Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial

Michael Sharpe, Kimberley A Goldsmith*, Anthony L Johnson, Trudie Chalder, Jane Walker, Peter D White*

Summary

Background The PACE trial found that, when added to specialist medical care (SMC), cognitive behavioural therapy (CBT), or graded exercise therapy (GET) were superior to adaptive pacing therapy (APT) or SMC alone in improving fatigue and physical functioning in people with chronic fatigue syndrome 1 year after randomisation. In this pre-specified follow-up study, we aimed to assess additional treatments received after the trial and investigate long-term outcomes (at least 2 years after randomisation) within and between original treatment groups in those originally included in the PACE trial.

Methods The PACE trial was a parallel-group randomised controlled trial of patients meeting Oxford criteria for chronic fatigue syndrome who were recruited from six secondary care clinics in the UK between March 18, 2005, and Nov 28, 2008. Participants were randomly allocated to receive SMC alone or plus APT, CBT, or GET. Primary outcomes (were fatigue measured with Chalder fatigue questionnaire score and physical functioning with short form-36 subscale score, assessed 1 year after randomisation. In this long-term follow-up, we sent postal questionnaires to assess treatment received after the trial and outcomes a minimum of 2 years after randomisation. We assessed long-term differences in outcomes within and between originally randomised groups. The PACE trial is registered at http://isrctn.org, number ISRCTN54285094.

Findings Between May 8, 2008, and April 26, 2011, 481 (75%) participants from the PACE trial returned questionnaires. Median time from randomisation to return of long-term follow-up assessment was 31 months (IQR 30–32; range 24–53). 210 (44%) participants received additional treatment (mostly CBT or GET) after the trial; with participants originally assigned to SMC alone (73 [63%] of 115) or APT (60 [50%] of 119) more likely to seek treatment than those originally assigned to GET (41 [32%] of 127) or CBT (36 [31%] of 118; p<0·0001). Improvements in fatigue and physical functioning reported by participants originally assigned to CBT and GET were maintained (within-group comparison of fatigue and physical functioning, respectively, at long-term follow-up as compared with 1 year: CBT –2·2 [95% CI –3·7 to –0·6], 3·3 [0·02 to 6·7]; GET –1·3 [–2·7 to 0·1], 0·5 [–2·7 to 3·6]). Participants allocated to APT and to SMC alone in the trial improved over the follow-up period compared with 1 year (fatigue and physical functioning, respectively: APT –3·0 [–4·4 to –1·6], 8·5 [4·5 to 12·5]; SMC –3·9 [–5·3 to –2·6], 7·1 [4·0 to 10·3]). There was little evidence of differences in outcomes between the randomised treatment groups at long-term follow-up.

Interpretation The beneficial effects of CBT and GET seen at 1 year were maintained at long-term follow-up a median of 2·5 years after randomisation. Outcomes with SMC alone or APT improved from the 1 year outcome and were similar to CBT and GET at long-term follow-up, but these data should be interpreted in the context of additional therapies having being given according to physician choice and patient preference after the 1 year trial final assessment. Future research should identify predictors of response to CBT and GET and also develop better treatments for those who respond to neither.

Funding UK Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions, National Institute for Health Research (NIHR), NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust, King's College London.

Lancet Psychiatry 2015

Published Online October 28, 2015 http://dx.doi.org/10.1016/S2215-0366(15)00317-X

See Online/Comment http://dx.doi.org/10.1016/S2215-0366(15)00475-7

*Joint first authors

Psychological Medicine Research, University of Oxford Department of Psychiatry, Oxford, UK (Prof M Sharpe MD, J Walker PhD)**; Department of Biostatistics** (K A Goldsmith PhD) **and Academic Department of Psychological Medicine** (Prof T Chalder PhD)**, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; Medical Research Council Clinical Trials Unit at UCL, London, UK** (Prof A L Johnson PhD)**; and Centre for Psychiatry, Wolfson Institute of Preventive Medicine, Bart's and The London Medical School, Queen Mary University of London, London, UK** (Prof P D White MD)

Correspondence to: Prof Michael Sharpe, Psychological Medicine Research, University of Oxford Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK **michael.sharpe@psych.ox.ac.uk**

Introduction

Chronic fatigue syndrome is characterised by chronic disabling fatigue in the absence of an alternative diagnosis (panel). Myalgic encephalomyelitis is thought by some people to be the same disorder and by others to be a different disease. The prevalence of chronic fatigue syndrome is between 0·2% and 2·6% of people worldwide,[5] and, if untreated, prognosis for recovery is poor.[6]

In March, 2005, we started the PACE trial, a multicentre randomised trial to compare outcomes after the most commonly used non-pharmacological treatments in patients with chronic fatigue syndrome.[7] When we planned the trial, some evidence had shown that cognitive behavioural therapy (CBT) and graded exercise therapy (GET) could improve patient outcomes. However, these rehabilitative treatments were controversial among patient organisations who regarded adaptive pacing therapy (APT) and specialist medical care (SMC) as better alternatives. The PACE trial aimed to compare the outcomes of patients who were randomly allocated to one of the following four interventions: SMC alone, SMC plus APT, SMC plus CBT, or SMC plus GET. The trial found

Research in context

Evidence before this study

For the original PACE trial report, we searched PubMed and the Cochrane Library for articles about non-pharmacological interventions for chronic fatigue syndrome published up to Nov 6, 2010. The previous Research in context panel concluded that the untreated outcome for patients with chronic fatigue syndrome was poor, and that evidence existed that cognitive behavioural therapy (CBT) and graded exercise therapy (GET) improved this. The PACE trial confirmed that CBT and GET with specialist medical care (SMC) were more effective than SMC alone in improving fatigue and physical functioning 1 year after randomisation, but that adaptive pacing (APT) plus SMC was not.

For this study we searched PubMed to Feb 1, 2015 for follow-up studies of more than 1 year in patients who had received a PACE trial treatment. The reports identified were almost all of small studies of CBT. They suggested that the benefits from CBT are maintained. We did not find any long-term follow-up study after GET (although a single follow-up of an educational intervention that included advice on graded activity found the benefits were maintained) or APT.

Added value of this study

This follow-up of participants in the PACE trial provides robust evidence that the improvements in fatigue and function with CBT and GET are maintained in the longer-term (after 2·5 years). It does not provide evidence that CBT and GET are better than SMC and APT in the longer term because patients allocated to these treatments had improved to a similar degree by the time of the follow-up. The interpretation of this finding is complicated by the fact that many of these patients had received CBT or GET after the trial final follow-up assessment. Importantly, no significant worsening in perceived health occurred during the follow-up period after any of the trial treatments.

Implications of all the available evidence

Taken together, the available evidence confirms that the rehabilitative treatments of CBT and GET for chronic fatigue syndrome are associated with long-term improvement in fatigue and functioning for patients with chronic fatigue syndrome. However, the observation that some patients remain unwell at long-term follow-up reminds us that more effective treatments are still needed for these patients.

Panel: Definitions of chronic fatigue syndrome and myalgic encephalomyelitis

Differing definitions

Chronic fatigue syndrome is a disorder usually characterised by chronic disabling fatigue of at least 6 months' duration in the absence of an alternative diagnosis. The overlap between chronic fatigue syndrome and myalgic encephalomyelitis is controversial. At least 20 different published case definitions now exist for chronic fatigue syndrome and myalgic encephalomyelitis; all emphasise fatigue, but they include different additional symptoms, have different exclusion criteria, and select patients with differing degrees of functional impairment. Definitions substantially overlap. A systematic review[1] found no good evidence that any definition identifies patients with a specific disease aetiology.

The definitions used in the PACE trial

The PACE trial used the Oxford definition for chronic fatigue syndrome to select patients.[2] This definition has been used widely to select patients into treatment trials. It has the advantage of simplicity of application and needing fatigue to be the patient's main symptom. The international case definition[3] for chronic fatigue syndrome proposed by the US Centers for Disease Control and Prevention is now the most widely used in research. This definition is similar to the Oxford criteria but requires additional symptoms; it was met by two-thirds of PACE trial participants. At the time of the trial, the London definition was the only available definition for myalgic encephalomyelitis that was usable for research;[4] it was met by half the trial participants. Subgroup analyses did not find that outcomes differed for participants meeting each of these different diagnostic criteria.

that at 1 year (52 weeks) follow-up from randomisation, patients allocated to CBT or GET had significantly greater improvements in their fatigue and physical functioning than had those allocated to either APT or to SMC alone.[7]

Other long-term follow-up studies of participants in trials of treatments for chronic fatigue syndrome have been reported.[8–12] We report the findings of a pre-specified long-term (minimum 2 years after randomisation) follow-up of the PACE trial participants. After the final 1 year trial outcome, participants were able to access additional trial therapies according to need. We aimed to describe additional therapy (APT, CBT, GET) that participants received after 1 year; compare the outcomes of participants within each randomised treatment group at long-term follow-up with the final 1 year outcome assessment; and compare the long-term outcomes between the original randomised trial treatment groups, bearing in mind the limitations on interpretation imposed by the provision of additional, non-randomly allocated therapy during the post-trial follow-up period.

Methods

The PACE trial

The trial protocol[13] and report[7] describe the PACE trial methods, including details of the trial treatments. In summary, the PACE trial was a four-arm, parallel-group, randomised controlled trial of non-pharmacological treatments for patients meeting the Oxford criteria for chronic fatigue syndrome, which requires fatigue to be the patient's main symptom.[2] 641 participants were recruited from six secondary care clinics in the UK from March 18, 2005, to Nov 28, 2008, and randomly allocated (1:1:1:1) to SMC alone, or SMC plus APT, CBT, or GET. Participants received the interventions (APT, CBT, and GET) in one-to-one sessions (maximum 14 sessions) during the first 6 months of trial participation, with an additional booster session offered at 9 months. The trial primary outcome measures were fatigue and physical

functioning, measured using self-report scales at mid-treatment (12 weeks), post-treatment (24 weeks), and the final outcome assessment, 1 year (52 weeks) after randomisation.[7]

After completing their final trial outcome assessment, trial participants were offered an additional PACE therapy if they were still unwell, they wanted more treatment, and their PACE trial doctor agreed this was appropriate. The choice of treatment offered (APT, CBT, or GET) was made by the patient's doctor, taking into account both the patient's preference and their own opinion of which would be most beneficial. These choices were made with knowledge of the individual patient's treatment allocation and outcome, but before the overall trial findings were known. Interventions were based on the trial manuals, but could be adapted to the patient's needs.

Ethical approval for both the trial and follow-up study was given by the West Midlands Multicentre research ethics committee (MREC 02/7/89). Written consent for the follow-up was obtained at time of original trial recruitment.

Procedures

Follow-up assessments were done with a brief questionnaire. The follow-up questionnaires were sent by post to eligible participants at a time that was at least 2 years after the date of their randomisation. Non-responders were contacted by post again and if they still did not respond were reminded by telephone.

The follow-up questionnaire included the following: questions about the nature and amount of any additional PACE therapies (CBT, GET, and APT) that participants had received for chronic fatigue syndrome since their final 1 year outcome assessment; the severity of their fatigue using the Chalder fatigue questionnaire (CFQ);[14] their physical functioning with use of the SF-36 physical functioning subscale (SF-36 PF);[15] their perceived change in overall health since trial enrolment with use of the participant-rated clinical global impression of change score (PCGI), a seven-point scale rated from "very much worse" to "very much better";[16] and their self-rated impairment of daily activities using the participant-rated work and social adjustment scale (WSAS) scored in five domains, each rated zero to eight, producing an overall score of 0–40, with lower scores indicating less impairment.[17] The questionnaire items and administration were identical to those used in the trial, apart from in the trial questionnaires were handed in at the assessment visit and in the follow-up they were self-rated at home and returned by post.

The CFQ and the SF-36 PF were included in the follow-up questionnaire because these were the primary outcome measures used in the PACE trial. We chose two of the secondary trial outcome measures (PCGI and WSAS) to enhance our estimation of patient wellbeing, while keeping the questionnaire sufficiently short to ensure a good response rate.

Statistical analysis

The variables to be analysed were first summarised using means and SDs, median and IQRs, or frequencies and proportions, as appropriate. We compared the proportions of eligible participants who returned follow-up questionnaires across the randomised treatment groups (SMC alone, SMC with APT, CBT, or GET) with Fisher's exact test. We compared the (pre-randomisation) baseline characteristics of PACE trial participants who did and did not take part in the follow-up study using Fisher's exact test, independent samples *t* tests, or the Mann-Whitney *U* test as appropriate. Baseline characteristics of participants in the subset who took part in the follow-up study were compared across original randomised treatment groups using Fisher's exact test, ANOVA, or the Kruskal-Wallis test as appropriate. Differences between the original treatment groups in the proportion of patients who received additional treatment after their final trial outcome assessment were compared with Fisher's exact test and differences in the number of additional treatment sessions between groups with the Kruskal-Wallis test.

We calculated differences in outcomes between the final trial assessment and long-term follow-up within each original treatment group using paired samples *t* tests for fatigue (CFQ score), physical functioning (SF-36 PF score), impairment of daily activities (WSAS score), and the exact McNemar's test for perceived change in overall health (PCGI score). For this analysis the PCGI was coded as a positive change for "very much better" or "much better";

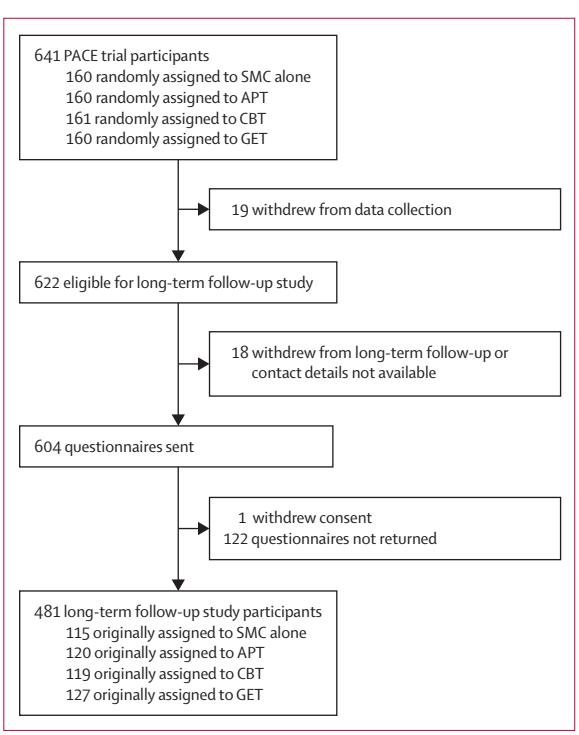

Figure 1: **Study profile**
SMC=standard medical care. APT=adaptive pacing therapy. CBT=cognitive behavioural therapy. GET=graded exercise therapy.

minimum change for "a little better", "no change", or "a little worse"; and negative change for "much worse" or "very much worse".

We constructed profile plots of fatigue (CFQ) and physical functioning (SF-36 PF) for follow-up study participants in each treatment group, including data from baseline, 12 week, 24 week, and final 1 year (52 week) trial outcome assessments, and the long-term follow-up assessment.

We assessed the differences in the measured outcomes between the original randomised treatment groups with linear mixed-effects regression models with the 12, 24, and 52 week, and long-term follow-up measures of outcomes as dependent variables and random intercepts and slopes over time to account for repeated measures. We included the following covariates in the models: treatment group, trial stratification variables (trial centre and whether participants met the international chronic fatigue syndrome criteria,[3] London myalgic encephalomyelitis criteria,[4] and DSM IV depressive disorder criteria),[18,19] time from original trial randomisation, time by treatment group interaction term, long-term follow-up data by treatment group interaction term, baseline values of the outcome, and missing data predictors (sex, education level, body-mass index, and patient self-help organisation membership), so the differences between groups obtained were adjusted for these variables. We calculated differences between treatment groups in perceived change in overall health (PCGI) for the derived categories (described above) of positive change (compared with minimum and negative change) and negative change (compared with minimum and positive changes). To do this we used a binary logistic generalised estimating equation model with an exchangeable working correlation and bootstrapped standard errors, and with similar covariates to those used in the models for the other outcomes.

Finally, we did a sensitivity analysis to control for the varying duration of follow-up in which time in the between-group difference models was coded as the number of days between randomisation and questionnaire administration, and compared treatment differences from these models to those obtained using the categorical coding of the time variable. The PACE trial was registered at http://isrctn.org, number ISRCTN54285094.

	Participated (n=481)	Did not participate (n=159)*	p value†
Age (years)	38·6 (12·0)	37·5 (11·4)	0·33
Women	366 (76%)	129 (81%)	0·23
White	451 (94%)	144 (91%)	0·45
CFS or ME patient group membership			0·015
Local self-help group for CFS or ME only	30 (6%)	3 (2%)	
National CFS or ME patient organisation only	46 (10%)	8 (5%)	
Both local and national member	11 (2%)	7 (4%)	
None	394 (82%)	141 (89%)	
International criteria for CFS met	319 (66%)	108 (68%)	0·71
London criteria for ME met	252 (52%)	77 (48%)	0·41
Depressive disorder	152 (32%)	61 (38%)	0·12
Any psychiatric disorder	220 (46%)	80 (50%)	0·36
Duration of CFS (months)	32 (16–66)	30 (18–76)	0·90
Body-mass index (kg/m²)	25·3 (4·8)	25·9 (5·4)	0·20

Data are mean (SD), n (%), or median (IQR). CFS=chronic fatigue syndrome. ME=myalgic encephalomyelitis. *One trial participant withdrew consent for any use of their data after completion of the trial and did not return a long-term follow-up questionnaire. †Fisher's exact test (categorical variables), independent samples *t* test (continuous variables), or Mann-Whitney *U* test (illness duration); p-value for difference between groups.

Table 1: **Baseline characteristics of PACE trial participants who did and did not participate in the follow-up study**

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. MS, KAG, ALJ, TC, and PDW had full access to data collected for the follow-up study and all authors had final responsibility for the decision to submit the report for publication.

Results

At the time of initial enrolment into the PACE trial, we obtained consent from all 641 participants to contact them for a long-term follow-up assessment (figure 1). 19 (3%) of

	Follow-up study participants with treatment data (n=479)*	SMC (n=115)	APT (n=119)	CBT (n=118)	GET (n=127)	p value†
Participants who received any additional sessions*	210 (44%)	73 (63%)	60 (50%)	36 (31%)	41 (32%)	<0·0001
Median number of additional sessions received	0 (0–8)	6 (0–12)	1 (0–8)	0 (0–3)	0 (0–6)	<0·0001
Participants who received an adequate number (≥10) sessions of therapy						
Received APT	15 (3%)	6 (5%)	0	2 (2%)	7 (6%)	0·016
Received CBT	65 (14%)	23 (20%)	20 (17%)	2 (2%)	20 (16%)	<0·0001
Received GET	26 (5%)	14 (12%)	7 (6%)	5 (4%)	0	0·0001

Data are n (%) or median (IQR). APT=adaptive pacing therapy. CBT=cognitive behavioural therapy. GET=graded exercise therapy. SMC=specialist medical care alone. *Two participants provided incomplete data; one in the CBT group had additional GET and one in the APT group had additional APT. †Fisher's exact test p value used for difference between treatment groups, except for number of additional sessions of therapy, which used a Kruskal-Wallis test p value.

Table 2: **Additional treatment received after final 12 month (52 week) trial outcome assessment**

these participants subsequently withdrew consent for further data collection. We sent questionnaires to 604 patients who had consented to long-term follow-up and for whom we had current contact details. Between May 8, 2008, and April 26, 2011, we received 481 (75% of full cohort; 80% of eligible participants) usable questionnaires which were included in the analysis (figure 1). The median time from randomisation to long-term follow-up assessment was 31 months (IQR 30–32) with a range of 24–53 months. The proportion of participants who returned questionnaires did not differ between randomised treatment groups (p=0·37; data not shown).

The baseline characteristics of the participants who did and did not take part in this follow-up did not differ apart from the fact that participants who were members of a patient organisation for myalgic encephalomyelitis or chronic fatigue syndrome were more likely to take part (table 1). Within the follow-up study sample, baseline characteristics of the randomised treatment groups did not significantly differ (appendix p 1).

Nearly half (44%; 210 of 479) of all the follow-up study participants reported receiving additional trial treatments after their final 1 year outcome assessment (table 2; appendix p 2). The number of participants who received additional therapy differed between the original treatment groups, with more participants who were originally assigned to SMC alone (73 [63%] of 115) or to APT (60 [50%] of 119) receiving additional therapy than those assigned to GET (41 [32%] of 127) or CBT (36 [31%] of 118; p<0·0001).

In the trial analysis plan we defined an adequate number of therapy sessions as ten of a maximum possible of 15. Although many participants in the follow-up study had received additional treatment, few reported receiving this amount (table 2). Most of the additional treatment that was delivered to this level was either CBT or GET.

Within-group long-term outcomes are shown in figure 2, table 3, and online (appendix pp 3–4). The improvements in fatigue and physical functioning reported by participants allocated to CBT or GET at their 1 year trial outcome assessment were sustained. The improvements in impairment in daily activities and in perceived change in overall health seen at 1 year with these treatments were also sustained for those who received GET and CBT (appendix p 4). Participants originally allocated to APT reported further improvements in fatigue, physical functioning, and impairment in daily activities from the 1 year trial outcome assessment to long-term follow-up, as did those allocated to SMC alone (who also reported further improvements in perceived change in overall health; figure 2; table 3; appendix p 4). In an exploratory post-hoc subgroup analysis requested by a reviewer, the within-group improvements were observed whether participants had received additional CBT or GET or not; however, this finding must be interpreted with great caution, as we discuss later.

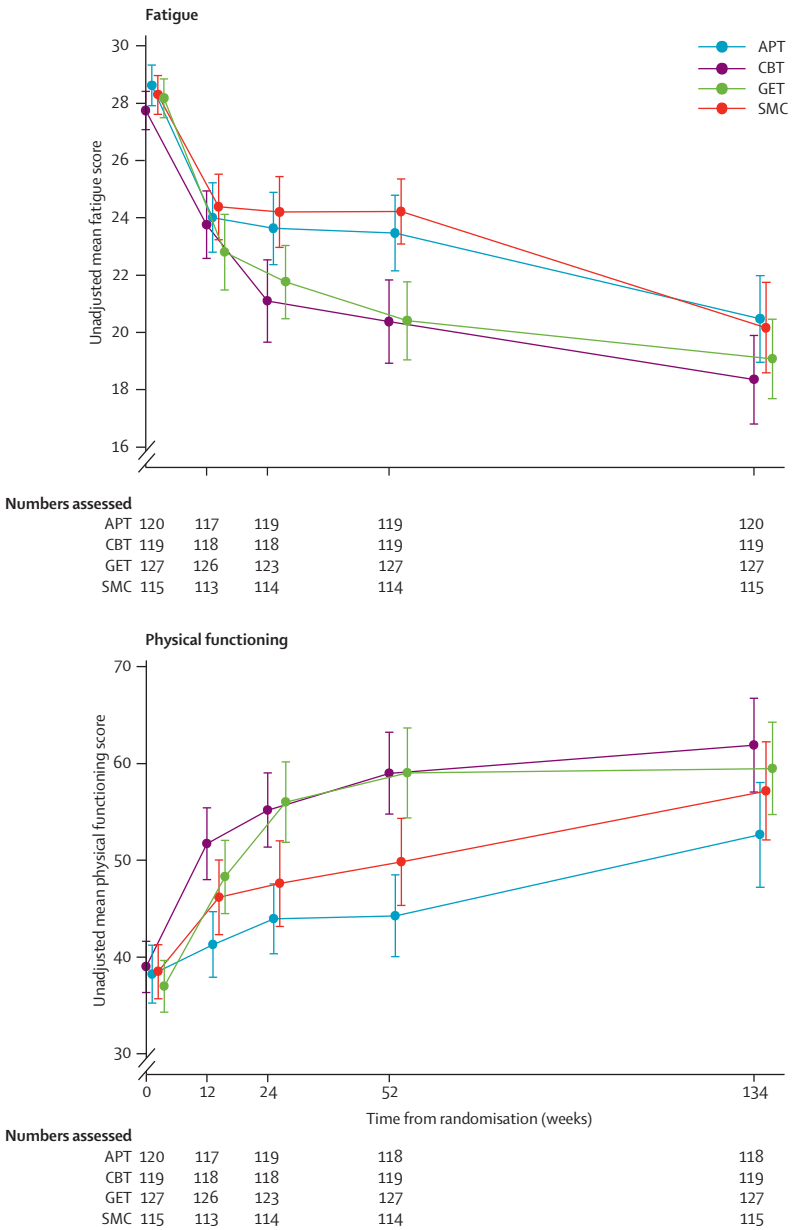

Figure 2: **Fatigue and physical functioning by treatment group for participants in the long-term follow-up study**
Data are unadjusted means and 95% CIs for the trial timepoints and long-term follow-up (median 134 weeks). APT=adaptive pacing therapy. CBT=cognitive behavioural therapy. GET=graded exercise therapy. SMC=specialist medical care alone.

The proportion of participants reporting deterioration (negative change) in their perceived overall health from the time they entered the trial at both the trial 1 year outcome and at long-term follow-up was small in all treatment groups (appendix p 4): the largest was 12% (n=14) in the APT group at long-term follow-up. There was no difference in the proportion of patients with negative change in each of the originally allocated treatment groups at either 1 year trial outcome or at long term-follow up (appendix p 4).

See Online for appendix

	SMC	APT	CBT	GET
Within-group differences				
Fatigue (CFQ)				
Participants at baseline	160	159	161	160
Mean score	28·3 (3·6)	28·5 (4·0)	27·7 (3·7)	28·2 (3·8)
Participants at 52 weeks	152	153	148	154
Mean score	23·8 (6·6)	23·1 (7·3)	20·3 (8·0)	20·6 (7·5)
Participants at long-term follow-up	115	120	119	127
Mean score	20·2 (8·6)	20·5 (8·4)	18·4 (8·5)	19·1 (7·9)
Participants in comparison	114	119	118	127
Mean difference between 52 weeks and long-term follow-up	−3·9 (−5·3 to −2·6); p<0·0001	−3·0 (−4·4 to −1·6); p<0·0001	−2·2 (−3·7 to −0·6); p=0·006	−1·3 (−2·7 to −0·1); p=0·059
Physical functioning (SF-36 PF)				
Participants at baseline	160	159	161	160
Mean score	39·2 (15·4)	37·2 (16·9)	39·0 (15·3)	36·7 (15·4)
Participants at 52 weeks	152	153	148	154
Mean score	50·8 (24·7)	45·9 (24·9)	58·2 (24·1)	57·7 (26·5)
Participants at long-term follow-up*	115	118	119	127
Mean score	57·4 (27·9)	52·8 (30·2)	62·2 (27·2)	59·8 (27·6)
Participants in comparison	114	117	118	127
Mean difference between 52 weeks and long-term follow-up	7·1 (4·0 to 10·3); p<0·0001	8·5 (4·5 to 12·5); p<0·0001	3·3 (0·02 to 6·7); p=0·049	0·5 (−2·7 to 3·6); p=0·78
Between-group differences				
Participants in comparison	157	159	155	159
Fatigue (CFQ)				
Mean difference compared with SMC	Ref	0·3 (−1·7 to 2·3); p=0·78	−1·4 (−3·4 to 0·7); p=0·19	−0·8 (−2·8 to 1·2); p=0·43
Mean difference compared with APT	..	Ref	−1·6 (−3·6 to 0·3); p=0·11	−1·1 (−3·0 to 0·9); p=0·28
Physical functioning (SF-36 PF)				
Mean difference compared with SMC	Ref	−3·6 (−9·6 to 2·4); p=0·24	2·8 (−3·2 to 8·8); p=0·36	2·0 (−4·0 to 7·9); p=0·51
Mean difference compared with APT	..	Ref	6·4 (0·4 to 12·4); p=0·035	5·6 (−0·3 to 11·5); p=0·064

Data are n, mean (SD), or mean difference (95% CI). Within group differences are between final trial 1 year outcome and long-term follow up. Lower scores are better for fatigue, higher scores are better for physical functioning. p values for within-group comparisons are from paired samples *t* tests. Mean between-group differences obtained from linear mixed effects models. CFQ=Chalder fatigue questionnaire. SF-36 PF=short form-36 physical functioning subscale. SMC=specialist medical care alone. APT=adaptive pacing therapy. CBT=cognitive behavioural therapy. GET=graded exercise therapy. Ref=reference category. *Two participants left the entire SF36 PF questionnaire blank at long-term follow-up and so were missing the physical functioning outcome measure.

Table 3: **Outcomes by original treatment assignments**

In the between-group analysis, adjusted findings from linear mixed-effects models show that the randomised treatment groups did not differ in mean fatigue scores at long-term follow-up (table 3). Physical functioning was significantly better for those allocated to CBT compared with those allocated to APT (mean difference 6·4 [95% CI 0·4–12·4]; p=0·035). However, given the number of comparisons made, this could be a chance finding. The findings were similar in the sensitivity analysis, which controlled for the varying duration of follow-up (data not shown). There were no significant differences between originally randomised groups in impairment in daily activities or in deterioration in perceived overall health at long-term follow-up (appendix p 4).

Discussion

The main finding of this long-term follow-up study of the PACE trial participants is that the beneficial effects of the rehabilitative CBT and GET therapies on fatigue and physical functioning observed at the final 1 year outcome of the trial were maintained at long-term follow-up 2·5 years from randomisation.

In interpreting the follow-up data it is important to note that many of the participants had received additional treatment for chronic fatigue syndrome since completing the trial. The decision whether to give each participant additional PACE treatments, and if so which, was made by the relevant PACE trial doctor in consultation with the patient. Participants originally allocated to SMC in the trial were the most likely to receive additional treatment,

followed by those who had APT; those originally allocated to the rehabilitative therapies (CBT and GET) were less likely to receive additional treatment. 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.

Participants originally allocated to SMC alone or to APT improved between their final trial outcome assessment and the long-term follow-up. This improvement might have been due to many factors, including the passage of time, regression to the mean, and long-term benefits of the treatment received in the trial. However, the finding that roughly a quarter and a third of the participants originally allocated to APT and SMC respectively had received a therapeutically adequate amount (ten or more sessions) of CBT or GET after the trial final trial outcome, makes it possible that this additional treatment was important in improving the long-term outcome for these patients. There was some evidence from an exploratory analysis that improvement after the 1 year trial final outcome was not associated with receipt of additional treatment with CBT or GET, given according to need. However this finding must be interpreted with caution because it was a post-hoc subgroup analysis that does not allow the separation of patient and treatment factors that random allocation provides. Importantly, the sustained benefit of CBT and GET was seen in those patients who did not have any additional treatment after the trial, as well as in those who did.

There was little evidence of deterioration (negative change) in perceived overall health measured with the (PCGI) in the whole sample at long-term follow-up and importantly there were no significant differences in deterioration rates between the originally allocated treatment groups. This finding suggests that none of the trial therapies are associated with long-term deterioration.

Between the original groups, few differences in outcomes were seen at long-term follow-up. This convergence in outcomes reflects the observed improvement in those originally allocated to SMC and APT, the possible reasons for which are listed above.

Several naturalistic follow-up studies have assessed outcomes in patients with chronic fatigue syndrome. A 2005 systematic review[6] found 14 studies of people meeting operational criteria for chronic fatigue syndrome with a range of follow-up durations and outcome measures and concluded that prognosis was generally poor; improvement was reported by a median of 40% of participants and recovery by only 7%.[6] Several small follow-up studies have also been done for specific treatments. The precise duration of follow-up varies between studies and was sometimes measured from randomisation and sometimes from the end of treatment. These studies are almost all of CBT: a 4 year follow-up of a small case series reported that most patients had maintained their improvement.[20] A 5 year follow-up of a small randomised trial of adults receiving CBT showed persisting improvement.[8] Similar sustained improvements were found after CBT in a 2 year follow-up of adolescents,[9] a 2 year follow-up of family focused CBT in adolescents,[11] and a 2·7 year follow-up of adolescents in a trial comparing internet-delivered CBT with usual care.[12] No follow-up study of GET has been done, although a 2 year follow-up of a randomised trial of an educational intervention that included advice on graded activity showed benefits to be maintained.[10] We are aware of no published follow-up studies of treatment with APT. Our findings confirm reports indicating that improvements from CBT are maintained in the long-term and report the new finding is that long-term benefit also occurs after GET.

This follow-up study has several limitations. First, the response rate was incomplete so some outcome data were missing; if these data were not missing at random it could have led to either overestimates or underestimates of the actual differences between the groups. Second, the duration of follow-up varied, although controlling for this in our mixed-effects regression model did not change the findings. Third, the outcomes were all self-rated, although these are arguably the most pertinent measures in a condition that is defined by symptoms. Finally, the supplementation of the originally randomly allocated treatment with additional treatment, given after the trial according to need, limits the interpretation of both the within-group and between-group comparisons.

We conclude that the benefits of CBT and GET on fatigue and physical functioning are maintained at a median of 2·5 years from randomisation and 2 years after the main treatment period ended. Participants who were originally allocated to APT, SMC, and to a lesser extent CBT, improved between 1 year and long-term follow-up, with outcomes remaining unchanged for participants in the GET treatment group. There was little evidence of differences between the four groups in fatigue or in physical functioning at long-term follow-up. We can also confirm that there was no evidence of deterioration in overall health from the final outcome assessment to follow-up for patients receiving any trial treatment. We note however that in all of the originally randomised treatment groups some patients remained unwell at long-term follow-up, an observation that reminds us that better treatments are still needed for patients with this chronically disabling disorder.

Contributors

PDW, TC, and MS were co-principal PACE trial investigators. MS, PDW, TC, and ALJ conceived and designed the follow up-study. KAG and ALJ designed and did the statistical analysis. The manuscript was written by MS, KAG, and JW. All authors contributed to the final manuscript.

Declaration of interests

PDW has done paid consultancy word for the UK Government and the Swiss Re insurance company. TC has received royalties from Sheldon Press and Constable and Robinson. MS has received royalties from Oxford University Press. KAG, ALJ, and JW declare no competing interests.

Acknowledgments

Funding for the PACE trial was provided by the UK Medical Research Council, Department of Health for England, The Scottish Chief Scientist Office, and the Department for Work & Pensions. TC and KAG were partly supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology, & Neuroscience, Kings College London. KAG was also funded by an NIHR Doctoral Fellowship. JW is partly supported by the NIHR Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. We gratefully acknowledge the help of the PACE Trial Management Group, which consisted of the authors of this paper, plus (in alphabetical order): B Angus, H Baber, J Bavinton, M Burgess, L V Clark, D L Cox, J C DeCesare, E Feldman, P McCrone, G Murphy, M Murphy, H O'Dowd, T Peto, L Potts, R Walwyn, and D Wilks, and the King's Clinical Trials Unit. We thank Hannah Baber for facilitating the long-term follow-up data collection.

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