

PACE: CBT and GET are not rehabilitative therapies

In a recent Article Michael Sharpe and colleagues¹ report on findings of a follow-up study of the PACE trial of proposed rehabilitative interventions for chronic fatigue syndrome: graded exercise therapy (GET) and cognitive behavioural therapy (CBT). Their main finding is that the beneficial effects of CBT and GET were maintained at follow-up (median: 2.5 years).¹ Both CBT and GET have been qualified by the PACE trial investigators as "moderately effective treatments".² However, looking at the data of the follow-up study¹ and other PACE trial studies,^{2,3} CBT and GET do not qualify as rehabilitative therapies for chronic fatigue syndrome or myalgic encephalomyelitis, as defined by the London criteria.¹

First, the PACE trial investigated the effects of CBT and GET in chronic fatigue, as defined by the Oxford criteria, not in chronic fatigue syndrome, let alone myalgic encephalomyelitis, as defined by the Ramsay criteria.⁴ The Oxford criteria have been criticised often. For that reason "consensus groups and researchers should consider retiring the Oxford case definition".⁴

Second, the positive effect of CBT and GET in subjective measures, fatigue and physical functioning, cannot be qualified as sufficient. Mean short form-36 physical functioning scores in the CBT group (62.2) and the GET group (59.8) at follow-up were below the inclusion cutoff score for the PACE trial (≤ 65)³ and far below the objective for recovery as defined in the PACE protocol (≥ 85).⁵ The mean fatigue scores in the CBT group (18.4) and GET group (19.1) were above subnormal (< 18)⁴ and far above the entry criterion for the PACE trial (> 12 , recalculated)³ and the recovery criterion in the PACE protocol (≤ 6).⁵

Third, the PACE trial follow-up study¹ concluded that outcomes with specialist medical care alone or adaptive pacing therapy (APT) were similar to CBT and GET at follow-up. The authors suggest that "it is important to note that many of the participants had received additional treatment for CFS since completing the trial". Looking at the data,¹ 23 (20%) of the patients in the specialist medical care arm received an adequate number of sessions (n=10) of CBT after the PACE trial and 14 (12%) received GET, while 20 (17%) of the patients in the APT group received CBT and 7 (6%) received GET afterwards. This finding implies that the vast majority of patients improved subjectively by specialist medical care and APT to the same level as by CBT and GET, without any additional therapies, including CBT and GET, or by other therapies.¹

Finally, looking at subjective outcomes at follow-up¹ and objective outcomes in earlier studies, such as physical fitness,² return to employment,³ social welfare benefits,³ and health-care usage,³ CBT and GET, like specialist medical care and APT, cannot be qualified as effective.

In conclusion, CBT and GET are moderately effective in subjective terms in chronic fatigue, but looking at the patients studied and the (subjective and objective) outcomes of the PACE trial,^{1,3-5} CBT and GET do not meet the requirements for rehabilitative or effective therapies for chronic fatigue syndrome, let alone myalgic encephalomyelitis.

I am associated with a Dutch ME/CFS patient foundation in a voluntary (non-paid) capacity.

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Results of the PACE follow-up study are uninterpretable

The PACE follow-up study¹ is something of a curate's egg, admirable in ambition, but interpretatively indigestible. Although the PACE programme of cognitive behavioural therapy (CBT) or graded exercise therapy (GET) led patients to report less fatigue or greater physical function than patients in the adaptive pacing therapy and specialist medical care groups in the short term, evidence in the long-term follow-up is unconvincing. The lack of between-group differences at follow-up takes precedence over within-group differences, which are inflated by attribution of any change associated with non-specific factors to the specific interventions. Re-assignment to new treatment also makes between-group comparisons uninterpretable, as we will see.

Although the investigators made heroic efforts to correct for attrition using linear mixed-effects regression models, such efforts depend on their unjustified assumptions of random missing data and of treatment received at follow-up not distorting any signal of effects of the earlier



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randomisation. Various covariates are introduced for statistical control, but without adequate rationale and documentation of diagnostics. It is therefore doubtful that the complexly adjusted results are reliable.

Several other unfortunate decisions further undermine the findings. Foremost, the unregulated crossover between treatments during follow-up. The follow-up outcome data³ in table 3 and figure 2 are uninterpretable because they refer to initial randomisation, without reflecting the—quite different treatments—received during follow-up.

The authors argued: “In so far as the need to seek additional treatment is a marker of continuing illness, these findings support the superiority of CBT and GET as treatments for chronic fatigue syndrome”.¹ More participants in the specialist medical care alone and the adaptive pacing therapy (APT) groups received additional treatments during follow-up than did those in the CBT and GET groups, but this finding is hardly surprising when half of participants in the specialist medical care group rated it as not being a logical treatment for them and only 41% were confident about being helped by specialist medical care.¹ This lack of equipoise was facilitated by the initial description of treatments investigators offered to patients and compounded by a mid-trial Newsletter for patients praising the PACE interventions. It is easy to see how specialist medical care effectively became a waitlist control of frustrated sufferers, who naturally awaited re-assignment. This limitation casts doubts not only on the validity of the follow-up data, but on the integrity of the trial itself.

Putting doubts about the validity of the PACE follow-up aside, let's take a close look at the unadjusted physical functioning follow-up data in figure 2.¹ There are no group differences, and the overall mean

short-form 36 (SF-63) physical functioning score is less than 60. It is useful to put this number in context. 77% of the PACE trial participants were women, and the mean age of the trial population was 38 years, with no other disabling medical conditions. Patients with lupus have a mean physical functioning score of 63,² patients with class II congestive heart failure have a mean score lower than 60,³ and normal controls with no long-term health problems have a mean score of 93.⁴

Lastly, the PACE investigators have previously complained in *The Lancet Psychiatry* of “the apparent campaign to bring the robust findings of the trial into question”.⁵ We think the further scrutiny that the follow-up study has brought casts further doubt on whether there ever were “robust findings”. The investigators should get more accustomed to rigorous post-publication peer review, which is not a campaign, but a reality of the 21st century.

We declare no competing interests.

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Patient reaction to the PACE trial

The long-term follow-up of the PACE trial,¹ which originally reported that cognitive behavioural therapy (CBT) and graded exercise therapy (GET) produced a significant and sustained improvement, even recovery, for some people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)² should, in theory, have been greeted positively by patients. However, Michael Sharpe and colleagues³ found very little difference in outcomes at long-term follow-up between any of the four interventions (which also included adapted pacing therapy and specialist medical care) and the patient community has expressed both anger and despair.

Anger because the media, along with many health professionals, has concluded that people can recover from ME/CFS through a simplistic approach to management involving exercise and positive thinking.³ Despair because the findings from the PACE trial have not been supported by patient evidence on CBT, GET, and pacing, which dates back to the 2002 Chief Medical Officer's Working Group report⁴ on ME/CFS.

The largest and most recent survey⁵ of patient evidence on the acceptability, efficacy, and safety of CBT, GET, and pacing was carried out by The ME Association and involved 1428 respondents. In this case, 73% of respondents reported that CBT had no effect on their symptoms and 74% that their symptoms were made worse by GET.

As a result, The ME Association has recommended that the National Institute for Health and Care Excellence should withdraw their recommendation that everyone with mild or moderate ME/CFS should be offered GET. And while accepting that some people may find CBT helpful when there are comorbid mental health problems, as can occur with any