# Psychiatric Disorder in Postural Orthostatic Tachycardia Syndrome and Ehlers-Danlos Syndrome–Hypermobility Type

Ahmed Saeed Yahya, MBBS, MRCPsych,[a,*] and Shakil Khawaja, MBBS, MRCPsych[a]


## ABSTRACT

Postural orthostatic tachycardia syndrome (POTS) and Ehlers-Danlos syndrome–hypermobility type (EDS-HT) are disorders that have a strong association and share a relationship with some mental illnesses. Both are commonly misdiagnosed as mental disorders possibly because they share a similar phenomenology to some. There is limited awareness and recognition of POTS and EDS-HT, which subsequently delays diagnosis. The presence of an underlying mental disorder can complicate the diagnosis and management of an already challenging case, which can cause further strain to patients and their loved ones whose lives have already been destabilized significantly. National support groups have been established to support during the stressful periods of diagnosis and adjustment. In this article, the evidence for the various mental disorders that have been linked to POTS and EDS-HT is reviewed, while highlighting the need to satisfactorily screen for mental disorders in this patient group.


*Prim Care Companion CNS Disord 2020;22(6):20nr02644*

***To cite:*** Yahya AS, Khawaja S. Psychiatric disorder in postural orthostatic tachycardia syndrome and Ehlers-Danlos syndrome–hypermobility type. *Prim Care Companion CNS Disord.* 2020;22(6):20nr02644.

***To share:*** https://doi.org/10.4088/PCC.20nr02644



[a]North East London NHS Foundation Trust, Waltham Forest Older Adults Mental Health Team, London, England

**Corresponding author:* Ahmed Saeed Yahya, MBBS, MRCPsych, North East London NHS Foundation Trust, Waltham Forest Older Adults Mental Health Team, Red Oak Lodge, London E11 4HU, United Kingdom (a.yahya@nhs.net).

Postural orthostatic tachycardia syndrome (POTS) is the most common type of orthostatic intolerance or dysautonomia (autonomic dysfunction) and can be a manifestation of Ehlers-Danlos syndrome–hypermobility type (EDS-HT), otherwise known as EDS type 3.[1,2] EDS-HT is an inherited connective tissue disorder of joint hypermobility and includes symptoms of joint instability, arthralgia, myalgia, soft tissue injury, and arthritis.[3] Patients with EDS-HT are susceptible to dysautonomia and POTS in particular.[4] POTS is a multifactorial disorder and is increasingly recognized as a nonmutually exclusive syndrome.[1] The connection between the 2 syndromes remains unclear, but the association is well documented, with EDS-HT a possible underlying mechanism for POTS.[1] There are 5 subtypes of POTS, which include the neuropathic, hypovolemic, primary hyperadrenergic, joint hypermobility–related, and immune-related forms.[1] We will be focusing primarily on the joint hypermobility subtype associated with EDS. POTS affects up to 1% of the US population, with predominance in females (4–5:1 ratio in comparison to males).[1,5] Statistics indicate that around 80% of patients with EDS-HT have either POTS or dysautonomia, while 18% of those with POTS meet the diagnostic criteria for EDS.[1]

Both POTS and EDS-HT can be debilitating and are associated with neuropsychiatric complications. These complications comprise the spectrum of anxiety disorders (including panic disorder and agoraphobia), depression, cognitive problems, eating disorders, and the neurodevelopmental disorders autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).[4,6–8] Patients with POTS more commonly report suicidal ideation and suicide attempts, although there are no data available to indicate a higher risk of completed suicide.[9] The associated mental disorders can cause further disruption to an already impaired quality of life and increasing level of disability. The following fictional case vignette presents both these disorders and highlights the diagnostic difficulties.

## CASE VIGNETTE

A 24-year-old woman presents to a specialist autonomic disorders clinic. She reports an 8-month history of fatigue, intolerance of standing, and light exercise. She gave birth to a healthy child 9 months previously. She has difficulty with attention and concentration. She experiences transient

## Clinical Points

- Postural orthostatic tachycardia syndrome and Ehlers-Danlos syndrome–hypermobility type are associated with neuropsychiatric complications.
- Treatment of associated mental illness in patients with postural orthostatic tachycardia syndrome or Ehlers-Danlos syndrome–hypermobility type should follow the biopsychosocial principles of management.
- A medication review is imperative in patients with postural orthostatic tachycardia syndrome or Ehlers-Danlos syndrome–hypermobility type, as they often present with polypharmacy, and some prescribed medications can potentially exacerbate symptoms.

palpitations, dizziness, epigastric discomfort, and anxiety. She was originally diagnosed with a generalized anxiety disorder. She also reports that she has hypermobile joints, for which she has a strong family history.

Eccles[8] postulates that dysregulation of the autonomic nervous system and the central representation of body arousal may be the mechanism for pervasive anxiety in joint hypermobility. Neuroradiologic findings of patients with hypermobility support the association with mental disorders, showing differences in the structure and functioning of brain areas responsible for emotional processing, including the amygdala and insula.[7]

Both POTS and EDS are underrecognized, with delayed detection and diagnosis. It can take between 8 and 10 years to make an accurate diagnosis of POTS, while the average time to diagnosis for EDS is 14 years and 22 years for those with a psychiatric comorbidity.[5,10] POTS is often misdiagnosed as an anxiety disorder.[5] Both POTS and anxiety disorders share a similar phenomenology including various cognitive distortions and somatic symptoms (Table 1).[1,7,11] Patients with EDS-HT have enhanced somatosensory awareness with pain amplification, which may be the driving mechanism for these abnormalities.[6,12] Chronic pain and insomnia can be debilitating for some patients. There is an association between EDS-HT and fibromyalgia, and many patients have comorbid rheumatic conditions.[8] EDS-HT is commonly misdiagnosed as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, depression, health anxiety, or in some cases even malingering.[3]

The delay in diagnosis and management of POTS and EDS increases the already high levels of patient and caregiver distress, with patients often feeling invalidated by health care professionals. The prognosis for POTS varies, with males having better outcomes and 80% of adolescents improving with appropriate treatment.[5] These data underscore the necessity for prompt identification and treatment of cases. In this narrative review, we describe the various neuropsychiatric disorders associated with POTS/EDS-HT in adults, which can prolong diagnosis and impact management. We summarize the latest evidence and use this information to guide our recommendations.

**Table 1. Shared Cognitive and Somatic Symptoms of POTS, EDS-HT, and Anxiety Disorders[1,5,7,11,12]**

- Catastrophizing
- Somatic hypervigilance
- Selective attention
- Avoidance
- Palpitations
- Dizziness
- Gastrointestinal disturbance

Abbreviations: EDS-HT = Ehlers-Danlos syndrome–hypermobility type, POTS = postural orthostatic tachycardia syndrome.

## METHODS

We conducted a comprehensive search of literature published within the last 5 years to assist our review. Our search included the electronic databases MEDLINE, EMBASE, Trip Database, Cochrane, CRDWeb (Centre for Reviews and Dissemination), Google Scholar, and NICE (National Institute for Health and Care Excellence) guidance. We additionally looked through the citation lists of sourced articles. The evidence search was restricted to articles published in the English language. Our initial search revealed 71 articles, which included several conference abstracts, but we were left with 37 relevant articles after screening.[1–37]

## RESULTS

### Postural Orthostatic Tachycardia Syndrome

POTS is a clinical syndrome that manifests with orthostatic intolerance and tachycardia upon standing. It presents with a constellation of significantly impairing cardiac and noncardiac signs that have been present for 6 months or longer.[1,5] There is temporary autonomic dysregulation in which sympathetic and parasympathetic responses exceed normal bodily hemostatic requirements.[1–5] Norepinephrine is the implicated catecholamine in the pathophysiology of POTS. The involvement of the monoamine neurotransmitter serotonin has also been suggested, with potential impairment in its central production and regulation.[1,5,13]

The estimated prevalence of POTS is 170/100,000, with an affected age range of 15–50 years (mean age at onset of 30 years).[5] The symptoms of orthostatic intolerance are usually episodic and can include various presyncopal symptoms (Table 2).

These symptoms noticeably occur in a standing position and can be exacerbated by dehydration, alcohol, higher temperatures, and exercise.[1,5,13] Approximately 30% of patients can have syncopal episodes.[1] These patients can present with nonorthostatic symptoms and symptoms related to autonomic dysfunction (Table 3). Estimates suggest that 40% of patients with chronic fatigue syndrome suffer with POTS.[5]

The diagnostic criteria for POTS include heart rate variability (HRV) with an increase of heart rate (HR) of ≥30 bpm within 10 minutes of movement from a lying to a standing position or ≥40 bpm in those between 12 and

**Table 2. Symptoms of Orthostatic Intolerance[1,5]**

- Dizziness
- Palpitations
- Shortness of breath
- Chest pain
- Tremor
- Weakness
- Fatigue
- Blurred vision
- Cognitive dysfunction
- Exercise intolerance

**Table 3. Symptoms of POTS[1,5,8]**

Nonorthostatic
- Migraine
- Tension headache
- Emotional dysregulation
- Chronic fatigue
- Sleeping problems
- Joint hypermobility

Autonomic dysfunction
- Gastrointestinal symptoms
- Urinary problems
- Sudomotor (sweat gland) abnormalities

Abbreviation: POTS = postural orthostatic tachycardia syndrome.

**Table 4. Investigations in POTS[1,5,13,14]**

- Clinical examination that can identify signs of acrocyanosis, rashes, hypermobility, and Raynaud's phenomenon
- Full blood count, electrolytes, bone profile, serum cortisol, thyroid function, and glucose
- Electrocardiogram
- 24-hr Holter monitoring
- Echocardiogram

Abbreviation: POTS = postural orthostatic tachycardia syndrome.

19 years of age.[1] There is usually no evidence of orthostatic hypotension, namely a drop in systolic blood pressure ≥ 20 mm Hg in patients.[1] It is noted that the standing HR in individuals is commonly ≥ 120 bpm with diurnal variation (more prominent HR increase in the morning rather than the evening).[1] The head up tilt table test (HUTT) and the active stand test (AST) are investigations used to diagnose POTS.[1,5]

The HUTT involves the patient lying on a table that can be tilted to an angle of 60–70 degrees and measures both positional HR and blood pressure. The AST works on a similar principle to the HUTT. Table 4 lists the other investigations utilized in the diagnosis of POTS.[13,14]

### Ehlers-Danlos Syndrome–Hypermobility Type

EDS is a multisystem inherited heterogeneous group of connective tissue disorders with 13 subtypes, and the type 3 hypermobile form is the most common, accounting for 80%–90% of cases.[3,15] EDS-HT is considered to be indistinguishable or even identical to joint hypermobility syndrome.[3] Joint hypermobility syndrome is described as an excessive range of joint movement when accounting for age, sex, and ethnicity.[16]

EDS-HT does not have the severe complications associated with some other EDS subtypes.[3] EDS-HT is characterized by musculoskeletal problems including joint instability, chronic pain, fatigue, sleep disturbance, and soft tissue problems, and individuals often have semitransparent skin.[3] Joint instability involves both peripheral and central joints, including the temporomandibular, sacroiliac, and hip joints.[3] The diagnosis of EDS-HT is based on specific clinical criteria, with the revised Beighton score and Brighton criteria the most popular. The Beighton score is a 9-point clinical scale, and a score ≥ 4 would fulfill the major criteria to aid diagnosis.[3,12,16,17]

For the diagnosis of EDS-HT to be met, there are certain prerequisite symptoms such as muscular pain, recurrent joint dislocations, rectal or uterine prolapse, and mitral valve prolapse.[8] Patients can present with extraarticular manifestations of the disorder, and various bodily systems can be affected including the cardiovascular, gastrointestinal, dermatologic, hematologic, immunologic, ocular, oral, gynecologic, neurologic (proprioception and vestibular dysfunction), and autonomic systems.[17–19]

### Depression and Anxiety

Evidence indicates that there are associations between EDS-HT and anxiety disorders, particularly panic disorder and agoraphobia.[6] There also may be a relationship with EDS-HT and mood disorders, although these associations appear more prominent when comorbid anxiety is present. Both anxiety and mood disorders can be exacerbated by fatigue and pain.[6] An incidence study[6] followed up patients for 15 years and observed that the cumulative incidence of panic disorder, agoraphobia, and simple and social phobia was significantly higher in the EDS-HT group, and the use of pharmacologic treatments was 4 times greater among these patients. Owens et al[20] concluded that affective symptoms in POTS were driven by anxiety and vigilance of physical sensations and symptoms rather than underlying trauma or neurosis.

A retrospective analysis[21] conducted in genetic clinics in Canada found that 42.5% of a total sample of 106 patients with EDS classic, EDS-HT, and overlapping diagnoses had an *ICD-10*–diagnosed psychiatric disorder with frequencies of 23.6% for anxiety disorders and 27.4% for mood disorders. Fewer studies overall have investigated a causal relationship between EDS-HT and mood disorders. A meta-analysis by Smith et al[25] reported that patients with EDS-HT more commonly experienced anxiety and depressive symptoms. Raj et al[11] concluded in their review that that there is consistent evidence of depression in those with POTS. The authors[11] also noted that the autonomic symptoms in POTS overlapped with anxiety symptoms and that it was important to adequately screen for comorbid anxiety disorder.

The treatment for clinically diagnosed depressive or anxiety disorder should follow the biopsychosocial model. Pharmacologic options include the use of selective serotonin reuptake inhibitors (SSRIs) or the serotonin-norepinephrine reuptake inhibitors (SNRIs) venlafaxine or duloxetine, which are also considered treatment options

for symptoms of POTS. These medications are usually well tolerated.[13] The serotonergic medications are recognized to increase nerve communication and stimulate the standing vasoconstrictor reflex, improving orthostatic intolerance by the reduction of venous pooling.[13] The SNRIs have also been investigated for their efficacy in treating the chronic pain associated with fibromyalgia.[22,38]

The norepinephrine-dopamine reuptake inhibitor bupropion is also recognized as a treatment for POTS and has established efficacy in clinical depression.[23] A combination of an SSRI and bupropion can be considered in some cases.[14,24] Bupropion has been approved in the United States for the treatment of depression for about 20 years but is only licensed in the United Kingdom as a treatment for smoking cessation.[39] Monoamine oxidase inhibitors and phenothiazines should be avoided, as they can worsen orthostatic intolerance. Tricyclic antidepressants should ideally be avoided, as they can exacerbate orthostatic symptoms while increasing drowsiness and affecting cognition because of their anticholinergic effects.[22] However, tricyclic antidepressants may be useful in the management of headache and abdominal pain in some cases.[1]

Psychological therapies warrant consideration, and patients should be supported to make the necessary psychosocial adjustment. There is much emphasis on using nonpharmacologic approaches to manage POTS. An adapted form of structured cognitive-behavioral therapy (CBT) may benefit pain perception and address dysfunctional coping mechanisms; however, there is a lack of robust evidence for the effectiveness of CBT in POTS.[11] Mindfulness and third-wave psychotherapies such as acceptance and commitment therapy and compassion-focused therapy are other potential therapeutic options.

### Cognitive Dysfunction

The published evidence investigating possible cognitive deficits in POTS is limited. Patients subjectively report cognitive difficulties including brain cloudiness/brain fog. Studies[11] demonstrate that there are selective impairments in attention, cognitive processing speed, memory, and executive functions, though these can be mild. Baeza-Velasco et al[26] found in their small controlled observational study that the EDS-HT patient group scored lower in attention, memory, and visuospatial problem solving than healthy controls. The fatigue associated with these disorders may be a potential causal factor for these deficits. It is also unclear if these deficits arise from orthostatic stress or form part of the illness process. Interestingly, patients have reported impairment in the seated and supine positions. Patients have also been shown to have these deficits when they were asymptomatic with the orthostatic tachycardia minimized.[27]

Treatment of the tachycardia and light headiness associated with POTS often improves these cognitive symptoms. Patients have reported benefits from stimulant medications including modafinil, intravenous saline, salt tablets, midodrine, and vitamin $B_{12}$ injections, although the effectiveness of these purported treatments has not been tested. Regular exercise programs have been reported to improve cognitive function.[22,24]

### Neurodevelopmental Disorders

There is a possible association of both EDS-HT and POTS with the neurodevelopmental disorders ASD, ADHD, and developmental coordination disorder. Eccles[7] reported that adults with ADHD had higher rates of joint hypermobility and dysautonomia. Other studies[6,15,28–30] have replicated the association with joint hypermobility. An observational study by Hollertz[35] found that both ADHD and EDS had high co-occurrence.

The management of ADHD in patients with either EDS-HT or POTS should also follow the biopsychosocial framework. Stimulants including methylphenidate, which is a long-acting α agonist, and modafinil have been used as treatments for POTS.[13,22] These medications have been found to be effective in the management of chronic fatigue syndrome and in the prevention of recurrent syncope. In 14 of 17 patients with refractory POTS, improvements in presyncope and fatigue were shown with methylphenidate.[22,24] Should the ADHD symptoms cause significant impairment, then these medications may warrant consideration. The α-2 adrenergic receptor agonist clonidine is useful in managing the autonomic symptoms of POTS and may provide benefit in the treatment of ADHD symptoms.[24,38]

The quality of current evidence is inconclusive in ascertaining the increased prevalence of ASD in EDS-HT. Lumley et al[36] found that children aged 7–12 years with EDS had some features congruent with ASD; however, subjects were not specifically investigated for ASD in this study. Eight case reports indicate a possible relationship between ASD and EDS.[15] A cohort study by Cederlöf et al[37] reported that the number of patients with ASD was disproportionately greater in those with EDS. ASD was diagnosed more in the patients with joint hypermobility than in controls (1.6% vs 1.4%, respectively). The number of siblings with ASD was also greater in the joint hypermobility group compared to controls (0.6% vs 0.5%).[37] If ASD is suspected in patients, they should be referred to specialist psychiatric services for multidisciplinary assessment and case management.

### Eating Disorders

It is difficult to differentiate signs such as weight loss that arise from EDS-HT or POTS rather than a comorbid eating disorder. The gastrointestinal symptoms of EDS-HT have been described as a potential risk factor for developing an eating disorder.[10,12] Both the articular and nonarticular features of EDS-HT may be a casual factor in the development and maintenance of disordered eating.[6] Case reports have described the co-occurrence of EDS and restrictive eating disorders such as anorexia nervosa.[10] A small comparative study[12] found joint hypermobility was significantly more common in patients with anorexia nervosa than in controls. The subjects with anorexia nervosa were found to have a higher prevalence of dysautonomia.

Also, secondary school pupils with hypermobility reported more "anorexic experiences" than those without this sign in another study.[12] We recommend that if an eating disorder is suspected, a prompt referral should be made to a local eating disorder service for assessment and specialist input.

### Chronic Pain and Sleep Disorders

Longstanding pain is debilitating for some patients with EDS-HT and POTS and can result in avoidance and limitation of physical activity, which is a perpetuating factor.[31–33] Hershenfeld et al[33] noted that any pain symptom increased the odds of having a psychiatric disorder. The presence of joint pain, abdominal pain, headache/migraine, and neuropathic pain was significantly associated with increased frequency of psychiatric disorder. Muscle and body pain was significantly associated with mood disorders, while neuropathic pain was linked to somatoform disorders.[31] It is thus important to be aware of this relationship and screen for mood and anxiety disorders with consideration of referral to psychiatric services for appropriate psychosocial management. Tailored exercise regimens to improve exercise tolerance and deconditioning have some efficacy in POTS.[23,32] Structured CBT is noted to have good face validity and may be considered along with other psychological therapies.[11]

Patients frequently struggle with insomnia, which can affect both sleep onset and maintenance.[34] CBT for insomnia is an evidence-based treatment that can be implemented in this group with subtle adjustment of behavioral techniques.[40] Pharmacologic treatments for insomnia have been poorly studied in these patients. One study[22] recorded that an acute oral dose of melatonin decreased HR while standing in patients with POTS when compared to placebo. Miller and Raj[22] reported that melatonin decreased the sympathetic response to orthostatic stress in subjects without POTS. The beneficial effects of melatonin on orthostatic symptoms and sleep in patients with POTS are unknown.[22] However, patients are frequently prescribed β-blockers, which can lower melatonin, so treatment may be useful in this particular group.[22]

## CONCLUSIONS

Both POTS and EDS-HT are heterogeneous conditions that have been associated with a variety of psychiatric disorders. The symptoms can be incredibly distressing and may be compounded by underlying psychiatric illness in some cases. The evidence linking them to certain psychiatric disorders is of low quality and derived mostly from case reports. However, the evidence base is growing, and there is more published literature on the relationship with anxiety and depressive disorders. We were unable to find any recent literature indicating that the existence of both these conditions together, rather than when present alone, increases the risk for psychiatric disorders. Overall, there remains a lack of awareness regarding the nature of these disabling disorders and the requirement for coordinated, personalized, and sensitive multidisciplinary care. There is clearly a need for further research on the efficacy and tolerability of pharmacologic agents guiding the management of the primary illness and multiple comorbidities.

***Submitted:*** April 22, 2020; accepted June 19, 2020.
***Published online:*** October 29, 2020.
***Potential conflicts of interest:*** None.
***Funding/support:*** None.
***Acknowledgments:*** The authors thank Lisa Burscheidt, MA (clinical librarian, North East London NHS Foundation Trust, Aubrey Keep Library and Knowledge Service, Ilford, Goodmayes Hospital site, Essex, United Kingdom) for her support with the literature search. Ms Burscheidt reports no conflicts of interest related to the subject of this article.

## REFERENCES

1. Zadourian A, Doherty TA, Swiatkiewicz I, et al. Postural orthostatic tachycardia syndrome: prevalence, pathophysiology, and management. *Drugs*. 2018;78(10):983–994.
2. Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Baroreflex dysfunction. *N Engl J Med*. 2020;382(2):163–178.
3. Gazit Y, Jacob G, Grahame R. Ehlers-Danlos syndrome-hypermobility type: a much neglected multisystemic disorder. *Rambam Maimonides Med J*. 2016;7(4):e0034.
4. Eccles J. 13 Hypermobility and autonomic dysfunction: insights from bench to bedside. *J Neurol Neurosurg Psychiatry*. 2019;90:A6.
5. Schmidt LL, Karabin BL, Malone AC. Postural orthostatic tachycardia syndrome (POTS): assess, diagnose, and evaluate for POTS treatment (ADEPT). *Integrative Medicine International*. 2017;4(3-4):142–153.
6. Bulbena A, Baeza-Velasco C, Bulbena-Cabré A, et al. Psychiatric and psychological aspects in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):237–245.
7. Eccles J. I045 Joint hypermobility and autonomic hyperreactivity: relevance to psychiatric disorder. *Rheumatology*. 2019;58(suppl 3):kez109.044.
8. Eccles J. Mind-body interactions in JH: relevance to psychiatric symptoms. Abstracts of the 73rd Annual Meeting of the American Psychosomatic Society; March 18–21, 2015; Savannah, Georgia. *Psychosom Med*. 2015;77(3).
9. Raj V, Raj SR. Postural tachycardia syndrome and suicide: what we don't know. *Clin Auton Res*. 2017;27(2):69–70.
10. Lee M, Strand M. Ehlers-Danlos syndrome in a young woman with anorexia nervosa and complex somatic symptoms. *Int J Eat Disord*. 2018;51(3):281–284.
11. Raj V, Opie M, Arnold AC. Cognitive and psychological issues in postural tachycardia syndrome. *Auton Neurosci*. 2018;215:46–55.
12. Baeza-Velasco C, Van den Bossche T, Grossin D, et al. Difficulty eating and significant weight loss in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Eat Weight Disord*. 2016;21(2):175–183.
13. Agarwal AK, Garg R, Ritch A, et al. Postural orthostatic tachycardia syndrome. *Postgrad Med J*. 2007;83(981):478–480.
14. Conner R, Sheikh M, Grubb B. Postural orthostatic tachycardia syndrome (POTS): evaluation and management. *Br J Med Pract*. 2012;5(4):a540.
15. Baeza-Velasco C, Cohen D, Hamonet C, et al. Autism, joint hypermobility-related disorders and pain. *Front Psychiatry*. 2018;9:656.
16. Bulbena-Cabre A, Bulbena A. Anxiety and joint hypermobility: an unexpected association. *Curr Psychiatr*. 2018;17(4):15–21.
17. Baeza-Velasco C, Pailhez G, Bulbena A, et al. Joint hypermobility and the heritable disorders of connective tissue: clinical and empirical evidence of links with psychiatry. *Gen Hosp Psychiatry*. 2015;37(1):24–30.
18. Baeza-Velasco C, Bulbena A, Polanco-Carrasco R, et al. Cognitive, emotional, and behavioral considerations for chronic pain management in the Ehlers-Danlos syndrome hypermobility-type: a narrative review. *Disabil Rehabil*. 2019;41(9):1110–1118.
19. Baeza-Velasco C, Bourdon C, Montalescot L, et al. Low- and high-anxious hypermobile Ehlers-Danlos syndrome patients: comparison of psychosocial and health variables. *Rheumatol Int*. 2018;38(5):871–878.
20. Owens AP, Low DA, Iodice V, et al. The genesis and presentation of anxiety in disorders of autonomic overexcitation. *Auton Neurosci*. 2017;203:81–87.
21. Hershenfeld S, Wasim S, McNiven V, et al. Frequency of psychiatric disorders in the classic and hypermobility types of Ehlers-Danlos syndrome and association with systemic findings. Abstracts of the 70th Annual Meeting of the Canadian Rheumatology Association; February 4–7, 2015; Quebec, Canada. *J Rheumatol*. 2015;42(7):1333–1334.

22. Miller AJ, Raj SR. Pharmacotherapy for postural tachycardia syndrome. *Auton Neurosci*. 2018;215:28–36.
23. Grubb BP. The postural tachycardia syndrome: when to consider it in adolescents. *Family Practice Recertification*. 2006;28(3):19–30.
24. Wells R, Elliott AD, Mahajan R, et al. Efficacy of therapies for postural tachycardia syndrome: a systematic review and meta-analysis. *Mayo Clin Proc*. 2018;93(8):1043–1053.
25. Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2014;53(1):114–122.
26. Baeza-Velasco C, Bourdon C, Polanco-Carrasco R, et al. Cognitive impairment in women with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Rheumatol Int*. 2017;37(6):937–939.
27. Arnold AC, Haman K, Garland EM, et al. Cognitive dysfunction in postural tachycardia syndrome. *Clin Sci (Lond)*. 2015;128(1):39–45.
28. Ghibellini G, Brancati F, Castori M. Neurodevelopmental attributes of joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: update and perspectives. *Am J Med Genet C Semin Med Genet*. 2015;169C(1):107–116.
29. Sinibaldi L, Ursini G, Castori M. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/ Ehlers-Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. *Am J Med Genet C Semin Med Genet*. 2015;169C(1):97–106.
30. Baeza-Velasco C, Sinibaldi L, Castori M. Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age. *Atten Defic Hyperact Disord*. 2018;10(3):163–175.
31. Wasim S, Suddaby JS, Parikh M, et al. Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers-Danlos syndrome and hypermobility spectrum disorders: a retrospective study. *Rheumatol Int*. 2019;39(7):1241–1248.
32. Krahe AM, Adams RD, Nicholson LL. Features that exacerbate fatigue severity in joint hypermobility syndrome/Ehlers-Danlos syndrome—hypermobility type. *Disabil Rehabil*. 2018;40(17):1989–1996.
33. Hershenfeld SA, Wasim S, McNiven V, et al. Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatol Int*. 2016;36(3):341–348.
34. Miglis MG, Muppidi S, Feakins C, et al. Sleep disorders in patients with postural tachycardia syndrome. *Clin Auton Res*. 2016;26(1):67–73.
35. Hollertz O. Searching for a biological marker common for both ADHD and EDS. *Lakartidningen*. 2012;109:41–42.
36. Lumley MA, Jordan M, Rubenstein R, et al. Psychosocial functioning in the Ehlers-Danlos syndrome. *Am J Med Genet*. 1994;53(2):149–152.
37. Cederlöf M, Larsson H, Lichtenstein P, et al. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. *BMC Psychiatry*. 2016;16(1):207.
38. Luty J. Medically unexplained syndromes: irritable bowel syndrome, fibromyalgia and chronic fatigue. *BJPsych Advances*. 2018;24(4):252–263.
39. Patel K, Allen S, Haque MN, et al. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol*. 2016;6(2):99–144.
40. Selsick H, O'Regan D. Sleep disorders in psychiatry. *BJPsych Advances*. 2018;24(4):273–283.