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White, PD; Goldsmith, KA; Johnson, AL; Potts, L; Walwyn, R; DeCesare, JC; Baber, HL; Burgess, M; Clark, LV; Cox, DL; Bavin-ton, J; Angus, BJ; Murphy, G; Murphy, M; O'Dowd, H; Wilks, D; McCrone, P; Chalder, T; Sharpe, M; PACE trial management group, [inc Fletcher, A.E.] (2011) Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet*, 377 (9768). pp. 823-36. ISSN 0140-6736 DOI: 10.1016/S0140-6736(11)60096-2

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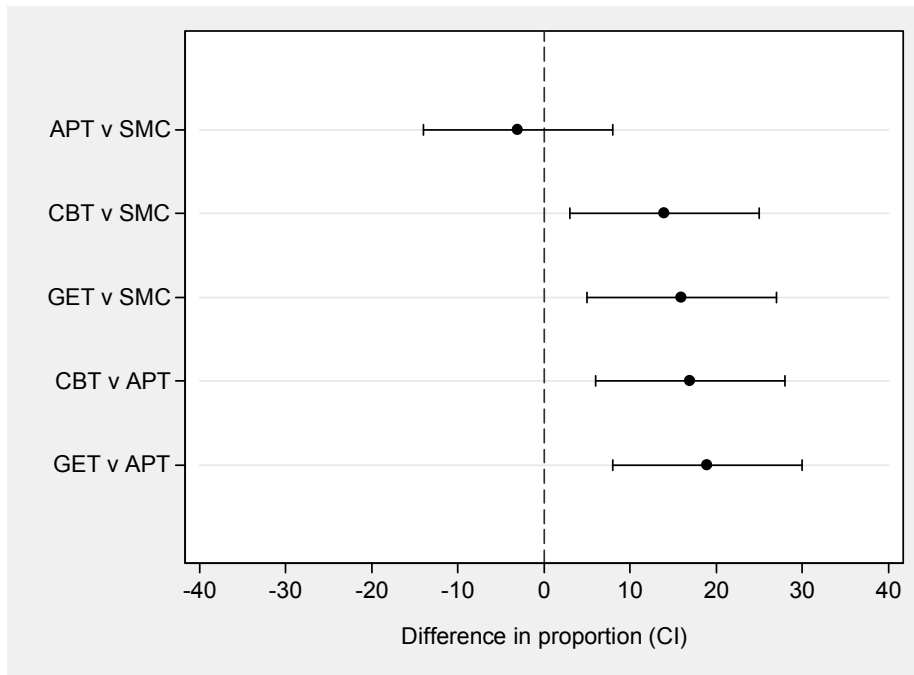
Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: White PD, Goldsmith KA, Johnson AL, et al, on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; published online Feb 18. DOI:10.1016/S0140-6736(11)60096-2.

Web appendix

	APT*	CBT†	GET‡	SMC§
Doctor/therapist profession: n	9 occupational therapists	7 clinical psychologists 4 nurse therapists 2 counselling psychologists	10 physiotherapists 1 exercise physiologist	4 general practitioners 7 physicians ¶ 27 liaison psychiatrists‡
Years of post-qualification experience:				
median (range)	7 (5-22)	3 (0-10)	5 (1-23)	-
Previous experience in a CFS or chronic pain service: N (%)	3 (33)	7 (54)	4 (36)	-
<p>*Adaptive pacing therapy. †Cognitive behaviour therapy. ‡Graded exercise therapy. §Specialist medical care. General practitioners with a special interest in CFS. ¶ All physicians specialised in infectious diseases. ‡ 22 of the 27 liaison psychiatrists were from one centre. 300 (47%) participants were treated by physicians, 184 (29%) by psychiatrists, and 149 (23%) by GPs. All the physicians and GPs had completed training. 4 psychiatrists had completed training; the rest were trainees. Therapists treated a median (range) of 14 (2-33) participants. Doctors provided SMC alone for a median (range) of 3 (1-19) participants.</p>				
Web Appendix Table A: Characteristics of therapists and doctors				



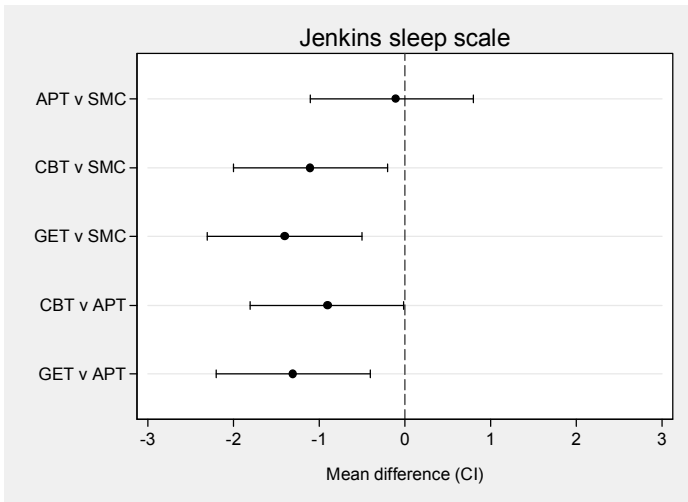
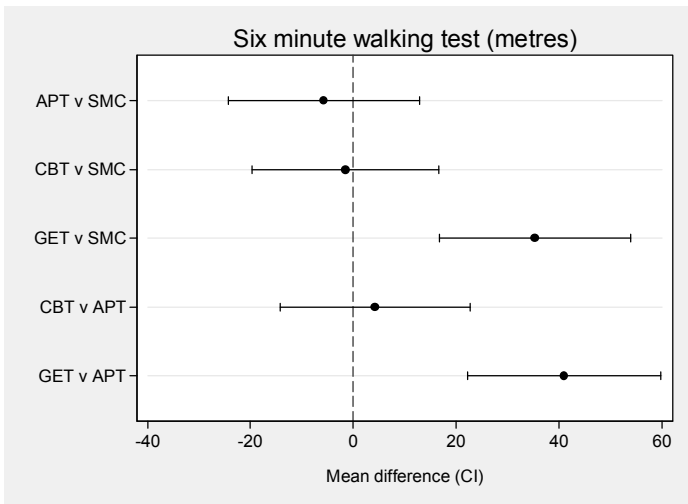
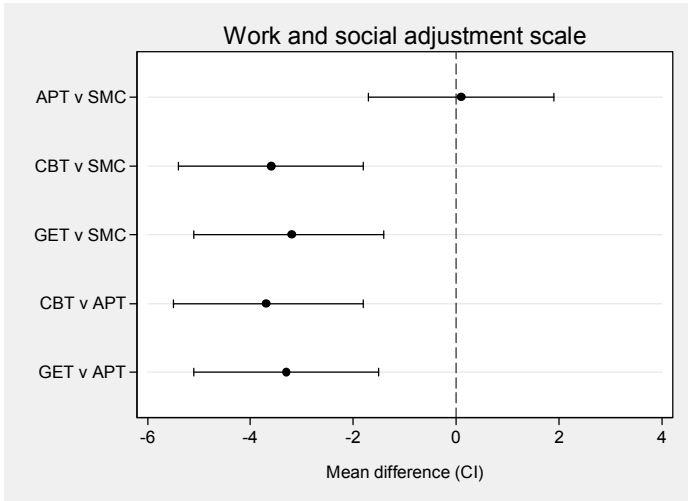
Data are mean differences (CIs). Positive values favour the first treatment arm of each pair compared. APT = adaptive pacing therapy. CBT= cognitive behaviour therapy. GET = graded exercise therapy. SMC = specialist medical care.

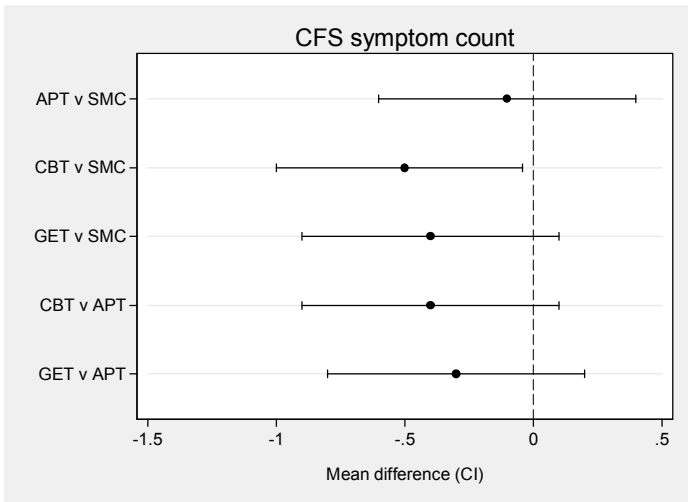
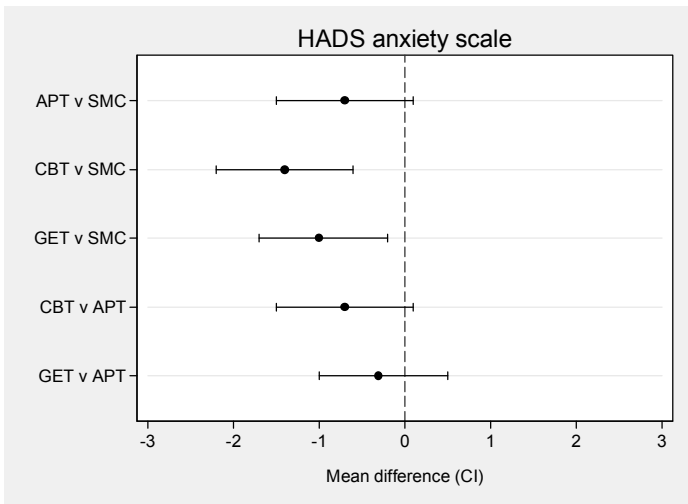
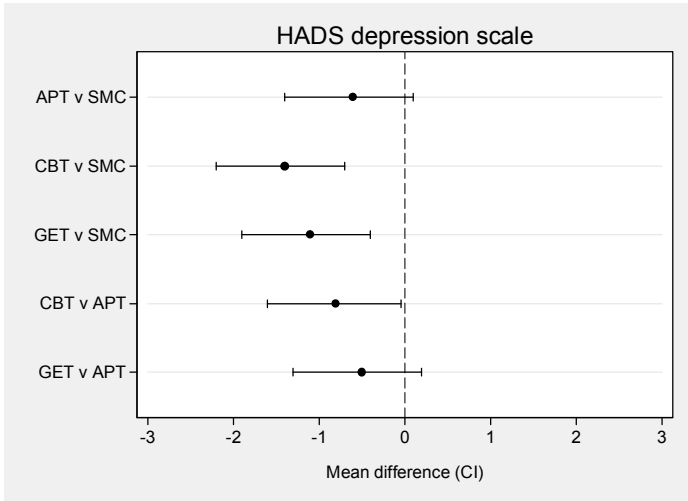
Web Appendix Figure A: Mean differences in the proportions that improved by both 2 or more points in fatigue and 8 or more points in physical function

Treatment arm	Fatigue*				Physical function†			
	APT‡	CBT§	GET	SMC¶	APT‡	CBT§	GET	SMC¶
Baseline n	142	138	134	142	142	138	134	142
Mean (SD)	28.6 (4.0)	27.9 (3.5)	28.2 (3.7)	28.4 (3.7)	38.1 (16.6)	39.5 (15.0)	36.7 (15.4)	38.6 (15.4)
12 weeks n	139	136	132	140	139	136	132	140
Mean (SD)	24.1 (6.4)	23.9 (6.3)	23.0 (7.5)	24.6 (6.4)	42.0 (19.5)	50.4 (20.2)	48.2 (21.2)	45.9 (20.4)
24 weeks n	140	135	132	140	140	135	132	140
Mean (SD)	23.9 (6.7)	21.8 (7.6)	22.0 (6.8)	24.4 (7.0)	43.0 (20.5)	54.2 (20.9)	56.4 (23.2)	47.6 (23.1)
52 weeks n	140	136	131	141	140	136	131	141
Mean (SD)	23.4 (7.3)	20.2 (8.0)	20.7 (7.5)	24.3 (6.2)	45.5 (24.7)	58.5 (23.6)	58.8 (26.9)	49.4 (24.3)
Compared to SMC: Mean difference (CI)	-1.0 (-2.5 to 0.4)	-3.7 (-5.2 to -2.2)	-3.4 (-4.8 to -1.9)	-	-4.1 (-8.9 to 0.8)	7.4 (2.5 to 12.3)	10.9 (6.1 to 15.8)	-
Unadjusted p values	0.16	<0.0001	0.0001	-	0.10	0.0038	<0.0001	-
Bonferroni adjusted p values	<i>0.78</i>	<i>0.0001</i>	<i>0.0003</i>	-	<i>0.50</i>	<i>0.0188</i>	<i>0.0002</i>	-
Compared to APT; Mean difference (CI)	-	-2.7 (-4.3 to -1.1)	-2.3 (-3.9 to -0.7)	-	-	11.5 (6.5 to 16.4)	15.0 (10.0 to 20.0)	-
Unadjusted p values	-	0.0030	0.0106	-	-	0.0001	<0.0001	-
Bonferroni adjusted p values	-	<i>0.0152</i>	<i>0.0530</i>	-	-	<i>0.0004</i>	<i><0.0001</i>	-
Data are mean (SD) scores, unless otherwise stated. *Chalder Fatigue Questionnaire (range 0-33, lower is better). ¹⁵ †SF36 physical function sub-scale score (range 0-100, higher is better). ¹⁶ ‡Adaptive pacing therapy. §Cognitive behaviour therapy. Graded exercise therapy. ¶ Specialist medical care. Comparisons made at 52 weeks are taken from the final adjusted models. P-values for comparisons are unadjusted and Bonferroni adjusted (in italics) for five comparisons within each primary outcome. This analysis included 556/640 (87%) participants. Those excluded were: 3 found ineligible after randomisation, 78/640 (12%) who had received inadequate treatment, 2 treated at a different centre from the one at which they were randomised, and one both ineligible and with inadequate treatment.								
Web Appendix Table B: Per protocol sample analysis of co-primary outcomes of fatigue and physical function								

Description	Relationship to treatment	SAR category*
Adaptive pacing therapy (2)		
1. Suicidal thoughts	possibly related	e
2. Worsened depression	possibly related	e
Cognitive behaviour therapy (4)		
1. Episode of self harm	possibly related	f
2. Low mood and episode of self harm	possibly related	e & f
3. Worsened mood and CFS symptoms	possibly related	d
4. Threatened self harm	possibly related	e
Graded exercise therapy (2)		
1. Deterioration in mobility and self-care	possibly related	d
2. Worse CFS symptoms and function	possibly related	d
Specialist medical care alone (2)		
1. Worse CFS symptoms and function	probably related	d
2. Increased depression and incapacity	possibly related	d
*SAR categories: a) Death; b) Life-threatening event; c) Hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included), d) Increased severe and persistent disability, defined as a significant deterioration in the participant's ability to carry out their important activities of daily living of at least four weeks continuous duration; e) Any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; f) Any episode of deliberate self-harm.		
Web Appendix Table C: Description of Serious Adverse Reactions		

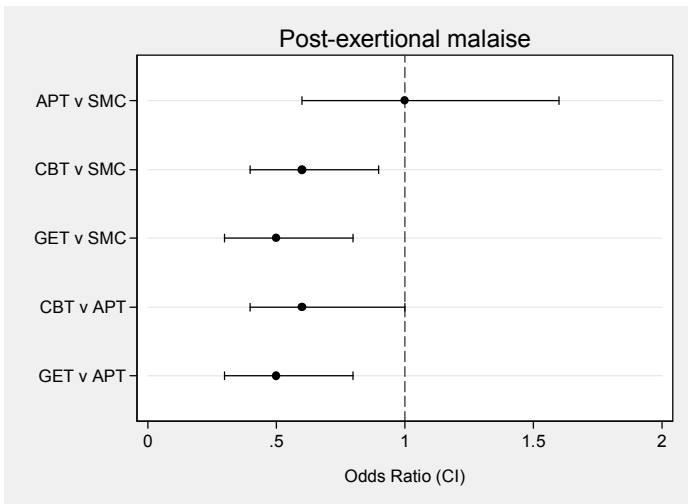
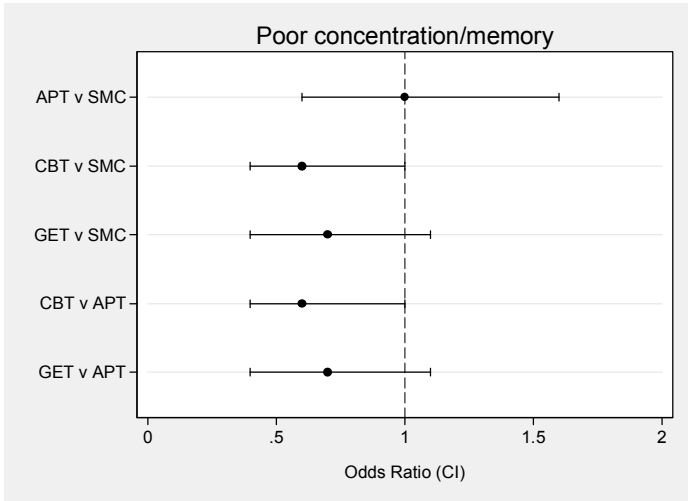
Description (n = 49)
b) Life threatening (1)
Laparotomy for ectopic pregnancy
c) Hospital admission (38)
<ul style="list-style-type: none"> • Surgery (18)
Arthroscopic subacromial decompression, repair of ankle tendon, total hip replacement, tonsillectomy (2), septoplasty, sinus wash-out and trimming of turbinates, removal of rectal abscess, abdominal adhesions release, laparoscopy for adhesions of endometriosis, Herniorrhaphy, stress incontinence repair, urethral dilatation and hysteroscopy, orchidectomy, prostatectomy, uterine cystectomy, colposcopy, hysteroscopy.
<ul style="list-style-type: none"> • Inpatient investigation (9)
Investigation of headache and drop attacks, epileptic seizure, polysomnography, chest pain, atrial fibrillation, abdominal pain (2), kidney pain, Neutropoenia.
<ul style="list-style-type: none"> • Respiratory (5)
Asthma attack (2), pneumonia, chest infection, bronchitis.
<ul style="list-style-type: none"> • Pregnancy complications (2)
Ectopic pregnancy, post-operative infection.
<ul style="list-style-type: none"> • Accident (2)
Accidental head injury (2)
<ul style="list-style-type: none"> • Other (2)
Anorexia nervosa, allergic reaction to bites.
d) Increase in severe and persistent significant disability/incapacity (10)
Breast cancer, cerebrovascular accident, prolapsed intervertebral discs, assault leading to disability, multiple life events leading to disability, upper respiratory infection leading to disability, acutely unwell, acute allergic reaction, blackout (2).
*SAE categories: a) Death; b) Life-threatening event; c) Hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included), d) Increased severe and persistent disability, defined as a significant deterioration in the participant's ability to carry out their important activities of daily living of at least four weeks continuous duration; e) Any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; f) Any episode of deliberate self-harm.
Web Appendix Table D: Description of Serious Adverse Events





Mean difference (CIs). Positive values for the Walk Test, and negative values for the rest, favour the first treatment group of each pair. WSAS = Work and social adjustment scale. Six Minute Walk Test = metres walked in six minutes. CFS = Chronic Fatigue Syndrome. JSS = Jenkins sleep scale. HADS = Hospital anxiety and depression scale. APT = adaptive pacing therapy. CBT= cognitive behaviour therapy. GET = graded exercise therapy. SMC = specialist medical care.

Web Appendix Figure B: Forest plot of treatment differences for secondary outcomes at 52 weeks



Odds ratios (CIs). Values below 1 favour the first treatment group of each pair. APT = adaptive pacing therapy. CBT= cognitive behaviour therapy. GET = graded exercise therapy. SMC = specialist medical care.

Web Appendix Figure C: Forest plot comparing individual symptoms across treatment arms