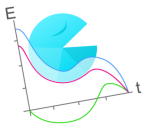

M.E. Analysis – Evaluating the results of the PACE study

a project supported by Phoenix Rising

Summary

The PACE trial was published in the March 2011 edition of The Lancet. Costing over £5 million and taking over 5 years in production, it was easily one of the largest and most expensive studies on the treatment of chronic fatigue syndrome (ME/CFS). Funded entirely by the British government, it studied and compared the effectiveness of three separate therapies* on 640 ME/CFS patients over the course of one year. The trial collected a large quantity of important data for analysis, but only a small proportion of this appears in the report.

Given the expense of the trial and its implications for future UK policy, the report caused a great deal of controversy. While the authors made moderate claims and recommendations based on these results, some media reports overstated the results and gave the impression that a magic cure for ME/CFS is readily available.

We, as people with scientific/mathematical backgrounds and who also have ME/CFS, believe that the PACE study deserved a thorough analysis. So we ask, "What has the PACE trial taught us, and where do we go from here?"

Here are our thoughts and conclusions.

* Cognitive Behaviour Therapy, Graded Exercise Therapy and a form of pacing called Adaptive Pacing Therapy.

The 10 Conclusions

❶ Future studies should not use the Oxford Criteria.

The UK is the only country to use the Oxford criteria as a matter of course, and then only in psychological studies of ME/CFS. According to the PACE figures, 38% of the patients participating in this trial would not be classified as having ME/CFS if judged by international standards. However, studies using the Oxford criteria have historically played a major role in shaping both opinion and treatment of ME/CFS in this country. Putting all of these patients together does not help with any analysis: all patients deserve treatments appropriate to their particular needs.

❷ Future studies should also use additional measures of average and variation.

The way in which averages were used in the PACE trial significantly overstated the effectiveness of the therapies used in the trial.

When results form a smooth and balanced distribution (such as people's heights), it can be useful to use the *arithmetic mean* as an average, and the *standard deviation* as a measure of variation between results. However, these measures can be quite deceptive when a distribution is unusual, as it is with the key measures in the PACE trial.

For example, the average number of fingers for everyone must be below 10: there are not enough with 11 or 12 to offset those born with few or none. But it would be misleading for me to say simply that I had more than the average number of fingers.

A more useful picture can be obtained by using the middle value (the median) as an average, and the quarter-way points (the quartiles) as a measure of variation.

❸ It has not been proven that we should continue to use GET and CBT with all ME/CFS patients.

The authors of the PACE study concluded that "*CBT and GET can safely be **added to** SMC (Specialist Medical Care) to moderately improve outcomes for chronic fatigue syndrome...*". The evidence does not support this.

It is not enough for a therapy or treatment to be safe: it also must be effective, and here the use of the term "**added to**" is highly significant. The average improvement added on to SMC by either GET or CBT is far too small to justify the universal investment either of resources or of patients' time. In fact, even for the key subjective measures chosen by the authors, the improvement in scores of patients who had only about 5 sessions of SMC was greater than the additional effect of the therapies. This is rather like having a minimum height requirement of 5 feet 10 inches for joining the police, then allowing applicants to stand on a box 3 feet high.

GET and CBT are effective therapies for a proportion of patients satisfying the Oxford criteria. The factors that define these patients need to be obtained from the vast wealth of the PACE data, so that these patients can continue to benefit.

It would, therefore, seem inappropriate for psychological theories to maintain any more importance to ME/CFS than they do for any other illness in which fatigue is a factor.

❹ All patients with CFS/ME should have better access to a specialist.

Patients in the PACE trial who received only Specialist Medical Care showed some improvement in all areas (more than the authors had anticipated). In fact, that improvement was generally greater than the extra improvement added on by giving the patients about 12 sessions of GET or CBT (which was *much less* of an improvement than the authors had anticipated). The level of Specialist Medical Care experienced by the patients in the PACE study is not normally provided at ME centres.

An analysis by the Newcastle NHS CFS Service found that 40% of patients sent to them with a provisional diagnosis of ME/CFS in 2008/09 did not have the condition, but had another, often treatable, condition. A similar proportion of people attending six specialist chronic fatigue centres who were screened for entry into the PACE trial were rejected because they did not have CFS. These findings underline the importance of ensuring that those diagnosed with ME/CFS are assessed more rigorously by specialists, rather than simply being referred for CBT and GET.

❺ We must find the factors which identify those patients who show greater benefit from these therapies.

The trial was based upon the model that patients with CFS (which includes patients with ME) suffer primarily from fear avoidance, deconditioning and exercise intolerance, and the authors clearly expected that the chosen therapies (CBT and GET) would produce a much greater improvement in patients' health. Given such a small average improvement, it would be sensible to conclude that this model is no longer useful for CFS as a whole, nor for ME/CFS in particular. In conclusion 6, we offer an alternative model.

But it would be wrong to deny these therapies to those who could benefit from them. The PACE trial has amassed a great deal of information about these patients. Priority should be given to determining how to recognise the characteristic symptoms of patients who benefit from these therapies, and to determining whether, in fact, it is these specific therapies that help, or whether other factors are at play.

⑥ We need better information about the prognosis of this illness.

There was no proper control group in the PACE trial. One group received just 5 sessions of Specialist Medical Care: the others received 3 or 4 sessions of SMC and a further dozen sessions with a therapist. If we were to assess GET and CBT (and their associated psychological assumptions), then we would need to start the assessment at the end of the sessions of Specialist Medical Care, and have a control group that experienced an equal number of sessions of a therapy which did not address those psychological assumptions. Only then could we separate out the specific effects of GET and CBT.

Results from our own survey have turned up an interesting number of points. For people with ME/CFS the natural variation between good and bad spells is often quite marked. Any focus on lessening the frequency and intensity of the bad spells, whether through medical means or through better management, would be welcomed by patients.

⑦ Future analysis of the results of the PACE trial should focus on individual improvements.

If everyone in a doctor's waiting room were given anti-depressants, there would probably be a weak overall benefit. Some people would benefit a lot, most would not and a few would be harmed. It would be a remarkably stupid and lazy idea: anti-depressants should only be given to an individual after a thorough and appropriate diagnosis has indicated that they are needed.

The PACE trial demonstrated weak overall improvements from therapies that were not selected on the basis of thorough, appropriate, individual diagnosis. It would be helpful if the individual data were to be released. There is so much information in this study that it would be a pity if it were not available for general analysis, and with modern technology it should be possible to analyse and present the results in a much more informative manner.

⑧ We need to find reliable bio-markers for ME.

While certain biomarkers and other assessments have been suggested for use in ME/CFS patients, agreement on which tests are diagnostic, or even useful in a majority of patients, has been complicated by a devastating lack of funding and by the use of varying definitions, some of which are overly broad.

It is not possible to identify biomarkers in a population that has been lumped together based on the failure to diagnose an alternate condition and on the manifestation of a single common, exceedingly vague symptom (or even a small group of symptoms which could arise from a number of causes).

In order to determine diagnostic biomarkers for ME/CFS, it will be essential to carefully perform differential diagnosis. We recommend the use of the International Consensus Criteria for the purpose of identifying which patients have ME. (Many people have started to use the term ME rather than ME/CFS when describing patients identified under tighter criteria.) These are the most up-to-date modern criteria supported by multiple researchers interested in differential diagnosis. Differential diagnosis also includes the careful identification of conditions other than ME, which might be causing fatigue.

⑨ There needs to be much more research and support for the seriously affected.

It doesn't say much for our society that we have done so little for the people who are the most affected by this illness. It is just too convenient to ignore those who remain trapped in their homes, and remain unnoticed – a view that was eloquently endorsed by the Countess of Mar in an address to the House of Lords (UK) .

Out of over 2400 studies and articles concerning ME that are listed in the AfME archives from 2000 onwards, only one specifically focuses on those whose needs are the greatest.

⑩ Future studies should aim for a more rigorous scientific structure.

The common advice for scientific studies is that if you want to prove that something ***is*** so, go out of your way to prove that it ***is not*** so. By beginning an experiment with the intention of confirming what you already believe to be true, you are likely to miss important possibilities, create misunderstandings, or make errors.

In our opinion, research into ME/CFS has been conducted on a piecemeal basis. The PACE trial is one of a very small number of comprehensive studies conducted since the analysis of pupil absences by Dowsett and Colby, published in 1997. Unfortunately, despite the authors' hopes, the results of the PACE trial have not taken us any further forward in terms of treatment, but at least they have made the limitations of the psychological model for ME/CFS quite clear. We hope that further analysis of individual data will enable doctors to target these therapies more appropriately for the small proportion of patients that might find them useful.

We also hope that the Medical Research Council's decisions on funding ME research, in November 2011, will result in a more integrated approach, especially in the selection of patients and in the consistency and quality of objective assessments.

Credits

The contents of this website were put together by Graham McPhee and Janelle Wiley, together with contributions, analysis, and support from Mark Berry, Robert Courtney, Tom Kindlon, Simon McGrath, Alex Young, and many others who prefer to remain in the background, and with lots of patient support and suggestions from friends both at Phoenix Rising and elsewhere. All of the contributors have ME, which is why the project has taken so long to complete.

The project was created as a way to consolidate some of the analysis on a Phoenix Rising thread discussing the PACE trial, together with analysis elsewhere, into a more accessible format. Phoenix Rising made Wiki software available to support collaboration on this project.

If you wish to contact Graham, please email Graham@meetup.org.uk