Review

Anomalies in the review process and interpretation of the evidence in the NICE guideline for chronic fatigue syndrome and myalgic encephalomyelitis


ABSTRACT

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a disabling long-term condition of unknown cause. The National Institute for Health and Care Excellence (NICE) published a guideline in 2021 that highlighted the seriousness of the condition, but also recommended that graded exercise therapy (GET) should only be used and cognitive–behavioural therapy should only be used to manage symptoms and reduce distress, not to aid recovery. This U-turn in recommendations from the previous 2007 guideline is controversial.

We suggest that the controversy stems from anomalies in both processing and interpretation of the evidence by the NICE committee. The committee: (1) created a new definition of CFS/ME, which ‘downgraded’ the certainty of trial evidence; (2) omitted data from standard trial end points used to assess efficacy; (3) discounted trial data when assessing treatment harm in favour of lower quality surveys and qualitative studies; (4) minimised the importance of fatigue as an outcome; (5) did not use accepted practices to synthesise trial evidence adequately using GRADE (Grading of Recommendations, Assessment, Development and Evaluations trial evidence); (6) interpreted GET as mandating fixed increments of change when trials defined it as collaborative, negotiated and symptom dependent; (7) deviated from NICE recommendations of rehabilitation for related conditions, such as chronic primary pain and (8) recommended an energy management approach in the absence of supportive research evidence.

We conclude that the dissonance between this and the previous guideline was the result of deviating from usual scientific standards of the NICE process. The consequences of this are that patients may be denied helpful treatments and therefore risk persistent ill health and disability.

INTRODUCTION

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is a disabling long-term condition, characterised by severe fatigue, and other symptoms that are typically made worse by minimal physical or mental exertion (postexertional fatigue and malaise).¹ ² In addition to fatigue, other common symptoms include cognitive difficulties, sleep disturbance and muscle pain.¹ ³

The UK National Institute for Health and Care Excellence (NICE) was founded in 1999. Although NICE has authority only in England, their publications are generally seen as providing high-quality evidence-based summaries that are highly influential in shaping clinical practice worldwide.”³ The NICE 2007 CFS/ME guideline recommended offering two specific forms of rehabilitation, namely graded exercise therapy (GET) and cognitive–behavioural therapy (CBT), to those with mild or moderately severe CFS/ME.⁴ These recommendations were based on the evidence review that NICE commissioned, which concluded that: ‘GET and CBT appeared to reduce symptoms and improve function, based on evidence from RCTs’.⁵

NICE published a new guideline in October 2021, which concluded that the evidence of benefit for rehabilitation in general and specifically for both CBT and GET was of low or very low certainty, using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) evidence appraisal approach.⁶ The guideline recommended that GET should not be provided and qualified the use of CBT, which they concluded was only useful for managing symptoms and treating distress, but was not a treatment of the core illness itself.⁶
Such a substantial change to the previous recommendations would be understandable if the balance of the evidence had fundamentally changed. An internal NICE Review in 2017 had concluded that there was no new evidence to justify a revision of the previous guideline. Table 1 provides the conclusions of the meta-analyses of behavioural intervention trials published since 2007. Although some reviews mentioned limitations in the evidence, every review concluded that CBT and GET improved fatigue and other outcomes.

Yet despite the findings of these reviews, NICE decided to revise the 2007 guideline. This revision has met considerable opposition. Three clinicians working in the field, who were on the NICE guideline committee, resigned before publication. Four Royal Colleges of Medicine concluded that ‘GET as defined in the guidance is not reflective of the personalised paced exercise programmes that are currently used in the National Health Service and termed GET. These have provided benefit to many patients and should not be discontinued.’ A Lancet commentary concluded that: ‘By selective use of the evidence from randomised studies, cherry-picking statements from qualitative studies, and relying on the opinions of the committee, NICE disregarded the best available research evidence and tarnished the guideline process.’

So, what went wrong? In this article, we raise concerns regarding the evidence synthesis, appraisal and interpretation that appear to have underpinned the revised guidance. Our criticisms are all based on our reviews of the new NICE guideline and the published appendices supporting the guideline.

The uncontroversial conclusions about CFS/ME in the guideline

First, we want to make clear that there are many things known about this illness, which are agreed by all, and which were included in the guideline. Some of the main points of agreement are summarised in Box 1.

The changes in recommendations regarding the management of CFS/ME

We suggest that the changes in recommendations concerning the management of CFS/ME derived from the processes chosen for identifying and synthesising data for the NICE guideline. For full details of concerns over the review process, please refer to the responses to consultation of the draft guideline by four Royal College of Medicine.

Table 1 Summary of meta-analyses published since 2007

<table>
<thead>
<tr>
<th>Meta-analyses</th>
<th>No of trials*</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price, 2008†</td>
<td>15 (only CBT)</td>
<td>‘CBT is effective in reducing the symptoms of fatigue at post-treatment compared with usual care, and may be more effective in reducing fatigue symptoms compared with other psychological therapies.’</td>
</tr>
<tr>
<td>Malouf, 2008‡</td>
<td>13</td>
<td>‘Results indicate that CBT for chronic fatigue syndrome tends to be moderately efficacious.’</td>
</tr>
<tr>
<td>Castell, 2011§</td>
<td>20</td>
<td>‘The results suggested that both CBT and GET are promising treatments for CFS, although CBT may be a more effective treatment when patients have comorbid anxiety and depressive symptoms.’</td>
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<tr>
<td>Marques, 2015¶</td>
<td>16</td>
<td>‘This meta-analysis of behavioural and psychological interventions targeting graded activity suggests that these interventions have sustained beneficial effects on chronic fatigue management, in particular on fatigue severity reduction for which a medium effect was found.’</td>
</tr>
<tr>
<td>Smith, 2015‖</td>
<td>21</td>
<td>‘Trials of rintatolimod, counselling therapies and graded exercise therapy suggest benefit for some patients meeting case definitions for CFS, although evidence for other treatments and harms is insufficient.’</td>
</tr>
<tr>
<td>Smith, 2016¶¶</td>
<td>16</td>
<td>‘Rintatolimod improves exercise performance in some patients (low strength of evidence), while counselling therapies and GET have broader benefit but have not been adequately tested in more disabled populations (low to moderate strength of evidence).’</td>
</tr>
<tr>
<td>Larun, 2019¶¶¶</td>
<td>8 (Only GET)</td>
<td>‘Exercise therapy probably has a positive effect on fatigue in adults with CFS compared with usual care or passive therapies.’</td>
</tr>
<tr>
<td>Casson, 2022¶¶¶¶</td>
<td>14§§</td>
<td>‘Activity pacing interventions are effective in reducing fatigue and psychological distress and improving physical function in CFS, particularly when people are encouraged to gradually increase exercise.’</td>
</tr>
<tr>
<td>Ingman, 2022¶¶¶¶¶</td>
<td>15</td>
<td>‘Results suggest some support for the positive effects of CBT and GET at short-term to medium-term follow-up although this requires further investigation given the inconsistent findings of previous reviews.’</td>
</tr>
<tr>
<td>Chou, 2022¶¶¶¶¶¶</td>
<td>22</td>
<td>‘CBT and exercise therapy were associated with improved fatigue, function and other outcomes vs inactive control therapies, but the magnitude of effects based on average benefits was small to moderate. … The strength of evidence supporting the use of graded exercise and CBT was low and the magnitude of benefits was small to moderate, with inadequate evidence in patients diagnosed with more current case definitions, limited reporting of harms, and inadequate evaluation in severely affected patients.’</td>
</tr>
</tbody>
</table>

*Number of trials of behavioural interventions reviewed.
†Reanalysis of Smith 2016 excluded trials using Oxford definition of CFS.
‡Activity pacing’ interventions included CBT and GET.
§Systematic review, not a meta-analysis.
¶CBT, cognitive–behavioural therapy; CFS, chronic fatigue syndrome; GET, graded exercise therapy.

Box 1 Uncontroversial conclusions about chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in the guideline

⇒ CFS/ME is a serious and debilitating condition.
⇒ Some patients are severely disabled, which may limit access to care and treatment.
⇒ Postexertional malaise is a common and important symptom of the illness.
⇒ CFS/ME shows pathophysiological changes, but there are no diagnostic tests.
⇒ People with CFS/ME may not have their illness taken sufficiently seriously by health and other professionals.
⇒ Treatments for CFS/ME should be negotiated between healthcare professionals and patients and should always be delivered collaboratively.
⇒ Simply telling patients to exercise more may make them worse.
⇒ Evidenced-based therapies for CFS/ME, such as cognitive–behavioural therapy and graded exercise therapy, do not benefit all patients.
Box 2 Eight anomalies of the National Institute for Health and Care Excellence (NICE) committee’s chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) 2021 guideline process and conclusions

- The use of a new definition of CFS/ME downgraded the certainty of trial evidence.
- Omission of outcome data from standard trial end points used to assess efficacy.
- Discounting trial data when assessing treatment harm in favour of lower-quality reports.
- Minimisation of the importance of fatigue as an outcome.
- Non-standard use of GRADE (Grading of Recommendations, Assessment, Development and Evaluations) to assess the trial evidence.
- Interpretation of graded exercise therapy as mandating fixed increments of change when trials defined it as collaborative, negotiated and symptom dependent.
- Inconsistency with NICE recommendations of rehabilitation for related conditions, such as chronic primary pain.
- Recommendation of an energy management approach in the absence of supportive research evidence.

Colleges of Medicine and the Association of British Neurologists, among others, which are available on the NICE Guideline website.11 There was a remarkable consistency in the criticisms made by these organisations. We have described our concerns regarding the process below (see Box 2 for a summary).

Use of a new definition of CFS/ME downgraded the certainty of trial evidence

A new set of diagnostic criteria for CFS/ME was devised by the NICE committee creating the guideline.6 Partially based on a previous review of the evidence,1 but not appearing to have been guided by the Guidelines International Network checklist for modifying disease definitions,13 the committee decided that a provisional diagnosis of CFS/ME should only be made if patients have all four symptoms of: debilitating fatigueability, post-exertional symptom exacerbation, unrefreshing sleep and cognitive difficulties.6 (The committee preferred the term ‘post-exertional symptom exacerbation’ to ‘post-exertional malaise’ (PEM)). While there is strong evidence that PEM is an important and common symptom of CFS/ME,1 the new guideline made it mandatory for making the diagnosis. This is problematic as PEM is not a mandatory symptom in the Centers for Disease Control and Prevention (CDC) definition which, with over 6000 citations on Google Scholar, is far and away the most widely researched definition of the condition.14 The NICE committee then instructed the UK National Guideline Centre, which was tasked with undertaking the systematic reviews and meta-analyses, to downgrade as indirect evidence all those trials that had not specifically and explicitly required participants to report the symptom of PEM as a mandatory criterion for recruiting participants.15–17 As this was a newly created definition, it downgraded nearly thirty years of research.

The emphasis NICE placed on PEM is debatable.18 Its prevalence varies according to how the symptom is defined and it is not specific to CFS/ME, being found in many conditions which present with pathological fatigue.19–22 PEM is also subjective, by definition, as are all the symptoms that make up the syndrome of CFS/ME. In contrast, the guideline authors criticised the outcome measures used in all the trials they considered as being too ‘subjective’ (see fourth error below), but did not apply the same tests or arguments to the equally subjective symptom of PEM itself. NICE’s own reviewers found only one study that tested the diagnostic utility of individual symptoms, which stated that PEM had a sensitivity of 0.50 and specificity of 0.57, that is, low.13 As NICE concluded: ‘The (established) diagnostic criteria have not been evaluated in terms of their measurement validity and accuracy in diagnosing ME/CFS.’13 This equally applies to the newly proposed NICE diagnosis.

Most trials have used either the CDC or Oxford definitions of CFS/ME, neither of which mandate PEM, although it is an optional symptom of the CDC definition.14 23 PEM is common in populations of patients with CFS/ME. Some 85% of participants reported PEM in eight CBT trials available for consideration, the prevalence depending on its definition.14 An individual patient data analysis found no moderating effect of PEM on the impact of CBT on either fatigue or functional outcomes.26 NICE did undertake a sensitivity analysis to assess whether the presence of PEM in trials affected outcomes. However, they arbitrarily set the threshold for trials with the prevalence of PEM at >94% of participants and did not include the data from the eight trials mentioned above.17

Furthermore, one trial of self-help based on the principles of GET, which did use an illness definition that mandated PEM, found the exercise intervention was effective in reducing fatigue.23 Another large trial (PACE) used a sensitivity analysis to show that using an ME definition that mandated post-exertional fatigue made no significant difference to the more positive outcomes after both CBT and GET, when compared with adaptive pacing therapy and usual care.25 Indeed, PEM improved more with CBT and GET compared with the comparison treatments.26

In summary, adopting PEM as a mandatory symptom for previous trial participants was not based on robust evidence. Therefore, downgrading the certainty of evidence on this basis (of indirectness or applicability) was inappropriate.16 17

Omission of primary outcome data from standard trial end points used to assess efficacy

Based on the published appendices it is clear that the NICE committee did not use data from all time points and overlooked predefined end-point timings of trials. To comprehensively assess treatment effects over time, meta-analyses should use all time points that directly evaluate the treatment effect.27 After the end of any trial, participants are free to take up any treatment they wish. Any longer-term follow-up is purely naturalistic and outcomes, good or bad, are progressively less attributable to the original treatment to which the participants were randomised. However, the NICE committee only considered outcomes for each trial at the data point furthest away from randomisation.16 17 The justification for this decision was to allow examination of long-term outcomes, such as mortality; but since CFS/ME is not a fatal disease, this is unconvincing.28 The decision sometimes led to excluding consideration of earlier trial outcomes assigned a priori as primary end-point times.16 17

Most trials only published outcomes at the predefined trial endpoint. The primary end-point for the PACE trial was at 12 months;26 trial participants were also followed up naturally for 2.5 years after randomisation; some 2 years after the allocated treatment had ceased. By this time, 44% of PACE trial participants had received either another course of the original therapy allocated or another trial therapy.29 An unknown number had additional non-trial treatments. Consequently, it
was unsurprising that no significant differences in the primary outcomes (of fatigue and physical function) were observed across the original randomly allocated groups by this time.\textsuperscript{29} The overall improvement in the CBT and GET groups was maintained in the PACE trial and the patients who had initially received other interventions also improved; that is, they caught up.\textsuperscript{29} This naturalistic follow-up finding was used by NICE to conclude incorrectly that these treatments were essentially ineffective.\textsuperscript{26} The 6 and 12 months’ findings of clear benefit for both CBT and GET, from the largest clinical trial in the literature, were not evaluated.\textsuperscript{26, 26} A cursory look at other current NICE guidelines to related or overlapping long-term conditions shows that this is not standard practice for NICE.\textsuperscript{30}

Discounting trial data when assessing treatment harm in favour of lower-quality reports

Harm is a critical issue to consider for all treatments, including psychological and physical therapies. As worsening can occur due to the natural history of the condition, harms should be assessed alongside benefits by extracting data from randomised clinical trials with comparisons made across interventions. The NICE committee inverted the usual evidence hierarchy by not adequately considering the reassuring evidence of the low risk of treatment harms found within randomised controlled trials, of GET in particular. Instead they prioritised qualitative studies and patient organisation surveys.\textsuperscript{16, 17}

Although the latest meta-analysis suggested that previous trials had limited reporting of harms,\textsuperscript{31} some relevant data are available. Both the PACE trial and a more recent trial systematically examined six measures of harm in all participants and found no evidence of harm after GET relative to comparison interventions.\textsuperscript{25, 26, 32} NICE was also provided with a summary of a meta-analysis of harm data from all 10 published trials of GET.\textsuperscript{25} This meta-analysis found no excess evidence of harm in relation to either the number of participants withdrawing from GET or rating their overall health as worse after treatment, when compared with controls.\textsuperscript{33} The meta-analysis did find that more participants dropped out of trial follow-up after GET, when compared with control interventions (11% vs 7%), but the authors suggested that this might have been related to the intensity of the initial exercise.\textsuperscript{33} So, while systematic studies of the safety of GET found no convincing evidence of harm with GET, NICE concluded that GET was not safe.

Minimisation of the importance of fatigue as an outcome

The NICE committee decided to downgrade all fatigue outcomes based on the premise that it is a subjective measure.\textsuperscript{16} This was inconsistent with the diagnosis of CFS/ME; all definitions depend on self-reported symptoms that are by definition, subjective. This subjectivity holds true for all four symptoms—debilitating fatigability, postexertional symptom exacerbation, unrefreshing sleep and cognitive difficulties. All these symptoms were included in the new NICE diagnostic criteria of CFS/ME.\textsuperscript{5} This is analogous to downgrading the importance of pain as an outcome in treatment trials of chronic pain. At the present time, there is no objective test that can tell us whether a patient has or does not have CFS/ME, so applying a different standard to outcome data from the diagnostic criteria is inconsistent.

The NICE committee took the view that therapy trials not being ‘blinded’, with both participant and therapist being aware of the intervention, impaired the validity of the results.\textsuperscript{26} Trials of complex non-pharmacological interventions often necessitate non-blinding of participants and therapists.\textsuperscript{14} Interestingly, a recent meta-epidemiological study of 142 Cochrane trial meta-analyses concluded that concerns over bias by lack of blinding in randomised trials may have been exaggerated.\textsuperscript{35}

The NICE guideline provided a description of what CBT entails.\textsuperscript{6} It suggested that CBT should focus primarily on support for managing symptoms and treating (emotional) distress, which was seen as a consequence of the illness. This is not what CBT was developed to do or how it was delivered in the trials for CFS/ME. The primary intention of CBT in the context of CFS/ME is to improve fatigue and function. We are not aware of any trial of CBT that had relief of distress as its primary outcome. Suggesting that CBT should only be used to manage symptoms and reduce distress associated with having a chronic illness implies that there is a ‘core illness’ that CBT cannot change.\textsuperscript{4} This assumption is puzzling given that CFS/ME is defined purely in terms of symptoms and impaired functioning. If the symptoms resolve and there is a sustained return to normal life, then the patient has recovered. A treatment such as CBT that reduces fatigue and improves functioning is therefore a treatment that improves the condition, as the clinical trial evidence shows (table 1).

Non-standard synthesis of GRADE to assess trial evidence

Based on the published reviews of the trial evidence, we consider that the research evidence was not presented adequately by NICE, resulting in the decision-making process being less robust. The application of the GRADE Evidence to Decision framework fell short of international expectations.\textsuperscript{36} Normal guideline development involves the research evidence being synthesised by methodological specialists, followed by the guideline development committee’s deliberations around benefits and harms being made transparently, with clear reasons for the resultant agreed recommendations.\textsuperscript{37} With complex interventions, NICE methodologists are available to characterise the components of the intervention, the theory of change and then characterise each trial to allow aggregated groupings. This did not happen. The NICE evidence tables were so disaggregated it is hard to interpret them.\textsuperscript{16, 17} The analysis was mainly at the level of the individual trial, which resulted in lower power and increased uncertainty in regard to primary outcomes.\textsuperscript{16, 17}

This lack of a robust process of evidence synthesis and guideline development was remarked on by four Royal Colleges of Medicine, which commented: ‘There is considerable disquiet in the medical profession and some patient groups about the way the data and evidence have been assessed...’\textsuperscript{7} The original GRADES methodologists described the review as ‘...a disastrous misapplication of GRADE methodology,...’\textsuperscript{36}

Interpretation of GET as employing fixed increments of change when the major trials defined it as collaborative, negotiated and symptom dependent

The description used by NICE is inconsistent with that of the 2007 guideline and trials of GET. In the current guideline, NICE described GET as incorporating fixed increments of exercise that are pursued irrespective of how the patient feels. We have been unable to find any trials that prescribed fixed increments of exercise. Trials and the previous guideline suggest that in GET, activity is determined collaboratively with the patient and only increased as the patient feels able, dependent on their symptomatic response. Table 2 illustrates important examples of this from: the very first RCT, the previous NICE guideline, the largest trials of GET and the Cochrane review of exercise therapy. Online supplemental table 3 provides examples from
all the other trials of GET. So, there are no ‘fixed increments of exercise’ in GET. The current guideline does describe an exercise programme, for those who wish to try it, but does not reflect the protocols used in the trials.6 37

Inconsistency with NICE recommendations of rehabilitation therapies for related conditions, such as chronic primary pain

NICE published a guideline for the management of chronic primary pain in 2021,40 6 3 months before the CFS/ME guideline. Chronic primary pain includes disorders such as fibromyalgia, which overlaps substantially with CFS/ME in terms of comorbidity and current aetiological and mechanistic thinking.38 Population-based studies show a considerable overlap between these two conditions.39 Indeed, the term ‘myalgic’ in ‘ME’ highlights how commonly people with CFS/ME experience pain.

Despite the strong clinical overlap, the conclusions were quite different in the primary pain guideline. For chronic primary pain, NICE recommends rehabilitation therapies, including graded exercise and psychological therapy.40 For clinicians seeing patients where CFS/ME coexists with chronic primary pain the contrasting advice is confusing. Furthermore, NICE recommends both CBT and exercise therapies in a range of neurological conditions, such as multiple sclerosis, where it can reduce fatigue and improve mobility.40 This inconsistent approach is confusing for the outside world.

NICE responded to these criticisms by suggesting that the pain in CFS/ME differs from that found in conditions such as fibromyalgia.11 12 The new guideline refers the reader to the NICE guideline on neuropathic pain.6 3 However, the pain of CFS/ME is not neuropathic pain, which is caused by a lesion or disease affecting the somatosensory nervous system.41 There is no evidence that this is the case in CFS/ME, and the International Association for the Study of Pain does not include CFS/ME as a cause of neuropathic pain.41 The category of nociceplastic pain, which is equivalent to chronic primary pain, is the correct category for the pain of CFS/ME.42

Recommendation of an energy management approach in the absence of supportive research evidence

Having downgraded the randomised trials of CBT and GET as primary treatments, NICE recommended ‘energy management’, in which patients are encouraged to stay within the energy limits imposed by their illness, and thus avoid exacerbating symptoms.5

This approach is often described as pacing. NICE recommended this approach based on the experience of the guideline committee, yet the (limited) research evidence suggests otherwise. The only substantial evaluation of pacing for CFS/ME published to date was as one arm of the PACE trial.26 This showed that adaptive pacing therapy, supported by an occupational therapist, was no more effective than specialist medical care alone and clearly less effective than either CBT or GET.26 32

CONCLUSIONS

The new guideline includes important statements about the nature and consequences of CFS/ME. But, in regard to management, we have presented evidence that suggests that both the processes of synthesis of the evidence and decision-making were problematic. It is difficult to understand the disconnect between the initial 2007 guideline that recommended CBT and GET, for which the research evidence has strengthened over the following decade, and the recent guideline that removes GET, qualifies CBT and replaces them with ‘energy management’, for which there is little evidence. We are concerned that this new guideline will effectively deny clinicians the ability to offer GET and evidence based CBT to those patients who want them and risks perpetuating chronic ill health and disability.

Since the guideline was published, three new systematic reviews have been published.31 41 44 The forthcoming individual patient data meta-analysis of exercise therapy trials for CFS/ME is a further step in the right direction.43 NICE should now reconvene a panel with an appropriate mix of specialists, methodologists and patients (both recovered and those still unwell), to revise the guideline, based on these new reviews. In the meantime, both patients and clinicians may wish to remember that NICE guidelines are advisory, not mandatory. Finally, there is also a great need for more rigorous clinical trial research into novel interventions for those who do not respond to either CBT or GET.

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Table 2 Descriptions of get prescriptions

<table>
<thead>
<tr>
<th>Trial/review/guideline</th>
<th>Description of GET incremental approach</th>
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<tbody>
<tr>
<td>Fulcher, 199826</td>
<td>‘If they [the patient] complain of fatigue in response to a new level of exercise, they should be advised to remain at the same level for an extra week, rather than progressing the duration, and to increase the exercise when the symptoms regress.’ (our italics)</td>
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<tr>
<td>NICE, 20074</td>
<td>‘When the low-intensity exercise can be sustained (our italics) for 5 days out of 7 (usually accompanied by a reduction in perceived exertion), the duration should be reviewed and increased, if appropriate, by up to 20%. For example, a 5-minute walk becomes 6 minutes…’</td>
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<tr>
<td>White, 201126</td>
<td>‘If it [exercise] can’t be done every day, then the starting level is too high … Keep to this level of activity until you are used to it and it feels OK. Once it feels OK (our italics) you’re getting stronger!, another small increase in time can be added.’</td>
</tr>
<tr>
<td>Clark, 201725</td>
<td>‘Importantly, if a participant found that their symptoms increased after an incremental change in their activity, they were advised to maintain their activity at the same level for longer than a week, until symptoms had settled. (our italics) before considering another incremental increase.’</td>
</tr>
<tr>
<td>Larun, 201937</td>
<td>‘Graded exercise therapy is characterised by establishment of a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active followed by an increase in intensity.’</td>
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</tbody>
</table>
Neuropsychiatry

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BAD reports NIH R13 infrastructure grant for 2022 Functional Neurological Disorders Society meeting in Boston. TC was co-investigator of several trials of behavioural interventions for CFS/ME, including the PACE trial, has received royalties for several books and book chapters on CFS/ME and received payments for workshops on CBT for CFS/ME. BAD is on the board of directors of the FNSD and receives royalties from Oxford University Press for ‘Psychogenic Nonepileptic Seizures: Towards the Integration of Care’. She does paid consultancy for Bioserity (EEG interpretations) and Best Doctors (clinical consultations). She received support to attend the American Epilepsy Society Board of Directors meeting in 2019. She chairs the data safety monitoring board of the DSMB NIH-ESETT trial 2015–2019, and received travel expenses to attend the American Epilepsy Society Board of Directors FNSD meeting and Epilepsy Foundation of New England PAB. MB reports royalties from Oxford University Press for the book ‘The Oxford Specialist Handbook of Movement Disorders’, consulting fees from UCB (personal) and Merz Pharma (to his institution), honoraria from the International Parkinson’s Disease and Movement Disorder Society (PD and MDS) and medicolegal fees for personal injury and clinical negligence cases, support to attend meetings from the FNSD, leadership roles in International Parkinson’s Disease and Movement Disorder Society and Dystonia UK, and is a medical board member of FND Action and FND Hope, and board member of the FNSD. JE was the President of the Faculty of Sport and Exercise Medicine at the time of the Royal College of Physicians’ review of this guideline and submitted comments on behalf of the Faculty. He is Medical Director of a company which occasionally manages patients with CFS/ME. 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SF was a co-founder of the Medical Working Group and a member of the GRADE guidance group. She has been engaged in debates related to the evidence regarding CFS/ME for many years from a biopsychosocial perspective. PGlasziou declares an NHMRC Investigator Award: ‘Neglected Problems in Health Care’ supporting his salary; grants from the National Heart Foundation, Commonwealth Department of Health and WHO for work unconnected to this paper; a Regeneron Pharmaceuticals, Samumed, Swing Therapeutics, and Acorda, and is a member of a company developing nonaggregating peptide analogues as replacement therapies for neurodegenerative diseases) and is co-owner of a patent that covers synthetic soluble nonaggregating peptide analogues as replacement treatments in proteinopathies. PMR has been engaged in debates related to the evidence regarding CFS/ME for many years from a biopsychosocial perspective. 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