroyd and Drew (Holroyd and Drew, 2006). These treatments are administered by trained mental health professionals using direct inter-personal interaction. Similar to work with physical therapists, patients are typically given techniques and exercises to perform on their own after or between treatment encounters.

Transcutaneous nerve stimulation has also been demonstrated to be effect for prevention of migraine (Schoenen et al., 2013), and has been reviewed elsewhere (Robbins and Lipton, 2017).

2.2.2. Pharmacologic management of migraine

Acute migraine treatment in the outpatient setting does not appear to differ between patients with POTS and the general population. Acute migraine treatments have been reviewed elsewhere (Becker, 2015).

In contrast to acute treatment for migraines, many of the medicines used for migraine prevention do raise particular considerations in the POTS population (see Table 2). For example, while TCAs are commonly used effectively for migraine preventive therapy, they may often worsen the dry mouth, constipation, and fatigue that are often seen in POTS patients. Nortriptyline, as a secondary amine, often has fewer anticholinergic side effects than tertiary amines, including amitriptyline (which is more widely studied in migraine prevention). Venlafaxine, a combined serotonin-norepinephrine reuptake inhibitor (SNRI), has level B evidence of its effectiveness in migraine prevention (similar to the TCA amitriptyline) (Silberstein, 2015). Some patients with bothersome tachycardia or palpitations may find these symptoms worsened when taking an SNRI.

Table 2
Diagnostic criteria for headache attributed to low cerebrospinal fluid (CSF) pressure (*Cephalalgia*, 2013).

- Any headache that develops in temporal relation to low cerebrospinal fluid (CSF) pressure or CSF leakage, or leading to its discovery
- With either or both of the following:
  1. Low CSF pressure (< 60 mm CSF)
  2. Evidence of CSF leakage on imaging (brain imaging showing sagging or pachymeningeal enhancement, or spine imaging showing extradural CSF)
- Not better accounted for by another ICHD-3 diagnosis

Topiramate, also commonly used for migraine prevention, has level A evidence for benefit in migraine prevention. Its use has been associated with restricted fetal growth (Hernandez-Diaz et al., 2014; Veiby et al., 2014), microcephaly (Veiby et al., 2014), and cleft lip and other fetal anomalies (Castilla-Puentes et al., 2014). At higher doses, topiramate increases the clearance of oral hormonal contraceptives. Women of childbearing potential must be counselled clearly about these considerations in its use. The cognitive slowing often reported with use of topiramate may be particularly bothersome for POTS patients already dealing with "brain fog".

The beta-blockers metoprolol, propranolol, timolol, atenolol, and nadolol all have level A or B evidence for their effectiveness in migraine prevention (Silberstein, 2015). However, many POTS patients cannot tolerate the higher doses typically used for migraine prevention (Raj et al., 2009). When used at lower doses, beta blockers, and perhaps propranolol in particular due to its pleiotropic effects (Wang et al., 2010), may be a particularly good choice for POTS patients with bothersome tachycardia and migraines.

Cyproheptadine, while only of level C evidence in terms of its effectiveness for migraine prevention in adults (Silberstein, 2015), may be particularly helpful in augmenting appetite in those with anorexia.

While the results of studies using magnesium supplementation for migraine prevention are mixed (Tepper, 2015), the treatment is often well tolerated in POTS patients. We will often use it as an adjunct to other treatments. Common side effects include diarrhea, and this makes the medication a good choice for patients with constipation. Paradoxically, occasional patients may have worsened constipation with magnesium. Magnesium citrate 600 mg daily has been most consistently effective in studies of migraine prevention. Though a study of magnesium oxide for migraine prevention in children was equivocal (Wang et al., 2003), we often use magnesium oxide dosed at 400–800 mg daily (for adults) due to its more widespread availability in tablet form in some pharmacies.

Riboflavin (vitamin B2) 400 mg (alone or in combination) has shown evidence of reducing migraine frequency in adults (Schoenen et al., 1998; Maizels et al., 2004). Two studies in the pediatric population using lower doses did not show a significant difference compared to placebo (MacLennan et al., 2008; Bruijn et al., 2010). This supplement is well tolerated. Diarrhea and polyuria rarely occur. It does typically cause bright yellow urine.

Feverfew (*Tanacetum parthenium*) is rated as having Level B evidence for migraine prevention (Holland et al., 2012). However, the variable concentration of proposed active chemicals in commercially available preparations, and the lack of long-term safety data challenge its widespread use in clinical practice.

Onabotulinum toxin A (Botox) injection has been shown to be effective for treatment of chronic migraine (see Table 1). While its use has not specifically been studied for migraine in patients with POTS, we have often found it useful in managing chronic migraine in POTS when response to first-line agents is not sufficient or not tolerated due to side effects. Common side effects of botulinum toxin injection include local pain or provocation of a headache. In our experience, side effects do not appear more commonly in POTS patients treated with botulinum toxin injection than the general population.

For women with prominent menstrual migraine, short term prophylaxis with either naproxen or a long-acting triptan (frovatriptan, naratriptan, or zolmitriptan) can be particularly helpful. Long acting triptan doses are "bridged" for a 6 to 7 day course across start of the menstrual period (see (MacGregor (2015) for dosing regimens).

With any given patient, a consideration must be given to the patient's overall symptoms and how they relate to the side effect profile of the medication and dose being considered. Some medications, like those affecting serotonin and dopamine pathways, may have a synergistic effect by preventing migraines directly while also improving sleep quality, adding additional benefit for migraine prevention in

those with sleep disturbance.

2.2.3. Treatment of other primary headache disorders

While the frequency of other primary headache disorders in POTS has not been explored separately from that of migraine, other primary headaches do occur in POTS patients. Most frequent among these is tension headache. Tricyclics, venlafaxine, and mirtazapine have all shown efficacy in preventive treatment of tension-type headache (Barbanti et al., 2014). Considerations regarding TCA and SNRI use are discussed above. Mirtazapine may be helpful in underweight patients or those with insomnia, as it promotes, appetite, reduces nausea, promotes sleep and has been used in chronic pain syndromes (Ansari, 2000).

Frequency of trigeminal autonomic cephalalgias has not been studied in POTS patients. While their occurrence is much less common than that of migraine and tension-type headache, recognition of the TACs is important (see Table 1) as the various TACs tend to respond to particular medication types or classes (Newman, 2015).

2.2.4. Starting preventive headache therapies

Like all other aspects of treatment, the decision to start preventive headache therapies must be individualized. As a general guide for migraine, if a patient is having two or more migraine days per week, it is often reasonable to start preventive pharmacotherapy. Other considerations in this decision include the degree to which the migraine impacts the patient's socioeconomic function and how well they respond to abortive therapies.

It is important that patients understand the expected timeframe and magnitude of benefit from a preventive headache therapy. Establishing expectations a priori seems to lead to better patient outcomes. Most preventive therapies do not have full effect until two or more months or regular use. Further, it is not expected that most headaches will entirely disappear with preventive therapy. With most preventive therapies, reduction of headache frequency of 50% is typically considered successful. Other markers of successful response to preventive therapies are decreased migraine duration or improved responsiveness to abortive medications. A headache log or diary is often very useful in gauging headache frequency, associated symptoms, duration, and response to medications. Such logs may be maintained in written form or electronically, and there are even applications for mobile devices for tracking headache-related data.

2.3. Secondary headache syndromes in POTS

Secondary headaches of particular concern in patients with POTS include 1) pain from insufficient orthostatic blood flow to head and neck structures and 2) pain related to spontaneous intracranial hypotension.

Orthostatic headache without orthostatic hypotension can occur in POTS and is at least partially responsive to volume expansion (Mokri and Low, 2003). The mechanism of these headaches is not known, but may be similar to the “coat-hanger”-type pain sometimes seen in people with orthostatic hypotension.

As discussed elsewhere in this issue, there is an overlap between POTS and hypermobility spectrum disorders (Francomano, 2018), and individuals with hypermobility spectrum disorders are at increased risk of spontaneous intracranial hypotension (sICH). All patients with POTS should be asked about orthostatic headaches. Headaches from spontaneous sICH arise from intracranial hypotension and often come on within 15 min of standing, but may take up to 2 h to manifest (Mea et al., 2009). The headache typically goes away within minutes of lying down and is typically symmetric and described as dull or throbbing (Mokri, 2013). About half of patients with sICH have symptoms besides headache, the most common being neck pain or stiffness, nausea, and vomiting (Schievink, 2006) (Table 3). Other less common side effect attributable to distortion or compression of structures of the base of the brain or the brainstem may also occur (Schievink, 2006; Mokri, 2014). The ICHD-3 emphasizes the exclusion of POTS in the diagnosis of headache attributed to low CSF pressure. While sICH should be suspected in any case of orthostatic headache, POTS may present with orthostatic headaches without sICH (Leep Hunderfund and Mokri, 2008).

Magnetic resonance imaging (MRI) of the brain with gadolinium in considered the initial study for confirming the presence of sICH. The mnemonic SEEPS has been proposed to help recall the prominent MRI features of intracranial hypotension: subdural fluid collections, enhancement of the pachymeninges, engorgement of venous structures, pituitary hyperemia, and sagging of the brain (Schievink, 2006). MRI does not detect all sICH and does not demonstrate the location of a CSF leak.

Lumbar puncture with a low CSF opening pressure ($< 60\ mmH_2O$) is a confirmatory finding, but intracranial pressure can be normal in patients with sICH. Therefore, many experts defer lumbar puncture in the workup of sICH. While computed tomographic (CT) myelography is considered the best test to detect dural defects causing CSF leak (Mokri, 2015), dynamic CT myelography may better detect rapid CSF leaks (Luetmer and Mokri, 2003). Magnetic resonance myelography and digital subtraction myelography may localize fluid leaks when in some CT-negative cases. In a comparison of imaging modalities in 19 patients with spontaneous intracranial hypotension, the sensitivity of MR and CT myelography were equivalent (Wang et al., 2009).

Acute (< 2 weeks), uncomplicated sICH in people without joint hypermobility can be managed conservatively, with bedrest and 200 to 300 mg caffeine given two to three times daily (Mokri, 2013). Epidural blood patch (EBP) is considered first-line therapy in people with connective tissue disease or joint hypermobility, CSF leak secondary to non-penetrating trauma, severe headache or disabling symptoms, or symptomatic headache for over two weeks (Mokri, 2013; Amoozegar et al., 2013). A retrospective study of 56 patients showed that targeted blood patch at the effected level was more effective than “blind” lumbar injection (Cho et al., 2011). However, lumbar injections often are effective even with more cranially-located defects. About half of patients with sICH will require more than one EBP (Sencakova et al., 2001; Berroir et al., 2004). Directed EPBs, fibrin sealant, or surgical closure may be needed in refractory cases.

3. Pain epidemiology in POTS

A percentage of patients with POTS experience visceral symptoms referred to the upper or lower gastrointestinal tract, bladder, and other abdominal and pelvic organs. In a large series of adult patients with POTS (Thieben et al., 2007), nausea was present in 39%, bloating in 24%, diarrhea in 18%, constipation in 15%, abdominal pain in 15%, and bladder symptoms in 9% of cases. These symptoms are similar to those typically reported by patients with functional motility disorders such as functional dyspepsia, irritable bowel syndrome, and interstitial cystitis, among others. Symptoms mimicking those of subjects with gastrointestinal motility disorders (such as gastroparesis) are also common, despite lack of objective evidence of true abnormalities on transit studies. Sixty-eight percent of a small cohort of women with POTS met criteria for a diagnosis of overactive urinary bladder (Kaufman et al., 2017). The underlying pathophysiology of these disorders includes variable mucosal inflammation, visceral hypersensitivity, and secondary visceromotor dysfunction. Behavioral amplification may also play a significant role. Gastrointestinal disorders and dysmotility are addressed more specifically elsewhere in this issue (Chelimsky, 2018).

Chronic fatigue (Okamoto et al., 2012; Ocon et al., 2012) and fibromyalgia (Staud, 2008) have been frequently associated with POTS. In the large survey referred to above, 21% of respondents reported having fibromyalgia. Eighty-five percent of Ojha et al.'s (2011) pediatric POTS patients reported chronic pain other than headache. In the other large series of adult patients with POTS (Thieben et al., 2007),

Table 3
Migraine preventive medications with high-level evidence of efficacy, with other selected preventive medications - dosing and considerations related to postural tachycardia syndrome. Evidence levels: A – Medications with established efficacy (≥2 class I trials); B – Medications with probable efficacy (1 class I or 2 class II studies).

Medication Class	Medication	Evidence level (Silberstein, 2015)	Typical daily dose	Comorbidities that may be worsened	Comorbidities that may be improved	Other considerations
Anti-seizure drugs	Divalproe × sodium, sodium valproate	A	500–2000 mg	Fatigue; dizziness; nausea; anorexia; abdominal pain; main worsen headache in some individuals	Mood disorders	Teratogenicity severely restricts use in women of childbearing potential Start at 250 to 500 mg daily
	Topiramate	A	50–200 mg	Anhidrosis/heat intolerance; cognition ("brain fog"); weight loss	May promote weight loss	Start 25 mg at bedtime, then increase 25 mg per week to 75–100 mg.
Beta-blockers	Metoprolol	A	100–200 mg daily	Fatigue, orthostatic intolerance, sexual	Palpitations/tachycardia	
	Propranolol	A	40–240 mg			The short-acting form dosed at 20 mg 2 or 3 times per day is often better tolerated.
	Atenolol	B	50–200 mg			
	Nadolol	B	20–160 mg			
Tricyclics	Amitriptyline	B	10–200 mg	Dry mouth, constipation, fatigue	Insomnia, chronic pain, depression	Start 10–25 mg at bedtime, increase weekly to 75–100 mg
	Nortriptyline	Anecdotal	10–150 mg	Insomnia	Insomnia, chronic pain, depression	Start 10–25 mg at bedtime, increase weekly to 75–100 mg. If insomnia occurs, take in the morning.
SNRI	Venlafaxine	B	75–225 mg	Tachycardia, insomnia	Chronic pain	
Natural supplements	Feverfew	B	50–300 mg			Lack of long-term safety data; varied potency of commercially-available preparations
	Riboflavin (vitamin B2)	B	400 mg			Maximal clinical effect starting at about two months
	Magnesium citrate	B	400–600 mg		Constipation	Effectiveness of oral magnesium oxide (9 mg/kg/day) was equivocal, but magnesium oxide is often used at the same dose due to availability. May paradoxically worsen constipation in some individuals.

many reported chronic fatigue (48%), sleep disturbance (32%), and myofascial pain (16%). There is a well-known overlap between chronic fatigue syndrome and POTS. Poor sleep, pain, and deconditioning all contribute to the cluster of such manifestations. Non-restorative sleep and pain can further amplify the already present sympathetic over-activity, thus worsening POTS symptoms.

3.1. Mechanisms of chronic pain

Multiple mechanisms may lead to chronic or maladaptive pain, including central sensitization (Kuner, 2010; Phillips and Clauw, 2011; Kuner, 2015), peripheral sensitization (Mickle et al., 2016; Berta et al., 2017), neuronal hyperexcitability (Berta et al., 2017; Ratte and Prescott, 2016), phenotypic switch of sensory neurons (Ueda, 2006; Wang et al., 2011), alterations of inhibitory pathways (Kuner, 2015; Prescott, 2015), and alterations in sensory gating as a result of afferent denervation (Woolf, 2004). These mechanisms are not mutually exclusive of one another. Such pain is labelled maladaptive as the pain no longer serves any protective factor. Despite the higher rates of occurrence, there is no evidence that mechanisms of chronic, non-nociceptive pain differ in POTS patients compared to the general population.

Higher rates of hypermobility spectrum disorders are seen in patients with POTS and may contribute to increased pain from joint dislocation and subluxation. However, pediatric POTS patients with joint hypermobility did not differ from those without joint hypermobility in their rates of migraine, functional abdominal pain, or fibromyalgia-like pain (Chelimsky et al., 2016).

As detailed above, functional pain syndromes, such as fibromyalgia, irritable bowel syndrome, functional abdominal pain, interstitial cystitis, and temporomandibular disorders seem to be more common in POTS patients, and share the common unifying factor of central sensitization. Alterations in brain activity related to autonomic nervous system function, immune and neuroendocrine activities, and genetic predispositions may be involved in the amplification of pain perception (Furquim et al., 2015).

Peripheral mechanisms may contribute to higher rates of pain disorders in POTS. Roughly a third to a half of all POTS patients has evidence of small fiber peripheral neuropathy (Thieben et al., 2007; Garland et al., 2015; Gibbons et al., 2013). While in some cases, the neuropathy may be related to the small fiber autonomic fibers, overlapping pathology with small fiber sensory fibers appears to occur in many cases. This corresponds with consistent evidence pointing to a peripheral neuropathic mechanism for about one-third of patients with fibromyalgia (Oaklander et al., 2013; Oaklander and Klein, 2013; Giannoccaro et al., 2014; Doppler et al., 2015).

3.2. Approaches to treating chronic pain

As with other patients with chronic pain, a multi-disciplinary and multi-modal approach to treating pain is most likely to be successful in the patient with POTS. Pain in people with POTS may be broadly categorized into four categories: neuropathic pain, pain due to central sensitization (including fibromyalgia), nociceptive pain due to joint hypermobility, and pain secondary to consequences of autonomic dysfunction (i.e., abdominal pain secondary to severe constipation).

Non-pharmacologic treatments are essential in managing chronic pain related to POTS. Physical exercise activates endogenous opioid pathways and increases pain-inhibiting serotonergic pathways in the central nervous system. There is concern that endogenous analgesic pathways are deficient in some individuals with chronic pain disorders and that physical exercise may provoke symptom flares secondary to inappropriate or excessive physical exercise (Daenen et al., 2015). Thus, an individually-tailored approach to exercise is necessary. Again, physical exercise for POTS patients is addressed elsewhere in this issue (Fu and Levine, 2018).

Cognitive behavioral therapy (CBT) has shown effectiveness in improving symptoms across a wide spectrum of chronic pain syndromes, populations, and delivery formats (Ehde et al., 2014). Resting-state functional MRI has demonstrated alterations in functional connectivity corresponding with improvement in chronic pain after CBT, providing evidence of an “unlearning” of chronic pain (Shpaner et al., 2014).

There is consistent evidence that insufficient sleep results in decreased pain thresholds acutely and the development of chronic pain syndromes over the long term (Finan et al., 2013). While pain can negatively affect sleep, the evidence indicates that sleep disturbance is a stronger predictor of future pain (rather than the other way around) (Finan et al., 2013). It is not clear whether or not improving sleep using pharmacologic therapy improves pain (Denucci et al., 1998; Smith and Haythornthwaite, 2004). The efficacy of pharmacologic options for treating insomnia has been reviewed elsewhere (Sateia et al., 2017). While cognitive behavioral therapies appear to improve sleep in chronic pain, the resulting effect on pain has been inconsistent (Tang, 2009), though measures of day-to-day function do improve (Finan et al., 2014). A focus on teaching and ensuring appropriate sleep hygiene, with judicious use of pharmacologic and cognitive behavioral interventions when needed, is probably the most beneficial approach.

There are currently no data to suggest that treatment responses to pharmacologic interventions for pain are any different in people with POTS compared to the general population. Some medicines, however, are likely to worsen other symptoms commonly seen in POTS, while others may have a synergistic or poly-modal effects (see Table 4). Pharmacologic approaches to treating non-nociceptive, non-inflammatory pain may be broadly categorized by their central or peripheral targets: 1) decreasing central excitation, 2) increasing endogenous central inhibitory pathways 3) decreasing peripheral excitation, and 4) directly stimulating receptors involved in increasing pain thresholds (i.e., cannabinoid receptor agonists).

Approaches to decrease central excitation include use of *n*-methyl-D-aspartate receptor antagonists (such as ketamine), alpha-2-delta calcium channel subunit antagonists (gabapentin and pregabalin), and other anti-epileptic drugs. Both gabapentin and pregabalin are considered first-line treatments for neuropathic pain (Dworkin et al.,

Table 4
Medications commonly used to treat neuropathic pain and fibromyalgia with side effect considerations and possible synergistic uses specific to postural tachycardia syndrome.

Medication or medication class	Comorbidities that may be worsened	Comorbidities that may be improved
Tricyclic antidepressants	Dry mouth, constipation, fatigue, orthostatic intolerance	Sleep disturbance; migraine; depression (may require higher doses); bladder pain
Serotonin reuptake inhibitors	Insomnia, headache, dizziness, fatigue, nausea, sexual dysfunction	Sleep disturbance
Cyclobenzaprine	Fatigue, dry mouth	Sleep disturbance
Alpha-2-delta calcium channel agonists (gabapentin, pregabalin)	Fatigue, weight gain	Sleep disturbance. May promote weight gain
Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine, desvenlafaxine, milnacipran)	Headache; nausea; palpitations; dry mouth (in adults); abdominal pain (in children and adolescents); weight loss (in children and adolescents)	Depression

2007). Gabapentin dosing is typically initiated at a low dose – 900 mg or less per day in three divided doses – and increased gradually until effectiveness or intolerable side effects are reached. Up to 3600 mg per day in three doses may be used. Pregabalin is typically started at 75 mg per day and increased to 150 mg daily after a week. Pregabalin may provide analgesia more quickly than gabapentin, and this is likely at least in part due to the ability to titrate more rapidly to an effective dose (Stacey et al., 2008).

Central inhibitory pathways, which are primarily serotonergic, may be augmented with tricyclics (TCAs), serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors (SNRIs). While TCAs are often beneficial in the general population with chronic pains of various origins, including neuropathic pain (Dworkin et al., 2007), their prominent anticholinergic effects may exacerbate many of the symptoms commonly seen in POTS.

Of the SNRIs, venlafaxine and duloxetine have demonstrated efficacy in treating neuropathic pain (Aiyer et al., 2017; Gao et al., 2015). Duloxetine and milnalcipran have both shown benefit in treating fibromyalgia (*Med. Lett. Drugs Ther.*, 2008; Cording et al., 2015). Duloxetine is also approved for the treatment of chronic musculoskeletal pain and chronic low back pain (Pergolizzi et al., 2013). Duloxetine is typically dosed at 60 mg per day. If SNRIs are to be discontinued, a very gradual taper is recommended in order to avoid withdrawal symptoms.

Peripheral nerve excitation may be targeted using medications that decrease voltage-gated sodium channel activation. Carbamazepine has shown moderate effectiveness for chronic neuropathic pain in short-term trials (Wiffen et al., 2011). However, these medications are less frequently used because of the better side effect profiles of the SNRIs and gabapentinoids.

While opioid medications do effectively treat many types of pain, any benefit has to be weighed against the potential risks of tachyphylaxis, dependence, overdose, and perhaps even potentiation of non-nociceptive pain (Heinl et al., 2011; Roeckel et al., 2016). The U.S. Centers for Disease Control and Prevention have published detailed guidelines regarding opioid prescription for chronic pain (Dowell et al., 2016).

Low dose naltrexone has emerged as a potential treatment of chronic pain. It is thought that the low-level opioid receptor blockade results in rebound production of endogenous opioids. While further studies are needed, this may be a well-tolerated and inexpensive treatment for chronic pain (Metyas et al., 2017; Patten et al., 2018).

The use of cannabis and cannabinoids in the treatment of chronic pain remains controversial. A recent meta-analysis of the use of cannabinoids in chronic non-cancer pain concluded that limited evidence suggests a potential benefit in relieving chronic neuropathic pain. However, there is insufficient evidence for any benefit toward other types of chronic pain (Nugent et al., 2017).

Topical medications, including anesthetics such as lidocaine or capsaicin-containing creams, may be helpful for some individuals with neuropathic pain, especially when that pain is localized.

4. Conclusion

Headache syndromes, particularly migraine, and chronic pain are common in the POTS population. While there is no data regarding different responses to treatments for migraine and chronic pain among people with or without POTS, co-existing conditions and symptoms must be considered when tailoring therapies for the POTS patient. In addition to the judicious use of pharmacologic therapies, non-pharmacologic therapies including exercise, treating sleep disorders and cognitive behavioral therapies are important for treating chronic pain and the most common primary headache syndromes in patients with POTS.

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