



## Review

## Cognitive and psychological issues in postural tachycardia syndrome

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## ABSTRACT

Postural tachycardia syndrome (POTS) is one of the most common forms of chronic orthostatic intolerance. In addition to orthostatic symptoms, many POTS patients report incapacitating cognitive dysfunction or “brain fog” even while lying down or seated. Consistent with these subjective reports, there is accruing objective evidence of specific cognitive difficulties in POTS, with studies showing mild to moderate cognitive impairment using standardized neuropsychological assessment batteries. The precise profile of cognitive dysfunction in POTS patients has been shown to vary among these studies potentially due to the neuropsychological tests used, postural position, comorbidities and length of illness, inclusion of adolescent versus adult patients, and sites of recruitment. The extent of the impact that this cognitive challenge has in patients justifies ongoing investigation and research into lifestyle and pharmacological treatments. Psychologically, patients face challenges congruent with many chronic illnesses, perhaps especially early in adjusting to the condition. POTS patients often exhibit mild to moderate depression symptoms as well as symptoms of anxiety disorders. Since even low levels of anxiety can exacerbate symptoms, and a high number of patients experience sub-clinical low mood and sleep disturbances, there is a likely role for psychotherapy in helping control adjustment-related issues, and possibly aberrant physiology, in POTS.

## 1. Introduction

Postural tachycardia syndrome (POTS) is a heterogeneous clinical syndrome characterized by sustained excessive postural tachycardia ( $\geq 30$  bpm within 10 min of standing or  $> 60^\circ$  head-up tilt) in the absence of orthostatic hypotension and with chronic symptoms of orthostatic intolerance (Freeman et al., 2011). In patients  $< 19$  years of age, the heart rate threshold for POTS is higher (increase  $\geq 40$  bpm within 10 min of standing or  $> 60^\circ$  head-up tilt) due to physiological orthostatic tachycardia in adolescents and children (Singer et al., 2012). POTS is one of the most common forms of orthostatic intolerance, having female predominance and affecting an estimated 0.1 to 1% of the population in the United States (Robertson, 1999; Schondorf et al., 1999; Low et al., 2009). Common orthostatic symptoms include lightheadedness, dizziness, tremulousness, palpitation, chest pain, fatigue, nausea, headache, and shortness of breath (Freeman et al., 2011; Low et al., 2009). While syncope is not a predominant feature, many POTS patients experience frequent presyncopal episodes that can contribute to impaired health-related quality of life (QOL) and functional disability (Anderson et al., 2014; Benrud-Larson et al., 2002; Benrud-Larson et al., 2003). It is estimated that approximately 25% of POTS

patients are disabled and unable to participate in routine activities of daily living (Benrud-Larson et al., 2002; McDonald et al., 2014).

It is less well appreciated that many POTS patients report cognitive dysfunction, (Anderson et al., 2014; McDonald et al., 2014; Arnold et al., 2015; Shanks et al., 2013; Ocon et al., 2012; Stewart et al., 2012; Ross et al., 2013) otherwise referred to as brain fog, mental fog, mental clouding, or mental fatigue. These terms all refer to a constellation of symptoms that impair intellectual functioning to a level that interferes with daily activities. For example, over 95% of POTS patients self-reported cognitive impairment in a social-media questionnaire-based study, with most experiencing symptoms on a daily basis (Ross et al., 2013). The most common patient descriptors included forgetful, cloudy, mental fatigue, slow, mind went blank, and difficulty thinking, focusing, and finding the right words (Ross et al., 2013). Importantly, this cognitive dysfunction can occur even while lying down or seated, limiting ability to engage in work and educational activities. Furthermore, POTS patients often exhibit mild to moderate depression and anxiety symptoms related to the presence of chronic illness, which can negatively impact cognition (Masuki et al., 2007; Moon et al., 2016; Raj et al., 2009). Despite the high prevalence and clinical impact of cognitive dysfunction in POTS, there are limited studies examining this

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phenomenon. This review will describe the psychiatric and neurocognitive profiles of POTS, as well as examine potential underlying mechanisms and treatment strategies for cognitive and psychological dysfunction in this patient population.

## 2. Quality of life and psychiatric profile of POTS

Patients with POTS often report reduced QOL as well as depression and anxiety symptoms (Anderson et al., 2014; Benrud-Larson et al., 2002; Benrud-Larson et al., 2003; Arnold et al., 2015; Masuki et al., 2007; Moon et al., 2016; Raj et al., 2009; Pederson and Brook, 2017; Umeda et al., 2015). In fact, many patients are diagnosed with anxiety or depressive disorders prior to receiving the diagnosis of POTS (Benrud-Larson et al., 2002; Raj et al., 2009). The question of whether depression and anxiety symptoms are an artifact created by an overlap with symptoms of POTS, or are independent of symptoms in their own right, remains an active area of debate and research (Khurana, 2006).

### 2.1. Quality of life

Studies consistently show reduced QOL in patients with POTS (using the 36-Item Short Form Health Survey, SF-36), with variable data related to the impact of physical versus mental health parameters (Anderson et al., 2014; Benrud-Larson et al., 2002; Moon et al., 2016; Pederson and Brook, 2017; Bagai et al., 2011). An initial study by Benrud-Larson et al. found that physical health-related QOL parameters, particularly vitality and role limitations, were significantly impaired in adult POTS patients (Benrud-Larson et al., 2002). This level of disability closely matched patients with congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) and correlated with autonomic symptom burden. Interestingly, mental health domain scores did not differ significantly between POTS patients, healthy subjects, CHF, or COPD patients (Benrud-Larson et al., 2002). Bagai et al. replicated the finding of impaired physical health-related QOL in adult POTS patients compared with healthy subjects (Bagai et al., 2011). They also found significant reduction in mental health composite score in POTS, but the magnitude was considerably less than for physical parameters. Approximately 50% of the variability in physical composite scores in this study was linked to sleep impairment, while this accounted for only 25% of variability in mental composite scores (Bagai et al., 2011).

Subsequent studies showed significant impairment in both physical and mental health QOL composite scores in POTS patients compared with healthy subjects (Anderson et al., 2014; Moon et al., 2016). A relatively small study by Anderson et al. found no correlation of physical or mental health scores with resting heart rate (HR) and blood pressure (BP) in adult POTS patients (Anderson et al., 2014). Another study by Moon et al. suggested that physical and mental health QOL scores correlated with orthostatic symptoms, but not HR, in adolescent and adult POTS patients. This study, however, did not evaluate for potential confounding factors such as comorbid conditions. Thus, the relationship of these QOL scores to hemodynamic and symptomatic responses during standing in POTS remains unclear. Importantly, even patients with mild orthostatic intolerance symptoms had significantly reduced QOL.

Pederson et al. recently examined the functional meaning of diminished QOL in adult POTS patients in a large survey-based study of symptoms (Pederson and Brook, 2017). They found that physical and mental health ratings were significantly lower in POTS compared with healthy subjects. POTS patients experienced more days of sadness with approximately 76% needing help with routine activities such as shopping, and 30% needing help with personal care. Limitations of this study included recruitment of POTS patients and controls from a social media-based website, unconfirmed POTS diagnoses, use of self-reported measures, and no information on comorbidities or non-pharmacological and pharmacological treatment approaches.

In conclusion, there is clear evidence for reduced QOL in POTS patients. This finding is consistent for physical health parameters, but is variable for mental health parameters. Multiple domains have been implicated in the reduced QOL including impaired sleep, cognitive impairment, fatigue, stamina, and pain. The finding that physical health-related QOL is impaired similarly among POTS, CHF and COPD is of particular concern (Benrud-Larson et al., 2002), as POTS patients are often premenopausal women that would otherwise have many productive years of life ahead of them.

### 2.2. Depression

Using structured clinical interview, Raj et al. found that adult POTS patients did not experience higher current or lifetime prevalence of major depressive disorder (Raj et al., 2009). Using validated self-rated questionnaires, however, these patients scored in the mildly depressed range with positive association to length of illness and no relationship with norepinephrine levels. In another study, Anderson et al. found that approximately 87% of adult POTS patients exhibited clinician-rated mild to moderate major depressive disorder compared with 3% of matched healthy subjects (Anderson et al., 2014). Interestingly, this study found that underlying levels of depression and anxiety largely influenced diminished performance on tests of intellectual function, concentration, and short-term memory in POTS (Low et al., 2009). Moon et al. similarly observed a mean self-rated depression score that fell in the mild range in adolescent and adult POTS patients compared with normative population scores (Moon et al., 2016). They found a positive correlation between depression scores and orthostatic intolerance symptoms, but no relationship with orthostatic HR increment. The orthostatic intolerance symptoms most strongly associated with depression were impaired concentration, chest discomfort, palpitation, lightheadedness, and nausea.

McDonald et al. found moderate to severe levels of self-rated depression and anxiety (these were measured together) in a large cross-sectional study of adolescent and adult POTS patients (McDonald et al., 2014). The level of depression and anxiety in POTS patients was significantly lower than in chronic fatigue syndrome (CFS), despite higher rating of orthostatic intolerance symptoms. This study was limited by use of self-reported survey measures, partial recruitment from a patient support group website, and a low response rate. Using a converse approach to the question of psychiatric pathology in patients with autonomic dysfunction, Lkhagvasuren et al. studied adult patients with diagnosed anxiety, depressive, and somatoform disorders for presence of autonomic disorders (Lkhagvasuren et al., 2011). In this small study, criteria for POTS were met in 17% of patients with depression, 3% of those with anxiety disorders, and 6% of somatoform patients compared with 10% of subjects without psychiatric disorders. While the authors concluded that POTS was not more prevalent in patients with psychiatric disorders compared with healthy subjects, a trend for increased POTS was observed in patients with depressive disorders versus controls. Thus, further studies including higher numbers of patients may be needed to confirm this conclusion.

In summary, there is consistent evidence of depression in POTS, with most studies finding the magnitude in the mild to moderate range. Several studies found a positive correlation between self-rated orthostatic symptom burden and magnitude of depression. No correlation has been found, however, between depression symptoms and physiological parameters such as orthostatic HR change or plasma norepinephrine levels. The natural history of depression in POTS is also unclear, with one study finding a reduction with increasing time from diagnosis.

### 2.3. Anxiety

Patients with POTS have long been perceived as anxious; however, many common orthostatic intolerance symptoms (e.g. palpitation, lightheadedness, nausea, chest discomfort) are also clinical features of

anxiety disorders (Raj et al., 2009). This has raised the important question of whether POTS patients truly experience increased prevalence of anxiety, or if these symptoms are part of the disease process itself. In reviewing the literature, this paper refers to somatic anxiety symptoms and psychological anxiety symptoms. Symptoms of anxiety include both somatic symptoms (such as tachycardia, tachypnea, palpitation) and psychological symptoms (such as fear and feeling detached). This distinction, although artificial in anxiety disorders, is of relevance in POTS patients as somatic symptoms overlap with some of the orthostatic intolerance symptoms in this population.

To address this, Khurana et al. examined panic-like symptoms after administering provoking stimuli in 11 adult POTS patients and 11 healthy subjects. This study used a validated 17-item self-rated questionnaire that measures severity of symptoms typically occurring during spontaneous attacks in patients with panic disorder (Acute Panic Inventory Questionnaire, API) (Khurana, 2006). The API evaluates four psychological symptoms (feeling afraid, fear of dying, feeling a sense of unreality, and feeling detached from part or all of the body) and 13 somatic symptoms (feeling faint, palpitations, difficulty breathing, difficulty concentrating, urge to urinate, urge to defecate, feeling dizzy, feeling confused, sweating, nausea, trembling, and difficulty doing a job). Provoking stimuli included head-up tilt table testing (HUTT) (an orthostatic stimulus), isoproterenol infusion (an adrenergic stimulus), and sodium lactate infusion (acute anxiety stimulus). None of the control subjects experienced panic symptoms in response to these three stimuli. All POTS patients experienced symptoms with HUTT (100%), 5 with isoproterenol (45%), and 4 with lactate (36%). POTS patients had a significant increase in 6 of the API symptom items after the three stimuli (palpitations, difficulty breathing, dizziness, difficulty concentrating, difficulty speaking, and trembling). These symptoms are strongly somatic, and not psychological, suggesting symptoms in POTS are phenomenologically distinct from panic disorder.

Raj et al. found that adult POTS patients did not have increased current or lifetime prevalence of anxiety disorders (Raj et al., 2009). POTS patients, however, scored as moderately anxious compared to the background population using a non-discriminating questionnaire that measured both somatic and psychological symptoms (Beck Anxiety Inventory). In contrast, POTS patients did not have elevated anxiety on a questionnaire weighted to measure psychological anxiety symptoms (Anxiety Sensitivity Index). They concluded that the clinical appearance of anxiety in POTS was likely related to the illness rather than representing an anxiety disorder. As further evidence for more somatically focused anxiety symptoms, Anderson et al. administered a self-rated questionnaire assessing the belief of POTS patients that various bodily sensations have harmful consequences (Anxiety Sensitivity Profile) (Anderson et al., 2014). They also obtained a clinician-rated score of anxiety using a questionnaire that rates both somatic and psychological anxiety symptoms (Hamilton Anxiety Rating Scale). Compared with healthy subjects, adult POTS patients scored significantly higher on the Hamilton rating, although their anxiety level still fell in the mild range. The Anxiety Sensitivity score was also higher in POTS patients, stemming from the belief that cardiac and dissociative symptoms were especially threatening. There was no relationship between anxiety scores and HR or BP. The authors concluded that patients with POTS have increased vigilance and anxiety related to perception of cardiac symptoms.

A study by Masuki et al. examined the relationship between orthostatic tachycardia and anxiety in POTS and healthy subjects (Masuki et al., 2007). They applied true lower body negative pressure (LBNP) to create orthostatic stress using a vacuum pump, and sham orthostatic stress using either LBNP and anti-shock trouser inflation or vacuum pump without LBNP. They found that HR and BP only increased significantly in POTS patients when true orthostatic stress was present. There was no increase in controls or in POTS patients receiving sham orthostatic stress. They also induced non-orthostatic mental stress using the Stroop word color test and asked POTS patients and controls to

complete self-rated questionnaires of anxiety (Anxiety Sensitivity Index, 16-item scale to measure anxiety-related bodily sensations), somatic vigilance (Body Vigilance Scale, 4-item scale to assess focus on internal body sensations), and catastrophic cognitions (Coping Strategies Questionnaire Catastrophizing Scale, 6-items reflecting thoughts of helplessness and inability to cope with pain). Despite similar hemodynamic responses to non-orthostatic mental stress, POTS patients had higher scores on all three measures of anxiety compared with controls. The anxiety scores in POTS were just above the upper end of normal in a larger general population dataset, but were significantly less than in panic disorder. The investigators concluded that HR responses to sham orthostasis and mental stress were similar in POTS patients and controls, and were not directly related to anxiety questionnaire scores. They deduced that anxiety is not the primary cause of excessive orthostatic tachycardia in POTS; however, the anxiety scores did appear slightly elevated in the POTS group in response to mental stress. This suggests that POTS patients may have elevated anxiety compared to healthy controls. Potential limitations of this study included a small sample size, failure of some POTS patients to meet HR criteria with active standing, and continued use of antidepressants.

To summarize, while POTS patients are commonly perceived to be anxious, studies suggest this is largely driven by orthostatic symptoms that overlap with common anxiety symptoms. Studies focusing on psychological anxiety symptoms suggest POTS patients are more anxious than healthy subjects, but significantly less anxious than patients with panic disorder. The anxiety symptoms themselves may be phenomenologically distinct, with studies to date observing increased somatic vigilance. Thus it is still clinically important to consider a comorbid anxiety disorder in patients with POTS.

#### 2.4. Suicide risk

The question of whether POTS patients are at increased risk of suicide is of great concern. The first studies have recently been published on this topic (Pederson and Brook, 2017; Pederson and Blettner Brook, 2017). In a large social media-based online survey, suicidal ideation and past suicidal behavior were quantified in POTS using the Suicidal Behaviors Questionnaire-revised (SBQ-R). An elevated score on this questionnaire predicts correlation with adult and adolescent psychiatric inpatients experiencing suicidal ideation or attempts. The mean total score in POTS just reached the threshold value for placement in a high-risk category. Compared with controls, POTS patients had significantly higher suicide risk and more had threatened, planned, or attempted suicide (Pederson and Brook, 2017). It is important to note that the SBQ-R score is largely driven by thoughts of suicide and is not predictive of completed suicide, which is much less common. A second publication analyzed the relationship between SBQ-R score and self-rated sleep quality using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. They found significant correlation between suicidal ideation and diminished overall sleep quality, delayed sleep latency, bad dreams, difficulty staying awake, and diminished enthusiasm in POTS. A linear regression model found that 15% of variance in suicidal ideation score was predicted by age, total sleep quality score, and having POTS (Pederson and Blettner Brook, 2017).

These studies suggest that POTS patients are at increased risk for mental distress and suicidal ideation. It is also concerning that more patients with POTS report attempting suicide than healthy subjects since prior suicide attempts are a strong predictor of future suicide attempts (Klonsky et al., 2016). It is vital to study whether this also translates to an increased risk of completed suicide in this population, and to examine factors correlating with increased risk of suicidal ideation. As previously mentioned, these studies recruited POTS patients with unconfirmed diagnosis from a social media-based website and used self-reported measures, and therefore these findings need be interpreted with caution.

**Table 1**  
Neuropsychological testing outcome measures in POTS.

Outcome	Result	Test	Authors
Premorbid intelligence	Normal seated	WTAR	Arnold et al., 2015
Current intellectual functioning	Reduced seated	WASI	Anderson et al., 2014
Attention	Reduced seated	Ruff 2&7 speed (selective attention)	Arnold et al., 2015
	Reduced seated	WAIS-III digits forward	Anderson et al., 2014
	Normal supine/reduced 60° HUT	CogState detection	Anderson et al., 2014
Memory	Normal seated	Randt memory test (semantic, associative, and working memory)	Arnold et al., 2015
	Reduced seated	WAIS-III digits back (short-term memory)	Anderson et al., 2014
	Normal supine and during 60° HUT	CogState one card learn (short-term memory)	Anderson et al., 2014
	Normal supine/reduced > 45° HUT	N-back (working memory)	Ocon et al., 2012; Stewart et al., 2012; Stewart et al., 2015
Cognitive processing speed	Reduced seated	Symbol digits modalities test	Arnold et al., 2015
	Normal supine/reduced 60° HUT	CogState identification	Anderson et al., 2014
Executive function	Reduced seated	Stroop word color and trails B	Arnold et al., 2015
Verbal fluency	Normal seated	Controlled Oral Word Association	Arnold et al., 2015
Psychomotor speed	Normal seated	Trails A	Arnold et al., 2015

Abbreviations: WTAR, Wechsler Test of Adult Reading; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale III.

### 3. Profile of cognitive dysfunction in POTS

POTS patients widely report problems with cognition including aspects of attention, concentration, memory, and complex information processing (Table 1). To date, however, only a handful of studies have performed standardized neuropsychological testing to define the profile of this cognitive dysfunction in POTS.

#### 3.1. Intellectual functioning

POTS patients are generally well educated, with most having received undergraduate to graduate level education (Benrud-Larson et al., 2002; McDonald et al., 2014; Arnold et al., 2015; Raj et al., 2009). Despite this, these patients are reported to spend approximately two years less time in formal education compared with age and gender matched healthy subjects (Anderson et al., 2014; Arnold et al., 2015). This finding likely reflects recruitment of healthy control subjects for research studies from communities surrounding the university environment, which may be more highly educated than general community-based cohorts. In a study by Anderson et al., adult POTS patients recruited from medical outpatient or cardiovascular clinics had reduced intellectual quotient (IQ) parameters using the Wechsler Abbreviated Scale of Intelligence (WASI) (Anderson et al., 2014). Compared with matched healthy subjects, POTS patients had significantly reduced percentile scores relative to normative data for verbal IQ ( $71 \pm 4$  healthy vs.  $52 \pm 6$  POTS), non-verbal IQ ( $78 \pm 3$  healthy vs.  $60 \pm 6$  POTS), and full scale IQ ( $78 \pm 3$  healthy vs.  $55 \pm 6$  POTS). In contrast, another study by Arnold et al. showed that adult POTS patients referred to a tertiary care center had a similar level of estimated intelligence compared with healthy subjects when using the Wechsler Test of Adult Reading (WTAR) (Arnold et al., 2015). A potential explanation for these disparate findings is that the WASI is a measure of current intellectual functioning, whereas the WTAR is a tool to estimate premorbid intelligence relying on abilities thought to be unaffected in individuals with neurocognitive damage.

#### 3.2. Neuropsychological testing

An initial study by Raj et al. provided evidence that seated adult POTS patients exhibit significant inattention when compared with healthy subjects using the Connors Adult Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale long form (Raj et al., 2009). Compared with ADHD patients, the impaired attention in POTS was less severe, developed later in life, and was not associated with significant hyperactivity suggesting a distinct cognitive phenotype. Another study by Anderson et al. similarly showed impaired focused

attention in seated adult POTS patients using the Wechsler Adult Intelligence Scale III (WAIS-III) (Anderson et al., 2014). This study also examined for acute changes in cognitive function in POTS in response to orthostatic stress using the CogState computerized test battery. In the semi-recumbent position, there were no differences in psychomotor function, attention, information processing, or short-term memory between POTS patients and matched healthy subjects. During 60° HUTT however, POTS patients exhibited increased response times during tasks of attention and information processing. These orthostatic-induced cognitive deficits were associated with magnitude of HR change, years of education, and depression and anxiety (Anderson et al., 2014).

A study by Arnold et al. examined the neuropsychological profile in semi-recumbent adult POTS patients and matched healthy subjects (Arnold et al., 2015). Compared with healthy subjects, POTS patients had similar premorbid intelligence. While the average cognitive test scores were within normal limits, a significantly higher proportion of POTS patients scored in a range consistent with clinically meaningful impairment for selective attention (ability to focus on competing informational cues). Mild impairment was also observed in cognitive processing speed (time to process information) and executive function (ability to plan, organize information, and adapt to changes) in POTS. There were no differences in other cognitive measures including sustained attention, memory function, psychomotor speed (reaction time), and verbal fluency (information retrieval from memory). It is important to note that there was substantial overlap in cognitive test scores between POTS patients and healthy subjects, perhaps reflecting disease heterogeneity. A limitation is that this study did not examine for postural changes in cognitive function.

Finally, three studies have examined the impact of orthostatic stress on cognitive function and cerebral hemodynamics in adolescent and adult POTS patients with comorbid chronic fatigue syndrome (POTS/CFS) (Ocon et al., 2012; Stewart et al., 2012; Stewart et al., 2015). In these studies, the n-back test of working memory (temporary holding of information available for processing) was performed in POTS/CFS patients and healthy subjects while supine and during graded HUTT. While no differences were observed while supine, POTS/CFS patients had impaired accuracy and longer response times during n-back testing when tilted to > 45° angles. As this is similar to previous reports in CFS alone, it is unclear if this finding represents the presence of chronic fatigue versus POTS. The impaired working memory was not due to altered cerebral blood flow velocity, but was associated with increases in critical closing pressure and oscillatory cerebral blood flow, perhaps suggesting uncoupling of the neurovascular unit during orthostatic stress in POTS/CFS.

In summary, studies have shown selective impairment of measures of cognitive function in POTS including attention, cognitive processing

speed, memory function, and executive function. The precise profile of cognitive dysfunction in POTS patients varies among studies perhaps due to the neuropsychological tests used, postural position, comorbidities and length of illness, inclusion of adolescent versus adult patients, and sites of recruitment. Importantly, cognitive dysfunction in POTS can be mild, with substantial overlap in cognitive test scores with healthy subjects, likely reflecting heterogeneity of the disease. While often attributed as an orthostatic symptom, many POTS patients report cognitive dysfunction in the supine and seated positions (Ross et al., 2013). Furthermore, cognitive deficits were shown in the semi-recumbent position, when patients were asymptomatic and orthostatic tachycardia minimized (Arnold et al., 2015). Thus, it remains unclear if cognitive dysfunction in POTS results from orthostatic stress, or is part of the disease. The broad self-reported cognitive impairment in POTS contrasts with the selective impairments observed during neuropsychological testing. It is unclear whether this represents a significant mismatch between patient perceptions and objectively measured cognitive dysfunction, or relates to the sensitivity of the measures currently available.

#### 4. Potential mechanisms underlying psychological and cognitive dysfunction in POTS

The underlying causes of psychological and cognitive dysfunction in POTS remain poorly understood. Several pathophysiological mechanisms have been proposed that could contribute to impaired psychological and cognitive function in POTS, all with limited to no supporting evidence.

##### 4.1. Central norepinephrine dysregulation

Dysregulation of catecholaminergic pathways within the central nervous system is associated with impaired cognition in psychiatric conditions including ADHD, depression, and panic disorder (Biederman and Spencer, 1999; Moret and Briley, 2011; Charney et al., 1990). Centrally acting norepinephrine transporter inhibitors, which increase synaptic levels of norepinephrine, improve attention and memory but can mimic clinical features of POTS (Schroeder et al., 2002). Approximately 50% of POTS patients exhibit a hyperadrenergic phenotype in which orthostatic tachycardia is accompanied by norepinephrine levels  $\geq 600$  pg/mL, increased BP, and symptoms of sympathetic activation (e.g. palpitation, tremulousness) (Low et al., 2009). One study showed no correlation between cognitive dysfunction and plasma norepinephrine levels in semi-recumbent POTS patients; however, this relationship was not assessed during standing when the hyperadrenergic phenotype would manifest (Arnold et al., 2015).

##### 4.2. Structural and functional brain abnormalities

An emerging theory is that constitutional differences in control of brain-body interactions underlie vulnerability to psychological symptoms and reactivity, with exaggerated patterns of autonomic responsiveness contributing to enhanced panic or anxiety symptoms (Eccles et al., 2015). An initial study by Umeda et al. examined processing of emotional and neural pictures in 12 POTS patients (half with joint hypermobility) and 12 healthy controls (Eccles et al., 2015). Compared with controls, POTS patients had accentuated and prolonged cardiac acceleration in orienting response, as well as enhanced deactivation of the ventromedial prefrontal cortex, in response to external stimuli. The authors suggest that a hyper-reactive bodily state in POTS may underlie disruption of emotional state by attenuating activity of the ventromedial prefrontal cortex. A more recent study by Umeda et al. used magnetic resonance imaging with voxel-based morphometry methods to examine for variations in regional brain structures between 11 POTS patients and 23 age-matched healthy subjects (Umeda et al., 2015). The authors found reduced gray matter volume in the left anterior insula,

right middle frontal gyrus, and right cingulate gyrus in POTS patients compared with healthy subjects, brain regions associated with autonomic control and emotional arousal. They also observed reduced white matter volume in primary somatosensory brain regions in POTS. Importantly, left insula volume negatively correlated with trait anxiety (measured by State-Trait Anxiety Inventory) and depression (measured by Beck Depression Inventory-II) scores in POTS patients. While this study included a relatively small sample size and did not establish relationships with comorbidities, it provides rationale for further research to replicate these findings and to better understand how structural changes may impact functional activity, physiological reactivity, and clinical features in POTS. These overall findings suggest that regional differences in brain structure and function may contribute to increased vulnerability to autonomic and psychiatric symptoms in POTS.

##### 4.3. Chronic fatigue

A significant proportion of POTS patients have comorbid CFS (McDonald et al., 2014; Rea et al., 2017). Similar to POTS, CFS patients self-report cognitive impairment to a level that negatively impacts daily functioning and health-related QOL (Shanks et al., 2013). Previous studies in CFS have shown problems with visual and verbal memory, attention, psychomotor speed, concentration, and executive function (Shanks et al., 2013). In a cross-sectional questionnaire-based study in POTS, mental fatigue scores positively correlated with self-reported brain fog severity and frequency (Ross et al., 2013). In this study, POTS patients with higher fatigue reported greater severity and frequency of cognitive impairment and reduced efficacy of therapies to improve cognitive symptoms. Despite these associations, the relationship between POTS and CFS in terms of cognitive dysfunction remains undetermined. Perhaps arguing against a causal relationship, CFS is characterized by memory and concentration deficits, which have not been consistently observed in POTS (Arnold et al., 2015). Furthermore, while both syndromes experience fatigue as a multi-dimensional construct, POTS patients have less distinct fatigue types compared to CFS (Wise et al., 2017).

##### 4.4. Sleep disturbances

Sleep plays a critical role in attention, learning, memory, and cognitive processing (Deak and Stickgold, 2010). POTS patients report nocturnal sleep disruption, sleep-related symptoms (e.g. daytime sleepiness, fatigue), longer sleep onset latency, and sleep disorders (e.g. insomnia, sleep apnea) (Ross et al., 2013; Bagai et al., 2011; Pederson and Blettner Brook, 2017; Bagai et al., 2013; Mallien et al., 2014; Xu et al., 2016). Poor sleep efficiency and sleep fragmentation have been correlated to reduced health-related QOL and suicidal ideation in POTS (Pederson and Blettner Brook, 2017). These sleep problems are thought to result from sympathetic or hypothalamic-pituitary axis activation to induce hyperarousal, or from comorbidities such as chronic pain. Consistent with patient reports, a small prospective study showed poor sleep efficiency and a trend towards increased sleep fragmentation using wrist actigraphy measures in POTS (Bagai et al., 2013). These patients did not display longer sleep onset latencies, perhaps suggesting sleep-state misperception. More recent studies using overnight polysomnograms, however, have not shown significant sleep problems or disorders in POTS (Mallien et al., 2014; Pengo et al., 2015; Bagai et al., 2016; Miglis et al., 2016). While lack of sleep is reported as one of the most frequent triggers of cognitive dysfunction in POTS (Ross et al., 2013), studies have not examined this relationship.

##### 4.5. Psychiatric and other comorbidities

Some POTS patients exhibit depression and anxiety symptoms, which alone can negatively impact cognitive function (Moret and Briley, 2011). Indeed, depression and anxiety symptoms were found to

influence current intellectual functioning and impairments in focused attention and short-term memory in seated POTS patients (Anderson et al., 2014). In contrast, clinically significant impairment in selective attention, cognitive processing speed, and executive function were still apparent in semi-recumbent POTS patients after adjustment for baseline depression and anxiety symptoms (Arnold et al., 2015). Thus, there are currently limited and disparate results regarding the impact of psychiatric comorbidities on cognitive function in POTS. Finally, POTS patients often have comorbidities known to negatively influence cognitive function including autoimmune disorders, chronic pain, irritable bowel syndrome, fibromyalgia, and Ehlers-Danlos syndrome hypermobility type (Moriarty et al., 2011; Dubey et al., 2016; Fadgyas-Stanculete et al., 2014; Baeza-Velasco et al., 2017).

## 5. Treatment strategies for cognitive dysfunction in POTS

### 5.1. Treatment overview

Applying emerging understanding of the dynamic interaction of psychological and physiological processes to relieve cognitive symptoms in POTS is a promising area. Encouragingly, there is increasing recognition that cognitive and emotional factors are a significant part of the illness burden and are important therapeutic targets (Raj et al., 2009; Kavi et al., 2016). The literature recognizes that multiple treatment strands, delivered by a multi-disciplinary team working from a biopsychosocial model, is likely optimal (Sheldon et al., 2015). There is increasing concurrence that psychological symptoms are both an adjustment and endogenous to the POTS clinical presentation (Ross et al., 2013). Some symptoms are seen to fluctuate with, and some remain independent of, postural changes. Thus, cognitive treatment approaches include those aimed to improve global POTS symptoms, as well as more tailored regimes for neuropsychological phenomena such as depression and anxiety symptoms and impaired cognition. It is clinically useful to conceptualize each patient having their own individual POTS thumbprint, requiring detailed clinical assessment and an individual plan to optimize treatment and outcomes.

Establishing clear treatment guidelines for cognitive dysfunction in POTS remains challenging as a unifying understanding of mechanisms involved remains elusive. There is no consistent treatment regimen prescribed, and no FDA approved medications, with most drugs prescribed off-label. Consequently, standard approaches advocate a step-wise treatment approach, starting conservatively with patient education and lifestyle changes, and pharmacological treatment when necessary. Importantly, there are no studies to date examining non-pharmacological or pharmacological treatment approaches for cognitive dysfunction in POTS. What follows is a suggested clinical management strategy using the limited data available and general standard of care treatment approaches.

### 5.2. Non-pharmacological interventions

Brain fog is reported as one of the most disabling and prevalent symptoms in POTS (Ross et al., 2013; Kavi et al., 2016). In a survey-based study, POTS patients self-reported that lying down, avoiding heat, and increasing fluid and sodium intake can non-pharmacologically alleviate cognitive symptoms. Conversely, brain fog was aggravated by excessive cognitive challenges, poor sleep, showering, and acute exercise (Ross et al., 2013). While exercise may acutely worsen patient perception of cognitive function, regular exercise programs are reported to improve cognitive symptoms (Ross et al., 2013), as well as physical symptoms of POTS (Fu et al., 2011). Patients can understandably be hesitant to engage in a challenging exercise regime with a delayed benefit and initial symptom escalation. There is a known positive correlation between exercise, cognition, and mood in the healthy (Hillman et al., 2008), which requires replication in POTS. Finally, POTS patients equally self-report caffeine as helpful or a hindrance

cognitively (Ross et al., 2013). Despite caffeine's vasoconstrictive qualities, perhaps in some cases diuresis and tachycardia outweighed benefit. Overall, there is a lack of objective data examining non-pharmacological approaches for cognitive dysfunction in POTS, and heterogeneity in terms of symptoms and treatment approaches for these patients.

### 5.3. Pharmacological interventions

In the same survey-based study as cited for non-pharmacological interventions, patients cited improvement in brain fog with intravenous saline (77%), stimulants (67%), salt tablets (54%), intramuscular vitamin B-12 injections (48%), and midodrine (45%) (Ross et al., 2013). To our knowledge none of these interventions have been robustly investigated regarding cognitive outcomes. This cohort reported that some treatments commonly used for POTS symptoms have a negative impact on brain fog including serotonin-norepinephrine reuptake inhibitors (SNRI),  $\beta$ 1-adrenergic receptor antagonists, and fludrocortisone. In the case of SNRI, it has been hypothesized that negative effects on brain function in POTS are due to high levels of synaptic norepinephrine (Stewart, 2012). Other studies have described mild cognitive impairment in healthy subjects following short-term selective serotonin reuptake inhibitors, but not SNRI treatment (Biringier et al., 2009). Raj et al. found that low-dose propranolol improved orthostatic symptoms in some POTS patients, but this study did not examine cognition (Raj et al., 2009). A better understanding of the mode of operation and effects on different subgroups within POTS is required to optimize treatment.

Cognitive benefit from modafinil has been documented in other neuropsychological conditions associated with brain fog such as adult ADHD patients (Turner et al., 2004). Encouraged by this, and the reassurance that this psychostimulant does not worsen hemodynamics in POTS as might be predicted (Kpaeyeh Jr. et al., 2014), there is currently an ongoing trial examining acute changes in cognitive function using neuropsychological testing (<https://clinicaltrials.gov/NCT01988883>). The effect of modafinil in combination with propranolol (to maintain HR control in susceptible patients) is also being examined. Based on patient observations (Ross et al., 2013), further examination of effects of vitamin B-12 injection and saline treatment are also warranted. Overall, more studies are needed to examine the effects of these interventions on cognitive function in POTS, and to determine if any effects are sustained and well tolerated in this population.

### 5.4. Cognitive therapies

Since there are documented associations of POTS with depression, anxiety, and suicidal ideation, it seems logical that addressing psychological, attention, and adjustment challenges would be beneficial either alone or in combination with non-pharmacological and pharmacological approaches. In this regard, stress-reduction techniques and Cognitive Behavioral Therapy (CBT) are typically advocated; however, there is a paucity of robust, high quality outcome research for cognitive-behavioral interventions in POTS. Much of the evidence for its recommendation stems from research on associated conditions with similar challenges such as chronic pain. There is good evidence that patients with medical conditions generally benefit from psychotherapies. This is born out, for example, in COPD (Smith et al., 2014), which has impaired health-related QOL comparable to POTS (Grubb, 2008). CBT has good face validity for treatment of physical health conditions with distressing symptoms (e.g. chronic pain, anxiety). It is centered on developing awareness of the interaction of physical responses with situations, thoughts, emotions, and actions with the ultimate goal of identifying and changing unhelpful patterns. As an example, catastrophic thinking, a standard target for modification with CBT, has been associated with functional disability in POTS (Benrud-Larson et al., 2002).

Evidence is growing rapidly for variants of traditional CBT approaches based on mindfulness, such as Mindfulness-based Cognitive Therapy (MBCT). Mindfulness is defined as paying attention to what is happening in the present moment with acceptance, curiosity, and compassion. Practicing mindfulness on a regular basis supports enhanced awareness of experiences and actions, and better adaptations (e.g. responding more flexibly and skillfully to changing symptoms such as palpitation). This can help break cycles of unhelpful thoughts and actions (such as avoidance), which can otherwise increase distress, exacerbate symptoms, and limit functioning. A large systematic review and meta-analysis, demonstrated that mindfulness-based interventions significantly improve mental health, QOL, and physical functioning in treatment of several patient populations including cancer, cardiovascular disease, chronic pain, depression, and anxiety disorders (Gotink et al., 2015). Mindfulness training has also been shown to improve autonomic responses to stress (Zeidan et al., 2010; Nyklíček et al., 2013), and relevantly to POTS, to reduce hypervigilance and catastrophic interpretations of symptoms (Vujanovic et al., 2007; Garland et al., 2012).

Some caution seems warranted, however, by a study reporting different outcomes following specialist CBT for patients with CFS/myalgic encephalomyelitis (CFS/ME) diagnosis according to whether they also had POTS. This study reported a lesser response rate and regression in some cases in the comorbid POTS-CFS/ME group (Roerink et al., 2017). There was a high attrition rate in this study, however, and fatigue was the only reported outcome measure. It would be useful to understand the specific elements of the intervention that were perhaps more challenging for POTS patients, and to explore mood, QOL, and psychosocial outcomes.

An interesting unanticipated finding emerged from a recent small outcome study of a Mindfulness-Based Stress Reduction (MBSR) program adapted for teenagers with cardiac diagnoses (in which category the investigators included POTS) (Freedenberg et al., 2017). That the comparison group, who received facilitated small group-support via video, had outcomes equivalent to the treatment group suggests that group support is perhaps best understood as intervention, not a non-treatment comparison. This is in line with accruing evidence of the pivotal role of reducing social exclusion and perceived helplessness for positive outcomes in chronic illness (Hawton et al., 2011). Indeed, reducing isolation may be a very significant factor in any therapeutic intervention. In a study examining adults with congenital heart disease, social adjustment was more predictive of health outcomes than medical variables (Kovacs et al., 2009). Isolation may be a significant factor for young bed-bound individuals with POTS. Many patients describe living a life un-fathomable to their peers and having been misbelieved and ostracized (Kavi et al., 2016). It is our opinion that clinicians who work with POTS patients have an opportunity to engender hope and reduce isolation.

Similar psychosocial adjustment factors could arguably be implicated in the case study of successful CBT treatment with a member of the American military with POTS (Ralston and Kanzler, 2016). Positive outcome was recorded in self-assessment of functional symptoms, improved mental well being, and return to work. As might be anticipated, significant emphasis was placed on the positive effects of challenging catastrophizing thoughts, reducing avoidance of symptom-triggering environments, and practicing tolerance of frightening symptoms. While this is a case study, many key aspects of this intervention concur with our own opinion of best practice psychological interventions for patients with POTS.

Finally, motivational interviewing is an evidence-based approach for exploring readiness to make life-style changes and treatment adherence (O'Halloran et al., 2014; Knight et al., 2006). Using patient-driven problem solving can be a useful method for improving patient's own engagement and active management of their condition. While currently having no evidence in POTS, motivational interviewing has been shown to produce good results in patients with other chronic

conditions such as anxiety, depression, chronic fatigue syndrome, chronic pain, hypertension, and obesity (Alperstein and Sharpe, 2016; Ma et al., 2014; Masterson Creber et al., 2016; Christie and Channon, 2014).

### 5.5. Suggested psychological treatment approach to POTS

A physical health clinician actively involved in patient care is probably best placed to introduce patients to the idea of engaging in psychological support without being misconstrued as suggesting symptoms are “all in the head”. Introducing this support early is likely to be an important factor in preventing QOL deterioration and associated secondary factors such as reactive depression, avoidance, and physical deconditioning (Kavi et al., 2016). A clinical or health psychologist is then well positioned with sufficient contact time and specialist skills to formulate, develop, and implement the integrated psychological, physiological, and behavioral/lifestyle treatment approach required.

Socializing a patient to the treatment approach is standard best practice for CBT and essential for engagement and active collaboration. We know that patients actively involved in their healthcare do better. The rationale for psychological intervention, all of which can be helpful to share with patients, include those specific to POTS, as well as those more broadly applicable to many chronic illnesses. It is worth emphasizing that we know that patients with many chronic illnesses do better with access to CBT. While we hope that more empirically validated CBT and third-wave interventions tailored specifically for POTS will soon be forthcoming, in the meantime, it is reasonable to make appropriate adjustments to protocols with proven efficacy for other chronic conditions (e.g. chronic pain, anxiety disorders) (Kaczurkin and Foa, 2015; Ehde et al., 2014). While a large number of diverse CBT protocols exist, all include elements of psychoeducation and the use of skill-focused approaches aimed to reduce psychological stress. Improvement in physical function is achieved by helping patients decrease unhelpful behaviors, identify and correct unhelpful thoughts, images, and beliefs, and increase adaptive behaviors.

CBT techniques used in many chronic health conditions that are almost universally helpful include: setting and working towards specific agreed goals (e.g. enhancing motivation to engage in appropriate lifestyle changes and adhere to pharmacological regimes more consistently); problem-solving training; and cognitive restructuring (e.g. identifying and changing unhelpful assumptions and thinking cycles including health and other fears about the future, harboring frustration at past mistakes, misdiagnosis, and failings among family and friends); and relaxation training to reduce the impact of chronic stress. Identifying any issues such as isolation, compromised sleep, poor diet, deconditioning, or self-medication, which can impact directly on disease prognosis and addressing these promptly. Guidance around appropriate pacing and engagement in the right activities for the right amount of time to live optimally; help with adjustment to diagnosis, grief, and fears for the future are all typical targets of assessment and intervention in a comprehensive CBT approach. In addition, effective protocols often include activities to be completed between sessions to document examples of thought or behavioral patterns, plan or practice new skills or conduct behavioral experiments to collate evidence for the positive effects of the approach.

In addition to the techniques described above, factors more specific to POTS that can be targeted for support include: getting the delicate balance right of responding appropriately to but not getting distressed or overwhelmed by somatic symptoms; learning strategies to calm down the fight/flight response and preventing anxious thinking from escalating the ‘anxiety-mimicking’ somatic symptoms; pre-syncope specific strategies including counter-maneuvers and not continuing on and ignoring physiological cues; addressing unhelpful dissociative tendencies, which can arise as a coping strategy in the wake of distress and discomfort (which untreated can exacerbate a vicious cycle of

deteriorating functioning); and challenging the unhelpful idea that the body is scary, unpredictable, out of control and has let them down.

Our experience with co-morbid difficulties and common challenges reported by POTS patients suggests some key therapeutic interventions, from both CBT and so-called ‘third-wave’ CBT approaches which incorporate mindfulness, self-compassion, and acceptance principles. After socialization to the model, and based on individual needs identified in case-formulation, these techniques should be considered for inclusion in treatment plans. They can be usefully adapted for individual or group interventions (please see Appendix Table A.1 for a detailed suggested treatment approach for psychologists). Given the rather contrary and unpredictable response to treatment of this complex syndrome, however, we would advocate that further work is needed to begin to construct and assess the incremental benefits of various elements of manualized therapy protocols, in addition to standard medical care. Adjustment to this challenging disorder will depend on their unique symptom profile, history and severity, as well as factors including extrinsic supports and acquired or intrinsic psychological resilience. Arguably, however, all will benefit from a paradigm for systemic illness, which moves beyond the unjustifiable separation of somatic and psychological phenomena, and tailors treatment to the whole person in their wider social context.

**6. Conclusions**

Overall, the presence of cognitive dysfunction in POTS is only now beginning to be appreciated by clinicians, although patients cite it as one of the most disabling aspects of their condition (Ross et al., 2013; Kavi et al., 2016). Effectively capturing the precise nature of the difficulties quantitatively has proven challenging. The limited studies to date have generally shown that POTS patients exhibit selective impairments in tests of attention, working memory, and executive function (Anderson et al., 2014; Arnold et al., 2015; Ocon et al., 2012; Stewart et al., 2012; Stewart et al., 2015); however, there is often considerable overlap in test scores with healthy subjects. This could

result from numerous factors including heterogeneity of disease as well as a mismatch between patient perceptions and objective measurements. The perception of cognitive symptoms as described in self-report questionnaires should therefore be interpreted with caution, with objective neuropsychological testing conducted to focus on the domains shown to be impaired in POTS. Importantly, cognitive symptoms severity does not always align with measurable hemodynamic irregularities, with impairments detected even in the absence of significant orthostatic stress (Anderson et al., 2014; Arnold et al., 2015). Cognitive dysfunction in POTS could therefore represent an independent consequence of disease pathophysiology. Proposed mechanisms include central NE dysregulation, structural and functional brain abnormalities, chronic fatigue, sleep disturbances, and psychiatric and other comorbidities; however, these potential mechanisms have not been adequately explored. Studies are needed to directly correlate cognitive outcomes with these physiological and psychological measures, with attention paid to the presence of comorbidities known to independently affect cognition including chronic fatigue syndrome, sleep disorders, and neuropsychiatric phenomena. Finally, effective clinical management of POTS requires attention to monitoring for psychological distress and treating as indicated. Currently the field is hampered by the limited research centers examining psychological treatment in this population. We are in great need of clinical trials comparing POTS patients receiving a specific psychological intervention with sham intervention or waitlist controls. This is essential to identify effective evidence based psychological treatment in patients with POTS.

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**Appendix A. Appendix**

Table A.1  
Psychological Treatment Approach to Cognitive Therapy in POTS.

Skill	Suggested techniques	Rationale
Core cognitive behavioral therapy skills for identifying and challenging unhelpful thinking	Thought records, coping cards (summary of coping statements to use when symptomatic), behavioral activation, behavioral experiments, and data gathering.	Understandable tendencies towards catastrophizing, minimizing achievements, black and white thinking, future related thoughts, and learned helplessness.
Acute anxiety skills	Psychoeducation, breathing skills, relaxation, visualization (including ‘turning down the dial’ of anxiety volume), defusing from emotions, refocusing/healthy distraction, self-soothing tool-kit. Treating any preexisting trauma that exacerbates difficulties.	Mismatch between measurable physiology and self-reported experiences. Managing scary sensations including a racing heart, dizziness and brain-fog. Preventing unhelpful responses e.g. avoidance or dissociation including conversion phenomena.
Worry skills	Decision trees, delayed ‘worry hours’ (including health anxiety/planning), generating alternative explanations with probabilities, rating importance of worries, challenging perfectionism and control.	Not only does managing chronic illness involve addressing worrying thoughts but the somatic symptoms of POTS (which mimic anxiety) make other emotion-congruent memories and worrisome thoughts more accessible. Compensatory over-control in another aspects of life can develop.
Adjusting to unpredictability	Enhancing belief in capacity to cope with situations as they arise. Flexible planning, acceptance and commitment based skills.	Difficulty planning activities due to not knowing how symptoms will be can generate ‘learned helplessness’ and avoidance.
Syncope and pre-syncope related skills	Skills in healthy body scanning, counter-maneuvers, life-style changes and ‘grounding’ (mindfully staying present).	Tendency to feel out of control, vulnerable and distressed by symptoms can cause lack of attunement to physical cues.
Improved sleep	Mindfulness for sleep strategies and sleep-hygiene	

(continued on next page)

Table A.1 (continued)

Skill	Suggested techniques	Rationale
Pain management	Mindfulness skills and behavioral activation	Patients report being ‘tired but wired’. Poor sleep is implicated in mood, anxiety, suicidal ideation and brain-fog. POTS patients report pain from migraine, coat-hanger (or neck and shoulder) pain and chest pain. Comorbid disorders such as headache are associated with significant additional pain.
Interpersonal skills	Appropriate assertiveness. Developing empathic awareness and compassion. Revising expectations of others. Role-play and ‘empty-chair’ strategies.	Illness places strains on interpersonal relationships. Preventing isolation is important for outcome. Socializing require creative adaptations in lieu of fatigue and physical limitations.
Managing grief and guilt	Psychoeducation, awareness and insight. Aim to ‘banish guilt’ and be compassionate of grief.	Losses include of the anticipated future, passions, and trust in body. Guilt about effect of illness on others.
Anger management	Reframing anger as a helpful ‘flag’ of issues to resolve or let go. Always valid, but needs to be harnessed usefully.	Often develops during period before diagnosis relating to not being believed, being misdiagnosed or feeling unsupported.
Mindfulness (presence in the moment with curiosity, compassion and acceptance)	Meditation, body scanning, adapted yoga or tai-chi.	Associated with improved energy, heart rate, blood pressure and glucose levels, interpersonal skills, sleep and quality of life.
Consolidating advice and over-seeing behavior changes	Practical skills for usefully undertaking life-style and daily planning (water, nutrition, medication, activities), motivation, priority setting, initiating action, & problem solving.	Actively coordinating own care plan improves engagement and outcome. Without being integrated, advice from multiple specialists can feel overwhelming and lead to inertia/helplessness.
Activity pacing	Developing an appropriately flexible regime for slowly and appropriately escalating challenges, and self-reward. Listening to body rather than continuing to burnout.	Fatigue and limited energy make choosing the right activities to stay fit and to enjoy life without setbacks more challenging and more critical.
Self-compassion, self-worth and self-care	Meditation skills, value-based living (rather than goal driven self-esteem), self-soothing.	Capacity to be a good friend to oneself essential for making positive health choices and valuing oneself even when not able meet previous goals or levels of productivity.
Challenging illness identity	Keeping interests and activities rich, varied and in keeping with pre-illness self, limiting time on health-related matters, maintaining key relationships, recognizing and celebrating individuality and achievements.	Managing appointments and health can begin to take up all time and energy, leaving patients feeling there is nothing else to them (further increasing isolation and despair).
Hope and positivity	Cognitive reframing, focusing on positives, life planning and prioritizing, and the therapeutic alliance itself (in generating hope).	The idea that when energy is compromised what really matters is brought sharply into focus, we potentially bring new appreciation and priorities to the fore in our day-to-day lives, which adds to and enriches pre-diagnostic lived experience.

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