ORIGINAL ARTICLE

Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial

J. H. Bourke[1]*, **A. L. Johnson**[2,3], **M. Sharpe**[4], **T. Chalder**[5] and **P. D. White**[1]

[1] *Centre for Psychiatry, Wolfson Institute for Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK*
[2] *MRC Biostatistics Unit, University of Cambridge Institute of Public Health*
[3] *MRC Clinical Trials Unit, London, UK*
[4] *Department of Psychiatry, University of Oxford, Oxford, UK*
[5] *Academic Department of Psychological Medicine, King's College London, UK*

Background. Pain is a common symptom of chronic fatigue syndrome (CFS). We investigated the effects of the treatments used in the PACE trial [cognitive behavioural therapy (CBT), graded exercise therapy (GET), adaptive pacing therapy (APT) and specialist medical care (SMC)] on pain in CFS.

Method. We compared pain outcomes including individual painful symptoms, taken from the CDC criteria for CFS and co-morbid fibromyalgia. We modelled outcomes adjusting for baseline variables with multiple linear regression.

Results. Significantly less frequent muscle pain was reported by patients following treatment with CBT compared to SMC (mean difference=0.38 unit change in frequency, p=0.02), GET *versus* SMC (0.42, p=0.01) and GET *versus* APT (0.37, p=0.01). Significantly less joint pain was reported following CBT *versus* APT (0.35, p=0.02) and GET *versus* APT (0.36, p=0.02). Co-morbid fibromyalgia was less frequent following GET *versus* SMC (0.03, p=0.03). The effect sizes of these differences varied between 0.25 and 0.31 for muscle pain and 0.24 and 0.26 for joint pain. Treatment effects on pain were independent of 'change in fatigue'.

Conclusions. CBT and GET were more effective in reducing the frequency of both muscle and joint pain than APT and SMC. When compared to SMC, GET also reduced the frequency of co-morbid fibromyalgia; the size of this effect on pain was small.

Introduction

Chronic fatigue syndrome (CFS)

CFS is a disorder characterized by chronic, post-exertional, disabling fatigue in the absence of an alternative explanatory diagnosis (Prins *et al.* 2006). It is sometimes called myalgic encephalomyelitis (ME), although some believe that ME is a separate condition. The prevalence of CFS is between 0.2% and 2.6% worldwide, depending on the definition used (Prins *et al.* 2006). Prognosis is poor if untreated (Cairns & Hotopf, 2005), although specific treatments can improve outcomes (NICE, 2007).

The PACE trial was a recently reported parallel-group randomized controlled trial of patients with CFS that tested the benefits and safety of adaptive pacing therapy (APT), cognitive behavioural therapy (CBT), and graded exercise therapy (GET), when added to specialist medical care (SMC), and SMC alone (White *et al.* 2011). The trial demonstrated that CBT and GET can be added to SMC to safely and moderately reduce fatigue and physical disability for CFS, but that APT was not an effective addition. This is consistent with meta-analyses and systematic reviews which also suggest that both CBT and GET are moderately effective treatments (Edmonds *et al.* 2004; Malouff *et al.* 2008; Price *et al.* 2008; Castell *et al.* 2011), something reflected in the guideline of the UK National Institute for Health and Clinical Excellence (NICE, 2007).

Pain in CFS

Pain is a common symptom in CFS that is reported by sufferers as being disabling and compromising to both

* Address for correspondence: Dr J. H. Bourke, Centre for Psychiatry, Wolfson Institute for Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Dominion House, 59 Bartholomew Close, London EC1A 7ED, UK.

(Email: j.bourke@qmul.ac.uk)

physical and social function (Meeus *et al.* 2007). The Centers for Disease Control (CDC) criteria for CFS contain five painful symptoms (muscle pain, joint pain, headache, sore throat, tender lymph nodes). Muscle pain is the most common of these, affecting as many as 93% of patients (Vercoulen *et al.* 1994; King & Jason, 2005). Chronic idiopathic pain, such as that which occurs in CFS, is poorly understood. Management strategies for chronic pain often include CBT and GET in combination with SMC, although with variable success (Morley *et al.* 1999; Andrews *et al.* 2012). Although the UK National Institute for Health and Clinical Excellence (NICE) recommend CBT and GET for CFS (NICE, 2007), no guidance specific to the management of pain in CFS currently exists and research in this area is sparse. It remains unknown whether CBT and GET individually combined with SMC alleviate pain as well as fatigue in CFS. It has been suggested that CBT is effective in reducing painful symptoms in CFS by one group (Knoop *et al.* 2007). However, this was examined in those who had recovered from CFS after successful treatment with this intervention, compared to those who had received CBT for CFS but had not recovered. This data alone is unable to clarify whether CBT is effective for painful symptoms as a consequence, or independent, of its effect on fatigue.

An overview of the precise use of therapies in the PACE trial has been described elsewhere (White *et al.* 2011). Briefly, CBT performed in the PACE trial was employed on the basis of the fear avoidance theory of CFS, suggesting that the cognitive (fear of engaging in activity) and behavioural (avoidance of activity) responses are linked and interact at the physiological level to perpetuate fatigue. The aim of treatment was to target these responses. GET performed in the PACE trial was employed on the basis of deconditioning and exercise intolerance theories of CFS. The aim of treatment was to help the participant gradually to habituate to appropriate physical activities, reverse the deconditioning, and thereby reduce fatigue and disability. The theories underpinning the use of CBT and GET in CFS for the PACE trial are also applicable to their use in the management of chronic pain (Ostelo *et al.* 2005; Lohnberg, 2007). APT was designed to help the patient better adapt to their illness by listening to their body and balancing activity against rest.

The aim of our study was to use data from the PACE trial to compare treatments for their effect on pain, reported by people with CFS, and to determine whether treatment responses were associated with changes in fatigue.

We hypothesized that CBT and GET would be more effective than SMC or APT for painful symptoms based upon prior literature and the evidence that these treatments were more effective for reducing both fatigue and disability (White *et al.* 2011).

Methods

We conducted an analysis of the PACE trial data, comparing the effects of APT, CBT, GET, and SMC on pain and co-morbid fibromyalgia.

In total, 641 patients were recruited into the PACE trial from secondary-care specialist CFS clinics in the UK, all of whom met the Oxford criteria for CFS (6 months of disability, with fatigue as a principal symptom, not otherwise explained by other diagnoses) (Sharpe *et al.* 1991). Participants were assessed by a research assistant for the presence of the international CDC criteria for CFS (Reeves *et al.* 2003) and diagnostic criteria for fibromyalgia (Wolfe *et al.* 2010). The international criteria for CFS require 6 months of disabling fatigue and at least four of eight associated symptoms (which include five pain symptoms), not otherwise explained by an alternative diagnosis (Reeves *et al.* 2003). We used the American College of Rheumatology criteria (Wolfe *et al.* 2010) to diagnose fibromyalgia, with the exception of tender points. These criteria require having 3 months of widespread pain in all four quadrants, above and below the waist, on both sides of the body, as well as axial pain (Wolfe *et al.* 2010). All measures and criteria were assessed at baseline (week 0, trial entry) and at the study endpoint (week 52). The methodology, including power calculations and descriptions of the interventions performed and primary outcome results of the PACE trial have been reported in detail elsewhere (White *et al.* 2007, 2011).

Painful symptom outcomes

While all patients in the PACE trial were required to meet the Oxford criteria for CFS for inclusion, data was also collected for the international (CDC) criteria. We have focused on these in the current analysis due to their description of painful symptoms. The international (CDC) criteria for CFS contain five painful symptoms central to a diagnosis of CFS: muscle pain, joint pain, headache, sore throat and tender lymph nodes. We chose muscle pain and joint pain as individual symptom outcomes, before analysis of outcome data, since these were the most commonly reported at baseline. Each of the symptom domains for the CDC checklist was scored with a 5-point scale: not at all present (score 0), present a little (1), present more than not (2), present most of the time (3), present all of the time (4).

A further categorical scoring system was generated for both CFS and non-CFS pain, based upon

Table 1. *Selected demographic and clinical characteristics at baseline, n (%)*

Treatment group	APT (*n*=159)	CBT (*n*=161)	GET (*n*=160)	SMC (*n*=160)
Age, years, mean (S.D.)	39 (11)	39 (12)	39 (12)	37 (11)
Female	121 (76)	129 (80)	123 (77)	122 (76)
Caucasian	146 (92)	151 (94)	148 (93)	150 (94)
International CFS criteria satisfied	107 (67)	106 (66)	106 (66)	108 (68)
London ME criteria satisfied	81 (51)	84 (52)	84 (53)	80 (50)
Any depressive disorder	54 (34)	52 (32)	54 (34)	53 (33)

APT, Adaptive pacing therapy; CBT, cognitive behavioural therapy; GET, graded exercise therapy; SMC, specialist medical care; CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis; S.D., standard deviation.

presence (1) or absence (0) of symptoms. For the CFS-related symptoms (CDC criteria), ratings of 0 and 1 were scored as 'absent' and ratings of 2, 3 or 4 were rated as 'present'.

We used the frequency scores for our comparisons of individual pain symptoms. This was a tertiary outcome chosen prior to the present analysis but after the main analysis of the PACE trial, which did not include painful symptoms. Diagnostic criteria for fibromyalgia were recorded as present (1) or absent (0) at baseline (study entry) and study endpoint (52 weeks) for all participants. Fibromyalgia is commonly co-morbid with CFS and since there is also a clinical overlap between the two disorders, in terms of painful symptoms, it was felt important to include this data in the analysis.

Analysis

Independent-sample *t* tests were used to compare the unadjusted means of pain frequency scores for individual and global pains between individual treatment arms, comparing two at a time (CBT *v.* APT, CBT *v.* GET, CBT *v.* SMC, APT *v.* GET, APT *v.* SMC, SMC *v.* GET). The PACE trial was not powered to investigate CBT *v.* GET (White *et al*, 2007). Pearson's χ^2 test was used to compare categorical data between trial arms for the presence or absence of the diagnostic criteria for fibromyalgia. We did not adjust for multiple comparisons because the pain outcomes were secondary in the PACE trial, and the five comparisons were stated *a priori* (White *et al.* 2007).

We calculated effect sizes for the unadjusted, significant differences between treatment arms by Cohen's *d* (Cohen, 1988) at 52 weeks.

To adjust for confounders, composite CFS pain scores and the most common CFS pain domains (muscle pain and joint pain) were individually modelled by multiple linear regression with baseline depressive disorder, international (CDC) criteria for CFS, and London ME criteria, in addition to trial arm

and the dependent pain score at baseline. The presence of fibromyalgia diagnostic criteria was modelled using binary logistic regression using the same covariates and the presence of the diagnostic criteria at baseline. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM, version 20, USA). Confidence intervals were calculated using Wilson's method (Bryant, 2000).

Results

A total of 641 patients were recruited, one of whom withdrew consent after participation. Demographic and clinical characteristics of participants were similar across treatment arms, apart from a shorter duration of illness in the SMC group (Table 1). Further details of the sample have been reported previously (White *et al.* 2011). The frequencies of the five individual pain symptoms were 70% for muscle pain, 51% for joint pain, 37% for headache, 31% for sore throat and 31% for lymph node pain.

Descriptive statistics

Frequencies of all painful symptoms and the presence of fibromyalgia diagnostic criteria are presented in Tables 2 and 3.

Unadjusted comparisons

Pain symptoms

Individual pain symptoms are given in Table 4. Both CBT and GET were associated with less frequent muscle pain compared to APT (*p*=0.04 and 0.03, respectively), and with SMC (*p*=0.02 and 0.01, respectively). Both CBT and GET were associated with less frequent joint pain compared to APT (*p*=0.04 and 0.03, respectively), but not compared to SMC.

The calculated effect sizes for these significant differences between treatment arms varied between 0.25 and 0.31 for muscle pain and 0.24 and 0.26 for joint pain.

Table 2. *Presence of individual symptoms, valid% (n)*

Symptom	APT		CBT		GET		SMC	
	Baseline (*n*=159)	52 weeks (*n*=151)	Baseline (*n*=161)	52 weeks (*n*=145)	Baseline (*n*=160)	52 weeks (*n*=144)	Baseline (*n*=160)	52 weeks (*n*=149)
Muscle pain	71 (113)	60 (91)	64 (102)	50 (73)	71 (114)	50 (72)	72 (115)	60 (89)
Joint pain	52 (84)	49 (74)	50 (81)	34 (49)	51 (81)	39 (56)	52 (83)	45 (67)
Headache	37 (59)	31 (47)	39 (63)	28 (40)	37 (59)	29 (42)	36 (58)	34 (50)
Sore throat	32 (51)	31 (50)	33 (53)	28 (41)	29 (46)	31 (44)	30 (48)	27 (40)
Tender lymph nodes	31 (50)	23 (35)	32 (51)	28 (41)	29 (46)	29 (41)	32 (51)	25 (37)

APT, Adaptive pacing therapy; CBT, cognitive behavioural therapy; GET, graded exercise therapy; SMC, specialist medical care;

Table 3. *Presence of fibromyalgia diagnostic criteria; valid% (n) and unadjusted trial arm comparisons,% difference (95% CI), p value*

	Valid% (*n*)	APT	SMC
APT			
Baseline (*n*=159)	25 (39)		
52 weeks (*n*=150)	24 (36)		
CBT			
Baseline (*n*=161)	17 (28)	4.0 (−5.5 to 13.4), 0.41	6.8 (−2.9 to 16.4), 0.17
52 weeks (*n*=145)	20 (29)		
GET			
Baseline (*n*=160)	21 (33)	9.4 (0.3 to 18.3), 0.04*	12.3 (3.0 to 21.3), 0.01*
52 weeks (*n*=144)	15 (21)		
SMC			
Baseline (*n*=160)	24 (38)	2.8 (−7.0 to 12.6), 0.57	
52 weeks (*n*=149)	27 (40)		

APT, adaptive pacing therapy; CBT, cognitive behavioural therapy; GET, graded exercise therapy; SMC, specialist medical care; CI, confidence interval.

* *p*<0.05.

Fibromyalgia

GET was associated with a significantly greater reduction in the frequency of fibromyalgia at 52 weeks, compared to APT (*p*=0.04) and SMC (*p*=0.01) (Table 3). The number needed to treat (NNT) for these comparisons were 11 and 13, respectively.

Regression modeling

Muscle pain

After adjusting for possible confounders using linear regression, reductions in muscle pain after both CBT (difference=0.14, *p*=0.05) and GET (difference=0.38, *p*=0.01) remained significantly greater than with SMC, and GET remained significantly greater than APT (difference 0.17, *p*=0.01). The difference between CBT and APT was confounded by baseline differences in muscle pain and was no longer significant (*p*=0.12). Adding change in fatigue score into the model had little effect on the treatment comparisons (CBT *v.* SMC: 0.14, *p*=0.05; GET *v.* APT: 0.18, *p*=0.01; GET *v.* SMC: 0.42, *p*<0.001). Participant subgroups meeting international criteria for CFS, London criteria for ME, and depressive disorder criteria did not differ in the pattern of treatment effects.

Joint pain

The effect of both CBT (difference=0.35, *p*=0.02) and GET (difference=0.15, *p*=0.02) on joint pain was significantly greater than that of APT after adjusting for baseline confounders. There was a trend for both CBT (difference=0.14, *p*=0.05) and GET

Table 4. *Trial arm comparisons for the most frequently occurring pain symptoms at 52 weeks – reduced score implies reduction in symptoms*

	Total number at 52 weeks		APT	SMC
	Muscle pain at 52 weeks, total score (0–4)	Mean score (S.D.)	Muscle pain, unadjusted trial arm comparisons, mean difference (95% CI), p value	
APT	151	2.07 (1.42)		
CBT	145	1.73 (1.33)	−0.34 (−0.02 to −0.65), 0.04*	−0.38 (−0.08 to −0.69), 0.02*
GET	144	1.69 (1.38)	−0.37 (−0.05 to −0.69), 0.03*	−0.42 (−0.11 to −0.73), 0.01*
SMC	149	2.11 (1.34)	0.05 (0.36 to −0.27), 0.76	
	Joint pain at 52 weeks, total score (0–4)		Joint pain; unadjusted trial arm comparisons, mean difference (95% CI), p value	
APT	149	1.64 (1.49)		
CBT	143	1.29 (1.38)	−0.35 (−0.02 to −0.68), 0.04*	−0.25 (0.08 to −0.58), 0.14
GET	144	1.28 (1.32)	−0.36 (−0.05 to −0.69), 0.03*	−0.25 (0.70 to −0.57), 0.12
SMC	151	1.54 (1.48)	−0.11 (0.23 to −0.44), 0.54	

APT, adaptive pacing therapy; CBT, cognitive behavioural therapy; GET, graded exercise therapy; SMC, specialist medical care; CI, confidence interval.

* $p < 0.05$.

(difference = 0.22, $p = 0.07$) to be associated with less joint pain compared to SMC, which was not evident in the unadjusted comparison ($p = 0.14$ and 0.12, respectively). Adding change in fatigue into the model had little effect on treatment comparisons, with the differences barely changing for CFS joint pain (CBT *v.* APT: 0.31, $p = 0.04$; CBT *v.* SMC: 0.13, $p = 0.08$; GET *v.* APT: 0.15, $p = 0.03$; GET *v.* SMC: 0.25, $p = 0.05$). As before, alternative diagnostic criteria and the presence of major depressive disorder did not alter the pattern of treatment effects.

Fibromyalgia diagnostic criteria

A statistically significantly greater reduction in the frequency of fibromyalgia at 52 weeks was seen for GET compared to SMC in the adjusted model (difference = 0.73, $p = 0.03$). Adding change in fatigue did not alter the model, with the difference barely changing (GET *v.* SMC: 0.70, $p = 0.05$). As before, alternative diagnostic criteria and the presence of major depressive disorder did not alter the pattern of treatment effects.

Discussion

This study found that GET was more effective than either APT or SMC in reducing the frequencies of both muscle and joint pain. It was also more effective than SMC in reducing the prevalence of fibromyalgia. CBT was more effective than SMC in reducing the frequency of muscle pain and more effective than either APT or SMC in reducing the frequency of joint pain. The beneficial effects of these therapies on painful symptoms in CFS were independent of their effects on reducing fatigue, i.e. their effects on painful symptoms were not dependent on generating an improvement in fatigue. However, the effect sizes were small.

Limitations

The timings of data collection during the PACE trial were such that we were unable to report a linear trend in the response to the interventions. Our measures of pain were based on frequencies of pain, rather than severity of pain and as such may not be as clinically meaningful. By virtue of the original power calculations for the PACE trial, we are unable to report on comparisons between the two most effective interventions, CBT and GET. The PACE trial also excluded patients unable to attend hospital, potentially excluding the more severely affected patients, who may have more pain that is less responsive, or differently responsive to the interventions assessed here. Similarly, the group of patients assessed by the PACE trial were those referred to secondary care, rather than those managed within general practice. These factors may affect the generalizability of our findings.

Strengths

This analysis has the benefit of the strengths of the original PACE trial data, which had only small numbers of dropouts (5%), high rates of compliance with the treatments, use of manual-defined treatments provided by competent therapists, with good therapeutic alliance and high rates of participant satisfaction

(White *et al.* 2011). Furthermore, we examined all trial participants by trial arm, irrespective of primary outcome, enabling an analysis of the effect of interventions on painful symptoms in CFS rather than an effect on painful symptoms that was dependent on the presence of or reduction of fatigue (Knoop *et al.* 2007).

We additionally examined the effects of treatments on fibromyalgia and demonstrated that GET directed at CFS improves outcome for co-morbid fibromyalgia as well as fatigue. CFS and fibromyalgia are similar disorders and commonly co-morbid (McKay *et al.* 2009). That GET is effective when the two co-exist has important clinical ramifications. However, the NNT for a positive outcome is greater than that reported for 'trial recovery' after 52 weeks of either GET or CBT in the PACE trial (White *et al.* 2013).

Comparisons with previous work in this area

CBT in CFS focuses on changing maintaining factors such as unhelpful avoidance in order to reduce fatigue and associated disabilities (Whiting *et al.* 2001). Although trials examining the effects of CBT in CFS report positive treatment effects, fatigue is normally the primary outcome and pain is rarely measured (Chambers *et al.* 2006). Two previous studies have shown improved pain outcomes after CBT for CFS (Stulemeijer *et al.* 2005; Knoop *et al.* 2007). A randomized controlled trial of CBT for CFS in adolescents reported reduced muscle pain and headaches in addition to reduction in fatigue (Stulemeijer *et al.* 2005). More recently Knoop and colleagues looked at adult patients with CFS who had recovered from fatigue *versus* those with CFS who had not recovered from fatigue after a CBT intervention for CFS (Knoop *et al.* 2007). They found that recovered patients reported a more significant reduction in pain and fewer pain locations compared to the non-recovered patients. The sampling of patients by the efficacy of an intervention for one outcome (fatigue) to examine the effect on another outcome (pain) is likely to be biased towards the intervention if there is an association between the two outcomes, and should therefore be interpreted with caution. This is consistent with the contrasting findings of this trial, which found that efficacy against pain was independent of the effect on fatigue.

Both CBT and GET are also commonly used in the management of other chronic idiopathic pain disorders although success in this regard seems to vary between treatments and disorders (Morley *et al.* 1999; Andrews *et al.* 2012). CBT is associated with greater effects for any psychological interventions used (Glombiewski *et al.* 2010). It is also effective in altering positive coping measures and reducing the behavioural expression of pain but is less effective against catastrophization, affective disturbance and social functioning as they relate to pain (Morley *et al.* 1999). This may lead to the hypothesis that GET might be superior to CBT in the treatment of chronic idiopathic pain. However, in the current analysis we are unable to report on this, as the PACE trial was not powered to examine this comparison directly (White *et al.* 2007, 2011).

We found significant advantages for both CBT and GET for the most common types of pain (particularly those affecting muscles). Joint pain was significantly better relieved by CBT compared to APT, while adjusted comparisons showed only a trend for CBT to be better than SMC. This may be related to the encouragement of self-help management incorporated within SMC.

GET was the most effective intervention for pain in this trial, with GET reducing muscle pain more than APT and SMC, reducing joint pain more than APT, and co-morbid fibromyalgia more than SMC. Physical activity (as compared to sustained sedentary behaviour) appears important in the central nervous system's regulation of pain in fibromyalgia, a condition closely related to and commonly co-morbid with CFS (Ellingson *et al*. 2012). GET is a moderately effective treatment for several pain disorders beyond CFS (Geraets *et al.* 2005; George *et al.* 2010). The differences in approach between APT and GET highlight the importance of a graded approach to increasing physical activity for improving outcomes for chronic pain.

APT has been used in other chronic idiopathic pain but recent studies report that it is ineffective (Kindermans *et al.* 2011; Andrews *et al.* 2012). The suggestion has been made that APT represents a combination of pain avoidance and activity avoidance, both of which are independently associated with worse pain outcomes and greater disability due to pain (Andrews *et al.* 2011). This might explain why our analysis was unable to demonstrate any beneficial effect of APT on pain in CFS and the same may be true of its lack of effect on fatigue as an outcome in CFS, as reported in the PACE trial (White *et al.* 2011).

Conclusions

Pain in CFS remains poorly understood. In spite of this, both CBT and GET show some efficacy compared to more passive forms of rehabilitation. It is important that GET directed at fatigue in CFS is also effective against co-morbid fibromyalgia, particularly given the frequency with which the two disorders co-occur. Advances in treatment may come from focusing these therapies towards pain as well as obtaining an improved understanding of the pathophysiology of pain in CFS.

Declaration of Interest

P.D.W. has done voluntary and paid consultancy work for the United Kingdom government and a reinsurance company. T.C. has received royalties from Sheldon Press and Constable and Robinson. M.S. has done voluntary and paid consultancy work for the United Kingdom government, has done consultancy work for an insurance company, and has received royalties from Oxford University Press.

References

Andrews NE, Strong J, Meredith PJ (2012). Activity pacing, avoidance, endurance, and associations with patient functioning in chronic pain: a systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation* **93**, 2109–2121.

Bryant TN (2000). Computer software for calculating confidence intervals (CIA). In: *Statistics with Confidence* (ed. D. G. Altman, D. Machin, T. N. Bryant and J. G. Gardner). BMJ Books: London.

Cairns R, Hotopf M (2005). A systematic review describing the prognosis of chronic fatigue syndrome. *Occupational Medicine (London)* **55**, 20–31.

Castell BD, Kazantis N, Moss-Morris RE (2011). Copgnitive behavioral therapy and graded exercise for chronic fatigue syndrome: a meta-analysis. *Clinical Psychology: Science and Practice* **18**, 311–324.

Chambers D, Bagnall AM, Hempel S, Forbes C (2006). Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/ myalgic encephalomyelitis: an updated systematic review. *Journal of the Royal Society of Medicine* **99**, 506–520.

Cohen J (1988). *Statistical Power Analysis for the Behavioural Sciences*. Lawrence Erlbaum Associates.

Edmonds M, McGuire H, Price J (2004). Exercise therapy for chronic fatigue syndrome. *Cochrane Database of Systematic Reviews*. Issue no. 3, Art. no. CD003200.

Ellingson LD, Shields MR, Stegner AJ, Cook DB (2012). Physical activity, sustained sedentary behavior, and pain modulation in women with fibromyalgia. *Journal of Pain* **13**, 195–206.

George SZ, Wittmer VT, Fillingim RB, Robinson ME (2010). Comparison of graded exercise and graded exposure clinical outcomes for patients with chronic low back pain. *Journal of Orthopaedic and Sports Physiotherapy* **40**, 694–704.

Geraets JJ, Goossens ME, de Groot IJ, de Bruijn CP, de Bie RA, Dinant GJ, van der Heijden G, van den Heuvel WJ (2005). Effectiveness of a graded exercise therapy program for patients with chronic shoulder complaints. *Australian Journal of Physiotherapy* **51**, 87–94.

Glombiewski JA, Sawyer AT, Gutermann J, Koenig K, Rief W, Hofmann SG (2010). Psychological treatments for fibromyalgia: a meta-analysis. *Pain* **151**, 280–295.

Kindermans HP, Huijnen IP, Goossens ME, Roelofs J, Verbunt JA, Vlaeyen JW (2011). 'Being' in pain: the role of self-discrepancies in the emotional experience and activity patterns of patients with chronic low back pain. *Pain* **152**, 403–409.

King C, Jason LA (2005). Improving the diagnostic criteria and procedures for chronic fatigue syndrome. *Biological Psychology* **68**, 87–106.

Knoop H, Stulemeijer M, Prins JB, van der Meer JW, Bleijenberg G (2007). Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? *Behaviour Research and Therapy* **45**, 2034–2043.

Lohnberg JA (2007). A review of outcome studies on cognitive-behavioral therapy for reducing fear-avoidance beliefs among individuals with chronic pain. *Journal of Clinical Psychology in Medical Settings* **14**, 113–122.

Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS (2008). Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clinical Psychology Review* **28**, 736–745.

McKay PG, Duffy T, Martin CR (2009). Are chronic fatigue syndrome and fibromyalgia the same? Implications for the provision of appropriate mental health intervention. *Journal of Psychiatric and Mental Health Nursing* **16**, 884–894.

Meeus M, Nijs J, Meirleir KD (2007). Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. *European Journal of Pain* **11**, 377–386.

Morley S, Eccleston C, Williams A (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* **80**, 1–13.

NICE (2007). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management, clinical guideline CG53 (http://guidance.nice. org.uk/CG53). National Institute for Health and Clinical Excellence. Accessed 17 September 2012.

Ostelo RWJG, van Tulder MW, Vlaeyen JWS, Linton SJ, Morley S, Assendelft WJJ (2005). Behavioural treatment for chronic low-back pain. *Cochrane Database of Systematic Reviews*. Issue no. 1, Art. no. CD002014.

Price JR, Mitchell E, Tidy E, Hunot V (2008). Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database of Systematic Reviews*. Issue no. 3, Art. no. CD001027.

Prins JB, van der Meer JW, Bleijenberg G (2006). Chronic fatigue syndrome. *Lancet* **367**, 346–355.

Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER (2003). Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Services Research* **3**, 25.

Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RH, Hawton KE, Lambert HP, Lane RJ (1991). A report – chronic fatigue syndrome: guidelines for research. *Journal of The Royal Society of Medicine* **84**, 118–121.

Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G (2005). Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *British Medical Journal* **330**, 14.

Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G (1994). Dimensional assessment of chronic fatigue syndrome. *Journal of Psychosomatic Research* **38**, 383–392.

White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M; PACE Trial Management Group (2013). Recovery from chronic fatigue syndrome after treatments given in the PACE trial. *Psychological Medicine*. Published online: 31 January 2013. doi:S0033291713000020.

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* **377**, 823–836.

White PD, Sharpe MC, Chalder T, DeCesare JC, Walwyn R (2007). Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise, as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurology* **7**, 6.

Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramirez G (2001). Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. *Journal of the American Medical Association* **286**, 1360–1368.

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care and Research (Hoboken)* **62**, 600–610.