THE PACE TRIAL: EXPLORATORY ANALYSIS OF PRIMARY FATIGUE OUTCOMES USING BIMODAL RATHER THAN CONTINUOUS LIKERT TYPE SCORING ON THE CHALDER FATIGUE SCALE

Introduction

We published the main results of the PACE trial in 2011 (White et al, 2011). PACE was a randomised controlled trial of four treatments for patients with chronic fatigue syndrome (CFS). These treatments were specialist medical care (SMC) and SMC supplemented by adaptive pacing therapy (APT), cognitive behaviour therapy (CBT) or graded exercise therapy (GET). We found that those patients allocated to CBT and GET were more improved in both fatigue and physical function that those allocated to SMC or APT.

The trial has been criticised on the basis that we changed the analysis of the primary outcomes from the outline plan in the published protocol (White et al, 2007) to the revised outcomes that were published in the statistical analysis plan (Walwyn et al 2013).

We have already explained that, in common with many trials, the statistical analysis plan was developed after the trial had started, but before any data were examined and was ratified by the trial steering committee. This final analysis plan used the same variables as primary outcomes but analysed these in a different way. One change was to use continuous 'Likert type' scoring (0, 1, 2, 3) of each Chalder fatigue scale item rather than bimodal scoring (0, 0, 1, 1) as originally proposed. We made this change following statistical advice that this would better reflect the data and improve statistical power.

We remain of the view that the pre-specified analysis we conducted for the main PACE paper was the best way of addressing the trial questions. However, to address the criticism we have redone the analysis using the bimodal scoring.

Methods

The bimodal scored CFQ variable was summarised using means, standard deviations and confidence intervals for the mean. We used prorated outcomes, as described in the main paper (White et al, 2011).

We analysed the differences in means between the treatment groups using mixed linear regression models with random intercepts and slopes over time. The outcomes in the model were the bimodal scored CFQ variables at 12, 24 and 52 weeks post-randomisation. Covariates in the models were baseline CFQ bimodal score, treatment group, time, and stratification factors (centre, present depressive disorder, and alternative criteria for chronic fatigue syndrome and myalgic encephalomyelitis; all as stratified at entry). Time by treatment interaction terms were included to allow extraction of contrasts at 52 weeks.

Results

Table 1 shows summary statistics for the bimodal scored CFQ. This shows generally lower scores in those patients who were allocated to CBT and GET. This pattern can also be seen in the unadjusted mean profile plots in Figure 1.

Figure 2 and Table 2 show that participants allocated to CBT and GET had significantly lower mean CFQ scores when compared to those allocated to APT and SMC. Those allocated to CBT had a bimodal CFQ score that was on average 1.8 points lower than those allocated to APT or SMCs, with those allocated to GET having a score that was on average 1.3 points lower.

All of these differences were statistically significant.

There was no significant difference in fatigue between those allocated to APT and those allocated to SMC.

Table 1. CFQ bimodal summary statistics and 95% confidence interval for the mean by treatment group and overall

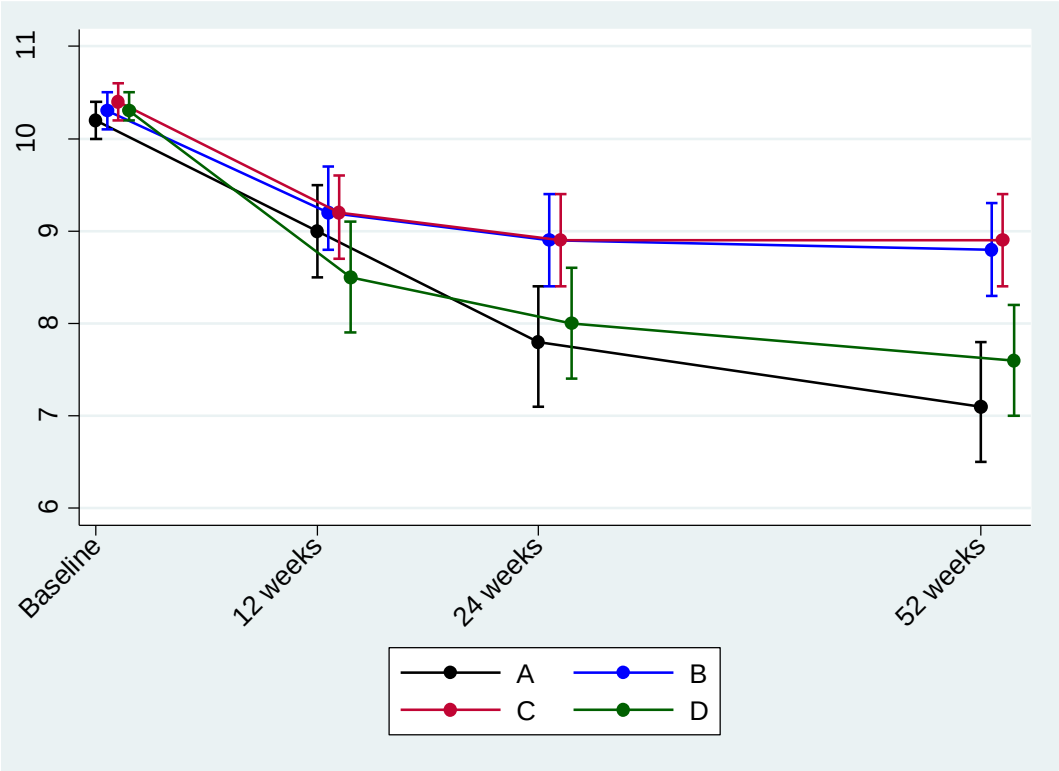
CFQ Bimodal scoring	**CBT n = 161**	**APT n = 159**	**SMC n = 160**	**GET n = 160**	**Overall n = 640**
Baseline	161	159	160	160	640
Mean (SD)	10.2 (1.2)	10.3 (1.2)	10.4 (1.1)	10.3 (1.1)	10.3 (1.2)
Mean (95% CI)	10.2 (10.0, 10.4)	10.3 (10.1, 10.5)	10.4 (10.2, 10.6)	10.3 (10.2, 10.5)	10.3 (10.2, 10.4)
12 weeks	153	153	154	153	613
Mean (SD)	9.0 (3.1)	9.2 (2.8)	9.2 (2.8)	8.5 (3.7)	9.0 (3.1)
Mean (95% CI)	9.0 (8.5, 9.5)	9.2 (8.8, 9.7)	9.2 (8.7, 9.6)	8.5 (7.9, 9.1)	9.0 (8.7, 9.2)
24 weeks	148	155	152	150	605
Mean (SD)	7.8 (3.9)	8.9 (2.9)	8.9 (3.3)	8.0 (3.6)	8.4 (3.5)
Mean (95% CI)	7.8 (7.1, 8.4)	8.9 (8.4, 9.4)	8.9 (8.4, 9.4)	8.0 (7.4, 8.6)	8.4 (8.1, 8.7)
52 weeks	148	153	152	154	607
Mean (SD)	7.1 (4.0)	8.8 (3.2)	8.9 (3.1)	7.6 (3.8)	8.1 (3.6)
Mean (95% CI)	7.1 (6.5, 7.8)	8.8 (8.3, 9.3)	8.9 (8.4, 9.4)	7.6 (7.0, 8.2)	8.1 (7.8, 8.4)

APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialised medical care, CI = confidence interval

Table 2. Bimodal scored CFQ differences between treatment groups

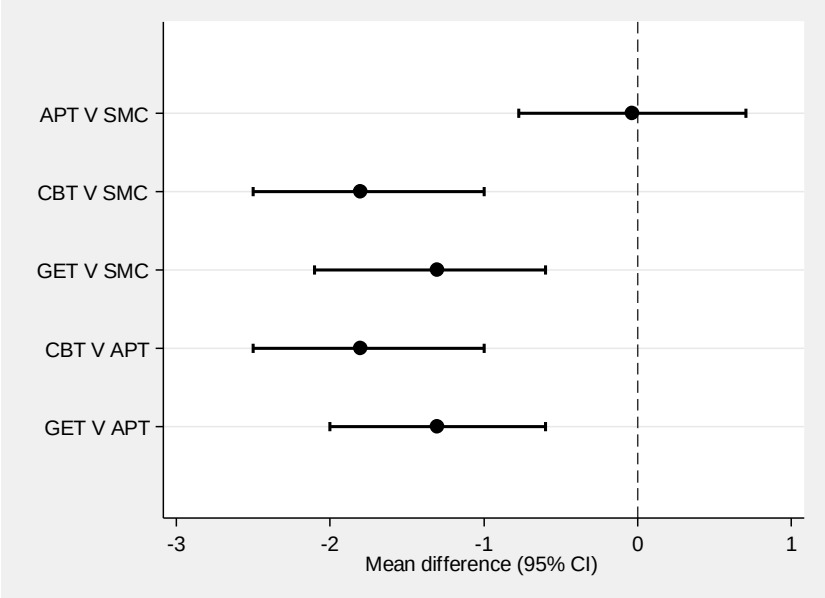
	Mean difference (95% confidence interval)	p-value
APT V SMC	-0.03 (-0.8 to 0.7)	0.93
CBT V SMC	-1.8 (-1.0 to -2.5)	$p < 0.001$
GET V SMC	-1.3 (-0.6 to -2.1)	$p < 0.001$
CBT V APT	-1.8 (-1.0 to -2.5)	$p < 0.001$
GET V APT	-1.3 (-0.6 to -2.0)	$p = 0.001$

Figure 1. Unadjusted CFQ bimodal score plotted over time by intervention arm



A = cognitive behaviour therapy, B = adaptive pacing therapy, C = specialised medical care, D = graded exercise therapy

Figure 2. Mean differences between treatment groups in bimodal CFQ score



APT = adaptive pacing therapy, CBT = cognitive behaviour therapy, GET = graded exercise therapy, SMC = specialised medical care, CI = confidence interval

Interpretation

The pattern of trial outcomes observed when the Chalder Fatigue scale was bimodally scored was very similar to that seen in the main PACE results paper (White et al 2011) for the Likert scored CFQ; i.e. there was a greater improvement in fatigue in those allocated to CBT and GET groups compared with those allocated to APT and SMC, with these differences being of moderate size.

In summary, these results support our initial interpretation that "CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition." (White et al, 2011).

References

Walwyn R, Potts L, McCrone P, Johnson AL, DeCesare JC, Baber H, Goldsmith K, Sharpe MC, Chalder T, White PD (2013). A randomised trial of adaptive pacing therapy, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome (PACE): Statistical analysis plan. Trials 14, 386.

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