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NHS Lothian submission of 23 August 2019

WHAT WAS THE PACE TRIAL?

- The PACE trial was a large clinical trial including 600 patients that was funded mainly by the Medical Research Council and published its main findings in 2011 in the Lancet.
- The trial aimed to compare four different ways of treating patients with CFS. A substantial proportion of participants also met one definition for ME (for which there are multiple research definitions).
- The treatments evaluated were:

    1. Specialist medical care, comprising visits to an interested hospital doctor (SMC)
    2. Adaptive Pacing Therapy, comprising seeing a therapist to help manage energy and live within limits (APT)
    3. Cognitive Behaviour Therapy, comprising seeing a therapist for a psychologically- informed treatment to help patients explore if their fears about worsening symptoms by being more active is excessive (CBT)
    4. Graded Exercise Therapy, probably better termed Graded Activity Therapy, comprising seeing a therapist for collaborative and gradual increases in activity (GET)

- The findings of the trial were clear. CBT and GET were superior to APT and SMC in improving both fatigue and physical function one year after entering the trial. The differences were clinically meaningful, but moderate in size.
- The study looked very carefully for harms and found no excess of harms with the rehabilitative-type treatments (CBT and GET).
- Secondary trial papers reported that a modestly greater proportion of patients could be regarded as 'recovered' with CBT and GET that with the other treatments. Whist there is no agreed definition of recovery the figures reported were approximately 20% with CBT and GET, and approximately 8% with the other conditions. These figures are consistent with other reports.
- The benefits of CBT and GET were maintained at 12 months and 18 months.

ALLEGATIONS ABOUT THE TRIAL

There have been many false allegations made about this research by activist groups and a small number of associated academics, which change over time. The main current ones are listed.

The trial finding that CBT and GET are superior to APT and standard medical care is false because it used patient rated outcomes.

- Patient-rated outcomes are the most important to patients. Bias in patient-rated outcomes is a risk if patients feel they have had greater attention from or have more faith in one treatment than another. This is a problem for all trials of therapies of which the patient must be aware of used for a condition, which is defined in subjective terms, such as pain fatigue or depression.
- However, in PACE whilst CBT and GET were found to be more effective than APT, which had similar therapist contact time and similar, if not better, credibility with participants. This finding makes bias participants ratings a very unlikely explanation of the differences found between these treatments.

The investigators changed the trial outcomes to make CBT and GET look better.

- The trialists used the originally registered primary outcomes to report the trial findings. There was no 'outcome-switching'.
- The precise way the outcomes were used in the analysis was changed from the initial protocol following statistical advice. Importantly this was done *before* looking at the data and was signed off by the Trial Steering Committee. This timing has been confirmed by the UK Health Research Authority review of the trial.
- Other ways of analysing the relative effects of the treatment produce similar findings.

The proportion of patients regarded as recovered was inflated and no better with CBT and GET than with the other treatments.

- The definition of recovery, especially with limited data (as in a trial), is contentious.
- A secondary paper exploring different definitions of recovery and found about twice as many people could be considered recovered with CBT and GET (about 20%) than with APT and SMC (about 10%).
- Whilst many definition of recovery are possible, and that these will alter the absolute percentage of those deemed recovered in each group, the relative effect of the treatments remains the same.
- The definition of recovery used yielded figures similar to those in the research literature.
- The allegation that people could be recovered when starting the trial is simply nonsense.

The trial was fraudulent or in some way influenced by the DWP or the insurance industry.

- The DWP contributed a small amount of the total cost (less than 5%) via the MRC as part of a recommended governmental department co-funding agreement. The DWP had no influence on the trial design analysis or presentation.
- Several of the investigators had done small amounts of independent consultancy for insurance companies, but this was in not relevant to the trial. The insurance companies played no part in the trial; this was confirmed by the HRA review
- The trial was run by a very large group of researchers to MRC standards with an independent Trial Steering Committee and Data Monitoring Committee and also independent statisticians.
- It is very hard to see that even if anyone had wanted to bias the results or to commit fraud, how they would have been able to do so.

The PACE authors refused to share or hid the trial data.

- The PACE trial data has been shared with a number of other scientists, including a Cochrane Collaboration Review group.
- The trial data was not shared with the public, as the trialists did not have participants consent to do this. Queen Mary University, London, which was the sponsor of the trial, therefore declined to release the data to the public in the face of dozens of Freedom of Information requests. Most of these refusals were upheld, but on one occasion, a FOI tribunal ordered the release of some of the trial data.
- This released data has been used to "reanalyse" the trial results, with a claim that the published results were misleading. The reanalysis was flawed and consequently misleading.

The PACE trial is universally regarded as flawed and consequently discredited.

- Many lengthy critiques have been produced alleging myriad flaws in the trial. Some of these include quotes from scientists, none of whom are experts in clinical trials.
- It is important to note that experts in clinical trials, including the many peer reviewers of the paper when it was published in The Lancet, have not found the trial to be flawed. Indeed, it is regarded as a high quality trial. The MRC and the Lancet stand by the trial.

WHY THE CRITICISM?

- The question arises why people are so keen to find fault with a robust trial published as long ago as 2011.
- The finding that CBT and GET are helpful has led some to believe that the study proves that "ME is a psychological condition". A treatment study cannot do that and the paper explicitly states that it does not prove that the condition is 'psychological'.

- Another reason is that patient experience of CBT and in particular, GET when received outside the trial is that it is often reported to be unhelpful or even harmful. These reports are probably explained by the treatment being given to people dissimilar to those who took part in the trial or by the treatments being given incorrectly. They require further research.

- These concerns do not however mean that the PACE trial was flawed or fraudulent.

HAVE SIMILAR FINDINGS BEEN MADE BY OTHERS?

- It is important to note that the PACE trial does not stand alone. There have been a number of trials from different universities and different countries with similar findings.
- The key arbiter of science is replication, and the PACE trial results have been replicated many times. There are Cochrane reviews of these multiple studies.

CONCLUSIONS

- The PACE trial and other similar trials find moderately better outcomes with CBT and GET than with SMC or APT. The evidence for the value and safety of CBT and GET as given in these trials is robust. These therapies are not a cure for all, but help many.
- The PACE trial does not show that CFS or ME are mental illnesses and does not suggest that biomedical factors are not relevant to ME.
- The reported adverse effects with GET and CBT in routine care requires further investigation. Reports of this may reflect misdiagnosis or poorly delivered treatment.
- It is most unfortunate that hostility to such treatments and associated misconceptions have led activist groups (not patients in general) to reject these treatments and to also to seek to discredit the science supporting them; see the Reuters and Guardian/Observer reports.

REFERENCES

PACE main paper

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