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PERSPECTIVE

Evidence-Based Care for People with Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

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Chronic fatigue syndrome (CFS), sometimes referred to as myalgic encephalomyelitis (ME) and often as CFS/ME, is an illness characterized by disabling fatigue and other symptoms, typically worsened by activity. The main evidence-based treatments are rehabilitative in nature and include specific types of cognitive behavior therapy (CBT) and graded exercise therapy (GET). In this article, we briefly review the evidence for their safety and effectiveness and propose that much of the controversy about them arises from misunderstandings about their nature and delivery. In particular, we emphasize that successful rehabilitation from CFS/ME does not indicate that the illness is not real. We recommend that rehabilitative treatment always be preceded by a thorough clinical assessment and delivered by appropriately trained therapists working in close collaboration with the patient. We conclude that properly applied rehabilitative treatments offer the best hope of safely improving fatigue and function for patients with CFS/ME. However, we also recognize the need for more research into the treatment of this neglected condition, especially for those most severely disabled by it.

Keywords Chronic fatigue syndrome · Myalgic encephalomyelitis · Management · Cognitive behavior · Therapy · Graded exercise therapy

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THE ILLNESS

Chronic fatigue syndrome (CFS) is a disabling and chronic illness that is characterized by fatigue and other symptoms that are typically exacerbated by exertion (a phenomenon often referred to as post-exertional malaise or PEM) and that are not better explained by an alternative diagnosis.[1–3] These symptoms are also ascribed to a condition referred to as myalgic encephalomyelitis (ME).[1, 2, 4] Whilst some view CFS and ME as distinct illnesses, others believe that they are essentially the same condition and refer to CFS/ME.[4, 5] No specific etiology for this condition has yet been established.[1, 4] Whilst all agree that there is a great need for better care of people with CFS/ME, the nature of that care has been much debated.[6] In this narrative review, we describe rehabilitative treatments and the evidence for such treatments.

MANAGEMENT OF CFS/ME

Once a thorough assessment of the patient is complete and alternative diagnoses have been excluded,[5, 7, 8] the physician is tasked with deciding which treatment the patient with a diagnosis of CFS/ME should be offered? The most researched approaches are the rehabilitative therapies of cognitive behavior therapy (CBT) and graded exercise therapy (GET).[9–12] These are non-pharmacological approaches that aim to relieve the symptoms and help the patient return to their desired activities.

In CBT, a therapist works collaboratively with the patient to review the way they understand and cope with their symptoms.[13] It is based on the observation that patients with CFS/ME often reduce their activity as a way of coping. This approach is an understandable consequence of the experience that activity leads to an increase in symptoms. As a consequence, they may become profoundly inactive, or get trapped in cycles of rest and activity. CBT aims to help the patient to stabilize and regularize their patterns of activity, rest and sleep, and then try out very gradual and consistent supervised increases in activity, whilst testing out their concerns that greater activity necessarily produces a persistent increase in symptoms. Together with this change in activity, patients are helped to address any social and emotional obstacles to a return to normal activities, using strategies such as problem-solving.[13]

In graded exercise therapy (GET), a therapist also works collaboratively with the patient to first stabilize activity and then to gradually increase it.[13] Incremental increases in the time spent physically active are carefully and mutually negotiated between patient and therapist. Target heart rate ranges are set when necessary in order to avoid overexertion, and increments in activity are informed by the patient's symptomatic response to

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it. The aim is to achieve 30 min of light exercise (such as walking) five times a week. Once this level of activity is attained, gradual increases in the intensity of exercise can be considered, depending on the patient's desire and ability to do so.[13]

Whilst the rehabilitative approaches of CBT and GET were developed separately, they have many similarities. For those seeking information on how to deliver these therapies, the manuals for both therapists and patients that were used in a trial that found them to be safe and effective, are freely available on line.[13]

SHOULD YOU RECOMMEND CBT AND GET TO YOUR PATIENTS?

So, should you recommend CBT or GET to your patients with CFS/ME? We suggest that you should as there are many randomized trials indicating the safety and efficacy of these treatments.[9–12] However, some commentators suggest that you should not and have disputed the evidence from the trials.[6, 15–18] The dispute has focussed on the largest trial of these treatments done to date, the PACE trial.[14] PACE was a four-arm trial that recruited over 600 patients. It compared specialist medical care (SMC) alone, with SMC supplemented by one of three therapies. The therapies evaluated in this way were the rehabilitative therapies of CBT, GET, and the non-rehabilitative, but therapist contact time matched, adaptive pacing therapy (APT), in which the patient was encouraged not to exceed limits imposed on their activity by their symptoms. The trial found that the rehabilitative therapies CBT and GET were more effective in both improving functioning and in reducing fatigue than SMC alone or SMC supplemented by non-rehabilitative APT.[14] In other words, active rehabilitation was found to be more effective than non-rehabilitative approaches.

Those questioning the validity of these findings have disputed the case definition of the illness used to recruit participants to the trials and the use of patient-reported rather than objectively measured outcomes. They have pointed to patient group surveys which report that, outside the trial rehabilitation and GET in particular has made some patients worse.[6, 15–18] Responses to these methodological criticisms have been published .[13, 19–22] However, to help the reader better understand the controversy, we will briefly summarize some of the main criticisms and responses to them.

There are many published diagnostic criteria for CFS and for ME.[2] Most of the published trials have used either the Oxford or the Centers for Disease Control (CDC) criteria.[3, 23] These definitions have been criticized as not capturing patients with the real illness of CFS/ME, by not requiring the symptom of post-exertional malaise. Whilst the generalizability of clinical trials to wider patient populations is an important issue, we find this argument unconvincing. Interestingly, none of the many case definitions of CFS or ME has been shown in a systematic review to be any more valid than any other.[2] One study reported that the Oxford definition was so broad that it identified over 20% of the US population as having CFS (compared to two percent as defined by CDC criteria) but the study had misapplied the criteria.[24, 25] A systematic review of studies reported a median prevalence of 1.5% for Oxford defined CFS in the population or in primary care.[2] In the context of the PACE trial, a sensitivity analysis found that the trial participants improved irrespective of the criteria. The London diagnostic criteria for ME require the patient to have post-exertional malaise.[26] These patients improved to a similar degree to *all* those in the trial, with both GET and CBT.[14] In light of this evidence, we suggest that the results of trials that used Oxford and other diagnostic criteria, which do not specifically require post-exertional malaise, are indeed generalizable to the wider population of patients with CFS/ME. Any reviews of the literature, which conclude there is insufficient evidence for rehabilitative therapies after excluding such trials, are therefore misleading.[27]

The use of patient-reported outcomes to judge effectiveness has been much debated as a source of bias. In the absence of any established objective test or 'biomarker' for CFS/ME, the condition is defined almost solely by patient report.[1–3] It is therefore both appropriate and necessary to determine the outcome of treatment for CFS/ME by asking patients about the same symptoms and associated disability that were used to make the diagnosis, using standardised and validated patient-reported outcome measures (PROMs). It is of course true that patient reports may suffer from bias in an unblinded trial if the patient felt more positively about a particular treatment. This issue was addressed in the PACE trial by measuring the expectations of participants about potential improvement, before they started their treatment. Whilst the lowest expectations of a therapy were for CBT, those who received it reported the greatest improvements.[14] On the issue of blinding more broadly, a recent meta-epidemiological study of 142 Cochrane collaboration meta-analyses found no evidence that lack of blinding leads to exaggerated estimates of treatment effects in clinical trials.[28]

Some people have expressed concern that CBT and GET may cause harm to patients. This concern arises both from the common experience of patients and patient surveys that sudden increases in activity causes an increase should in symptoms.[6] All trials be they medicinal or otherwise report on safety as well as benefits. In the PACE trial, six safety outcomes were examined and there was no evidence of harm found from the very gradual and collaboratively planned increases of activity used in CBT or GET.[14, 29] A more recent trial of guided self-help, based on GET, used the same six safety measures, and also found there were no significant differences in safety outcomes between this intervention and specialist medical care.[30] It is of course likely that outside clinical trials, rehabilitative therapy is not always applied correctly; any medical intervention can cause harm if given at the wrong dose or frequency. In particular, rigidly applied programmes that are not collaborative or tailored to the patient's symptom severity and disability may lead to worsening of symptoms.[31] The discrepancy between the reported findings of patient surveys and randomised controlled trials clearly merits further exploration. However, it seems likely that any harm reported from patient community surveys reflects poorly implemented therapy, as well as possible misdiagnosis of CFS/ME.[31, 32] In summary, the available trial evidence indicates that these therapies are safe, if given properly.[33, 34]

One issue that is perhaps the most central to the debate about rehabilitation concerns the theoretical underpinning of such treatments. Rehabilitation, including CBT and GET, for CFS/ME assumes that disability and symptoms, once established, are at least in part maintained by factors that are reversible. The reversible factors include psychological and behavioural factors, such as the patients' worries about their symptoms and how they cope with them, as well as by associated physiological changes.[35, 36] A major concern of those who argue against rehabilitation is that such reversibility implies that the symptoms and disability of CFS/ME means CFS/ME is not a 'real physical illness'.[6] Whilst this concern is understandable, the conclusion drawn is surely wrong. A degree of reversibility of an illness, demonstrated by successful rehabilitation, does not imply that the illness was not real. Notably in this regard, both CBT and GET have been found to be effective in improving the fatigue and disability accompanying many established medical conditions.[37, 38].

ALTERNATIVES TO REHABILITATION

If we abandon rehabilitation as a treatment, what are the alternatives? The only widely described and advocated alternative management approach is a form of 'pacing' in which patients are encouraged to stay within the 'energy envelope' imposed by the illness and not to attempt rehabilitation.[6] However, the PACE trial found that such an approach was relatively ineffective in improving either patients' ability to do things or their symptoms and no better than specialist medical care alone.[14, 29] Furthermore, a systematic review of pharmacological interventions concluded 'that there is no clear recommended pharmaceutical therapy for CFS/ME.'[39] Given the lack of an effective alternative treatment to rehabilitation, we need to think twice before dismissing it as a treatment, given that trials continue to find that rehabilitative treatments are both safe and moderately effective for patients with CFS and related syndromes.[40, 41]

CONCLUSION

In conclusion, the available research evidence from randomized trials supports the use of the rehabilitative therapies of CBT and GET for patients with CFS/ME. More research is of course needed into these approaches, as well as into other treatments for this neglected group of patients. However, it would be a disservice to our patients to tell them we have nothing to offer them when the evidence suggests that we have evidence-based therapies that are both safe and moderately effective for many.

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Declarations

Conflict of Interest The authors were all members of the PACE trial research team. Trudie Chalder and Michael Sharpe have authored several books and book chapters on chronic fatigue syndrome and have received royalties for these. Peter White is an unpaid member of the Independent Medical Experts Group, which advises the UK Ministry of Defence regarding its Armed Forces Compensation scheme. He also provides paid consultancy to a re-insurance company. Trudie Chalder has conducted workshops on CBT for CFS and has received payment.

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