THE PACE TRIAL: ANALYSIS OF PRIMARY OUTCOMES USING COMPOSITE MEASURES OF IMPROVEMENT

Introduction

We published the main results of the PACE trial in 2011. PACE was a randomised controlled trial of four treatments for patients with chronic fatigue syndrome (White et al, 2011). 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 how we analysed the primary outcomes from the outline plan in the original published protocol (White et al, 2007) to the statistical analysis plan (Walwyn et al, 2013). We have 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 differed from the protocol in that: (a) we used a continuous 'Likert type' scoring (0, 1, 2, 3) of each Chalder fatigue scale item rather than bimodal scoring (0, 0, 1, 1), (b) we analysed fatigue and physical function as continuous variables rather than as dichotomous (improved v not improved) categorical variables and (c) we omitted a composite measure of improvement which combined the categorical variable of improvement in both fatigue and physical function. In writing the analysis plan we made these changes in order to best use all the data collected, improve the trials statistical power and to aid interpretability of the findings.

We remain of the view that the pre-specified analysis we conducted was the best way of addressing the trial questions. However, as critics of the trial have requested that we also analyse the trial with the primary outcomes in the form outlined in the published protocol, we have done this as an analysis to see if this changes the trial's conclusions.

Methods

For this analysis, the primary outcomes were recoded to define dichotomous improvement versus non-improvement as outlined in the PACE protocol (White, Sharpe, Chalder, DeCesare, & Walwyn, 2007). This coding was as follows: for physical functioning, participants were coded as improvers if they had either a score of 75 or more (out of 100) at 52 weeks post-randomisation, or a 50% increase from the baseline score at that time point. For fatigue, participants were coded as improvers if they had either a score of 3 or less (out of 11) at 52 weeks post-randomisation, or a 50% decrease from the baseline score on the bimodal scored Chalder fatigue scale at this time point. We used prorated outcomes, as described in the main paper (White et al, 2011).

An additional composite outcome of overall improvement in which participants were coded as improved or not improved in both physical functioning and fatigue was created.

Participants meeting the improvement criteria were summarised using frequencies and proportions.

We analysed differences in proportions of those who improved between the treatment groups, using binary logistic generalised estimating equations regression with an exchangeable working correlation over time and bootstrapped standard errors. Separate models were run for physical functioning, fatigue and the composite measure. The outcomes in the model were the binary improvement variables at 12, 24 and 52 weeks post-randomisation in each case. Covariates in the models were 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 improvement in physical function, fatigue and the composite measure for all post-randomisation time points. The general pattern was of higher proportions showing improvement in those allocated to CBT and GET.

Physical functioning

Figure 1 and Table 2 show that participants allocated to CBT had 1.6 times the odds of improving in their physical functioning: as compared to those allocated to APT (95% CI 1.0 to 2.6, p = 0.035), with those allocated to GET having 2.4 times the odds of improving compared to APT (95% CI 1.5 to 3.7, p < 0.001). Participants allocated to GET also had greater odds of improving in physical functioning compared to SMC (odds ratio 1.9, (95% CI 1.2 to 3.1, p = 0.004). Participants allocated to CBT had 1.3 times the odds (95% CI 0.9 to 2.1, p = 0.20) of improving compared to SMC; however this was not a statistically significant difference.

Fatigue

Figure 2 shows that participants allocated to CBT and GET also had significantly greater odds of improvement in fatigue as compared to APT and SMC. The effects were of a similar magnitude, with the odds being between 2.0 and 2.7 times greater in those allocated to CBT and GET across the comparisons (Figure 2 and Table2).

Composite outcome

With improvement on both physical functioning and fatigue, Figure 3 shows a similar pattern of effects; participants allocated to CBT or GET had significantly greater odds of improving on the composite outcome than for APT and SMC.

The odds of being improved on the composite outcome were between 2.4 and 2.7 times greater with CBT and GET than with APT and SMC (Figure 3 and Table2).

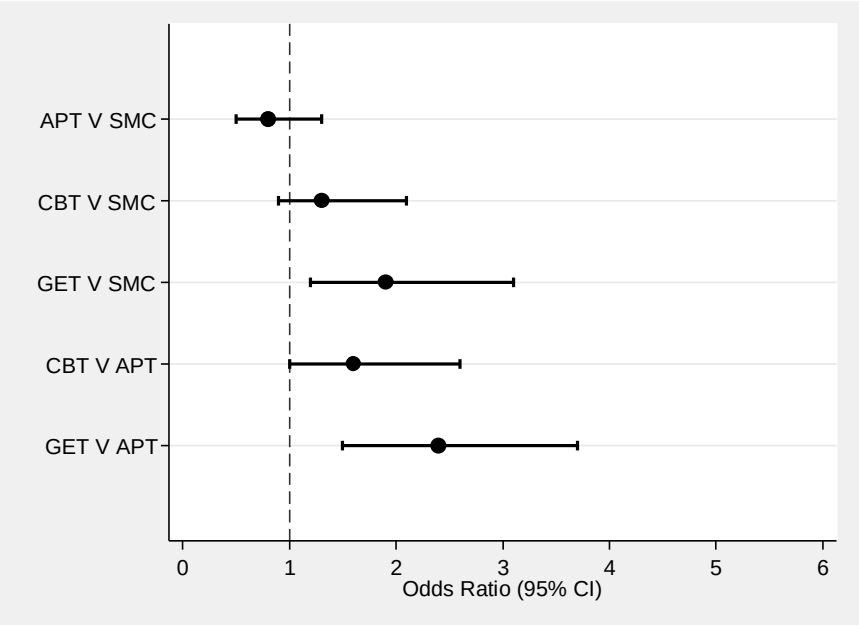
There were no significant differences between APT and SMC on any of the measures.

Table 1. Proportion of improvers (N (%)) by treatment group*

	CBT n = 161	**APT n = 159**	**SMC n = 160**	**GET n = 160**	**Overall n = 640**
12 weeks					
Physical functioning	60 (37)	45 (28)	54 (34)	68 (43)	227 (35)
Fatigue	16 (10)	16 (10)	13 (8)	27 (17)	72 (11)
Both	11 (7)	4 (3)	6 (4)	18 (11)	39 (6)
24 weeks					
Physical functioning	68 (42)	46 (29)	57 (36)	79 (49)	250 (39)
Fatigue	33 (21)	19 (12)	21 (13)	31 (19)	104 (16)
Both	23 (14)	7 (4)	13 (8)	27 (17)	70 (11)
52 weeks					
Physical functioning	79 (49)	64 (40)	70 (44)	97 (61)	310 (48)
Fatigue	42 (26)	23 (14)	21 (13)	38 (24)	124 (19)
Both	32 (20)	15 (9)	16 (10)	33 (21)	96 (15)

*Denominator for proportions is the number randomised into each group

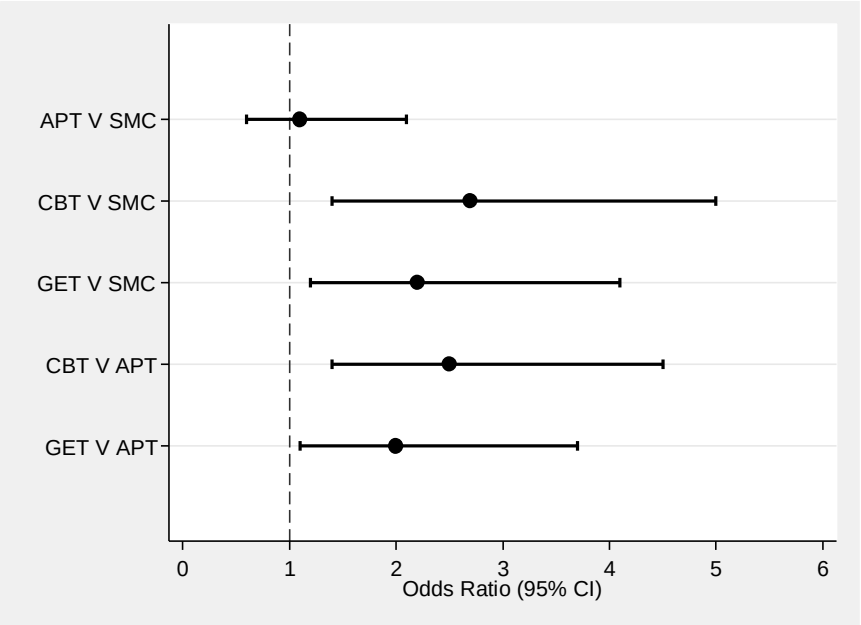
Figure 1. Odds ratios for differences between treatment groups in improvement in physical functioning*



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

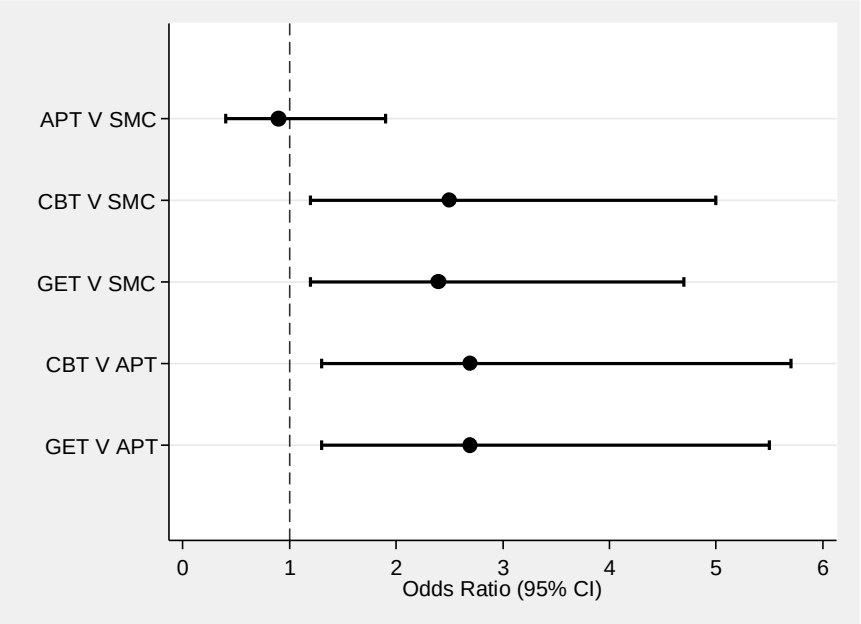
**Lower limit of the CBT v APT confidence interval is 1.03.

Figure 2. Odds ratios for differences between treatment groups in improvement in fatigue



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

Figure 3. Odds ratios for differences between treatment groups in a composite measure requiring improvement in both physical functioning and fatigue



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

Table 2. Treatment group comparisons for proportions improving in physical functioning, fatigue and both*

	Odds ratio (95%CI)	**p-value**
Physical functioning		
APT V SMC	0.8 (0.5 to 1.3)	0.40
CBT V SMC	1.3 (0.9 to 2.1)	0.20
GET V SMC	1.9 (1.2 to 3.1)	0.004
CBT V APT	1.6 (1.0 to 2.6)**	0.035
GET V APT	2.4 (1.5 to 3.7)	< 0.001
Fatigue		
APT V SMC	1.1 (0.6 to 2.1)	0.83
CBT V SMC	2.7 (1.4 to 5.0)	0.002
GET V SMC	2.2 (1.2 to 4.1)	0.016
CBT V APT	2.5 (1.4 to 4.5)	0.003
GET V APT	2.0 (1.1 to 3.7)	0.023
Both		
APT V SMC	0.9 (0.4 to 1.9)	0.79
CBT V SMC	2.5 (1.2 to 5.0)	0.010
GET V SMC	2.4 (1.2 to 4.7)	0.011
CBT V APT	2.7 (1.3 to 5.7)	0.007
GET V APT	2.7 (1.3 to 5.5)	0.008

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

*These results are from a GEE model with 12, 24 and 52 week variables as dependent variables (see Methods), however, the results from a logistic regression model with the 52 week variable as a dependent variable gave almost identical results.

**Lower limit of the CBT v APT confidence interval is 1.03.

Interpretation

All three of these outcomes are very similar to those reported in the main PACE results paper (White et al, 2011); physical functioning and fatigue improved significantly more with CBT and GET when compared to APT and SMC. One difference was found however; in this analysis with CBT compared to SMC, the difference for physical functioning was no longer statistically significant at p = 0.20.

When we look at a composite outcome which requires participants to have improved on both of the primary outcomes, we see the same pattern as reported in the main PACE paper with better outcomes with CBT and GET compared to those with APT and SMC.

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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