

Conceptual Model for Physical Therapist Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

Todd E. Davenport, Staci R. Stevens, Mark J. VanNess, Christopher R. Snell, Tamara Little

T.E. Davenport, PT, DPT, OCS, is Assistant Professor, Department of Physical Therapy, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, 3601 Pacific Ave, Stockton, CA 95211 (USA). Address all correspondence to Dr Davenport at: tdavenport@pacific.edu.

S.R. Stevens, MA, is Executive Director, Pacific Fatigue Laboratory, Department of Sport Sciences, University of the Pacific.

M.J. VanNess, PhD, is Associate Professor, Department of Sport Sciences, University of the Pacific.

C.R. Snell, PhD, is Professor and Chair, Department of Sport Sciences, University of the Pacific.

T. Little, PT, EdD, DMT, FAAOMPT, is Associate Professor, Department of Physical Therapy, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific.

[Davenport TE, Stevens SR, VanNess MJ, et al. Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. *Phys Ther*. 2010; 90:602–614.]

© 2010 American Physical Therapy Association

Fatigue is one of the most common reasons why people consult health care providers. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is one cause of clinically debilitating fatigue. The underdiagnosis of CFS/ME, along with the spectrum of symptoms that represent multiple reasons for entry into physical therapy settings, places physical therapists in a unique position to identify this health condition and direct its appropriate management. The diagnosis and clinical correlates of CFS/ME are becoming better understood, although the optimal clinical management of this condition remains controversial. The 4 aims of this perspective article are: (1) to summarize the diagnosis of CFS/ME with the goal of promoting the optimal recognition of this condition by physical therapists; (2) to discuss aerobic system and cognitive deficits that may lead to the clinical presentation of CFS/ME; (3) to review the evidence for graded exercise with the goal of addressing limitations in body structures and functions, activity, and participation in people with CFS/ME; and (4) to present a conceptual model for the clinical management of CFS/ME by physical therapists.



Post a Rapid Response or
find The Bottom Line:
www.ptjournal.org

Fatigue is a symptom common to many illnesses, such as cancer, depression, autoimmune diseases, hormonal disorders, and infections, and it is associated with poorer health outcomes and a high degree of recidivism in the general population.^{1,2} Most health conditions that cause fatigue, such as fatigue secondary to deconditioning, cancer, and neuromuscular disorders, have etiologies that are attributable to specific pathologies that may respond favorably to various forms of intervention, such as physical therapist management. However, some people may demonstrate fatigue related to causes that remain unclear.

Recent studies have begun to improve the collective understanding of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) as one cause of clinically debilitating fatigue. Chronic fatigue syndrome/myalgic encephalomyelitis affects 1 to 4 million adults in the United States,³ with women accounting for up to 75% of cases.⁴ Prevalence in the United States ranges from 230 to 420 per 100,000 adults,⁵ with the mean age at onset ranging from 29 to 35 years.⁴ Up to 85% of CFS/ME cases may be undiagnosed,³ and the actual prevalence of CFS/ME may be 6 to 10 times higher than presently understood,⁶ suggesting that a vast majority of CFS/ME cases are untreated and unaccounted for by epidemiological studies.⁷ The large number of cases that may remain undiagnosed places a premium on the recognition and management of CFS/ME and CFS/ME-like conditions by physical therapists.

The purpose of this analysis was 4-fold. First, we summarize the diagnosis of CFS/ME with the goal of promoting the optimal recognition of this condition by physical therapists. Second, we discuss aerobic system and cognitive deficits that may lead to the clinical presentation of CFS/

ME. Third, we review the evidence for graded exercise with the goal of addressing limitations in body structures and functions, activity, and participation in people with CFS/ME. We conclude by presenting a conceptual model, based on current scientific evidence, for the clinical management of CFS/ME by physical therapists.

Characteristic Clinical Findings of CFS/ME That Guide Diagnosis

Chronic fatigue syndrome/myalgic encephalomyelitis is not a new health condition. The neurologists Beard⁸ and Goetz⁹ were among the first to characterize a health condition that they called *neurasthenia* in the latter half of the 19th century; neurasthenia was described as a combination of fatigue, anxiety, headache, impotence, and neuralgia. In the early 20th century, Gilliam¹⁰ documented an outbreak in Los Angeles, California, of a health condition that resembled poliomyelitis and that he called *atypical poliomyelitis*. Various outbreaks of health conditions resembling CFS/ME were recorded in the United States and elsewhere throughout the 20th century.¹¹ Each of these outbreaks was described by its own region-specific and sometimes pejorative terminology. The term *epidemic myalgic encephalomyelitis* was coined as a result of a Royal Society of Medicine symposium in 1978.¹² This development was notable because it represented the medical community's first acknowledgement that CFS/ME was a distinct disease process rather than a behavioral disorder. Chronic fatigue syndrome/myalgic encephalomyelitis reached the popular consciousness in the United States after an outbreak in the Reno-Lake Tahoe, Nevada, region in the 1980s. Research involving this outbreak resulted in the name *chronic fatigue syndrome*.¹³ This term is considered

to be most representative of the clinical features of the health condition by many clinicians and researchers,¹⁴ although the term *myalgic encephalomyelitis* continues to find common usage in the clinical community secondary to popular support from people with CFS/ME.¹⁵ Therefore, both terms were adopted for the purposes of this analysis.

Various attempts to characterize CFS/ME were made in the late 20th and early 21st centuries.¹³ The most current and common case definition was created when the Centers for Disease Control and Prevention convened an international working group in 1994. To meet the case definition criteria for CFS/ME, an individual must report persistent or relapsing, debilitating fatigue for which a preexisting illness or psychiatric comorbidity cannot be found as an explanation. According to the 1994 case definition of Fukuda and colleagues,¹⁶ to meet the criteria for CFS/ME, an individual must have persistent or relapsing fatigue for greater than 6 months (Fig. 1). The fatigue of CFS/ME may be characterized by either gradual or sudden onsets, and it may be progressive or relapsing and remitting during the course of the condition.

In addition to the specific criteria for fatigue, CFS/ME is characterized by a broad spectrum of nonspecific physical examination findings. Therefore, to meet the case definition criteria for the diagnosis of CFS/ME, an individual concurrently must exhibit



Available With
This Article at
ptjournal.apta.org

• Audio Abstracts Podcast

This article was published ahead of print on February 25, 2010, at ptjournal.apta.org.

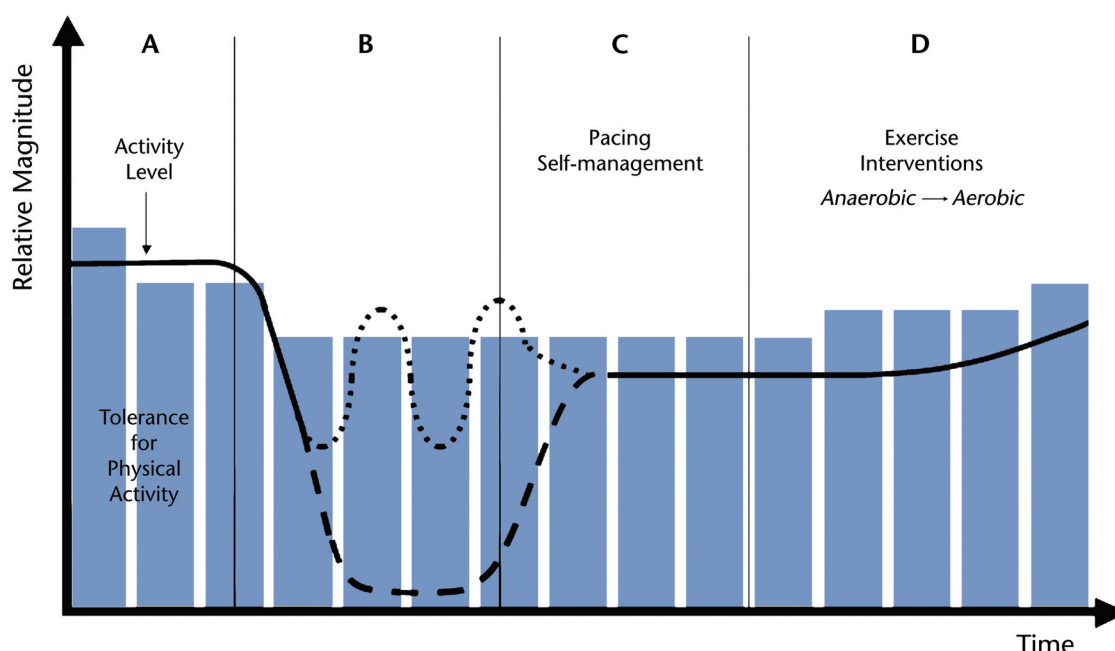


Figure 1.

Conceptual model for clinical management of people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). (A) The first presentation of symptoms in people with CFS/ME hypothetically occurs when the intensity of physical activity (solid line) exceeds the tolerance for physical activity (bars). (B) In response to symptoms, people with CFS/ME adapt their behaviors by either activity and symptom avoidance (dashed line) or activity and symptom fluctuation (dotted line). (C) The initiation of a pacing self-management program is hypothesized to stabilize activity levels within the tolerance for physical activity, such as that indicated by heart rate biofeedback below the anaerobic threshold. (D) After symptoms and function are stabilized, progression of anaerobic exercise to graded aerobic exercise may be used to increase tolerance for physical activity.

at least 4 additional symptoms, such as postexertion malaise (PEM) for at least 24 hours after exercise, impaired memory or concentration, nonrefreshing sleep, muscle pain, pain in multiple joints without signs of inflammation, headaches of a new type or severity, sore throat, and tender cervical or axillary lymph nodes. Secondary symptoms of joint pain and headaches may facilitate entry into physical therapy settings for people with CFS/ME. Perhaps the most prominent feature of CFS/ME is PEM, which is usually defined as a general feeling of discomfort or unease after even minimal physical activity.¹⁶ Indeed, among the various health conditions that are associated with fatigue, increased PEM that can alter daily activities for up to 2 weeks¹⁷ appears to be unique to CFS/ME.^{18,19}

Other diagnostic systems that have been described in the literature are the Oxford criteria²⁰ and the Canadian Consensus Document.²¹ The Canadian Consensus Document case definition for CFS/ME²¹ (Tab. 1) may be useful because it displays significantly greater power than the criteria established by Fukuda and colleagues¹⁶ to differentiate people with CFS/ME from people with fatigue related to psychiatric health conditions.²² Across all definitions, it is important to emphasize that the fatigue of CFS/ME must be unexplained by another somatic or psychiatric health condition, making CFS/ME a diagnosis of exclusion. Given the prominence of pain and fatigue in the symptomatology of CFS/ME,^{16,23} physical therapists may be among the first health care providers to recognize this health condition and direct appropriate management.

Aerobic System and Cognitive Changes Contributing to the Clinical Presentation of CFS/ME

A growing body of research confirms the presence of oxidative impairments in CFS/ME. Our research group²⁴ and others²⁵ have identified clinical evidence of oxidative metabolic impairments during graded exercise tests. VanNess and colleagues²⁴ identified a range of oxidative impairments during graded exercise testing in participants meeting the case definition criteria of Fukuda and colleagues¹⁶ for CFS/ME. Although the maximum oxygen consumption ($\dot{V}O_2\text{max}$) for participants in that study²⁴ ranged from 36% to 76% of the $\dot{V}O_2\text{max}$ predicted for matched sedentary participants, in only half of the participants were

Table 1.

Case Definition Criteria for Identification of Chronic Fatigue Syndrome/Myalgic Encephalopathy

Case Definition of Fukuda et al ¹⁶		Oxford Criteria, ²⁰ Requiring the Presence of Severe Disabling Fatigue as the Main Symptom and Further Defined as Follows:	Case Definition of Canadian Consensus Document ²¹	
Requires the Presence of Profound Fatigue, Defined as Follows:	Also Requires 4 or More of the Following Features:		Requires the Presence of the Following Features:	Also Requires at Least 1 Symptom From 2 of the Following Categories:
<ul style="list-style-type: none"> • Symptom duration of ≥ 6 mo • Causes a substantial reduction in occupational, personal, social, or educational activities • Unrelieved with rest • Other medical or psychiatric conditions excluded 	<ul style="list-style-type: none"> • Postexertion malaise lasting >24 h • Impaired memory or concentration • Nonrefreshing sleep • Muscle pain • Pain in multiple joints without signs of inflammation • Headaches of new type or severity • Sore throat • Tender cervical or axillary lymph nodes 	<ul style="list-style-type: none"> • Symptom duration of ≥ 6 mo • Affects both physical and mental functions • Symptoms are present $\geq 50\%$ of the time • Definite onset and not lifelong • Other medical or psychiatric conditions excluded 	<ul style="list-style-type: none"> • Symptom duration of ≥ 6 mo for adults and ≥ 3 mo for children • New onset of unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity levels • Postexertion malaise • Other medical or psychiatric conditions excluded 	<ul style="list-style-type: none"> • Autonomic manifestations (eg, orthostatic intolerance, light-headedness, extreme pallor, nausea, irritable bowel syndrome, urinary frequency, bladder dysfunction, palpitations with or without cardiac arrhythmias, exertional dyspnea) • Neuroendocrine manifestations (eg, loss of thermostatic stability, intolerance of extremes of heat and cold, marked weight change, loss of adaptability, worsening of symptoms with stress) • Immune manifestations (eg, tender lymph nodes; recurrent sore throat; recurrent flulike symptoms; general malaise; new sensitivities to food, medications, or chemicals)

American Medical Association guidelines for moderate to severe aerobic impairments met. This finding suggests that a spectrum of aerobic energy system impairments may be responsible for the reduced tolerance of physical activity observed in people with CFS/ME despite their common medical diagnosis.

Evidence suggests that disruption of the aerobic energy system may be associated with a combination of genetic, cellular, and systemic metabolic deficits.^{26–28} Investigators also have found evidence at the cellular level of mitochondrial dysfunction and impaired energy metabolism,²⁹ oxidative damage to mitochondrial deoxyribonucleic acid,³⁰ and poor recovery of adenosine triphosphate after exercise,³¹ which may be responsible for the observed deficits in repeated graded exercise test performances. These cellular and systemic impairments in the aerobic energy

system lead to a reduced functional capacity that limits an individual's ability to sustain and repeat functional activities. Aerobic system impairments appear to be related to maladaptive sympathetic autonomic responses,³² perhaps in response to a triggering event, such as an injury or illness, in people with an apparent genetic predisposition.³³ Over time, these maladaptive responses are suspected of causing dysregulation of the normal hypothalamus-pituitary axis³⁴ and sympathetic autonomic responses³² and an overall reduction in tolerance for physical effort.³⁵ Autonomic dysregulation is thought to be responsible for the orthostatic intolerance³⁶ and abnormal heart rate (HR) responses to exercise³⁷ exhibited by some people with CFS/ME.

In addition to aerobic system impairments, people with CFS/ME exhibit centrally mediated disturbances in attention, perception, and affect.³⁵

On average, people with CFS/ME rate their effort during physical tasks significantly higher than do people who are healthy³⁸; this factor may lead to an overall decrease in maximal exertion. Paradoxically, however, anecdotal observations from various sources^{35,39} indicate that behavioral responses to symptom exacerbations in people with CFS/ME range from the maintenance of a sedentary lifestyle to abrupt increases in activity during periods of symptom remission that serve to exacerbate symptoms (Fig. 1). Patient-reported mental fatigue¹⁹ and maladaptive overactivity⁴⁰ are cognitive and psychological correlates of morbidity in people with CFS/ME. Some authors have suggested that comorbid kinesiophobia⁴¹ or depressive symptoms⁴² also may be responsible for these disablements in CFS/ME; however, these findings are inconsistent,⁴¹ and functional deficits remain even after these variables are controlled for.⁴³

Arguably, the cognitive effects of CFS/ME may serve as the greatest barrier to optimal research, diagnosis, and effective management of this health condition. Early attempts to characterize CFS/ME involved the assumption that it was primarily a psychiatric disorder.⁹ Our experience suggests that some clinicians still seem to view CFS/ME through this lens; this belief could be a source of stigma for people with CFS/ME.

Clinical Outcomes Associated With Graded Exercise in People With CFS/ME

Graded aerobic exercise as an intervention for people with CFS/ME has been the focus of several studies, even though, as a general rule, deconditioning may not play a role in disabilities secondary to CFS/ME.⁴⁴ To assess the clinical effects of exercise in people with CFS/ME, we conducted a literature search with the search terms “exercise” AND “chronic fatigue syndrome” OR “myalgic encephalomyelitis” in the Cochrane Database of Systematic Reviews and the EMBASE, ERIC, MEDLINE, PEDro, Ovid Healthstar, Ovid Global Health, and PSYCHINFO databases. The initial search yielded 694 distinct citations. The abstracts of these citations were scanned for references to treatment responses in people with chronic fatigue, yielding 94 citations. These citations were then analyzed for observational, comparison, or randomized studies that reported on the effects of an exercise intervention in adults with CFS/ME according to existing diagnostic criteria, yielding 9 citations for consideration in this analysis. These studies are summarized in Table 2.

Body structure and function deficits (eg, fatigue, muscle strength [force-generating capacity], cognitive processing, maximal and submaximal exercise test variables) and personal

factors (eg, mood) in people with CFS/ME appeared to improve consistently with graded aerobic exercise (Tab. 2). Fulcher and White⁴⁵ found a significantly lower mean HR during treadmill testing in participants in a graded exercise group than in participants in a flexibility exercise group, as well as significantly lower ratings of perceived exertion (RPEs) in participants who received graded exercise than in participants who received flexibility exercise. Physiologic improvements were maintained at the 3-month follow-up in the graded exercise group. Moss-Morris et al⁴⁶ reported significant improvements in physical, mental, and total fatigue in the exercise group compared with the control group. Pardaens and colleagues⁴⁷ identified significant improvements in duration, peak power (ability to perform work over time), and peak respiratory exchange ratio, as well as a significant improvement in isokinetic hamstring muscle strength, in response to a graded exercise intervention combined with cognitive behavioral therapy. Wearden and colleagues⁴⁸ found significantly greater functional work capacity in people who received graded exercise than in people in comparison groups, but fatigue ratings did not differ among the groups. Wallman et al⁴² noted significant improvements in resting HR, resting blood pressure, power, peak oxygen consumption, respiratory exchange ratio, and net blood lactate production in participants who received graded exercise compared with participants who received flexibility and relaxation exercises. Significant improvements also were documented in depression, anxiety, physical fatigue, and mental fatigue in participants who received graded exercise compared with participants who received flexibility and relaxation exercises. Modified Stroop word color identification test performance was significantly better in participants who received graded exercise. Despite the consistent im-

provements in body structure and function deficits in response to graded exercise across studies, Pardaens and colleagues⁴⁷ reported that these improvements were weakly correlated with or were not significantly correlated with functional improvements.

Although there seemed to be a qualitative trend toward improvement, observations of qualitative and quantitative improvements at the levels of activity and participation were more mixed (Tab. 2). Fulcher and White⁴⁵ and Pardaens et al⁴⁷ found that scores on subscales of the Medical Outcomes Study 36-Item Health Survey Questionnaire (SF-36) were significantly higher in participants who received graded exercise than in participants who received a comparison intervention. Powell and colleagues⁴⁹ identified significantly higher SF-36 physical functioning subscale scores in the intervention groups than in the control group. At the 2-year follow-up⁵⁰, all groups maintained significant improvements, and no significant differences persisted among the groups. Moss-Morris et al⁴⁶ documented no significant differences in SF-36 physical functioning subscale scores among the groups, and Wallman et al⁴² did not identify significant changes in activity. It is notable that many studies conducted to examine the effectiveness of graded exercise had high drop-out rates, suggesting the presence of a subpopulation for whom graded exercise interventions may be ineffective at the levels of body structure and function, activity, and participation. Additional research seems to be necessary to clarify the effects of different exercise volumes on activity and participation in people with CFS/ME.

A major challenge of research and clinical practice related to exercise prescription for people with CFS/ME is the phenomenon that increased self-reported activity levels during intervention may be a direct result of the exercise program at the expense

Table 2.

Studies of Comparative Effectiveness Involving Graded Aerobic Exercise in People With Chronic Fatigue Syndrome/Myalgic Encephalomyelitis^a

Study	Intervention Program	Participants	Outcome Measures	Main Study Findings
Pardaens et al ^{47,b}	Evaluated the effect of a 6-mo program of cognitive behavioral intervention (consisting of group discussions, relaxation and breathing exercises, and psychiatric and medical consultations, as needed) combined with graded exercise on exercise capacity measures. Intervention was provided in 4-h treatment sessions twice per week for the first month and once per week for the next 5 mo.	116 participants meeting the criteria proposed by Fukuda et al ¹⁶ 48% of the sample had an additional diagnosis of fibromyalgia	<ul style="list-style-type: none"> SF-36 Symptom Checklist-90 Causal Attribution List Self-Efficacy Scale Graded exercise testing on stationary bicycle with analysis of expired gases Isokinetic dynamometry of the right and left quadriceps and hamstring muscles 	<ul style="list-style-type: none"> Significant improvements in all SF-36 subscale scores except emotional limitations Significant improvement in Causal Attribution List nonphysical subscale score Significant improvements in duration, peak power, and peak respiratory exchange ratio with graded exercise testing Significant improvement in isokinetic hamstring muscle strength Vo₂max was not correlated with or was weakly correlated with changes in quality-of-life measures
Fulcher and White ⁴⁵	Tested the effect of a 12-wk graded aerobic exercise program with a home exercise component provided in weekly sessions on global impression of change in status. The home exercises were to be completed at least 5 d/wk, with initial sessions of 5–15 min at an intensity of 40% of Vo ₂ max. The daily prescription was increased in consultation with the subject to maxima of 30 min/d and 60% of Vo ₂ max. Control intervention consisted of relaxation and flexibility exercises.	66 participants meeting the Oxford criteria ²⁰ (49 women)	<ul style="list-style-type: none"> Individual global impression of change Graded treadmill walking test with analysis of expired gases Perceived exertion on exercise testing Isometric quadriceps muscle testing SF-36 Visual analog scale for physical, mental, and total fatigue 	<ul style="list-style-type: none"> Significantly more participants in the exercise group (51%) than in the control group (27%) rated themselves as “much better” or “very much better” Significantly lower mean heart rate during treadmill testing in the graded exercise group than in the flexibility exercise group Significantly lower ratings of perceived exertion in the graded exercise group than in the flexibility exercise group SF-36 total, physical functioning, and general health subscale scores were significantly higher in the graded exercise group than in the flexibility exercise group Physiological improvements were maintained at 3-mo follow-up in the graded exercise group Qualitatively, larger proportions of participants in the graded exercise group than in the flexibility exercise group rated themselves at 1-y follow-up as improved, were working or studying at least part time, and considered themselves regularly active
Moss-Morris et al ⁴⁶	Investigated the effectiveness and mechanisms of change attributed to graded exercise. Intervention group participated in 12 wk of graded walking, starting at 40%–50% of Vo ₂ max, 4–5 times/wk. Specific intensity was set at a level unlikely to exacerbate symptoms, as determined in collaboration with the subject. Exercise duration was increased 3–5 min/wk, with final goals of 30 min and 70% of Vo ₂ max. Control group received standardized medical care and advice.	61 participants meeting the criteria proposed by Fukuda et al ¹⁶	<ul style="list-style-type: none"> Individual global impression of change SF-36 14-item fatigue questionnaire Graded treadmill exercise testing Perceived exertion on exercise testing Illness Perceptions Questionnaire-Revised Illness Management Questionnaire 	<ul style="list-style-type: none"> Significantly more participants in the graded exercise group (48%) than in the control group (21%) rated themselves as “much better” or “very much better” at the end of 12 wk and at the 6-mo follow-up Significant improvements in physical, mental, and total fatigue in the exercise group compared with the control group No significant differences between groups in SF-36 physical functioning subscale scores

(Continued)

Table 2.
Continued

Study	Intervention Program	Participants	Outcome Measures	Main Study Findings
Powell et al ⁴⁹	Documented the effect of a psycho-educational intervention to encourage graded exercise at 1-y follow-up. Intervention groups received medical assessments and then evidence-based explanations of symptoms to encourage graded activity. Interventions included minimum intervention (2 in-person sessions), telephone intervention (minimum intervention + seven 30-min telephone contacts), and maximum intervention (minimum intervention + seven 1-h in-person contacts). Control group received standardized medical care, consisting of medical assessment, advice, and an information booklet that explained symptoms to encourage graded activity.	148 participants meeting the Oxford criteria ²⁰	<ul style="list-style-type: none"> SF-36 Hospital Anxiety and Depression (HAD) Scale 4-item sleep problem questionnaire Individual global impression of change 	<ul style="list-style-type: none"> Significantly more participants in the intervention groups (84%) than in the control group (12%) rated themselves as "much better" or "very much better" Significantly higher SF-36 physical functioning subscale scores in the intervention groups than in the control group Significantly lower fatigue scores in the intervention groups than in the control group
Powell et al ⁵⁰	Measured the effect of a psycho-educational intervention to encourage graded exercise at 2-y follow-up. Intervention groups received medical assessments and then evidence-based explanations of symptoms to encourage graded activity. Interventions included minimum intervention (2 in-person sessions), telephone intervention (minimum intervention + seven 30-min telephone contacts), and maximum intervention (minimum intervention + seven 1-h in-person contacts). Control group received standardized medical care, consisting of medical assessment, advice, and an information booklet that explained symptoms to encourage graded activity.	114 participants meeting the Oxford criteria and participating in the original trial of Powell et al ⁴⁹	<ul style="list-style-type: none"> SF-36 HAD Scale 4-item sleep problem questionnaire Individual global impression of change 	<ul style="list-style-type: none"> All groups maintained significant improvements compared with baseline measurements, and no significant differences in physical functioning and fatigue scores persisted among the groups Significant improvements in physical functioning and fatigue scores over time in control group participants who were allowed to cross over into treatment groups after the conclusion of the first study period
Wallman et al ⁴²	Tested the effectiveness of a 12-wk program of graded exercise with pacing on physiological, psychological, and cognitive function. Intervention group participated in 5–15 min of exercise for large muscles; intensity was based on the mean heart rate during exercise testing. Participants were instructed to exercise every other day, unless they had a symptom relapse. In that case, subsequent exercise sessions were reduced to a length assessed by the participants to be manageable. Control group received relaxation and flexibility exercises.	61 participants meeting the criteria proposed by Fukuda et al ¹⁶	<ul style="list-style-type: none"> Submaximal bicycle exercise testing with analysis of expired gases and periodic blood sampling Perceived exertion on exercise testing Older Adult Exercise Status Inventory 14-item fatigue rating scale HAD Scale Modified Stroop word color identification test 	<ul style="list-style-type: none"> Significant improvements in resting heart rate, resting blood pressure, power, $\dot{V}O_2$max, respiratory exchange ratio, and net blood lactate production in participants who received graded exercise compared with participants who received flexibility and relaxation exercises Significant improvements in depression, anxiety, physical fatigue, and mental fatigue in participants who received graded exercise compared with participants who received flexibility and relaxation exercises

(Continued)

Table 2.
Continued

Study	Intervention Program	Participants	Outcome Measures	Main Study Findings
Wallman et al (continued)				<ul style="list-style-type: none"> • Activity levels among groups were not significantly different • Significant improvements in modified Stroop word color identification test performance in participants who received graded exercise compared with participants who received flexibility and relaxation exercises
Wearden et al ⁴⁸	Assessed the effect of a 26-wk regimen of fluoxetine and graded exercise on fatigue, general health status, physical work capacity, and mood. Participants were randomized among 4 groups: fluoxetine + graded exercise, fluoxetine placebo + graded exercise, fluoxetine + graded exercise placebo, and fluoxetine placebo + graded exercise placebo. The fluoxetine dose was 20 mg. Participants who received fluoxetine placebo received an inert substance. Participants who received graded exercise were encouraged to exercise 3 times/wk for 20 min at an intensity at or exceeding 75% of $\dot{V}O_2$ max. Participants who received graded exercise placebo were instructed to exercise when they felt capable but did not receive specific instructions.	n=136 meeting Oxford criteria ²⁰	<ul style="list-style-type: none"> • Graded exercise testing with analysis of expired gases • 14-item fatigue rating scale • Medical Outcomes Survey • HAD Scale 	<ul style="list-style-type: none"> • Significant improvement in mood in participants who received fluoxetine at 12 wk • Functional work capacity was significantly increased at week 12 and week 26 in the exercise groups • Neither intervention was significantly associated with reduced fatigue ratings, although a qualitative trend toward improvement in the exercise groups was noted • Dropouts were significantly more frequent in the exercise groups than in the nonexercise groups

^a All studies were controlled studies, unless otherwise noted. One observational study⁶¹ was excluded because the description of the exercise intervention was incomplete. Two controlled studies^{51,52} were excluded because the criteria for inclusion were unclear. SF-36=Medical Outcomes Study 36-Item Health Survey Questionnaire, $\dot{V}O_2$ max=maximum oxygen consumption.

^b Observational study.

of actual increases in daily activities. For example, Black and colleagues⁵¹ studied the effectiveness of advice to increase physical activity on daily physical activity, fatigue, mood, and pain in participants who were diagnosed with CFS/ME by a physician and in matched sedentary control participants. Participants were requested to increase their physical activity during the first 2 weeks of the program in an incremental manner. Intervention included a 6-week walking program

consisting of an increase in daily walking time to a total of 30% more than pretreatment levels. The authors documented a significant increase in physical activity in participants with CFS/ME by use of an accelerometer, leading to their conclusion that the intervention was a feasible and effective way to facilitate increased physical activity in this population. However, self-reported mood became significantly worse in participants with CFS/ME than in control participants over time.

Ratings of fatigue and pain, which were already significantly different between groups throughout the study, increased over time in participants with CFS/ME. A secondary analysis of the data revealed that participants with CFS/ME could actually maintain the increase in physical activity for the first 4 to 10 days of the study, exercising for a mean of 23 minutes.⁵² In contrast, during the final 3 weeks of the study, physical activity time fell to approximately 8 minutes per day. The

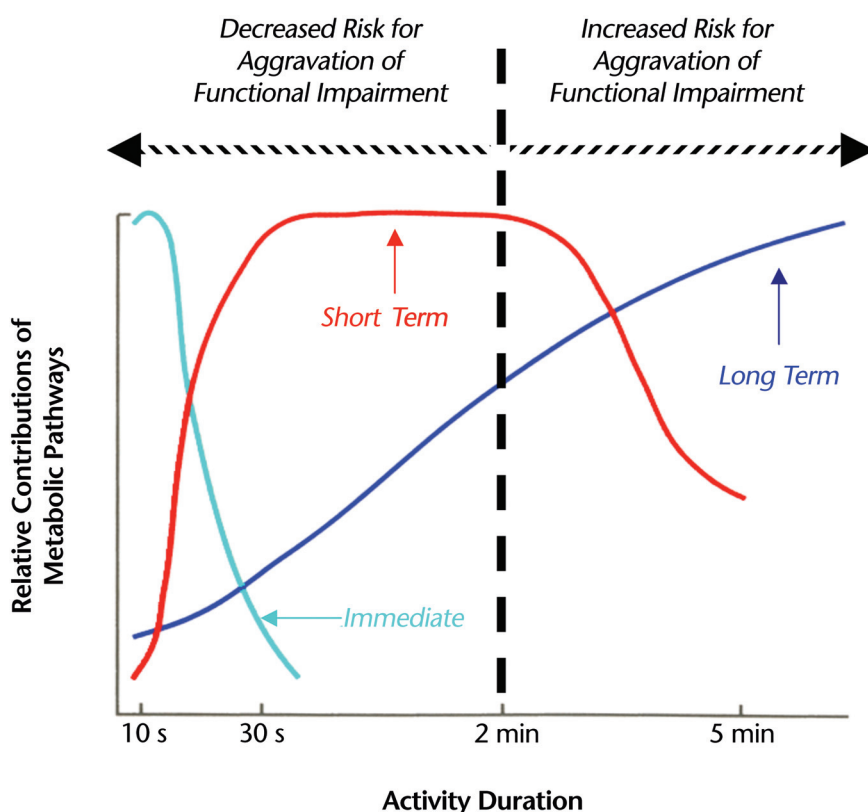


Figure 2.

Hypothetical relationship among duration of functional activity, metabolic energy pathways, and functional impairments in people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). The creatine phosphate-adenosine triphosphate immediate (teal line) and anaerobic short-term (red line) energy systems predominate during the first 2 minutes of activity (dashed black line). Activities longer than 2 minutes in duration are characterized by a rapid decrease in the contributions of these short-term energy systems and an exponential increase in the contribution of the aerobic long-term energy system (blue line). It has been hypothesized that activities longer than 2 minutes in duration aggravate symptoms and functional deficits in people with CFS/ME because they have aerobic system impairments.

decrease in physical activity appeared to be coincident with the timing of the worsening mood and increased symptoms. It is possible that a similar trend has been observed in studies documenting significant increases in functioning in association with graded exercise in people with CFS/ME, but the use of quantitative measurements to document daily physical activity and secondary analyses of existing studies are uncommon.

Model for Clinical Management of CFS/ME

The goal for the clinical management of CFS/ME should include an individ-

ual's return to an optimal level of function. Disablement attributable to CFS/ME results from maladaptive physiologic responses that lead to overloaded body systems (Fig. 1). This assertion is consistent with the predictions of physical stress theory,⁵³ which suggests that changes in relative stress in tissues result in predictable tissue adaptations ranging from decreased stress tolerance to increased stress tolerance. Therefore, consistent with physical stress theory⁵³ and other models for the clinical management of CFS/ME,^{35,39} optimal functioning for people with CFS/ME first de-

pends on the achievement of a level of tissue stress that corresponds to symptom and functional maintenance. This objective will require the implementation of strategies that focus on pacing self-management to promote energy conservation and rest. After maintenance is achieved, physical stress must be provided in a manner that results in improved stress tolerance. As mentioned before, earlier models encouraged the use of graded exercise to achieve increased tissue stress tolerance.^{35,39} However, our experience has been that an approach beginning with therapeutic activities and exercises that avoid excessive use of the impaired aerobic system also is promising because it may mitigate the subsequent functional impairments associated with PEM. This approach involves short-duration exercises that are completed at intensities below an estimated anaerobic threshold (AT). After anaerobic activities are initiated without symptom exacerbation, progression to graded aerobic exercise can be undertaken. Finally, the chronic and episodic nature of this health condition⁴ requires physical therapists to ensure that people with CFS/ME demonstrate adequate development of the cognitive and physical skills necessary to facilitate long-term symptom self-management and optimal functioning.

Pacing Self-Management: Criteria and Strategies

Strategies to promote energy conservation appear to be important in people with CFS/ME. To date, recommendations for pacing self-management in people with CFS/ME have been made on the basis of symptom acuity and irritability.^{35,39} Although these criteria seem to be intuitive, they may fail to account for the rapid changes in function that are characteristic of CFS/ME. An impaired perception of effort in people with CFS/ME may interfere with the optimal maintenance of symptom-free activity levels if pacing

self-management criteria that are based solely on symptomatology are used. Also, the ability to predict when activities might cause a flare-up of symptoms and functional deficits would be most helpful. The metabolic impairments observed in people with CFS/ME suggest the need to limit the intensity of activity to avoid excessive use of the aerobic energy system (Fig. 2). Therefore, we suggest that AT may be a critical objective limit for ensuring that physical activity is maintained at an appropriate level to facilitate optimal pacing self-management.

The use of criteria based on HR biofeedback for pacing self-management may be helpful in people with CFS/ME.⁵⁴ We assert that HR biofeedback should be used to ensure that activities are conducted at intensities below the AT. The gold standard for establishing the HR at the AT is a graded exercise test with periodic blood sampling. However, even in clinical settings in which graded exercise and blood sampling procedures are prohibitive in terms of cost, time, or expertise, the need to index activity pacing recommendations to quantitative data remains. Therefore, the HR at the AT may be estimated indirectly from $\dot{V}O_{2\max}$ measurements obtained during submaximal exercise testing; alternatively, the HR corresponding to RPEs of 13 to 15 during submaximal exercise testing may be used. Clinicians should bear in mind that although submaximal exercise testing demonstrates good discriminative validity for people with CFS/ME versus people without CFS/ME,⁵⁵ such testing also demonstrates high within-subject variability.⁵⁶ Frequent reassessment will be necessary to maintain confidence in the AT estimates obtained from submaximal testing. In untrained people, the AT has been approximated at 55% $\dot{V}O_{2\max}$.⁵⁷ Thus, we suggest that clinicians may approximate the HR at the AT by calculating

55% of the HR at the $\dot{V}O_{2\max}$ as a starting point, although specific establishment of the HR at the AT in this population requires additional research.

We suggest that people's RPEs during submaximal exercise testing also may be used to approximate the threshold for pacing self-management, in which ratings below 13 to 15 represent activity at an intensity below the AT.⁵⁷ Although exercise testing is an important clinical tool for guiding the clinical management of CFS/ME, we emphasize that it should be conducted with extra care secondary to the risk for orthostatic impairments and the high likelihood of symptom exacerbation. Extra care includes adequate individual education regarding expected outcomes, with the goal of achieving appropriate consent for testing, as well as close symptom and physiologic monitoring to determine the need for test cessation or modification.

In line with earlier models for the clinical management of CFS/ME,^{35,39} the importance of energy conservation in reducing symptom exacerbation and promoting optimal functioning in people with CFS/ME indicates that pacing self-management strategies should be provided in the context of a comprehensive psychoeducational program. The 5 A's construct, originally proposed by the Canadian Task Force on Preventive Health Care,⁵⁸ has been applied to individual education as part of clinical management programs for other chronic health conditions.⁵⁹ The components of the 5 A's construct⁵⁸—assess, advise, agree, assist, and arrange—also may be applied to people with CFS/ME. This construct contains a learning needs assessment, which includes determining the presence of behaviors that may exacerbate symptoms as well as the individual's preferred behavior change goals, methods, and constraints. An

individual's level of knowledge related to CFS/ME and overall health literacy also should be ascertained. Advice for people with CFS/ME includes specific and personalized behavior change counseling based on the learning needs assessment and centered on maintaining physical exertion below the HR at the AT. People should be encouraged to wear an HR monitor for this purpose. Given the variability inherent in the use of many tests for establishing the HR at the AT, we suggest that a 10% margin below the estimated HR should be used as the critical threshold for pacing self-management to account for variability and ensure that an individual's exertion remains below the AT. Therefore, the monitor's alarm should be set to sound if the HR exceeds 10% below the HR at the AT. Frequent breaks including diaphragmatic breathing, alternate positions, and adaptive equipment should be prescribed to assist people in maintaining the target level of physical exertion. Further identification of activities that exacerbate symptoms and, as a result, necessitate attention may be aided by the use of activity logs, in which an individual with CFS/ME records the time of day, type and duration of activity, and symptoms for systematic analysis by the individual and the physical therapist. People with CFS/ME and their attending physical therapists should agree on the goals and methods of psychoeducational interventions for behaviors. The behavior change plan should be a collaborative effort between the individual and the attending physical therapist. People with CFS/ME may require assistance in implementing the behavior change plan; physical therapists may provide such assistance during both clinic visits and distance consultations. Finally, arrangement of follow-up contacts allows for additional assistance and alteration of the behavior change plan and reinforces the importance of behavior change to the individual.

Physical therapists are in a unique position to follow up with clinical brief counseling strategies because of their relatively frequent contact with people (compared with that of other health care providers).

Exercise Interventions

Exercise interventions for people with CFS/ME must be carefully customized to reflect the unique needs of each individual. The existing literature mentions 2 critical issues in prescribing physical activity for people with CFS/ME. First, clear communication between the individual and the physical therapist about the effects of the exercise program is critical to avoid the perception that physical activity has been increased because of increased physical capacity instead of the self-fulfilling prophecy associated with starting an exercise program. Second, aerobic system impairments associated with CFS/ME result in functional impairments that may not be amenable to training in people with CFS/ME compared with people who are sedentary.

We assert that exercise interventions for people with CFS/ME require a combination of compensation and rehabilitation approaches to physical training in which training begins with activities that provide stress to the unimpaired anaerobic energy system before the impaired aerobic energy system is stressed. Therefore, we advocate a training approach in which initial therapeutic activities are short duration, low intensity, and directed toward specific contributing impairments in body structures and functions. Because oxidative phosphorylation serves as the primary metabolic pathway in activities lasting longer than 2 minutes (Fig. 2), aerobic system impairments in people with CFS/ME would seem to limit activities longer than 2 minutes because of the risk of developing symptoms and functional deficits associated with PEM. Therefore, we recommend thera-

peutic activities that last less than 2 minutes and are conducted at an intensity consistent with an HR that is 10% below the HR at the AT or RPEs below 13 to 15. Previous studies demonstrated that reducing exercise time and intensity is effective in reducing symptoms of PEM in people with CFS/ME.⁶⁰ These recommendations regarding duration and intensity are flexible; clinicians should be guided by the individual's immediate and latent responses to therapeutic activities to determine appropriate exercise volume.

We recommend that activities initially consist of stretching and active-range-of-motion (AROM) exercises to improve region-specific strength and flexibility, because deficits in strength and flexibility may be the source of increased energy expenditure through suboptimal movement mechanics. The specific exercises incorporated into the flexibility and AROM program depend on the clinician's thorough examination and evaluation of potentially contributing pathomechanics. After participating in a stretching and AROM program that does not reproduce symptoms of PEM, people may advance to strength training in which the focus is on short-duration, low-intensity strengthening with maintenance of adequate rest intervals. Clinicians should use caution during the creation and progression of the resistance training program because the safety and effectiveness of these interventions in people with CFS/ME require additional research. Finally, people with CFS/ME may advance to short-duration, low-intensity interval training. As starting criteria, the duration of the intervals should not exceed 2 minutes, and the intensity should not exceed an HR that is 10% below the HR at the AT. Progression of interval training should involve increasing the number and intensity of intervals while maintaining a training range that prevents excessive use of the impaired aerobic sys-

tem in people with CFS/ME. Interval training should involve functional retraining whenever possible, according to the physical therapist's evaluation of the individual's disablement. When short-duration interval training can be completed successfully, clinicians should consider initiating short-duration aerobic interval training, which can be advanced in an incremental manner according to people's symptoms, as described elsewhere.³⁹

Despite the importance of exercise to address physical conditioning in some people with CFS/ME, the health-related quality of life of people with CFS/ME is only weakly correlated with exercise capacity measurements. This fact underlines the importance of multimodal treatment, including individual education and pacing self-management, to address the activity and participation limitations in people with CFS/ME.

Summary

The prevalence of CFS/ME emphasizes the importance of the recognition and management of CFS/ME and CFS/ME-like conditions by physical therapists. The prominent features of CFS/ME include aerobic system impairment and centrally mediated disturbances in attention, perception, and affect. Pacing self-management criteria based on HR biofeedback may be helpful in ensuring that activities are conducted at an intensity below the AT in people with CFS/ME. The mode and intensity of exercise-based interventions for people with CFS/ME must be carefully customized to reflect the unique needs of each individual. Future studies should continue to clarify the roles of pacing self-management and exercise in the context of a comprehensive clinical management program for people with CFS/ME.

All authors provided concept/idea/project design. Dr Davenport, Dr Snell, and Dr Little provided writing. Dr VanNess and Dr Snell provided data collection and analysis, fund

procurement, and facilities/equipment. Dr Davenport and Dr Snell provided project management and institutional liaisons. Dr Davenport provided clerical support. Dr Davenport, Ms Stevens, Dr Snell, and Dr Little provided consultation (including review of manuscript before submission).

This article was received February 16, 2009, and was accepted November 15, 2009.

DOI: 10.2522/ptj.20090047

References

- van der Windt DA, Dunn KM, Spies-Dorgelo MN, et al. Impact of physical symptoms on perceived health in the community. *J Psychosom Res.* 2008;64:265-274.
- Nijrolder I, van der Horst H, van der Windt D. Prognosis of fatigue: a systematic review. *J Psychosom Res.* 2008;64:335-349.
- Centers for Disease Control and Prevention. Chronic fatigue syndrome. Available at: <http://www.cdc.gov/cfs/>. Accessed December 12, 2008.
- Cairns R, Hotopf M. A systematic review describing the prognosis of chronic fatigue syndrome. *Occup Med (Lond).* 2005;55:20-31.
- Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med.* 1999;159:2129-2137.
- Reeves WC, Jones JF, Maloney E, et al. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. *Popul Health Metr.* 2007;5:5.
- Prins JB, van der Meer JW, Bleijenberg G. Chronic fatigue syndrome. *Lancet.* 2006;367:346-355.
- Beard G. Neurasthenia, or nervous exhaustion. *The Boston Medical and Surgical Journal.* 1869;3:217-221.
- Goetz CG. Poor Beard!! Charcot's internationalization of neurasthenia, the "American disease." *Neurology.* 2001;57:510-514.
- Gilliam AG. *Epidemiological Study on an Epidemic, Diagnosed as Poliomyelitis, Occurring Among the Personnel of Los Angeles County General Hospital During the Summer of 1934.* Washington, DC: US Government Printing Office; 1934.
- Ramsay AM. *Postviral Fatigue Syndrome: The Saga of Royal Free Disease.* New York, NY: Gower Medical Publishing; 1986.
- Epidemic myalgic encephalomyelitis. *Br Med J.* 1978;1:1436-1437.
- Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108:387-389.
- Evengard B, Schacterle RS, Komaroff AL. Chronic fatigue syndrome: new insights and old ignorance. *J Intern Med.* 1999;246:455-469.
- Jason LA, Eisele H, Taylor RR. Assessing attitudes toward new names for chronic fatigue syndrome. *Eval Health Prof.* 2001;24:424-435.
- Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121:953-959.
- Sisto SA, Tapp WN, LaManca JJ, et al. Physical activity before and after exercise in women with chronic fatigue syndrome. *QJM.* 1998;91:465-473.
- Cook DB, Nagelkirk PR, Peckerman A, et al. Exercise and cognitive performance in chronic fatigue syndrome. *Med Sci Sports Exerc.* 2005;37:1460-1467.
- Sorensen B, Streib JE, Strand M, et al. Complement activation in a model of chronic fatigue syndrome. *J Allergy Clin Immunol.* 2003;112:397-403.
- Sharpe MC, Archard LC, Banatvala JE, et al. A report—chronic fatigue syndrome: guidelines for research. *J R Soc Med.* 1991;84:118-121.
- Carruthers BM, Jain AK, DeMeirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols (a consensus document). *Journal of Chronic Fatigue Syndrome.* 2003;11:7-115.
- Jason LA, Torres-Harding SR, Jurgens A, Helgeson J. Comparing the Fukuda et al. criteria and the Canadian case definition for chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome.* 2004;12:37-52.
- Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in individuals with the chronic fatigue syndrome: a systematic review. *Eur J Pain.* 2007;11:377-386.
- VanNess JM, Snell CR, Strayer DR, et al. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc.* 2003;35:908-913.
- De Becker P, Roeykens J, Reynders M, et al. Exercise capacity in chronic fatigue syndrome. *Arch Intern Med.* 2000;160:3270-3277.
- Bains W. Treating chronic fatigue states as a disease of the regulation of energy metabolism. *Med Hypotheses.* 2008;71:481-488.
- Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. *Mol Med.* 2009;15:34-42.
- Whistler T, Jones JF, Unger ER, Vernon SD. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. *BMC Physiol.* 2005;5:5.
- Whistler T, Taylor R, Craddock RC, et al. Gene expression correlates of unexplained fatigue. *Pharmacogenomics.* 2006;7:395-405.
- Fulle S, Mecocci P, Fano G, et al. Specific oxidative alterations in vastus lateralis muscle of individuals with the diagnosis of chronic fatigue syndrome. *Free Radic Biol Med.* 2000;29:1252-1259.
- Wong R, Lopaschuk G, Zhu G, et al. Skeletal muscle metabolism in the chronic fatigue syndrome: in vivo assessment by ³¹P nuclear magnetic resonance spectroscopy. *Chest.* 1992;102:1716-1722.
- Cordero DL, Sisto SA, Tapp WN, et al. Decreased vagal power during treadmill walking in individuals with chronic fatigue syndrome. *Clin Auton Res.* 1996;6:329-333.
- Fang H, Xie Q, Boneva R, et al. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. *Pharmacogenomics.* 2006;7:429-440.
- Van Den Eede F, Moorkens G, Van Houdenhove B, et al. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. *Neuropsychobiology.* 2007;55:112-120.
- Van Houdenhove B, Verheyen L, Pardaens K, et al. Rehabilitation of decreased motor performance in individuals with chronic fatigue syndrome: should we treat low effort capacity or reduced effort tolerance? *Clin Rehabil.* 2007;21:1121-1142.
- Naschitz JE, Rosner I, Rozenbaum M, et al. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. *QJM.* 2003;96:133-142.
- Broderick G, Craddock RC, Whistler T, et al. Identifying illness parameters in fatiguing syndromes using classical projection methods. *Pharmacogenomics.* 2006;7:407-419.
- Wallman KE, Sacco P. Sense of effort during a fatiguing exercise protocol in chronic fatigue syndrome. *Res Sports Med.* 2007;15:47-59.
- Nijs J, Paul L, Wallman K. Chronic fatigue syndrome: an approach combining self-management with graded exercise to avoid exacerbations. *J Rehabil Med.* 2008;40:241-247.
- Van Houdenhove B, Bruyninckx K, Luyten P. In search of a new balance: can high "action-proneness" in individuals with chronic fatigue syndrome be changed by a multidisciplinary group treatment? *J Psychosom Res.* 2006;60:623-625.
- Nijs J, De Meirleir K, Duquet W. Kinesophobia in chronic fatigue syndrome: assessment and associations with disability. *Arch Phys Med Rehabil.* 2004;85:1586-1592.
- Wallman KE, Morton AR, Goodman C, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust.* 2004;180:444-448.
- Blackwood SK, MacHale SM, Power MJ, et al. Effects of exercise on cognitive and motor function in chronic fatigue syndrome and depression. *J Neurol Neurosurg Psychiatry.* 1998;65:541-546.
- Bazelmans E, Bleijenberg G, Van Der Meer JW, Folgering H. Is physical deconditioning a perpetuating factor in chronic fatigue syndrome? A controlled study on maximal exercise performance and relations with fatigue, impairment and physical activity. *Psychol Med.* 2001;31:107-114.
- Fulcher KY, White PD. Randomised controlled trial of graded exercise in individuals with the chronic fatigue syndrome. *BMJ.* 1997;314:1647-1652.

- 46 Moss-Morris R, Sharon C, Tobin R, Baldi JC. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. *J Health Psychol.* 2005;10:245-259.
- 47 Pardaens K, Haagdorens L, Van Wambeke P, et al. How relevant are exercise capacity measures for evaluating treatment effects in chronic fatigue syndrome? Results from a prospective, multidisciplinary outcome study. *Clin Rehabil.* 2006;20:56-66.
- 48 Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry.* 1998;172:485-490.
- 49 Powell P, Bentall RP, Nye FJ, Edwards RH. Randomised controlled trial of individual education to encourage graded exercise in chronic fatigue syndrome. *BMJ.* 2001;322:387-390.
- 50 Powell P, Bentall RP, Nye FJ, Edwards RH. Individual education to encourage graded exercise in chronic fatigue syndrome: 2-year follow-up of randomised controlled trial. *Br J Psychiatry.* 2004;184:142-146.
- 51 Black CD, O'Connor PJ, McCully KK. Increased daily physical activity and fatigue symptoms in chronic fatigue syndrome. *Dyn Med.* 2005;4:3.
- 52 Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. *Dyn Med.* 2005;4:10.
- 53 Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "physical stress theory" to guide physical therapist practice, education, and research. *Phys Ther.* 2002;82:383-403.
- 54 Nijs J, Almond F, De Becker P, et al. Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial. *Clin Rehabil.* 2008;22:426-435.
- 55 Wallman KE, Morton AR, Goodman C, Grove R. Physiological responses during a submaximal cycle test in chronic fatigue syndrome. *Med Sci Sports Exerc.* 2004;36:1682-1688.
- 56 Nijs J, Demol S, Wallman K. Can submaximal exercise variables predict peak exercise performance in women with chronic fatigue syndrome? *Arch Med Res.* 2007;38:350-353.
- 57 Demello JJ, Cureton KJ, Boineau RE, Singh MM. Ratings of perceived exertion at the lactate threshold in trained and untrained men and women. *Med Sci Sports Exerc.* 1987;19:354-362.
- 58 Whitlock EP, Orleans CT, Pender N, Allan J. Evaluating primary care behavioral counseling interventions: an evidence-based approach. *Am J Prev Med.* 2002;22:267-284.
- 59 Davenport TE, Kulig K, Matharu Y, Blanco CE. The EdURP model for nonsurgical management of tendinopathy. *Phys Ther.* 2005;85:1093-1103.
- 60 Clapp LL, Richardson MT, Smith JF, et al. Acute effects of thirty minutes of light-intensity, intermittent exercise on individuals with chronic fatigue syndrome. *Phys Ther.* 1999;79:749-756.
- 61 Sadlier M, Evans JR, Phillips C, Broad A. A preliminary study into the effectiveness of multi-convergent therapy in the treatment of heterogeneous individuals with chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome.* 2000;7:93-101.