

Review

Managing fatigue in postural tachycardia syndrome (PoTS): The Newcastle approach

Victoria Strassheim^a, Jenny Welford^b, Rob Ballantine^c, Julia L. Newton^{d,e,*}

^a *Fatigue Cresta, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK*

^b *Occupational Therapy, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK*

^c *Research and Development, Northwick Park Hospital, Harrow, UK*

^d *Institute of Cellular Medicine, Newcastle University, Newcastle, UK*

^e *Research & Innovation Hub, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK*

ARTICLE INFO

Keywords:

Fatigue
Activity
Multidisciplinary

ABSTRACT

Fatigue is a significant symptom that is frequently reported by those with postural tachycardia syndrome (PoTS). There are a variety of reasons why those with PoTS might experience fatigue and as a consequence an individualised approach to management is most appropriate.

In this chapter we will examine the prevalence of fatigue in those with PoTS, its overlap with conditions such as chronic fatigue syndrome and describe a clinical approach to the management of fatigue in those with PoTS.

1. Introduction

Fatigue is a common symptom that is being increasingly identified in association with a broad range of chronic medical illnesses, including musculoskeletal conditions such as rheumatoid arthritis and Sjogrens syndrome, neurological disorders such as stroke, multiple sclerosis and Parkinson's Disease and others such as post cancer, cardiac failure and chronic respiratory disease (Krupp et al., 1988; Yoshii et al., 2006; Newton et al., 2008; Newton and Jones, 2007; Newton et al., 2009; Ng and Bowman, 2010).

Fatigue can be acute (lasting less than a month), prolonged (< 6 months duration) or chronic (6 or more months). Definitions of what is considered chronic differ between the US and the UK (3 vs 6 months) and are sometimes described and/or perceived in different ways by clinicians, researchers and those who experience the symptom (mental versus physical fatigue) making its description, quantification and study difficult.

Fatigue is generally not relieved by sleep or rest and in studies it has been shown consistently to be distinct from depression (Skapinakis et al., 2003; Pawlikowska et al., 1994) (although some people affected by fatigue will have reactive depression secondary to their symptoms) (Newton and Jones, 2010). Fatigue is described in 25% of all primary care consultations. It is the main reason for attendance in 6.5% (Cullen et al., 2002). In UK Community surveys, over 10% of adults have had substantial fatigue for over one month (David et al., 1990).

Fatigue impacts quality of life and has consequences for individuals across all aspects of their activities of daily living; including self-care leisure and productivity domains. This can, in addition, impact society, as those who are fatigued are less able to work, and if they do work, they may feel they are less productive (Ricci et al., 2007; Collin et al., 2017).

2. How common is fatigue in those with PoTS?

A recent survey performed with the United Kingdom PoTS charity, PoTS UK received responses from 779 UK patients identifying themselves as having been diagnosed with PoTS by a doctor or a specialist nurse (Kavi et al., 2016). Of these patients, 92% were female and 81% were aged 18 to 49. The three most common symptoms described by PoTS patients were fatigue (91%), presyncope and dizziness (90%), and palpitations (86%). Interestingly 58% of the cohort had a history of syncope.

3. What might cause fatigue in PoTS?

Table 1 lists a number of potential explanations for fatigue in PoTS. In a clinical encounter, when considering causes of fatigue in any chronic disease it is important to exclude common fatigue associated conditions such as iron deficiency, hypothyroidism or vitamin D deficiency (Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Abbreviations: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis; EDS, Ehlers Danlos Syndrome

* Corresponding author at: Institute of Cellular Medicine, The Medical School, Newcastle University, Newcastle, UK.

E-mail address: julia.newton@ncl.ac.uk (J.L. Newton).

Table 1
What might cause fatigue in PoTS?

PoTS itself
PoTS plus other associated co-morbidity such as CFS (McDonald et al., 2014; Wallman et al., 2014), EDS (Hakim et al., 2017), fibromyalgia, anxiety, migraine, irritable bowel syndrome, mast cell disorders (Theoharides et al., 2005) and Chiari malformation (seen more commonly among those with EDS).
Medications for PoTS or other conditions such as beta-blockers, tricyclic antidepressants or anticonvulsants for management of co-morbid pain, or medications used for nausea and sleep.
Problems with sleep that might be associated with PoTS
Managing a chronic illness whilst trying to lead a normal life

(Encephalopathy); *Diagnosis and Management*, 2007).

PoTS itself appears to be a fatigue-associated condition, although intriguingly not all PoTS sufferers describe fatigue, suggesting this might not be the case. Some of the recognised physiological variables seen in those with PoTS may contribute to fatigue; such as inadequate hydration, heat intolerance, low blood volume, decreased cerebral blood flow, increased noradrenaline levels, increased sympathetic tone, or activation of reflex pathways as would be seen in those with PoTS and vaso-vagal syncope.

The PoTS UK survey confirms that a significant proportion of those with PoTS describe symptoms of fatigue. Fatigue may occur because of other comorbid conditions that are recognised in PoTS, such as chronic fatigue syndrome or Ehlers-Danlos joint hypermobility syndrome (McDonald et al., 2014; Wallman et al., 2014; Hakim et al., 2017). It may occur in association with medication, for example beta blockers which are commonly used in PoTS patients and are known to be associated with fatigue.

Further research is needed to understand those PoTS sub-types that might be more associated with a fatigue phenotype which could point towards more likely physiological fatigue associated phenomena and as a consequence targeted treatments.

Currently, we are recognising an increase in the association between problems with PoTS patients and sleep where patients describe themselves as feeling “wired” and as a consequence find it difficult to get to sleep. More research needs to be done in this area but certainly patient descriptions of problems with sleep are very frequently heard in the clinic. Finally, fatigue can occur because of all of these issues, plus the impact of having to live your life with a condition that is poorly understood and for which there are few evidence based treatments.

4. How common is chronic fatigue syndrome in those with PoTS?

In addition to fatigue occurring in association with a range of chronic diseases, it can occur with a constellation of other symptoms recognised as chronic fatigue syndrome (CFS) (*Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine*, 2015). CFS is a neurological disorder classified by the World Health Organisation in ICD10 (G93.3). CFS, sometimes referred to as myalgic encephalomyelitis (ME), is a medically unexplained condition, physiologically distinct from depression. Over recent years, a large number of immunological, neurological and endocrine abnormalities have been identified in those with CFS that are consistent across research studies (*Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (Encephalopathy); Diagnosis and Management*, 2007; Nacul et al., 2011).

The prevalence of PoTS in those with CFS varies between studies. This wide variability in prevalence is (at least in part) related to differences in orthostatic testing methods which might influence the reported prevalence, together with differences in definitions of CFS between studies. Rates as high as 50% PoTS prevalence in adults with CFS have been reported in the US (Freeman and Komaroff, 1997) with other studies reporting (Miwa, 2016) a prevalence of 42% of those with CFS

meeting the diagnostic criteria for PoTS. Interestingly in this study, 97% had symptoms of orthostatic intolerance, and a proportion hypo-tension without PoTS, emphasizing the importance of considering the broader problem of orthostatic intolerance in this population.

In paediatric patients (Stewart, 2004) 64% of CFS participants had PoTS, but up to 96% of those with a diagnosis of CFS had some form of orthostatic intolerance. UK studies, in those with CFS, have shown approximately one third of individuals have haemodynamic findings consistent with postural tachycardia syndrome (PoTS) (Hoad et al., 2008; Reynolds et al., 2013). This highlights the considerable overlap between PoTS and CFS. The British Journal of Cardiology PoTS UK survey (Kavi et al., 2016), also confirmed that up to 30% of those with PoTS describe having comorbid chronic fatigue syndrome.

5. Quantifying fatigue

Fatigue is often perceived as a subjective problem and as a result can be difficult to identify and quantify. Currently there are no gold standard objective assessments of fatigue although surrogate markers such as accelerometry or assessment of neuromuscular function may provide some objective evidence of fatigability.

In a clinical setting, fatigue is most frequently quantified using subjective questionnaire based assessment tools such as the Fatigue Impact Scale (Fisk et al., 1994) or the Fatigue Severity Scale (Krupp et al., 1989). The measure that is most frequently used in the UK Chronic Fatigue Syndrome services to quantify fatigue is the Chalder Fatigue Scale (Chalder et al., 1993). Making a diagnosis of chronic fatigue syndrome in those with comorbid PoTS requires fulfilment of a defined symptom set (in the UK this would be symptoms consistent with the NICE guidelines (*Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (Encephalopathy); Diagnosis and Management*, 2007)).

6. What might the consequences of fatigue be in PoTS

In individuals with PoTS, fatigue can be associated with a number of consequences, some of which are shown in a word cloud developed with our patients (Fig. 1). It can lead to frustration, problems with decision-making and poor performance. This may impact upon the affected individual's ability to have a fulfilling career, or complete appropriate schooling. Fatigue can also impact upon productivity, make those affected irritable and therefore adversely affect social and personal relationships. Stress can also arise as a result of fatigue, in addition to low mood and reduction in memory function.

7. Managing fatigue

Managing fatigue is possible, but it is not easy. It takes commitment, persistence, trial and error with no immediate quick fix. There is no medication that will cure fatigue in general, or specifically in those with PoTS and a multi-disciplinary approach is needed to aid its management.

First, it is important to find a stable start point. In our fatigue clinic, in Newcastle UK (Hackett et al., 2016; Lambson et al., 2015) we frequently ask people to complete activity diaries and to grade whether their activities are high, medium or low, defining periods when they are resting or asleep. When people do this, they can often see patterns in their activity that highlight how they may be booming and busting, or pacing their activity appropriately.

The management booklet that we use in Newcastle is available via <http://www.ncl.ac.uk/medicalsciences/research/centres/fatigue/>, and the components of our multidisciplinary approach shown in Fig. 2.

When managing fatigue in PoTS patients, much of the advice that we use in our clinical practice is generic and some extrapolated from information available in the CFS literature (*Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (Encephalopathy); Diagnosis and*



Fig. 1. Symptoms described by those with PoTS as consequences of their fatigue.

Management, 2007). However, by understanding the mechanisms that might lead to symptoms in PoTS, exacerbations can be avoided in order to help find a stable base line from which to manage and improve. We consider fatigue management as being a package of advice that we provide for PoTS patients, it is unlikely that one thing alone will make the difference people want, it is most likely that approaching management of fatigue from multiple perspectives will have the best result.

7.1. Managing energy

Managing fatigue in any condition is about managing energy. In our clinic we use multiple analogies to explain this, such as the utilisation of a pie of energy, or having an energy bank account, where if you use up

your money there will be less to spend the following day. When using the bank analogy, it is useful to understand which activities ‘make you money’ and which ‘spend it’.

As PoTS is an autonomic disturbance characterised by orthostatic intolerance where orthostatic intolerance means intolerance to gravity (Agarwal, 2007); activity management can be difficult as we live in an environment of gravity.

We therefore recommend to our patients that in order to start to manage fatigue and improve it, a point of stability must be reached. That point is when activity is consistent day after day, week after week. This makes planning more predictable as we can then identify what depletes energy and what restores it. To begin to stabilise fatigue in people with PoTS, it is helpful to understand the mechanisms at play

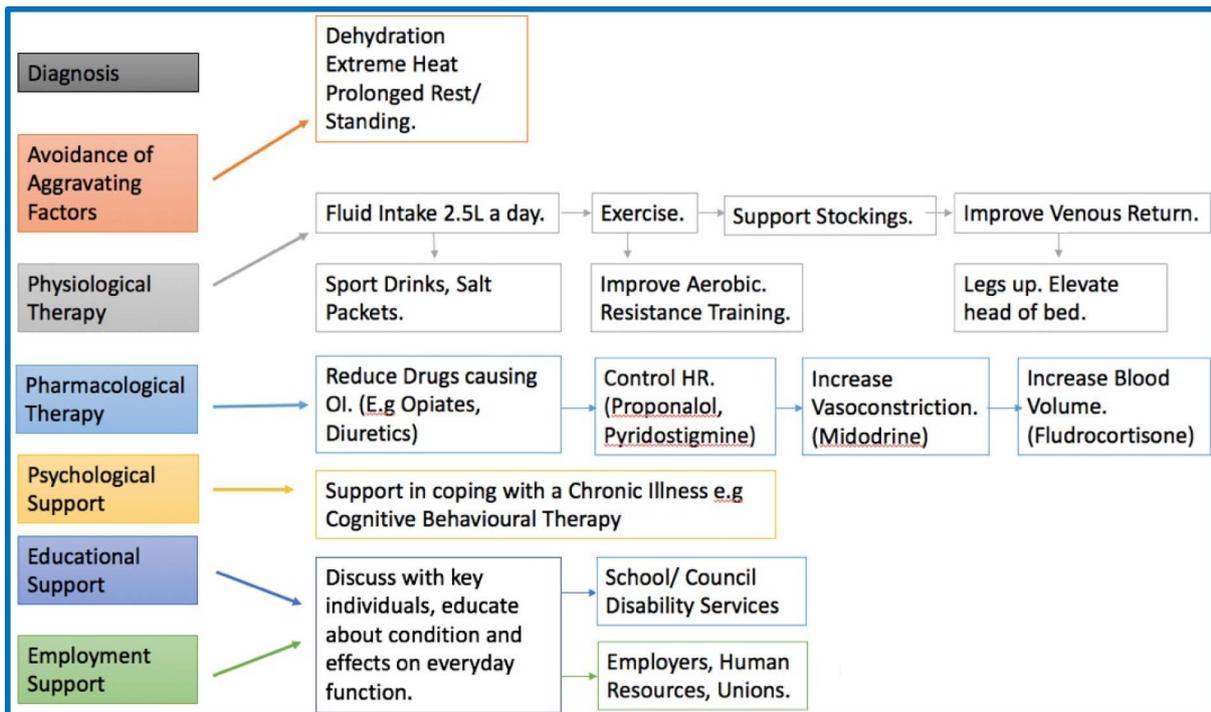


Fig. 2. Multidisciplinary approach to managing fatigue in PoTS.

when they move:

The autonomic nervous system regulates blood flow as the body moves. This is performed in two areas:

1. The pooling areas – the volume of blood below the level of the heart.
2. The hydrostatic column – the line between the heart and the head over which the heart must pump blood to ensure brain perfusion.

This mechanism is dynamic and changes depending on the challenge (Antonutto, 2003). Blood pressure has a hydrostatic component and when exposed to a gravitational stress, the appropriate physiology must be in place to maintain adequate circulation to the heart and brain. Understanding that certain movements may cause physiological stress and may need to be modified or limited helps to manage energy expenditure.

7.2. Avoidance of movement

Fear of movement and avoidance behaviour towards physical activity has been reported in CFS/ME and other fatigue associated conditions (Nijs et al., 2012; Vergauwen et al., 2015). Activity avoidance has been related to various clinical characteristics of CFS/ME, including symptom severity, reduced quality of life and disability (Vergauwen et al., 2015; Scerbo et al., 2017; Nijs and Malfliet, 2016). When seeing patients with CFS/ME it is crucial to identify movement behaviour, be it persisting, avoiding or boom and busting. We use a similar approach with patients with PoTS.

Some people with PoTS are aware they avoid certain movements which exacerbate their symptoms, thereby limiting their movement patterns. The movements which are avoided could be identified as a therapeutic challenge to be gradually increased once stability has been reached. Others with PoTS, persist with activity despite experiencing extreme autonomic symptoms. The activities which individuals persevere with, could be modified with equipment or behaviour change to help stabilise activity and physiological challenge and improve function. It is increasingly clear that an individualised approach is likely to achieve the best outcomes for PoTS sufferers.

It is our group's experience that once PoTS physiology improves, people with CFS/ME are then able to exercise, suggesting that it is the orthostatic intolerance keeping PoTS patients less active rather than an unwillingness to exercise in the first place.

7.3. Activity management

In terms of activity management, exercise at low level can improve fatigue over time in some sufferers whilst others describe their symptoms as worsening with increased activity. It is important therefore to tailor advise to individuals with PoTS and to ensure that activity programmes are monitored closely. This is particularly important in the most severely affected patients. Furthermore, recognising the high prevalence of orthostatic intolerance symptoms in PoTS and ensuring that activity management strategies take these into consideration may lead to improved compliance. Furthermore, taking into consideration co-morbidities such as EDS will lead to modifications in the management programme for example resistance training with weights could lead to joint trauma in these patients, exacerbating their pain and thus their PoTS symptoms.

Two weeks of physical inactivity for those that are physically fit leads to a 30% loss of muscle strength. Muscle mass at that time will decrease to that of someone over age 65. It takes about three times the amount of time you were inactive to get your muscle mass back (Vigelsø et al., 2016). Restoring that muscle mass is difficult when you need to exercise against gravity in order to do so, the very thing that exacerbates PoTS symptoms. Restoring muscle mass, particularly in the lower limbs, where venous return is reliant upon muscle activity to 'pump' blood pooled in the extremities back to the central circulation, often

against gravity.

A way to improve weakness could be recumbent strength training. Thereby removing the hydrostatic challenge of the heart pumping upwards towards the brain and allowing the focus to be strengthening. This could be using static weights or resistance bands to improve lower limb muscle strength. Understanding that gravity is the challenge may help modify activity to increase energy levels. The Levine protocol is often used in the US (George et al., 2016). It is however, important to emphasise that research in this area is limited and taking a flexible, individualised approach is the most likely to be successful.

7.4. Managing sleep

Sleep is one of the most problematic areas for those with POTS. As many patients with POTS have a delayed sleep phase syndrome (DSPS), the most important anchoring point is their wake time, rather than their bedtime. The time at which they go to bed can vary (though should be as consistent as possible), however the time at which they wake up should be held constant to help lock in a more regular circadian rhythm. This is a central tenant of cognitive behavioral therapy for insomnia (CBT-I). The potential benefits of CBT-I in those with PoTS requires further study.

Managing sleep in PoTS is critical and there are four points to consider when thinking about how to improve your sleep, as outlined in Table 2.

The best way to achieve a regular bedtime is to work out a wake up time. It is often helpful to work backwards in order to ensure 7–9 h per night is achieved. Secondly, it is important to wind down using whichever method works. Some people like to read a book, others prefer mindfulness or meditation. One thing to note is that electronic devices such as mobile phones, laptops, tablets or TVs are very unhelpful during the wind-down phase. This is due to the fact that they emit blue light, which tricks the brain in to thinking it is daytime. Finally, ensure that the environment in which sleep occurs is appropriate. For example, a very dark room, with a temperature of 15–18 °C is optimal. People who struggle to sleep are also encouraged to get out of bed if they remain awake for longer than thirty minutes. This is because staying awake in bed leads the brain to associate bed with wakefulness, which is unhelpful for sleep.

Many patients with POTS spend too much of their time in bed. In our clinic, we frequently use the important sleep hygiene concept of only using the bed for sleep. If a patient cannot fall asleep within 30 min, they should leave the bed and go to another room, try and do something that is relaxing, and only return to bed when they are sleepy.

Additionally, some patients describe difficulty falling asleep because of their autonomic cardiovascular symptoms (palpitations, light-headedness, chest pains), or symptoms of sympathetic hyperactivity (excessive sweating, feelings of anxiety, etc.), and medications such as beta blockers and central sympatholytics such as clonidine may be helpful if dosed around bedtime.

7.5. Modifying for environmental challenges

The other aspect to allostasis in PoTS is understanding environmental demand. An aspect of that is the weather, in particular heat.

Table 2

Clinical factors to consider when managing sleep in fatigued PoTS patients.

-
- Having a regular bedtime and wake time
 - Avoid daytime naps particularly if they are longer than 30 min
 - Wind down prior to going to bed.
- Having a fixed bedtime routine allows your body to 'switch off' from the day.*
- Ensure that the environment in which you are sleeping is appropriate.
- Generally, this would be a quiet, dark setting with a lack of blue light from electronic devices.*
-

Warm weather causes vasodilation, which reduces the body's efficiency to regulate blood flow to where it is most needed. Compression stockings may help aid this process along with advice regarding elevating feet to aid venous return.

Through identifying the mechanisms which exacerbate symptoms in the context of energy use, people with PoTS can be empowered to modify their behaviours to minimise boom and busts, and reach a stable baseline from which to start to increase activity.

7.6. Rest and recovery

Finally, following periods of activity it is important to encourage rest time to allow recovery.

Particularly following an exacerbation of symptoms. Rest allows modification of the effects of gravity on the body. It allows blood to travel from dependent lower limbs, back into central circulation aiding faster restoration of autonomic balance.

It can often be difficult for clinicians and patients to understand the opposing treatment paradigms in POTS and CFS. In the former, exercise is encouraged; in the latter, exercise is sometimes discouraged. This conflict is often addressed in our clinic by individualising treatment programmes, ensuring the appropriate balance between activity and rest, something that varies from one person to another.

7.7. Pharmacological management of fatigue in PoTS

As in other fatigue associated conditions, there are no pharmacological management strategies for fatigue in PoTS. Currently, all treatments in PoTS are symptomatic rather than curative, something that patients often find difficult to understand. Physiologically it might be expected that achieving heart rate control using medications might lead to symptomatic benefit including improvements in fatigue. Anecdotally, however, even after improved heart rate control, not all PoTS patients report improvement in fatigue, suggesting that other mechanisms might be involved in the pathogenesis of their fatigue. More research is needed to understand the relationship between PoTS symptomatology and physiology.

There are many treatment strategies that are used to address symptoms in those with fatigue (antidepressants, autonomic cardiovascular medications, stimulant medications), and many can produce significant results. However, few have been systematically evaluated, data are limited, and thus most treatments are used off label.

8. In summary

Fatigue is a common symptom described by those with PoTS. Its pathophysiology is poorly understood and there are no evidence based treatments. Taking an individualised approach and modifying management strategies from other conditions has the potential to improve symptoms and develop patterns that will allow PoTS patients to function better.

More research is clearly needed to understand the causes of fatigue in PoTS, define its prevalence and overlap with other frequently recognised comorbid conditions. It is also important that in view of the gravitational challenges faced by those with PoTS that specific therapeutic options are considered and subject to rigorous research.

Acknowledgements

PoTS UK.

References

- Agarwal, A.K., 2007. Postural orthostatic tachycardia syndrome. *Postgrad. Med.* 83, 478–480.
- Antonutto, G., 2003. Cardiovascular deconditioning in microgravity: some possible

- counter measures. *Eur. J. Appl. Physiol.* 90, 283–291.
- Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., Wallace, E.P., 1993. Development of a fatigue scale. *J. Psychosom. Res.* 37, 147–153.
- Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (Encephalopathy); Diagnosis and Management. www.nice.gov.org (NG53).
- Collin, S.M., Bakken, L.J., Nazareth, I., Crawley, E., White, P.D., 2017. Health care resource use by patients before and after a diagnosis of chronic fatigue syndrome (CFS/ME): a Clinical Practice Research Datalink study. *BMC Fam. Pract.* 18.
- Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations; Institute of Medicine, 2015 Feb 10. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Redefining an Illness*. National Academies Press (US), Washington (DC) (ISBN-13: 978-0-309-31689-7 ISBN-10: 0-309-31689-8).
- Cullen, W., Kearney, Y., Bury, G., 2002. Prevalence of fatigue in general practice. *Ir. J. Med. Sci.* 171, 10–12.
- David, A., Pelosi, A., McDonald, E., Stephens, D., Ledger, D., Rathbone, D., Mann, A., 1990. Tired, weak, or in need of rest: fatigue among general practice attenders. *BMJ* 301, 1199–1202.
- Fisk, J.D., Ritvo, P.G., Ross, L., Haase, D.A., Marrie, T.J., Schlech, W.F., 1994. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin. Infect. Dis.* 18, S79–83.
- Freeman, R., Komaroff, A.L., 1997. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am. J. Med.* 102, 357–364.
- George, S.A., Bivens, T.B., Howden, E.J., Saleem, Y., Galbreath, M.M., Hendrickson, D., Fu, Q., Levine, B.D., 2016 Apr. The international POTS registry: evaluating the efficacy of an exercise training intervention in a community setting. *Heart Rhythm.* 13 (4), 943–950. <http://dx.doi.org/10.1016/j.hrthm.2015.12.012>. (Epub 2015 Dec 9).
- Hackett, K.L., Lambson, R.L., Strassheim, V., Gotts, Z., Deary, V., Newton, J.L., 2016. A concept mapping study evaluating the UK's first NHS generic fatigue clinic. *Health Expect.* 19 (5), 1138–1149.
- Hakim, A., De Wandele, I., O'Callaghan, C., Pocinki, A., Rowe, P., 2017. Chronic fatigue in Ehlers-Danlos syndrome—Hypermobile type. *Am. J. Med. Genet. C. Semin. Med. Genet.* 175C, 175–180.
- Hoad, A., Spickett, G., Elliott, J., Newton, J.L., 2008 Sep 19. Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. *QJM* 101 (12), 961–965.
- Kavi, L., Nuttall, N., Low, P.A., Opie, M., Nicholson, L., Caldwell, E., Newton, J.L., 2016. A profile of patients with postural tachycardia syndrome and their experience of healthcare in the UK. *Br. J. Cardiol.* 23 (33). <http://dx.doi.org/10.5837/bjc.2016.010>.
- Krupp, L.B., Alvarez, L.A., et al., 1988. Fatigue in multiple sclerosis. *Arch. Neurol.* 45, 435–437.
- Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The Fatigue Severity Scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch. Neurol.* 46, 1121–1123.
- Lambson, R., Newton, J.L., Strassheim, V., Gotts, Z.M., Deary, V., Hackett, K.L., 2015. The evolution of the Newcastle CRESTA Fatigue Clinic: a unique NHS multidisciplinary approach to fatigue. *J. Rheumatol. Occup. Ther.* 29 (1), 7–11.
- McDonald, C., Koshi, S., Busner, L., Kavi, L., Newton, J.L., 2014. Postural tachycardia syndrome is associated with significant symptoms and functional impairment predominantly affecting young women: a UK perspective. *BMJ Open* 4 (6), e004127.
- Miwa, K., 2016. Variability of postural orthostatic tachycardia in patients with myalgic encephalomyelitis and orthostatic intolerance. *Heart Vessel.* 31, 1522–1528.
- Nacul, L.C., Lacerda, E.M., Pheby, D., Campion, P., Molokhia, M., Fayyaz, S., Leite, J.C.D.C., Poland, F., Howe, A., Drachler, M.L., 2011. Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross sectional study in primary care. *BMC Med.* 9, 91.
- Newton, J.L., Jones, D.E.J., 2007. Population prevalence of autonomic dysfunction and daytime somnolence in Primary Biliary Cirrhosis. *Hepatology* 47, 1496–1505.
- Newton, J.L., Jones, D.E.J., 2010. Making sense of fatigue. *Occup. Med.* 60, 326.
- Newton, J.L., Jones, D.E., Henderson, E., Kane, L., Wilton, K., Burt, A.D., Day, C.P., 2008. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. *Gut* 57, 807–813.
- Newton, J.L., Brown, A., Jones, D.E.J., et al., 2009. Fatigue in early renal disease. *Br. J. Ren. Med.* 14, 10–14.
- Ng, W.F., Bowman, 2010. Primary Sjögren's syndrome: too dry and too tired. *Rheumatology* 49, 844–853.
- Nijs, J., Malfliet, A., 2016. Rehabilitation for patients with myalgic encephalomyelitis/chronic fatigue syndrome: time to extend the boundaries of this field. *J. Intern. Med.* 279, 265–267. <http://dx.doi.org/10.1111/joim.12431>.
- Nijs, J., Meeus, M., Heins, M., Knoop, H., Moorkens, G., Bleijenbergh, G., 2012. Kinesiophobia, catastrophizing and anticipated symptoms before stair climbing in chronic fatigue syndrome: an experimental study. *Disabil. Rehabil.* 34, 1299–1305.
- Pawlikowska, T., Chalder, T., Hirsch, S.R., Wallace, P., Wright, D.J., Wessely, S.C., 1994. Population based study of fatigue and psychological distress. *BMJ* 308, 763–766.
- Reynolds, G.K., Lewis, D.P., Richardson, A.M., Lidbury, B.A., 2013 Nov 29. Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. *J. Intern. Med.* 275 (4), 409–417.
- Ricci, J.A., Chee, E., Lorandeanu, A.L., Berger, J., 2007. Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. *J. Occup. Environ. Med.* 49, 1–10.
- Scerbo, T., Colasurdo, J., Dunn, S., Unger, J., Nijs, J., Cook, C., 2017. Measurement properties of the central sensitization inventory: a systematic review. *Pain Pract.* 29. <http://dx.doi.org/10.1111/papr.12636>.
- Skapinakis, P., Lewis, G., Meltzer, H., 2003. Clarifying the relationship between

- unexplained chronic fatigue and psychiatric morbidity: results from a community survey in Great Britain. *Int. Rev. Psychiatry* 15, 57–64.
- Stewart, J.M., 2004. Chronic orthostatic intolerance and the postural tachycardia syndrome (POTS). *J. Pediatr.* 145, 725–730.
- Theoharides, T.C., Papaliadis, D., Tegen, M., et al., 2005. Chronic fatigue syndrome, mast cells, and tricyclic antidepressants. *J. Clin. Psychopharmacol.* 25 (6), 515–520.
- Vergauwen, K., Huijnen, I.P., Kos, D., Van de Velde, D., van Eupen, I., Meeus, M., 2015. Assessment of activity limitations and participation restrictions with persons with chronic fatigue syndrome: a systematic review. *Disabil. Rehabil.* 37, 1706–1716. <http://dx.doi.org/10.3109/09638288.2014.978507>.
- Vigelso, A., Gram, M., Dybboe, R., Kuhlman, A.B., Prats, C., Greenhaff, P.L., Constantin-Teodosiu, D., Birk, J.B., Wojtaszewski, J.F.P., Dela, F., Helge, J.W., 2016. The effect of age and unilateral leg immobilization for 2 weeks on substrate utilization during moderate-intensity exercise in human skeletal muscle. *J. Physiol.* 594, 2339–2358. <http://dx.doi.org/10.1113/JP271712>. (PMCID: PMC4933116).
- Wallman, D., Weinberg, J., Hohler, A.D., 2014. Ehlers-Danlos Syndrome and Postural Tachycardia Syndrome: a relationship study. *J. Neurol. Sci.* 15:340 (1–2), 99–102. <http://dx.doi.org/10.1016/j.jns.2014.03.002>.
- Yoshii, F., Takahashi, H., Kumazama, R., Kobori, A., 2006. Parkinsons and fatigue. *J. Neurol.* 253 (supp 7), V1148–53.