

Chronic Fatigue in Ehlers–Danlos Syndrome—Hypermobile Type

ALAN HAKIM,* INGE DE WANDELE, CHRIS O'CALLAGHAN, ALAN POCINKI, AND PETER ROWE

Chronic fatigue is an important contributor to impaired health-related quality of life in Ehlers–Danlos syndrome. There is overlap in the symptoms and findings of EDS and chronic fatigue syndrome. A proportion of those with CFS likely have EDS that has not been identified. The evaluation of chronic fatigue in EDS needs to include a careful clinical examination and laboratory testing to exclude common causes of fatigue including anemia, hypothyroidism, and chronic infection, as well as dysfunction of major physiological or organ systems. Other problems that commonly contribute to fatigue in EDS include sleep disorders, chronic pain, deconditioning, cardiovascular autonomic dysfunction, bowel and bladder dysfunction, psychological issues, and nutritional deficiencies. While there is no specific pharmacological treatment for fatigue, many medications are effective for specific symptoms (such as headache, menstrual dysfunction, or myalgia) and for co-morbid conditions that result in fatigue, including orthostatic intolerance and insomnia. Comprehensive treatment of fatigue needs to also evaluate for biomechanical problems that are common in EDS, and usually involves skilled physical therapy and attention to methods to prevent deconditioning. In addition to managing specific symptoms, treatment of fatigue in EDS also needs to focus on maintaining function and providing social, physical, and nutritional support, as well as providing on-going medical evaluation of new problems and review of new evidence about proposed treatments. © 2017 Wiley Periodicals, Inc.

KEY WORDS: hypermobility; fatigue; Ehlers Danlos

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INTRODUCTION

Fatigue can be temporally categorized as recent, prolonged, or chronic that is less than 1, 1–6, and more than 6 months, respectively. Its persistence and impact on daily activities and quality of life are recognized in the descriptors of the condition Chronic Fatigue Syndrome (CFS), also known as myalgic encephalomyelitis (ME).

Fatigue may be a principal presenting symptom in Ehlers–Danlos syndrome—hypermobile type (hEDS). However a clinician may diagnose CFS without appreciating the presence or pre-existence of features that may have led to a diagnosis of hEDS. The risk then is attention may be taken away from specific triggering factors for fatigue and adaptations to management specific to hEDS such as physical therapies.

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appreciating the presence or pre-existence of features that may have led to a diagnosis of hEDS.

The purpose of this review is to explore what is known of the association between fatigue and hEDS; provide guidance on the assessment and management of fatigue in the context of hEDS; and consider areas for further research in this field.

METHODS

The committee on Chronic Fatigue of the International Ehlers–Danlos Syndrome Consortium met by teleconference or through electronic correspondence throughout 2015 and 2016 to discuss the associations of chronic fatigue with hEDS and its assessment and management. The following reflects the Committee’s literature review and professional experience as well as insights from various contributing members of the international effort on EDS through the Consortium.

LITERATURE REVIEW

Fatigue is common and often disabling in hEDS [Rowe et al., 1999; Hakim and Grahame, 2004; Voermans et al., 2010; Castori et al., 2011; Voermans and Knoop, 2011; Murray et al., 2013; Schepers et al., 2016]. It has been associated in hEDS with muscle weakness [Voermans et al., 2011; Celletti et al., 2012], and kinesiophobia [Celletti et al., 2013]. However, there are no large randomized trials of the management of fatigue in EDS. The few publications that offer management advice are based on either small cohort studies or expert opinion.

There is no specific definition for chronic fatigue in hEDS. The authors recommend the following definitions of fatigue, similar in concept and substance to that published by the Institute of Medicine [2015]. Chronic fatigue is defined by:

- Persistent and/or recurrent fatigue, that has been present for more than 6 months,

- unexplained by other conditions,
- not the result of ongoing exertion,
- not substantially alleviated by rest,
- resulting in a substantial reduction or impairment in the ability to engage in normal levels of activities.

CAUSAL ASSOCIATIONS

A full history (including exacerbating and alleviating factors, sleep disturbance and stressors, and perceived impact on wellbeing) should be taken, and include assessment of psychological wellbeing both as a cause and an impact. Because fatigue is such a common symptom in systemic illnesses not related to hEDS, and can be associated with disease in any organ system, it is fundamentally important that a thorough history and physical examination is undertaken.

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The following causes for fatigue are common findings in hEDS.

- Poor sleep quality—in hEDS initiation, maintenance and restoration of sleep may be disturbed by factors such as pain, nocturnal tachycardia, or sleep disordered breathing.¹
- Chronic pain—typically both neuropathic in nature and from acute and chronic mechanical joint and soft tissue injury.

¹While daytime napping may be beneficial as part of rest and relaxation, it may in some cases lead to either a shift or reversal of the day–night sleep cycle, with resultant difficulty sleeping at night and daytime somnolence, and therefore be more detrimental than beneficial.

- Physical deconditioning (as opposed to physical “weakness”)—that arises from poor physical activity.
- Orthostatic intolerance [De Wandele et al., 2016], and cardiovascular dysregulation (e.g., tachycardia, hypotension, syncope).
- Bowel dysfunction (e.g., malabsorption and subsequent nutritional deficiencies).
- Nocturnal micturition due to bladder dysfunction or polyuria which is usually secondary to increased fluid consumption but may also be a consequence of increased urine production during recumbent posture, eliminating fluid “pooled” in the lower body during the day.
- Anxiety and/or depression.
- Headaches/migraines.

It is important to recognize that chronic fatigue may be the result of a co-existing condition. “Red flag” alerts of a serious different condition include:

- Weight loss,
- significant lymphadenopathy,
- clubbing,
- persistent shortness of breath on exertion (exertional dyspnoea is often a consequence of cardiovascular dysfunction),
- fevers,
- red, swollen joints,
- bronzing of the skin,
- abnormalities on the neurological examination,
- later age of onset.

The following should then be excluded or investigated further if thought to be present:

- Chronic infection (e.g., hepatitis, tuberculosis, brucellosis, endocarditis, Lyme disease),
- endocrine disorders (e.g., diabetes, thyroid disease, adrenal insufficiency),
- autoimmune inflammatory conditions (e.g., joints, skin, bowel, liver, and renal disorders),
- cardiorespiratory disease,
- sleep disordered breathing,
- neurological disorders (e.g., myasthenia gravis, multiple sclerosis).

CONTROVERSIES

It is the authors’ opinion that the criteria used for diagnosing CFS and hEDS are

inadequate and contribute to diagnostic confusion. To meet a diagnosis of CFS, fatigue must be “unexplained by other conditions.” Therefore, a diagnosis of hEDS must exclude a diagnosis of CFS. However, hEDS is likely to be substantially under-diagnosed and it is likely that some patients diagnosed with CFS may meet or would previously have met the criteria for diagnosis of hEDS. Also it is the authors’ opinion that the literature and diagnostic methods for CFS and hEDS are of insufficient strength to reliably differentiate between these conditions in a given individual. We would conclude that in the context of hEDS one would simply use the term chronic fatigue.

Treatment of fatigue in hEDS is based on guidance from the general literature on management of chronic fatigue, and expert opinion. There is no evidence for use of specific pharmacological therapies in hEDS, though these are, within licencing regulation, recommended.

MANAGEMENT AND CARE GUIDELINES

Assessment of Severity and Impact of Fatigue

There is no single tool for the assessment of patients with fatigue that allows a global appraisal of its severity and impact. Also fatigue may be an expression of an underlying disorder, and it is the severity and impact of that disorder per se that is the issue.

More formal questionnaires that address fatigue include the Multidimensional Fatigue Inventory—Short Form (MFI-SF), a 30-item self-report instrument designed to measure fatigue. The full MFI is 83 questions [Smets et al., 1995]. It explores general, physical, and mental fatigue, reduced motivation and reduced activity. Subsections of it can be used to look at specific areas such as mental fatigue.

Simple tools such as the Wood Mental Fatigue Inventory can be used in the clinic to explore the cognitive symptoms of fatigue [Bentall et al., 1993].

Scales for functional assessment, such as the Medical Outcomes Study

Short-Form General Health Survey (SF-36[®]) and Sickness Impact Profile (SIP) may be helpful.

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Whitehead [2009] analyzed of the scales most often used in research. The review identified three short instruments demonstrate good psychometric properties (namely the Fatigue Severity Scale [FSS], Fatigue Impact Scale [FIS], and Brief Fatigue Inventory [BFI]), as did three comprehensive instruments (namely the Fatigue Symptom Inventory [FSI], Multidimensional Assessment of Fatigue [MAF], and Multidimensional Fatigue Symptom Inventory [MFSI]). Of these four measures (BFI, FSS, FSI, and MAF) demonstrated the ability to detect change over time and might therefore be more suitable in the assessment of chronic long-term conditions.

Perhaps the most useful information clinically is that gained from patient self-record of their daily activities, general function, and the degree of disability perceived, for example how far a patient can walk without having to stop to rest, or how many flights of stairs. By logging a list of these activities and functions, the patient

has a baseline from which to set goals, and the opportunity to judge improvement in wellbeing by achieving these goals. This process can be repeated to challenge and record further improvements over time.

Personal electronic devices are now available to measure activity and these can be useful in monitoring physical exertion particularly during therapeutic programs.

Advice and Treatment

General principles

To facilitate effective management the clinician needs to establish a collaborative relationship with the patient and their carers. Engagement with the family is particularly important for children and young people, and for people with severe fatigue.

The patient and their clinician should share decision making both in identifying the causes of, recognising the impact of, and the phases in the management of fatigue. Together this might include:

- Understanding the need to exclude underlying diseases and disorders.
- Recognizing the reality and impact (physical, emotional, social [including education and employment]) of the condition and the symptoms.
- Setting realistic goals and timelines for improvement, being prepared to manage set-backs/relapses.
- Exploring the range of interventions and management strategies available, taking account of the patients’ age (particularly for children), the severity of their symptoms, their preferences and experiences, and the outcome of previous treatment.
- Negotiating other areas of healthcare provision, supporting applications for financial benefits and social care, as well as concerns related to education or employment.

People with severe fatigue may need support from a multidisciplinary team for example, nursing, occupational therapy, dietetics, psychology, physiotherapy, and pain management. This should be coordinated by a named

healthcare professional, and usually their general practitioner/general physician.

Treatment is based on addressing the underlying issues. These might include medications directed at orthostatic intolerance, antidepressants, anti-anxiety drugs, management of allergies, use of sleep aids, and pain management [Castori et al., 2012], as well as a lifestyle changes including pacing, changing sleep pattern, exercise, and even a change of job or hours of work.

There is no known pharmacological treatment or cure for fatigue per se. Large systematic reviews have not identified consistently effective medications for CFS symptoms in general, but many medications are effective for specific symptoms (e.g., headaches) and co-morbid conditions that result in fatigue [Smith et al., 2014]. Unless there is an underlying medical disorder, the following medications should be avoided as they may cause harm if used inappropriately:

- Glucocorticoids (in the absence of other indications),
- thyroxine (in the absence of hypothyroidism),
- antiviral agents² (in the absence of confirmed active viral infection).

There is insufficient evidence to recommend the use of complementary therapies and supplements for fatigue. However, some patients choose to use these therapies and find them helpful, and there is little evidence of harm. Typical agents include co-enzyme Q10, Carnitine, alpha-lipoic acid, magnesium, nicotinamide adenine dinucleotide (NADH), and multivitamins and minerals. Co-enzyme Q and Riboflavin have been shown to be effective in migraine prophylaxis.

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²The authors recognize that clinicians try these, however, there is very little evidence of efficacy in the literature.

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In some cases, patients with bowel dysfunction may need supplements because of a restricted diet. A dietician's expertise may be required in this situation if the attending clinician is not confident to advise.

Clinicians and patients should remain aware that some patients do not show meaningful responses to therapy. Patients with intractable, chronic and disabling conditions are prone to feelings of abandonment and may be vulnerable to potentially toxic therapies or exploitative practitioners. For such patients, the long-term supportive and protective role of the physician can be invaluable.

Maintaining independence

For people with moderate or severe fatigue that has not responded to treatment, equipment and adaptations (e.g., a wheelchair) should be considered as part of the management plan, after assessing the risks and benefits for the individual patient. Such adaptations may be valued ways of gaining more independence and improving quality of life.

Disruption of education or employment is generally detrimental to health and wellbeing. The ability to continue in these should be addressed early. The clinician should assist, following consent from their patient, by proactively and as needs be regularly advising colleagues on their patients' fitness for work and education, and the adjustments or adaptations required for them to remain in or return to studies or work.

Treatment modalities

Sleep management, rest, and relaxation and key approaches. Advice on sleep management includes:

- Explaining the effect disordered sleep or a poor sleep pattern can have on causing

and exacerbating fatigue can help an individual understand how their behaviors might affect the normal day–night sleep cycle.

- Identifying poor sleep patterns such as insomnia, hypersomnia, an altered sleep–wake cycle, and non-refreshing sleep despite either an apparent normal cycle or prolonged sleep.
- Providing general advice on what good sleep hygiene means (see below).
- Introducing changes to sleep patterns gradually.

Good sleep hygiene includes:

- Avoiding stimulants such as caffeine or nicotine too close to bedtime.
- Exercise during the day to promote good sleep.
- Avoiding large meals too close to bedtime.
- Relaxation techniques—establishing a regular relaxing bedtime routine, avoiding emotional upset/dwelling on problems before trying to go to sleep. Calm music or reading may be relaxing for some.
- Associate bed with sleep. Avoid watching TV, playing computer games, sending text messages, e-mails, etc. Calm music or reading may be relaxing for some.
- The sleep environment should be pleasant and relaxing. The bed should be comfortable, and the room dark, quiet, and neither too hot or too cold.

During the day, exercise may also encourage wakefulness, as should adequate exposure to natural light. Especially early in the day, light exposure helps to maintain a healthy sleep–wake cycle.

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Chronic pain may be a dominant influence on sleep; it should be managed accordingly. Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, should be considered.

Other medications may assist sleep. These include:

- Melatonin,
- doxepin,
- cyproheptadine,
- diphenhydramine,
- trazodone,
- propranolol,
- clonazepam,
- zolpidem,
- a variety of others including benzodiazepines, beta blockers, muscle relaxants, and eszopiclone.

As part of pacing, rest periods may be required. Rest periods can be introduced into daily routine, but the frequency, length, and types of activities undertaken should be adapted for each individual. It is important to maintain as normal a level of activity as possible, whilst avoiding over-exertion. There is always a balance here and advice requires individual assessment. Rest advice might include:

- Limiting the length of rest period to, say, 30 min.
- Undertaking low-level physical (arts, crafts, etc.) and cognitive (reading, puzzles, etc.) activities depending on the severity of symptoms.
- Using relaxation techniques.
- Trying to avoid complete rest as the only management during a setback/relapse.

Prolonged bed rest should be avoided if possible. It is associated with significant physical deconditioning, psychological risks, and medical disorders including severe postural hypotension, venous thrombosis, osteoporosis, and pressure sores.

Relaxation techniques may help in the management of pain, sleep problems, and comorbid stress or anxiety. It is important that patients rest when tired, and not use caffeine or stimulating medications to “push through” periods of severe fatigue. Common relaxation techniques include:

- Progressive muscle relaxation. In this technique the individual focuses on

slowly tensing and then relaxing each muscle group.

- Visualization. For example the individual may imagine a peaceful setting and then focus on controlled, relaxing breathing, slowing the heart rate.
- Other techniques include:
 - Massage,
 - meditation,
 - yoga,
 - music and/or art therapy.

Graded exercise therapy (GET) and management of daily activities are also fundamental therapeutic approaches. Before advising on exercise the clinician should consider the impact of joint hypermobility and joint instability in EDS, as well as the negative influence on exercise that arises from uncontrolled pain, fear of movement (kinesiophobia), and other associated conditions such as cardiovascular autonomic dysfunction.

Gradual exercise programmes may be beneficial for some patients, improving physical, psychological, and cognitive aspects of wellbeing. The main objectives in EDS of an exercise programme are the progressive prevention of physical deterioration, optimization of functional capacity without triggering injury, and pain control.

A suitably trained therapist or instructor should deliver GET. Recommendations such as “go to the gym,” “exercise more,” or “go swimming” are not helpful without supported advice on what this actually means, and should be avoided. It is recommended that exercise should be supervised, structured, and gradually increased in intensity (both in muscle strengthening and aerobic fitness as appropriate). Unstructured and unsupervised exercise may worsen symptoms, as can a rigid or inflexible escalation of activity.

GET should be based on the individuals’ current level of activity and individual goals. When planning GET, it is important clinicians and/or therapists:

- Undertake an assessment of current activity analysis—while also ensuring

that this does not of itself already lead to a “boom and bust” cycle.

- Discuss both short and long-term goals important and relevant to the individual.
- Agree on a level of additional low-intensity exercise that is sustainable
- Recognize that it can take weeks, months, or even years to achieve goals, and ensure that this is taken into account in the therapy structure and the ways services deliver treatment.
- Advise that increased levels of exercise may increase symptoms for a few days (e.g., stiffness and fatigue), but explain that this is normal.

Before completing a GET programme, it is important the individual has been advised on maintaining the exercise and strategies for managing set backs, including access to their clinician and/or therapist. Treatment of existing movement restrictions and biomechanical dysfunction using manual techniques can be a bridge to tolerating exercise for some individuals.

Activity management is a form of pacing, controlling activities by means that include:

- Planning daily activities to allow for a balance and variety of different types of activity, rest, and sleep.
- Spreading out difficult or demanding tasks over the day or week.
- Splitting activities into small achievable tasks.
- Monitoring, regulating, and planning activities to avoid a “boom and bust” cycle.
- Goal setting, planning, and prioritising activities.

Cognitive Behavioral Therapy (CBT) has both formal and informal approaches.³ At an informal level, this involves education about symptoms, demystification of the medical problems, and explanation of how inactivity can aggravate a number of the problems that contribute to fatigue (e.g., deconditioning, orthostatic intolerance).

³The authors caution that the effect size of CBT is modest, that improvements are not always sustained, and that CBT has not been studied in those with more severe symptoms and impairment.

An individualized, person-centred programme should be offered to people with fatigue. The objectives of the programme should be to:

- Sustain or gradually extend, the person's physical, emotional, and cognitive capacity.
- Manage the physical and emotional impact of their symptoms.

The components, and progression throughout the programme should be based on the person's age, preferences and needs, and should be delivered only by a healthcare professional with appropriate training in CBT.

WHAT WE NEED TO KNOW

The incidence, prevalence, and natural history of fatigue in the hEDS population is unknown, so therefore also the distribution and types of (co-associated) mechanisms that trigger this phenomenon.

Also, it is unclear as to how many patients diagnosed with CFS actually really have EDS, not CFS.

Subgroup clinical trials of efficacy and safety of treatments are required to move beyond the limitations of case study and expert opinion evidence. Future studies are also needed to assess the effect of treatment on quality of life and fatigue.

The influence of anxiety disorders/mental health factors on presentation and response to treatment are also not clear.

SUMMARY

Fatigue is a common finding in EDS. It may present in a manner that is indistinguishable from CFS. Diagnosis of fatigue remains an area of uncertainty: the definition of fatigue remains uncertain and diagnostic tests are not available. The initial approach to fatigue in EDS is to exclude other conditions that may produce fatigue.

Conditions which are commonly seen in EDS and which may manifest as or exacerbate fatigue include sleep

disorder, chronic pain, deconditioning, cardiovascular dysregulation, bowel and bladder dysfunction, psychological issues and nutritional deficiencies.

Treatment algorithms for fatigue are poorly defined and therapy is frequently ineffective and so aims of treatment should be realistic. Treatment should focus on improving symptoms, maintaining function and providing social, physical and nutritional support.

Where medical and physical interventions fail to provide substantial symptomatic or functional improvement, it is essential that clinicians provide on-going support to patients who are at risk of feelings of abandonment.

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REFERENCES

- Bentall RP, Wood GC, Marrinam T, Dears C, Edwards RHT. 1993. A brief mental fatigue questionnaire. *Br J Clin Psychol* 32:375–379.
- Castori M, Celletti C, Camerota F, Grammatico P. 2011. Chronic fatigue syndrome is commonly diagnosed in patients with Ehlers-Danlos syndrome hypermobility type/joint hypermobility syndrome. *Clin Exp Rheumatol* 29:597–598.
- Castori M, Morlino S, Celletti C, Celli M, Morrone A, Colombi M, Camerota F, Grammatico P. 2012. Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers-Danlos syndrome, hypermobility type): Principles and proposal for a multidisciplinary approach. *Am J Med Genet A* 158A:2055–2070.
- Celletti C, Galli M, Cimolin V, Castori M, Albertini G, Camerota F. 2012. Relationship between fatigue and gait abnormality in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Res Dev Disabil* 33:1914–1918.
- Celletti C, Castori M, La Torre G, Camerota F. 2013. Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Biomed Res Int* 2013:580460.
- De Wandele I, Rombaut L, De Backer T, Peersman W, Da Silva H, De Mits S, De

- Paeppe A, Calders P, Malfait F. 2016. Orthostatic intolerance and fatigue in the hypermobility type of Ehlers-Danlos syndrome. *Rheumatology (Oxford)* 55:1412–1420.
- Hakim AJ, Grahame R. 2004. Non-musculoskeletal symptoms in Joint Hypermobility syndrome: Indirect evidence for autonomic dysfunction. *Rheumatology* 43:1194–1195.
- Institute of Medicine, Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations. 2015. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an illness*. Institute of Medicine. Washington, D.C.: The National Academies Press, February 10.
- Murray B, Yashar BM, Uhlmann WR, Clauw DJ, Petty EM. 2013. Ehlers-Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. *Am J Med Genet A* 161A:2981–2988.
- Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. 1999. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers Danlos syndrome. *J Pediatr* 135:494–499.
- Scheper MC, Juul-Kinstensen B, Rombaut L, Ramekers EA, Verburt J, Engelbert RH. 2016. Disability in adolescents and adults diagnosed with hypermobility-related disorders: A meta-analysis. *Arch Phys Med Rehabil* 97:2174–2187.
- Smith MEB, Nelson HD, Haney E, Pappas M, Daeges M, Wasson N, McDonagh M, Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. 2014. Evidence Report/Technology Assessment No. 219. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 15-E001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December.
- Smets EMA, Garssen B, Bonke B, De Haes JCJM. 1995. The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 39:315–325.
- Voermans NC, Knoop H, van de Kamp N, Hamel BC, Bleijenberg G, van Engelen BG. 2010. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. *Semin Arthritis Rheum* 40:267–274.
- Voermans NC, Knoop H. 2011. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. *Disabil Rehabil* 33:706–707.
- Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. 2011. Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: An explorative study. *Physiotherapy* 97:170–174.
- Whitehead L. 2009. The measurement of fatigue in chronic illness: A systematic review of unidimensional and multidimensional fatigue measures. *J Pain Symptom Manage* 37:107–128.