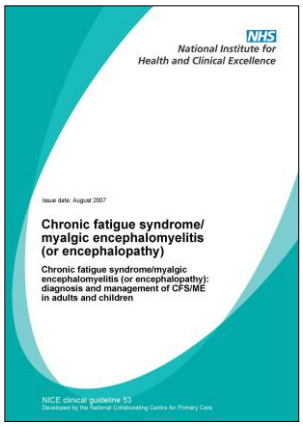
Falling Off the PACE
Analysis of the *Lancet* study

A paper published Feb. 18, 2011 in the *Lancet*, "Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial" compares four treatment approaches in a population of 641 patients in the United Kingdom (U.K.). The study reported that patients who received a six-month course of cognitive behavioral therapy (CBT) or graded exercise therapy (GET) had improvement in self-reported symptom scores at higher rates than those who were provided specialized medical care alone (SMC) or adaptive pacing therapy (APT). In the Discussion section of the paper, the authors led by Peter D. White acknowledge, "Our finding that studied treatments were only moderately effective also suggests research into more effective treatments is needed. The effectiveness of behavioural treatments does not imply that the condition is psychological in nature."

The study has received a great deal of media attention following a London press conference held on Feb. 17, 2011 and a press release circulated that day by the journal. White et al, begin the paper by drawing attention to the controversy the application of these therapies in CFS has generated over the years, "Trial findings show CBT and GET can be effective treatments for CFS, but patients' organisations have reported that these treatments can be harmful and favour pacing and specialist health care." This opening statement set up the rather adversarial nature of the study itself and its conclusions, and it flavored much of the news coverage. As we have seen with other recent studies, statements made in the press release and press conference get more attention than somewhat more tempered statements or details of the paper itself. Headlines have touted more conclusive results than the data support, as described in Kim McCleary's commentary about the study, "Too Big to Fail."



NICE Guidelines for CFS/ME

The study and services, called the PACE Trial, were designed by a large steering committee and the service providers were specially trained to deliver the highly structured programs for the benefit of the National Health Service. It was funded by the U.K. Medical Research Council, the U.K. Department of Health and the U.K. Department for Work and Pensions. The patient population was selected using the Oxford criteria for CFS. 3,148 patients diagnosed with CFS recruited from six CFS specialty clinics in England and Scotland were screened to identify 641 subjects who met study criteria. The Oxford criteria are broader than either the 1994 international research case definition or the 2003 Canadian criteria for ME/CFS, suggesting that the term CFS is used by physicians in the U.K. to identify a broad spectrum of medically unexplained illness. According to the Trial's Frequently Asked Questions,

> "The Oxford criteria will allow researchers to generalise their findings to the largest possible number of people with CFS/ME and ensure the trial can recruit enough people to give meaningful results. Assessing participants using International and London criteria once they've been enrolled into the trial may shed light on whether different groups of people respond differently to different treatments. The ultimate aim is to rigorously evaluate all the treatments on offer so that patients and doctors can make informed choices about which treatment might best improve an individual's quality of life."

There are no data in the paper indicating how many subjects might have been excluded on the basis of neurologic or cardiovascular signs or symptoms. The National Health Service guidelines for CFS state that the presence of these symptoms warrants further investigation and consideration of alternate diagnoses.

	Adaptive pacing therapy (n=159)	Cognitive behaviour therapy (n=161)	Graded exercise therapy (n=160)	Specialist medical care alone (n=160)	Overall (n=640)
Demographic data					
Age (years)	39 (11)	39 (12)	39 (12)	37 (11)	38 (12)
Female	121 (76%)	129 (80%)	123 (77%)	122 (76%)	495 (77%)
White	146 (92%)	151 (94%)	148 (93%)	150 (94%)	595 (93%)
Any ME group membership	31 (19%)	26 (16%)	25 (16%)	23 (14%)	105 (16%)
Clinical data					
International CFS criteria[12]					
As randomised	99 (62%)	100 (62%)	98 (61%)	100 (63%)	397 (62%)
Actual	107 (67%)	106 (66%)	106 (66%)	108 (68%)	427 (67%)
London ME criteria[13]					
As randomised	89 (56%)	90 (56%)	89 (56%)	89 (56%)	357 (56%)
Actual	81 (51%)	84 (52%)	84 (53%)	80 (50%)	329 (51%)
Any depressive disorder					
As randomised	55 (35%)	55 (34%)	54 (34%)	55 (34%)	219 (34%)
Actual	54 (34%)	52 (32%)	54 (34%)	53 (33%)	213 (33%)
Any psychiatric disorder*	75 (47%)	75 (47%)	73 (46%)	77 (48%)	300 (47%)
Duration of illness (months)	33 (16–69)	36 (16–104)	35 (18–67)	25 (15–57)	32 (16–68)
Body-mass index (kg/m²)	25·9 (5·5)	25·4 (5·2)	25·5 (4·6)	25·1 (4·5)	25·5 (5·0)

Data are mean (SD), n (%), or median (IQR). ME=myalgic encephalomyelitis. CFS=chronic fatigue syndrome. *Psychiatric disorders included any depressive disorder and any anxiety disorder, including phobias, obsessive-compulsive disorder, and post-traumatic stress disorder.

Table 1: **Baseline demographics and clinical characteristics**

Table 1 describes study participants

Two-thirds of the subjects met the international CFS criteria and about half met the M.E. criteria, which require the presence of post-exertional relapse and exclude individuals with depressive or anxiety disorders. One-third had depression and almost half had a history of some depressive disorder. The authors state, "Our findings were much the same for participants meeting the different diagnostic criteria for CFS and for M.E., for those with depressive disorder, and after allowing for clustering effects."

It is important to note that study participants had to be able to attend sessions at a hospital or clinic, and therefore more severely ill or homebound patients were not included. The study recruited patients age 18 and older. The average duration of illness was about three years and no subject had been ill longer than six years. The average age was 38; 77 percent of the subjects were women and 93 percent were Caucasian.

Assessments using self-report measures were taken at baseline, 12 weeks into therapy, at 24 weeks (post-therapy) and at 52 weeks for follow-up. Improvement and adverse events were also assessed using several self-report measures. Subjects were also asked to rate how successful they thought the treatment would be before sessions began and how satisfied they were at the end of therapy. There were no biological

	Adaptive pacing therapy (n=159)	Cognitive behaviour therapy (n=161)	Graded exercise therapy (n=160)	Specialist medical care alone (n=160)
Change from baseline				
12 weeks	153 (96%)	153 (95%)	151 (94%)	151 (94%)
Positive change	20 (13%)	32 (21%)	37 (25%)	7 (5%)
Minimum change	126 (82%)	113 (74%)	111 (74%)	133 (88%)
Negative change	7 (5%)	8 (5%)	3 (2%)	11 (7%)
24 weeks	155 (97%)	149 (93%)	148 (93%)	151 (94%)
Positive change	37 (24%)	56 (38%)	54 (37%)	28 (19%)
Minimum change	111 (72%)	82 (55%)	89 (60%)	107 (71%)
Negative change	7 (5%)	11 (7%)	5 (3%)	16 (11%)
52 weeks	153 (96%)	147 (91%)	152 (95%)	152 (95%)
Positive change	47 (31%)	61 (41%)	62 (41%)	38 (25%)
Minimum change	96 (63%)	77 (52%)	80 (53%)	100 (66%)
Negative change	10 (7%)	9 (6%)	10 (7%)	14 (9%)
Odds ratio (positive change vs negative or minimum changes)				
Compared with specialist medical care	1·3 (0·8–2·1); p=0·31	2·2 (1·2–3·9); p=0·011	2·0 (1·2–3·5); p=0·013	..
Compared with adaptive pacing therapy	..	1·7 (1·0–2·7); p=0·034	1·5 (1·0–2·3); p=0·028	..

Data are n (%) or odds ratio (95% CI). Comparisons made at 52 weeks were taken from the final adjusted models. Positive change was defined as very much better or much better. Minimum change was defined as a little better, no change, or a little worse. Negative change was defined as much worse or very much worse.

Table 5: **Participant-rated clinical global impression of change in overall health**

Table 5 provides data about participants' impressions of their therapy

measures reported. Studies of CBT in other conditions including HIV/AIDS and cardiovascular disease, routinely collect data on immune markers or other biological measures in attempt to understand how and why CBT works in the context of the condition studied.

The services delivered in this study were highly structured and are described in the study and in several detailed manuals. At least three sessions of medical care were provided to all 641 participants over the six-month study period, and additional sessions were available as needed. These sessions included basic pharmacologic support, especially for sleep, pain and mood. For all groups the medical services were delivered by specialists with experience treating CFS. The pacing group received its services from occupational therapists, using a modified "energy envelope" approach that encouraged patients to "plan and pace activity to reduce or avoid fatigue, achieve prioritized activities and provide the best conditions for natural recovery." CBT services were delivered by clinical psychologists and nurse therapists. They guided patients to establish a baseline of activity and rest and a regular sleep pattern, and then make collaboratively planned gradual increases in both physical and mental activity. Participants were helped to address social and emotional obstacles to improvement through problem-solving. GET services were provided by physiotherapists and one exercise physiologist. Therapeutic strategies in the GET group consisted of establishing a baseline of achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active. Target heart rate ranges were set when necessary to avoid overexertion, which eventually aimed at 30 minutes of light exercise five times a week. The subjects receiving only specialized medical care were seen 5-6 times during the study, while the subjects in the other three programs were seen a total of 16-17 times during the study.

	Adaptive pacing therapy (n=159)	Cognitive behaviour therapy (n=161)	Graded exercise therapy (n=160)	Specialist medical care alone (n=160)
Non-serious adverse events	949	848	992	977
Participants with non-serious adverse events	152 (96%)	143 (89%)	149 (93%)	149 (93%)
Non-serious adverse events per 100 person-years	597 (559–636)	527 (492–563)	620 (582–660)	611 (573–650)
Serious adverse events	16	8	17	7
Participants with serious adverse events	15 (9%)	7 (4%)	13 (8%)	7 (4%)
Serious adverse events per 100 person-years	10·1 (5·8–16·3)	5·0 (2·2–9·8)	10·6 (6·2–17·0)	4·4 (1·8–9·0)
Serious adverse reactions	2	4	2	2
Participants with serious adverse reactions	2 (1%)	3 (2%)	2 (1%)	2 (1%)
Serious adverse reactions per 100 person-years	1·3 (0·2–4·5)	2·5 (0·7–6·4)	1·3 (0·2–4·5)	1·3 (0·2–4·5)
Serious deterioration (composite)*	13 (8%)	14 (9%)	10 (6%)	15 (9%)
Physical functioning reduction	7 (4%)	5 (3%)	5 (3%)	6 (4%)
PCGI worse	5 (3%)	7 (4%)	1 (<1%)	10 (6%)
Withdrawn due to worsening	3 (2%)	0	2 (1%)	1 (<1%)
Serious adverse reactions	2 (1%)	3 (2%)	2 (1%)	2 (1%)
Differences in serious deterioration				
Comparison with specialist medical care	−1·2%; p=0·71	−0·7%; p=0·83	−3·1%; p=0·30	..
Comparison with adaptive pacing therapy	..	0·5%; p=0·87	−1·9%; p=0·51	..

Data are n, n (%), or rate (95% CI), unless otherwise stated. Adverse events were considered serious when they involved death, hospital admission, increased severe and persistent disability, self-harm, were life-threatening, or required an intervention to prevent one of these. There were no suspected unexpected serious adverse reactions. PCGI=participant-rated clinical global impression. *Serious deterioration composite is either of a short form-36 physical function subscale score reduction at two consecutive visits, a PCGI score of much worse or very much worse at two consecutive visits, withdrawal from treatment due to explicit worsening, or a serious adverse reaction; the numbers withdrawn from treatment due to worsening is a subset of all those withdrawing from treatment shown in table 2.

Table 4: Safety outcomes

Table 4 reports safety outcomes for each group

Although the patient organization Action for M.E. participated in the planning and design of the adaptive pacing program, it doesn't completely mirror the type of pacing advocated by many expert CFS physicians or that has been tested formally by Leonard Jason, PhD's group at DePaul University. Dr. Jason's latest published study in the *Journal of Clinical Psychology* found that increasing activity was associated with more improvements for those who started treatment within their energy envelope compared with those outside of their energy envelope.

The PACE Trial reported a moderate beneficial effect of CBT and GET compared to adaptive pacing therapy and specialized medical care alone. Participants' global impressions of the therapy report positive change by 41 percent of those receiving CBT or GET at the one year mark; 31 percent of the pacing group had positive change and 25 percent of the specialized medical care (alone) group had positive change. Negative change was reported by six percent of the CBT group, seven percent of the GET and pacing groups, and nine percent of the group receiving specialized medical care alone. Serious

adverse events were lowest in the CBT and medical care alone group with four percent; highest was the pacing group with nine percent. Rates of serious adverse reactions and serious deterioration did not differ between treatment groups.

The characteristic feature of CFS is post-exertional relapse and provoking the relapse of all symptoms after even modest physical or mental activity is of great concern to patients who experience it. Eighty-four percent of the subjects reported this symptom at baseline and the distribution of subjects into the four groups resulted in fairly even distribution of this symptom across the four treatment groups. The greatest improvement in this symptom was seen in the GET group, where participants were advised to gradually return to appropriate physical activities and reverse deconditioning. At the one-year mark the report of post-exertional relapse in this group had dropped from 82 percent to 44 percent of participants. In the CBT group where participants were encouraged to do more than they thought they could, post-exertional relapse was reported by 49 percent of the participants at follow-up. In the pacing group, participants were advised not to undertake activities that demanded more than 70 percent of participants' perceived energy envelopes. Increased activities were encouraged, if the participant felt able, and as long as they did not exacerbate symptoms. At the end of the study, 63 percent of the pacing participants reported post-exertional malaise. In the group that received specialized medical care only, participants were simply counseled to avoid the extremes of rest and activity; 63 percent of them reported post-exertional malaise at follow-up.

Given the size of this study and its potential implications for health policy in the U.K. and other countries, it is deeply disappointing that there was no attempt to include measures that might provide a biologic explanation for the outcomes reported. In fact, the word biology is not mentioned once in this paper. The lack of biological explanation for observed improvements reinforces the perception that CFS is mind over matter, even while the paper says it should not. While most people recognize that CBT and GET can be effective in many chronically ill populations as an adjunct to medical care, the news coverage of studies like this one often fails to underscore this point. In several studies of CBT and infection, CBT is shown to work by helping decrease chronic inflammation and tempering the number and activity of harmful immune cell activity. A walking program was shown to improve memory by increasing brain volume in aging sedentary people, as shown by functional MRI studies. Again, no such correlations were attempted in the PACE trial. Further, it is unclear whether the moderate benefits achieved from such an intensive course of CBT and GET are sustained. The authors indicate that long-term follow-up will be reported in other papers, along with a cost-effectiveness assessment and breakdowns of treatment benefits by subgroup analysis according to different case definitions used.

The takeaway message from this study is that the current standard medical care available to people with CFS (by any definition) remains very limited and is relatively ineffective on its own. Structured programs that seek to expand function and reduce symptoms may provide modest benefits when added to standard medical care, but they do not offer complete resolution of symptoms or cure, and the benefits are equivalent to those seen in other studies of chronic illness. Younger, less severely ill and more recently ill individuals may benefit more, according to the effects seen in this select study population. It is worth noting that the specialized medical care provided to all subjects in this study – at least three sessions over a 12-month period – represents more access to medical care delivered by professionals educated about CFS than most CFS patients in the United States (and other countries) can obtain, regardless of their financial resources. Without that important adjunct, it is unknown how successful these behavioral treatment modalities would be, especially if delivered outside this type of structured program by lesser trained professionals who lack basic information about the rather specific and unique challenges posed by CFS.

The CFIDS Association of America is committed to advancing research that leads to the early detection, objective diagnosis and effective treatment of CFS. The scientific and medical communities are obligated to understand the biological roots of CFS so that targeted and effective treatments can be made available to the millions of people around the world whose lives have been derailed by CFS.

References:

White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M, on behalf of the PACE trial management group. Comparison of adaptive pacing therapy, cognitive behavior therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet.* February 18, 2011. DOI:10.1016/S0140-6736(11)60096-2. (Abstract and paid access to full text at http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)

National Institute for Health and Clinical Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management (Clinical guideline CG53). http://guidance.nice.org.uk/CG53 (accessed Feb. 19, 2011).

Brown M, Khorana N, Jason LA. The role of changes in activity as a function of perceived available and expended energy in nonpharmacological treatment outcomes for ME/CFS. J Clin Psychol. J Clin Psychol 00:1-8, 2010.

Revised Feb. 21, 2011