Evaluating Pacing Therapy (PT) versus Graded Exercise Therapy (GET) for improving fatigue, pain, and quality of life in adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Systematic Review

Journal of Bodywork & Movement Therapies 44 (2025) 319–327

Contents lists available at ScienceDirect

Journal of Bodywork & Movement Therapies

journal homepage: www.elsevier.com/jbmt

Evaluating pacing therapy (PT) versus graded exercise therapy (GET) for improving fatigue, pain, and quality of life in adults with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A systematic review

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ARTICLE INFO

Handling editor: Jerrilyn Cambron

Keywords:
ME/CFS
Physical therapy
Graded exercise therapy
Fatigue
Pain
Quality of life
Adverse events

ABSTRACT

This study aimed to evaluate the effectiveness of Pacing Therapy (PT) and Graded Exercise Therapy (GET) in improving fatigue, pain, and Quality of Life in adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), while also considering adverse events. Data were sourced from PubMed Central, Academic Search Complete, CINAHL, MEDLINE, Cochrane Library, Google Scholar, and manual citation searches from 2013 to 2023. Studies were related to PT, GET, and outcomes of fatigue, pain, and QOL. Out of 925 studies, six met the inclusion criteria, analyzing a total of 2280 participants. The methodological quality of these studies, assessed using the PEDro scale, ranged from good to poor. GET showed the highest recovery rates for ME/CFS, with 33 % on the CFQ and 53 % on the SF-36PF, compared to 21–22 % and 35–41 % for APT and SMC. Symptom improvements were reported by 44 % post-PT, compared to 12 % in GET ($p < 0.001$). GET also resulted in less frequent muscle and joint pain compared to APT and SMC. GES participants scored 4.2 points lower on the CFQ and 6.3 points higher on the SF-36PF than SMC. APT and SMC showed significant improvements in fatigue and physical function at 2.5 years ($p < 0.0001$). Adverse events were reported in two studies, with over 50 % experiencing NSAEs, and serious deteriorations in fatigue and physical functioning noted across all groups. In conclusion, PT and GET are more effective than SMC, with GET being particularly favoured for improving pain, fatigue, and physical function. Adverse effects suggest that GET and PT are safer options than SMC.

1. Introduction

The terms myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS), and ME/CFS describe the same condition (NICE, 2021). ME/CFS is a serious, chronic, complex, and systemic disease with a wide range of symptoms associated with neurological, immunological, musculoskeletal, cardiovascular, endocrine, gastrointestinal, and energy metabolism dysfunction (Carruthers et al., 2011; Bateman et al., 2021; NIH, 2022). The World Health Organisation (1969) classifies ME/CFS as a neurological disease, "characterised by a sudden or gradual onset of persistent disabling fatigue, post-exertional malaise (PEM), unrefreshing sleep, cognitive and autonomic dysfunction, myalgia, arthralgia, headaches, sore throat, and tender lymph nodes, with symptoms lasting at least 6 months. Symptoms do not improve with sleep or rest" (Komaroff, 2015). Patients with (Pw) ME/CFS also experience orthostatic intolerance, sensory intolerance, and flu-like symptoms (NIH, 2022). It is not clear what causes ME/CFS, however, in many cases symptoms are triggered by an infection (NICE, 2021). The main feature seen in PwME/CFS is the occurrence of additional symptoms (exacerbation) due to physical, cognitive, sensory, or emotional exertion (Bateman et al., 2021). Symptom severity fluctuates greatly, impacting activities of daily living (Carruthers et al., 2011), with some individuals experiencing symptom improvements or complete remission (Bateman et al., 2021). In many cases, remission occurs between bouts of recurring relapses (Shepherd and Chaudhuri, 2019). There is currently no known cure (Carruthers and van de Sande, 2012), therefore the primary goals of treatment are to manage symptoms and improve functional capacity (BMJ Best Practice, 2022).

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https://doi.org/10.1016/j.jbmt.2025.05.048
Received 7 September 2024; Received in revised form 6 May 2025; Accepted 25 May 2025
Available online 30 May 2025

1.1. Epidemiology

Prevalence of ME/CFS is hard to determine due to varying diagnostic criteria and lack of reliable assessment tools (Lim et al., 2020). Lim et al. (2020) found an average ME/CFS prevalence rate of 1.4 % (±1.57 %) based upon 56 prevalence data reports, similar to their general population data whereby they found an average ME/CFS prevalence to be 1.45 % (±1.68 %). Recent estimates suggest 0.8 % prevalence globally (Leslie et al., 2023). UK Biobank data indicates over 250,000 people in England and Wales have ME/CFS, with about 25 % being housebound or bedbound (NICE, 2021). Peak onset ages are 11–19 and 33–39 (Rowe et al., 2017). The condition is more common in females than males at a 3:1 ratio (Bateman et al., 2021). Gender studies show females (55 %) are more likely to have ME/CFS than males (Lim et al., 2020).

1.2. Pathophysiology

One theory of ME/CFS involves abnormalities in the central and autonomic nervous systems, metabolic system, and immune system (Komaroff, 2019). Recurrent infections or chemical exposures can lead to hypersensitivity of these systems (Jason et al., 2009), causing physiological changes (Proal and Marshall, 2018). An 11-month case study found fluctuations in immune, metabolic, neurological, and mitochondrial functions correlated with symptoms (Helliwell et al., 2022).

Some PwME/CFS have lower muscular pain thresholds (Meeus et al., 2010) but normal skin and subcutaneous thresholds (Vecchiet et al., 1996). The cause is unknown, though one theory involves reduced adrenal gland function (Meeus et al., 2008). Studies found normal muscle energy production (Byrne and Trounce, 1987) but abnormalities in muscle structure and enzyme activity (Vecchiet et al., 1996). Pain in PwME/CFS often indicates central nervous system dysfunction (Meeus et al., 2008).

1.3. Pacing/energy management for ME/CFS

Pacing, also known as energy/activity management, is a strategy that involves managing a person's activities to stay within their available energy levels/envelope (Pesek et al., 2000; NICE, 2021). If PwME/CFS only expend the energy available within the envelope, and not exceed this, they can reduce the frequency of symptom exacerbation (Jason, 2008). Optimal activity levels involve remaining within energy boundaries (Jason et al., 2009). Previous research into the efficacy of energy management in ME/CFS is limited, with suggestions that pacing is effective in decreasing ME/CFS symptoms (Jason et al., 1999; Pesek et al., 2000).

Pacing is effective in a multitude of other chronic health conditions (Antcliff et al., 2019), balancing activities and rest to aid symptom management (Goudsmit et al., 2012). In cancer patients, a combination approach of cognitive behavioural therapy (CBT) and PT demonstrated reduced fatigue severity and improved QOL after the intervention and at 3-month follow-up when compared to chemotherapy alone, although the effects of CBT or pacing alone were not assessed (Getu et al., 2023). Similar to ME/CFS, fibromyalgia presents with high levels of pain and fatigue. Many patients partake in activity-avoidance behaviours, but research determined pacing to be a more appropriate strategy essential for self-management of pain (Karsdorp and Vlaeyen, 2009), contributing to improved QOL via appropriate activity management strategies (Attali et al., 2023). In the chronic pain population, a meta-analysis suggested activity pacing may lead to fatigue reduction, although more success can be attained by tailoring treatment to the individual (Abonie et al., 2020).

The quota-contingency pacing theory describes "undertaking activities according to an amount, distance, or goal with the aim of improving function" (Leslie et al., 2023). In clinical practice, this theory is widely used for those with chronic pain and chronic fatigue. The symptom-contingent theory (envelope theory) describes activities that are driven by perceived symptom levels to avoid symptoms and conserve energy, however in clinical practice, only 1.8 % of healthcare professionals prescribe PT for energy conservation due to lack of research and knowledge gaps in this area (Antcliff et al., 2019; Leslie et al., 2023). The primary aim of pacing for ME/CFS should be to allow as much normal functioning as possible within the individual's available energy levels whilst simultaneously avoiding symptom exacerbation. A survey distributed to 92 healthcare professionals found 50 % use quota-contingency pacing techniques, compared to 17.4 % who use symptom-contingent pacing (Antcliff et al., 2019). Although symptom-contingent pacing is proven to be more effective (White et al., 2011), it is used less frequently in clinical practice. More recently, quota-contingency pacing has been found to still be favoured by clinicians, but interpretations of pacing styles can impact the effectiveness of the intervention. Within this study a physiotherapist explained that quota pacing took the focus away from the patient's symptoms, enabling them to focus more on enjoyable activities, rather than purely managing their symptoms (Antcliff et al., 2022). Investigations have been limited to objectifying the energy envelope within the ME/CFS population, potentially due to individuals experiencing a large array of symptom severities making it difficult to have set values for the whole population. Jason et al. (2009) surveyed 110 PwME/CFS, asking them to rate their perceived energy levels to prompt the researcher's development of a daily energy quotient. They found 86 % of participants subjectively indicated they were expending more energy than they had available, therefore higher energy expenditure coincided with higher fatigue severity. Subsequently, another study found those who have higher levels of functioning also demonstrate higher severity PEM if they exceeded their energy envelope compared to those with lower baseline functioning (O'Connor et al., 2019), suggesting energy management is more prudent in those with milder forms of any CFS, and having less impact on those suffering with severe forms of the condition.

1.4. Graded exercise therapy (GET) for ME/CFS

The overall aim of GET is to help the patient become more independent in their everyday life by increasing functional capacity and reducing symptoms (The Royal Australian College of General Practitioners, 2015). GET aims to achieve this by preventing/reversing physical deconditioning and exercise intolerance by encouraging people to extend their physical functioning further than their current ability (The Royal Australian College of General Practitioners, 2015).

In most diseases, exercise-based interventions can improve symptoms, however, research into exercise for PwME/CFS focused on addressing deconditioning and improving fatigue is limited (Chalder et al., 2015). This is probably because physical exertion in those with ME/CFS can trigger symptom exacerbation, presenting as PEM. Therefore, a balance should be found between combating deconditioning through exercise and triggering a symptom flare-up (Leslie et al., 2023).

GET, also known as Graded Activity Management (GAM) or Graded Activity Therapy (GAT), is defined as "establishing a baseline of achievable exercise or physical activity and then making fixed incremental increases in the time spent being physically active" (NICE, 2021), via incremental increases in frequency, duration, and intensity (White et al., 2011). GET "is a therapy based on the deconditioning and exercise avoidance theories of ME/CFS" (NICE, 2021). Prolonged physical inactivity maintains ME/CFS symptoms, and in some cases, symptoms worsen, leading to further activity avoidance (Fulcher and White, 1998). However, this theory has been criticised as a "flawed model of causation involving abnormal beliefs and behaviours and deconditioning" (NICE, 2021), although they stated that "evidence here is lacking".

Incremental exercise programmes have been considered effective in reversing deconditioning post-operatively (Wu et al., 2020), in people with spinal cord injury (Maher et al., 2017), and stroke (Ivey et al., 2008). Therefore, the principle of GET for ME/CFS is to reverse deconditioning to increase exercise tolerance (Fulcher and White, 1998). Research has shown improvements in subjective fatigue and physical

functioning following GET under physiotherapy guidance compared to self-guided GET and SMC (Wilshire et al., 2018; Cheshire et al., 2020; Smakowski et al., 2022). Previous guidance has recommended GET but these have been controversial, providing uncertainty about the effectiveness among PwME/CFS (NICE, 2021). Therefore, with the limited high-quality research base, the efficacy of GET is questionable when based on deconditioning theories, which have more recently been said not to be the primary cause of ME/CFS.

1.5. Objectives

The objective of this systematic review was to investigate, synthesize, and analyse existing literature on PT and GET for improving fatigue, pain, and quality of life (QOL) in adults with ME/CFS. The main goal was to determine which treatment modality is more effective and to identify any adverse effects based on the available evidence.

2. Methods

This systematic review was registered with PROSPERO (registration number: CRD420251010815.

2.1. Eligibility criteria

This systematic review used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Page et al., 2021). Inclusion and exclusion criteria are shown in Table 1 The PICOT format is an evidence-based acronym that provides detailed information that is useful as an initial base for the search criteria to enable the retrieval of highly relevant articles for the study question (Scells et al., 2017; Eriksen and Frandsen, 2018). COMET Initiative (2022) outlined plans to produce a core outcome set for ME/CFS throughout 2022, but this is yet to be made available. Hence, core outcome measures for this review have been determined by utilising a preliminary ICF core set (Bileviciute-Ljungar et al., 2020) combined with the NICE (2021) critical outcomes for ME/CFS.

2.2. Sources

Article retrieval was conducted via online database searches on PubMed Central, Academic Search Complete, CINAHL Complete, MEDLINE and Cochrane Library. Within healthcare, these databases are highly recommended as a researcher's top priority when conducting a literature search for reviews (Bramer et al., 2017; Vassar et al., 2017). The inclusion of grey literature is imperative, so searches were conducted on Google Scholar, screening the first 200 results. Online searches were filtered to articles within the years 2013–2023. This recent timespan was chosen to avoid repeating the same search that the NICE guidelines conducted. To further increase the scope of the search, manual citation searching of included articles and excluded systematic reviews was also conducted.

Table 1
Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
• Peer-reviewed journals • English language • Full text available (open access or via University of Worcester) • PICOTS: o Population must be adults with ME/CFS o Intervention must be pacing (energy management) and/or GET o Outcome measures must be fatigue and/or pain and/or quality of life o Time – longest follow-up available o Study designs – RCTs, cohort studies, non-randomised clinical trials, controlled before-after studies, and case studies. • Articles may outline treatment-related adverse effects for pacing and/or GET in ME/CFS	• Participants with no ME/CFS diagnosis • Long COVID, COVID-19 or other neurological conditions • Co-morbidities • Paediatric population • Study not published within years 2013–2023 • Systematic reviews • Failing to meet search terms or inclusion criteria

2.3. Search strategy

Mixed search methods were used with Boolean operators and synonyms (Rao and Moon, 2021) as per the following: ('myalgic encephalopathy' or 'myalgic encephalomyelitis' or 'chronic fatigue syndrome' or 'ME' or 'CFS' or ME/CFS' or 'post viral fatigue syndrome') AND ('pacing' or 'energy management' or 'activity management' or 'energy envelope') AND ('graded exercise therapy' or 'GET' or 'graded exercise' or 'graded activity management' or 'GAM' or 'graded activity therapy' or 'GAT') AND ('adults' or 'adult') AND ('fatigue' or 'fatiguability' or 'tiredness' or 'exhaustion' or 'post-exertional malaise' or 'PEM' or 'sleepiness') OR ('pain' or 'joint pain' or 'muscle aches' or 'chronic pain' or 'neuropathic pain') OR ('quality of life' or 'well-being' or 'health--related quality of life' or 'QOL'). The search entailed studies from 2013 to 2023, therefore, where databases allowed, a limiter was applied to search within the last 10 years. This timescale has been determined to find new developments, avoiding replicating the searches completed as part of the updated NICE guidelines (NICE, 2021), hence the wider scope of this review investigating all primary research to uncover further literature in this area.

2.4. Selection process

Database search results were exported into Rayyan for the study selection process. Although many reference management software are available, Rayyan is considered the 'best scoring free tool' when screening literature for a systematic review in biomedical research (Van der Mierden et al., 2019). More recently, a comparison study undertaken by Dos Reis et al. (2023) investigating the usefulness of Rayyan, Abstrackr and Colandr, revealed Rayyan as the most sensitive software, with raters able to correctly identify 78 % of true positives, compared to 60 % and 65 % in Abstrackr and Colandr respectively. Rayyan automatically sifts through duplicates for removal. Manual scanning through the titles enabled duplicate removal that may have been missed in the automatic process. Practical screening involved removing articles whereby their title, abstracts, or keywords were irrelevant. Subsequently, the inclusion and exclusion criteria were applied to the abstract of each article, removing any unsuitable articles. Consequently, the remaining articles were methodologically screened for critical appraisal, an essential element before proceeding with the review (Ma et al., 2020). Both authors independently conducted the search and screening process. Authors discussed the points of disagreement and tried to reach a consensus through discussion. A third independent researcher was available to be consulted if a consensus could not be reached. However, this was not needed as a consensus was reached at all times.

2.5. Data collection

Two researchers were involved in extracting data from the included studies. For each of the included studies, the following data were extracted: author, date and country of study, study design, recruitment data (sample size, gender, mean age), ME/CFS classification, and illness duration. Further extracted details include interventions, outcome measures (relating to fatigue, pain, and QOL), a summary of the main results, and program duration.

2.6. Risk of bias assessment

All included studies were assessed for quality using the PEDro scale, an 11-item criterion for external and internal validity (Maher et al.,

2003). The primary aim of conducting the risk of bias assessment was to determine study quality in relation to their methodology. Cashin and McAuley (2020) evidenced the PEDro scale has good construct validity and is able to discriminate between high- and low-quality studies. In addition, the PEDro scale is widely used worldwide with recognised reliability and validity (de Morton, 2009; Elkins et al., 2013), enabling identifiable assessment of the included trials and their applicability within clinical practice (Kamper et al., 2015). As a result, the PEDro scores were not used to exclude articles but to consider the applicability and trustworthiness of the results. Study quality was categorized as <4 poor, 4–5 fair, 6–8 good, and 9–10 excellent (Cashin and McAuley, 2020). Papers were additionally evaluated for publication bias and potential conflicts of interest.

Both researchers were involved in assessing the risk of bias of the included studies. Both researchers discussed the points of disagreement and tried to reach a consensus through discussion. A third independent researcher was available to be consulted, however, this was not needed as a consensus was reached at all times.

3. Results

3.1. Study selection

Database searching returned 567 records. After removing duplicates, 452 records remained for screening. After screening the titles and abstracts, 25 full-text articles were retrieved. Additionally, 358 records were identified via search engine and manual citation searching. 56 were retrieved, and 28 were assessed for eligibility. Overall, 6 articles met the inclusion criteria for this review (Fig. 1). Thereafter, data collection

Commenced whereby key demographic data was extracted from the included articles.

3.2. Study characteristics

Five of the included studies in this review compared the effectiveness of PT versus GET for improving fatigue, pain, and QOL in adults with ME/CFS (White et al., 2013; Bourke et al., 2014; Sharpe et al., 2015; Clark et al., 2017; Geraghty, Hann and Kurtev, 2019). One study explored the adverse effects of these interventions (Dougall et al., 2014). Across the 6 studies, with adjustments for the 4 PACE trial follow-up studies (White et al., 2013; Bourke et al., 2014; Dougall et al., 2014; Sharpe et al., 2015), the total sample size equates to 2280. Drop-outs (n = 486) meant the final analysis across the studies included 77 % of the initial sample. The age of participants ranged from 35 to 39. 78.5 % (n = 1420) of recruits identified as female. Ethnicity data showed 92 % (n = 783/852) identified as White/Caucasian, excluding one study where ethnicity data was not reported (Geraghty et al., 2019). ME/CFS illness duration ranged from 16 months to 9.5 years. Study duration ranged from 3 months to 2.5 years (see Table 2).

3.3. Risk of bias

The methodological quality assessment revealed varying levels of quality among the included studies. Specifically, three studies (Bourke et al., 2014; Dougall et al., 2014; Clark et al., 2017) were deemed to be of good quality, two studies (White et al., 2013; Sharpe et al., 2015) were rated as fair, and one study (Geraghty et al., 2019) was assessed as poor quality (see Table 3).

3.4. Individual study results

3.4.1. Effectiveness of PT versus GET

Bourke et al. (2014) analysed 640 participants (77 % female) across four trial arms (GET, APT, and SMC) with a mean age of 38.5 ± 12 over 52 weeks. Eligibility required a confirmed CFS diagnosis per the Oxford criteria, with 66 % also meeting the International CDC criteria. GET was associated with less frequent muscle pain compared to APT (p = 0.03) and SMC (p = 0.01) with effect sizes of 0.25–0.31. After Bourke et al. (2014) used multiple linear regression to adjust for possible confounders (baseline depressive disorder, CDC criteria for CFS, London ME criteria, and baseline dependent pain score), reductions in muscle pain remained significantly greater in the GET group compared to APT (p = 0.01, difference = 0.17) and SMC (p = 0.01, difference = 0.38). GET also resulted in less frequent joint pain compared to APT (p = 0.03) with effect sizes of 0.24–0.26. After linear regression, reductions in joint pain

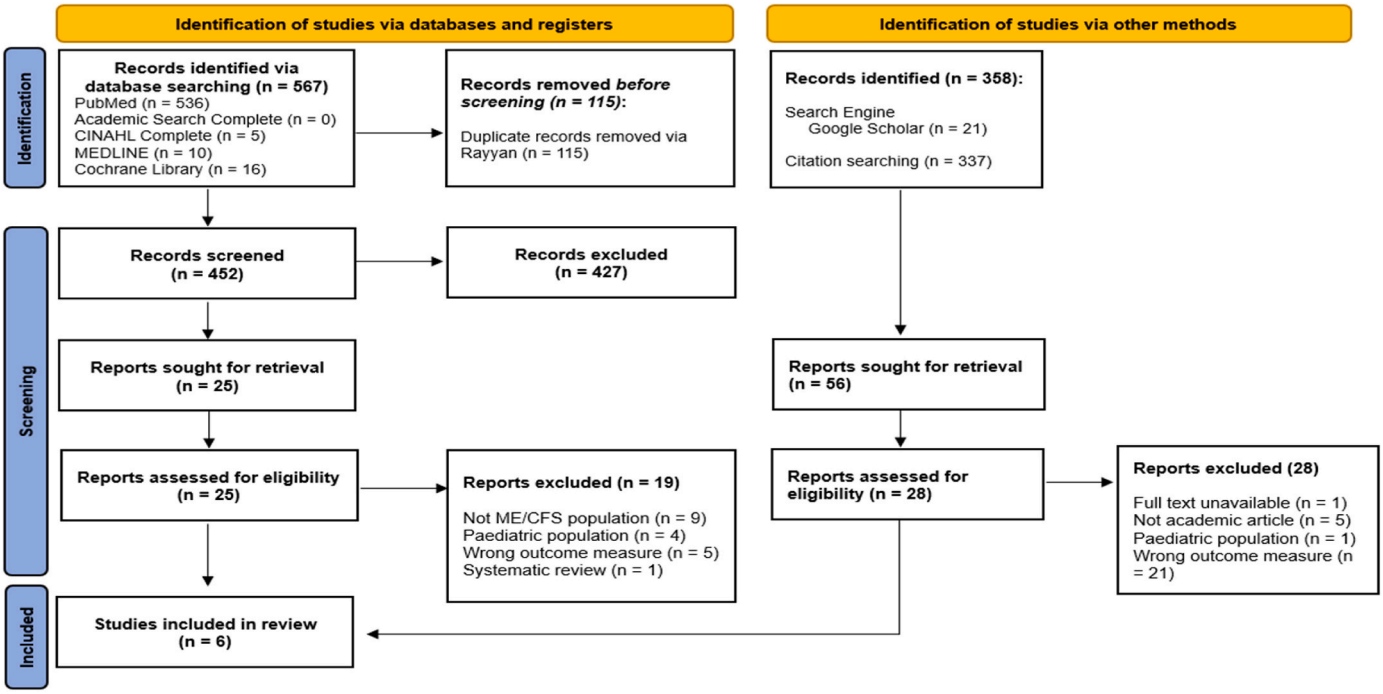

Fig. 1. Prisma Flow Diagra.

Table 2
Table of study characteristics.

Citation (author, year)		Bourke et al. (2014)	Clark et al. (2017)
Country		United Kingdom	United Kingdom
Study Design		RCT	RCT
Recruitment	**Sample Size**	641 (GET = 160; APT = 159; SMC = 160)	211 (GES = 107; SMC = 104)
	N analysed	640 (GET = 160; APT = 159; SMC = 160)	197 (GES = 95; SMC = 102)
	Gender (M:F)	145:495 (GET = 123 F; APT = 121 F; SMC = 122 F)	44:167 (GES = 88 F; SMC = 79 F)
	Age (mean, SD)	38.5 ± 12 (GET = 39 ± 12; APT = 39 ± 11; SMC = 37 ± 11)	GES = 38.1 ± 11.1; SMC = 38.7 ± 12.7
ME/CFS Classification		Oxford criteria for CFS International CDC criteria for CFS	Diagnosis of NICE-defined ME/CFS Oxford Criteria for CFS CDC Criteria for CFS
Intervention(s)		GET, APT, SMC	GES + SMC, SMC
Outcome Measures		Muscle pain score; Joint pain score	CFQ; SF-36 PF
Main Results		Muscle pain: GET v APT ↑ (p = 0.01, difference = 0.17) GET v SMC ↑ (p = 0.01, difference = 0.38) Joint pain: GET v APT ↑ (p = 0.02, difference = 0.15) GET v SMC ↑ (p = 0.07, difference = 0.07)	Baseline to FU (GES) CFQ ↑ (p = 0.005) SF-36PF ↑ (p < 0.0001) GES + SMC v SMC alone CFQ ↑ (p < 0.0001) SF-36PF ↑ (p = 0.006) Adverse Events Reported (GES:SMC) **NSAEs** 27:23 ↔ (p = 0.41) **SAEs** 1:2 (NR) **Serious deterioration** Physical functioning 20:25 ↔ (p = 0.49) CGI-health 1:8 ↑ (p = 0.04) CGI-CFS 0:9 ↑ (p = 0.003)
Program Duration		52 weeks	12 weeks
Citation (author, year)		Dougall et al. (2014)	Geraghty, Hann & Kurtev, 2019
Country		United Kingdom	United Kingdom
Study Design		RCT	Survey
Recruitment	**Sample Size**	641 (GET = 160; APT = 159; SMC = 160)	1428
	N analysed	640 (GET = 160; APT = 159; SMC = 160)	957
	Gender (M:F)	145:495	199:758
	Age (mean, SD)	38 ± 12	Age at symptom onset: 35
ME/CFS Classification		Oxford criteria for CFS	ME/CFS diagnosis from a qualified medical professional.
Intervention(s)		GET, APT, SMC	GET, PT
Outcome Measures		NSAEs, SAEs, SARs and Serious Deteriorations	Respondents' views of their therapy treatment.
Main Results		Adversities Reported (GET:APT)	302 patients (32 %) reported symptoms worsening. 455 (49 %) reported symptoms stayed the same. 176 (19 %) reported improved symptoms. More symptom improvements reported in PT (44 %) versus GET (12 %) (p < 0.001). GET had more negative

Table 2 (*continued*)

Citation (author, year)		Bourke et al. (2014)	Clark et al. (2017)
			symptom change (74 %) versus 14 % in PT (p < 0.001).
		NSAEs 992:949 ↔ (p = 0.47) [median number per participant per annum was 4; IQR 2–8]. 46 % attributed to CFS.	Independent associations with change in symptoms post-therapy:
		SAEs 13:15 ↔ (p = 0.15)	Patients rating the course 'not appropriate' reported worse symptoms (p < 0.001).
		SARs 2:2 ↔ (p = 0.96)	Patients who did not attend the full course reported worse symptoms (p = 0.001).
		Serious deteriorations	Compared with 35–44-year-olds all other adult age groups reported some symptom improvement (p = 0.041).
		Physical function 18:39 ↑ (p = 0.0007)	Men reported a better improvement in symptoms (p = 0.018).
		Fatigue 11:21 ↔ (p = 0.12)	Patients who had ME > 12 months reported worse symptoms (p = 0.008).
		Function and fatigue 5:11 ↔ (p = 0.21)	The belief that ME was psychological resulted in worsening of symptoms.
		CGI 10:10 ↔ (p = 0.69)	
Program Duration		1-year post-intervention	Survey open for 4 months
Citation (author, year)		Sharpe et al. (2015)	White et al. (2013)
Country		United Kingdom	United Kingdom
Study Design		Questionnaire	RCT
Recruitment	**Sample Size**	604	641
	N analysed	481 (GET = 127; APT = 120; SMC = 115)	640 (GET = 160; APT = 159; SMC = 160)
	Gender (M:F)	115:366	145:495
	Age (mean, SD)	38.6 ± 12	38 ± 12
ME/CFS Classification		Oxford criteria for CFS	Oxford criteria for CFS
Intervention(s)		GET, APT, SMC	GET, APT, SMC
Outcome Measures		CFQ; SF-36PF	CFQ; SF-36PF
Main Results		WITHIN GROUP *(1 yr trial outcome to long-term follow up)* GET CFQ ↔ (p = 0.059) SF-36PF ↔ (p = 0.78) APT CFQ ↑ (p < 0.0001) SF-36PF ↑ (p < 0.0001) SMC CFQ ↑ (p < 0.0001) SF-36PF ↑ (p < 0.0001) BETWEEN-GROUP: GET v APT CFQ ↔ (p = 0.28) SF-36PF ↔ (p < 0.064) GET v SMC CFQ ↔ (p = 0.43) SF-36PF ↔ (p = 0.51) APT v SMC CFQ ↔ (p = 0.78) SF-36PF ↔ (p = 0.24)	Participants meeting criteria for recovery % (n/total): Within CFQ normal range GET 33 % (51/154) APT 22 % (34/154) SMC 21 % (32/152) Within SF-36PF normal range GET 53 % (81/154) APT 35 % (53/154) SMC 41 % (62/152) In both CFQ and SF-36PF normal range GET 28 % (43/154) APT 16 % (25/154) SMC 15 (22/152)
Program Duration		2.5 years post-randomisation	52 weeks

SD standard deviation; RCT randomised controlled study; ME myalgic encephalomyelitis; CFS chronic fatigue syndrome; IQR interquartile range.
Interventions (of relevance to this review) - GET graded exercise therapy; APT adaptive pacing therapy; PT pacing therapy; GES graded exercise self-help; SMC specialist medical care. Outcomes - CFQ Chalder fatigue questionnaire; SF-36PF short-form 36 physical function subscale; NSAEs non-serious adverse events; SAEs serious adverse events; SARs serious adverse reactions. ↑ significant change; ↔ no significant change; NR not reported.

were greater for GET compared to APT ($p = 0.02$, difference = 0.15) and SMC ($p = 0.07$, difference = 0.22). Fatigue score, alternative diagnostic criteria, and depression did not significantly alter these outcomes.

White et al. (2013) conducted a follow-up study on the PACE trial, with a median illness duration of 32 months. Recovery at 52 weeks was highest in the GET group (CFQ = 33 %, SF-36PF = 53 %) compared to APT (CFQ = 22 %, SF-36PF = 35 %) and SMC (CFQ = 21 %, SF-36PF = 41 %). The likelihood of recovery was over three times higher with GET versus APT ($p = 0.001$) and SMC ($p < 0.001$). Missing data was 11 % for GET and 6 % for APT and SMC, deemed not significant.

Sharpe et al. (2015) followed up 2.5 years post-PACE trial, with 75 % (n = 481) of participants returning the questionnaire. Baseline characteristics were similar to the original study. Significant improvements in fatigue and physical functioning were found in the APT and SMC groups ($p < 0.0001$), but not in the GET group. No significant differences were seen in between-group analyses.

Geraghty et al. (2019) surveyed 957 patients (79 % female) over 4 months. Average age of symptom onset was 35, with an illness duration of 72 months. Post-therapy, 32 % reported worsening symptoms, 49 % saw no change, and 19 % reported improvement. PT led to 44 % improvement versus 12 % in the GET group ($p < 0.001$). GET had 74 % reporting worse symptoms versus 14 % from pacing ($p < 0.001$). Factors for symptom deterioration included inappropriate course rating ($p < 0.001$), incomplete course attendance ($p = 0.001$), and belief in ME as psychological.

Clark et al. (2017) analysed 197 participants (79 % female) over 12 weeks, comparing GES plus SMC versus SMC alone. The GES group scored 4.2 points lower on the CFQ scale ($p < 0.0001$) and 6.3 points higher on the SF-36PF scale ($p = 0.006$) than the SMC group. Effect sizes were 0.53 for fatigue and 0.2 for physical function. From baseline to 12 weeks, 64 % of GES participants improved in fatigue and 45 % in physical functioning, compared to 44 % and 22 % in the SMC group. The IPAQ showed significant improvement in self-reported physical functioning ($p < 0.0001$).

3.5. Adverse effects of interventions on PwME/CFS

Clark et al. (2017) conducted the GETSET trial, reporting NSAEs in both GES and SMC groups ($p = 0.41$). Three SAEs (GES = 1, SMC = 2) involved A&E attendance with no long-term injuries. Serious deteriorations were defined as a physical functioning decline of >10 points ($p = 0.49$).

Dougall et al. (2014) identified adverse events in the PACE trial, with baseline characteristics matching Bourke et al. (2014). The average NSAEs per participant per year was 4, with no significant differences between treatment groups ($p = 0.47$). Significant differences were found between trial centres ($p < 0.001$). 46 % attributed their NSAE to ME/CFS, correlating with baseline depressive disorder ($p = 0.03$), CFS symptoms ($p = 0.006$), and physical symptoms ($p = 0.09$). Physical functioning decline was significant in pacing (25 %), SMC (18 %), and GET (11 %) groups ($p = 0.0007$). No significant differences were found for SAEs ($p = 0.15$), SARs ($p = 0.96$), or fatigue deterioration ($p = 0.12$) (see Table 4).

3.6. Reporting Biases

A loss of 486 participants across the 6 studies led to a final analysis rate of 77 %. White et al. (2013), Bourke et al. (2014), Dougall et al. (2014), and Sharpe et al. (2015) all reported on 1 participant withdrawing their consent after participation during the original PACE trial. None of these studies gave a reason for this withdrawal. In addition, Sharpe et al. (2015) failed to retrieve complete questionnaires from 122 participants who had initially proved consent to take part in their follow-up study. Clark et al. (2017) had a drop-out of 14 participants, losing 12 to follow-up (GET n = 10, pacing n = 2) and 2 withdrawing during the GET intervention. Again, no reason was provided for the withdrawals. Geraghty et al. (2019) experienced the largest drop-out rate (n = 471) due to the application of eligibility criteria to the completed questionnaires, whereby 957/1428 participants had provided an affirmative ME/CFS diagnosis by a professional and had completed an appropriate intervention. With the lack of reasoning provided within these studies, it is difficult to determine whether the loss of participants via personal choice to leave the trial was due to the intervention or not.

Table 4
Adverse effects of treatments at 12-week and 52-week follow-up (%) (data from Dougall et al. (2014) and Clark et al. (2017)).

	GES/GET		Pacing	SMC	
	12-wks (n = 97)	52-wks (n = 160)	52-wks (n = 159)	12-wks (n = 101)	52-wks (n = 160)
NSAEs	28	93	96	23	93
SAEs	1	8	9	2	4
SARs	0	1	1	0	1
Fatigue worse	0	7	13	9	14
Physical function worse	21	11	25	25	18

% = percentage of participants. GES (graded exercise self-help); GET (graded exercise therapy); SMC (standard medical care); wks (weeks) NSAEs (non-serious adverse events); SAEs (serious adverse events); SARs (serious adverse reactions).

Table 3
PEDro Scale - methodological quality of included studies.

Study	PEDro scale											Total (2–11)
	1	2	3	4	5	6	7	8	9	10	11	
Bourke et al. (2014)	*1*	*1*	*0*	*1*	*0*	*0*	*0*	*1*	*1*	*1*	*1*	***6***
Clark et al. (2017)	*1*	*1*	*0*	*1*	*0*	*0*	*1*	*1*	*1*	*1*	*1*	***7***
Dougall et al. (2014)	*1*	*1*	*0*	*1*	*0*	*0*	*1*	*1*	*0*	*1*	*1*	***6***
Geraghty, Hann and Kurtev, 2019	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*0*	*1*	*1*	***3***
Sharpe et al. (2015)	*1*	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*1*	*1*	*1*	***5***
White et al. (2013)	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*1*	*1*	***5***

1: Eligibility criteria; 2: Random allocation; 3: Concealed allocation; 4: Groups similar at baseline; 5: Blinded participants; 6: Blinded therapy administration; 7: Blinded assessors of outcomes; 8 Outcomes obtained from >85 % of participants; 9: Intention-to-treat analysis; 10: Statistical between-group comparisons for at least one key outcome; 11: Point estimates and variability.
0 indicates no; 1 indicates yes.

All included studies reported declarations of interest. Geraghty et al. (2019) declared no conflicts of interest. White et al. (2013) reported royalty conflicts. Similar declarations were made in studies by Bourke et al. (2014), Dougall et al. (2014), Sharpe et al. (2015), and Clark et al. (2017), with P.D. White as a contributing author. Clark et al. (2017) also noted that authors received grants and provided unpaid advice to the UK Department for Work and Pensions until 2015.

4. Discussion

4.1. Findings in context of related studies

This systematic review explored the current literature regarding PT versus GET for improving fatigue, pain, and QOL outcomes in PwME/CFS. Identification of six suitable studies for review demonstrated the scarcity of research in this area. Amongst the included studies, treatment arms included GET (n = 5; one used GES), PT (n = 5), and SMC (n = 4). Across the included studies, GET has been associated with less frequent joint and muscle pain compared to PT (Bourke et al., 2014). GES resulted in reduced pain, and improved quality of life and physical functioning when compared to SMC (Clark et al., 2017). Post intervention questionnaires found 44 % of PT patients reporting symptom improvement compared to 12 % in GET group (Geraghty et al., 2019). Recovery 1-year post-intervention was highest after GET compared to PT and SMC (White et al., 2013), however at 2.5 year follow up, fatigue and physical functioning had improved in APT and SMC groups, but not GET (Sharpe et al., 2015).

4.2. Effectiveness of interventions

Fatigue:

The CFQ questionnaire measures fatigue severity (Jackson, 2015) and is widely used in ME/CFS research (Kim et al., 2020; Leslie et al., 2023) due to its reliability and validity (Chalder et al., 1993). Despite a low ceiling effect, 56 % of RCTs on physiotherapy for ME/CFS used this scale (Wormgoor and Rodenburg, 2021). In this review, 50 % of studies used the CFQ as the primary fatigue measure.

White et al. (2013), Sharpe et al. (2015), and Clark et al. (2017) used the CFQ Likert Scale. Clark et al. (2017) and White et al. (2013) found significant CFQ score improvements in their GET groups at 12 and 52 weeks, respectively. The SMC group also improved at 12 weeks, but less than the GET group. Most recoveries were in the GET group at 52 weeks. However, Sharpe et al. (2015) found significant fatigue improvements in the PT and SMC groups at 2.5 years follow-up, but not in the GET group.

Bearing in mind the limited scope of the literature, and lack of a universal method of PT and GET across the studies, preliminary suggestions are that GET provides initial improvements in fatigue levels immediately post-intervention. However, the studies with follow-up at 1-year and 2.5 years, suggest that without maintaining these initial improvements, they become more fatigued again over time post-GET; whereas those who partook in PT showed better fatigue outcomes in the years following PT intervention. This could be due to pacing being easier to continue once the skills have been learnt, without being encouraged by clinician-led sessions in terms of motivation and applying these techniques to their already established daily routine (Barry et al., 2024). Previous literature has shown fatigue outcomes to be one of the most important measures in ME/CFS research (NICE, 2021).

4.2.1. Pain

ME/CFS pain often manifests as muscle, joint, or nerve pain (Bateman et al., 2021) due to symptoms like PEM (Chu et al., 2018), complicating pain management. Only Bourke et al. (2014) studied pain response to physiotherapy, using the CDC checklist for muscle and joint pain. Scores of 0–1 indicated no symptoms, while 2–4 indicated symptoms. They found GET reduced muscle and joint pain compared to APT and SMT, but did not compare APT to SMC, limiting conclusions on pacing effectiveness. Methodological screening rated the study as good, despite non-concealed allocation and non-blinding.

Pain in PwME/CFS may stem from fatigue, PEM, and could be musculoskeletal or neurological (Gerwyn and Maes, 2017). The lack of comparative studies makes it hard to assess GET and pacing effectiveness on pain in ME/CFS.

4.2.2. Quality of life

The SF-36 is the most frequently used tool to measure QOL in PwME/CFS, with 69 % of RCTs using it (Kim et al., 2020; Van Campen et al., 2020; Wormgoor and Rodenburg, 2021). In this review, 50 % of studies used the SF-36PF as a primary outcome measure. Of the included studies in this review, 50 % (n = 3) used the SF-36PF as a primary outcome measure. Clark et al. (2017) and White et al. (2013) both found their GET groups resulted in significantly improved scores in SF-36PF at 12-weeks and 52-weeks post-intervention respectively. The SMC group also saw significant improvements in physical functioning at 12-weeks. At 12-weeks, SF-36PF scores were significantly higher as a result of GES when compared to SMC. At 52-weeks more recoveries were recorded due to GET compared to SMC and pacing, and no significant changes were noted between APT and SMC. Opposing these results, at 2.5 years follow-up, Sharpe et al. (2015) found significant within-group improvements from PT and SMC for physical functioning scores. Geraghty et al. (2019) took a different approach by surveying patients' views of previous therapy interventions for their ME/CFS. The study findings seem promising as a preliminary search, although considerations need to be made given the study's methodological quality was rated poor, the lowest of all included studies. That being said, they had the largest recruitment of almost 1000 participants. Therefore, this data can be useful in context of the other findings in determining the appropriateness of physiotherapy treatments for PwME/CFS going forward. In their study, they found PT to lead with 44 % of participants reporting improvements in symptoms, whereas 74 % of participants reported worse symptoms after attending GET. The authors also reported that certain factors were directly correlated with poor outcomes such as the participant rating the course as inappropriate, not attending the full course, clinician belief that ME was psychological rather than a physical illness, and those who had ME for longer than 12 years were more likely to have reported deterioration of symptoms.

4.2.3. Adverse effects of interventions

Phillips et al. (2019) highlighted inconsistencies in reporting adverse effects in clinical trials, raising safety concerns. Treatment harms and side effects must be routinely considered (Barry et al., 2024). Two studies in this review addressed adverse effects of PT, GET, or SMC for ME/CFS. Dougall et al. (2014) focused on the PACE trial, while Clark et al. (2017) reported all adverse effects in their research on GET for fatigue and physical function in PwME/CFS. Both studies categorized adverse effects into non-serious adverse events (NSAEs), serious adverse events (SAEs), serious adverse reactions (SARs), and serious deteriorations, as suggested by the Cochrane Handbook (Peryer et al., 2023). The Cochrane Handbook also suggests these as commonly used terms in reported adverse effects (Peryer et al., 2023). Across the two studies, less than 10 % of the 677 participants experienced an SAE (5 %), SAR (<1 %), or worsening of fatigue (9 %). 19 % reported worsening physical function, mainly due to PT (25 %), with GET and SMC both under 10 %. NSAEs were most common (74 %), with over 25 % in each treatment arm, but no significant differences between groups. Less than 50 % of NSAEs were attributed to ME/CFS symptoms. SMC appeared safest, followed by GET, while PT had more NSAEs and serious deteriorations. However, Clark et al. (2017) did not report pacing adverse effects, limiting direct comparisons.

Current guidelines suggest PT is superior to GET and CBT for ME/CFS, but the PACE trial's exercise recommendations and updated NICE guidelines (2021) highlight uncertainties about GET risks (Barry et al., 2024). Previous research shows GET can harm PwME/CFS (NICE, 2021),

while PT lacks evidence of direct harm (Barry et al., 2024).

The PACE trial should have considered adverse effects, as Dougall et al. (2014) did, to better understand GET and PT safety for ME/CFS. Dougall et al.'s (2014) delayed study included long-term adverse effects not immediately noticeable.

5. Strengths and limitations

5.1. Strengths

The analysis rigorously appraised evidence, ensuring quality control and defined outcomes. It included six studies with 200–1000 patients, representing the ME/CFS population and impacting conclusions on GET and PT effectiveness.

5.2. Limitations of the evidence

The review faced several limitations, including limited literature availability and varied outcome measures. Only one study assessed pain outcomes, and another used a unique survey. Physiotherapy interventions varied in delivery methods, such as clinician-led GET and self-led GES, and different approaches by clinicians. The lack of a universal method for GET or pacing led to diverse approaches, affecting outcomes. Comparisons were hindered by varied timescales, though PACE trial studies provided long-term insights up to 2.5 years post-intervention.

5.3. Limitations of the review process

Limiting searches to English led to all studies being UK-based, restricting generalizability to the global ME/CFS population and potential publication bias. Only studies available via the institution's library subscription services were included.

5.4. Clinical implications

Controversy over treatment approaches for PwME/CFS hinders access to appropriate care (Sanal-Hayes et al., 2023). Healthcare professionals, including physiotherapists, often lack sufficient knowledge of ME/CFS, leading to generic physiotherapy prescriptions (Sanal-Hayes et al., 2023; Wormgoor and Rodenburg, 2021). Understanding ME/CFS is crucial for optimal patient outcomes. The CDC (2021) and NICE (2021) recommend a multidisciplinary, individualized approach using both pharmaceutical and non-pharmaceutical methods. This review shows promise for GET and PT but staying updated with emerging research is essential.

5.5. Recommendations for future research

High-quality research on physiotherapy for ME/CFS is limited. Future studies should include participants across the severity spectrum, including housebound or bedbound individuals. Long-term studies are needed to assess the longevity of improved outcomes and inform therapy recommendations.

6. Conclusion

This review suggests that both pacing and graded exercise (GET/GES) show significant improvements immediately post-intervention when compared to SMC alone and, therefore, can be considered preferred options for ME/CFS, provided they are appropriately tailored to individual needs. Graded exercise shows the most promise for improving pain, fatigue, and physical function. At the 2.5-year follow-up, symptoms were maintained after PT; however, improved outcomes in GET had not been maintained at this stage. While GET shows short-term improvements, pacing provides more stable long-term outcomes. A combination of graded exercise and pacing could offer optimal short- and long-term benefits, but further high-quality research is needed to confirm this approach for ME/CFS management.

CRediT authorship contribution statement

Charlotte Cooper: Writing – original draft, Resources, Conceptualization. **Konstantinos Papadopoulos:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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