Response to the editorial by Dr Geraghty

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Abstract

This article is written in response to the linked editorial by Dr Geraghty about the adaptive Pacing, graded Activity and Cognitive behaviour therapy; a randomised Evaluation (PACE) trial, which we led, implemented and published. The PACE trial compared four treatments for people diagnosed with chronic fatigue syndrome. All participants in the trial received specialist medical care. The trial found that adding cognitive behaviour therapy or graded exercise therapy to specialist medical care was as safe as, and more effective than, adding adaptive pacing therapy or specialist medical care alone. Dr Geraghty has challenged these findings. In this article, we suggest that Dr Geraghty's views are based on misunderstandings and misrepresentations of the PACE trial; these are corrected.

Keywords

chronic fatigue syndrome, clinical trials, cognitive behaviour therapy, graded exercise therapy, treatment

The PACE trial compared four treatments for people diagnosed with chronic fatigue syndrome (CFS) (White et al., 2011). A recent editorial about this trial (Geraghty, 2016) contains a number of inaccuracies which we now correct.

1. Dr Geraghty states that '… there are accepted scientific procedures and standards that appear to have been neglected, or bypassed, by the PACE-Trial team', although he has not said which procedures and standards we neglected or bypassed. The trial was extensively peer reviewed by the Medical Research Council, which funded it. It followed the consolidated standards of reporting Trials (CONSORT) guidance on how to report and conduct a high-quality trial (http://www.consort-statement.org/). A Research Ethics Committee gave ethical

approval, and it was overseen throughout by the independent Trial Steering Committee and Data Monitoring and Ethics Committee; patient members sat on the Trial Management and Steering Committees. The protocol was published some 3 years before the analysis began, and 4 years before the first outcome paper was published (White et al., 2007). The papers reporting the trial findings were peer reviewed before their publication in high-impact journals, such as The Lancet (White et al., 2011). So far, we have published 16 papers from the trial (http://www.wolfson.qmul.ac.uk/current-projects/pace-trial), as well as contributing data to an individual patient data Cochrane Collaboration review, which has been submitted for publication.

2. We reject the accusation that our 'actions have arguably caused distress to patients', for which Dr Geraghty offers no evidence. People with CFS and/or myalgic encephalomyelitis (ME) want treatments that help them to improve (Action for ME, 2011). In this ME charity member survey of National Health Service (NHS) clinics, 85 per cent of those surveyed wanted the charity to campaign to save these services and 92 per cent wanted more such services; 46 per cent had received cognitive behaviour therapy (CBT) and 65 per cent thought that CBT should be made available; 31 per cent had received graded exercise therapy (GET) and 48 per cent thought it should be made available (Action for ME, 2011). The PACE trial simply confirmed what previous smaller trials had already found (Edmonds et al., 2004; Price et al., 2008): that patients are more likely to get better with either CBT or GET than with other treatments or usual care.

3. We reject the suggestion that the fact that we use these therapies for our patients and have tested them in previous trials is 'a major source of investigator bias'. Clinical research often arises from questions thrown up by clinical practice. The clinicians among us have dedicated their careers to care for thousands of patients with CFS/ME and we always want the best for them. We are therefore obliged to conduct trials to test the effectiveness and cost-effectiveness of treatments that we use. If Dr Geraghty's proposal, that trials should only be conducted by investigators with no previous experience of an illness and its treatments, was followed, it would prevent any clinician or researcher from attempting to replicate or refute the results of their earlier trials. While steps should always be taken to minimise bias, as we did, this suggestion is not sensible.

4. In our long-term follow-up paper, we reported that the benefits of CBT and GET were maintained some 2 years after treatment (Sharpe et al., 2015). Dr Geraghty suggests that 'The trial authors have since [the paper was published] argued that the SMC and APT groups [who improved over the follow up period], probably went to get CBT or GET privately after the end of the formal trial'. The reality is that we clearly reported within the paper the numbers of participants who went on to receive the additional therapies (most commonly CBT and GET), which were offered by trial NHS therapists to all participants who needed and wanted further help.

5. Regarding our paper on recovery, Dr Geraghty stated that we defined it partially on the basis of 'a patient reporting feeling "better" or "much better"' when in reality ratings of overall health as 'much better' or 'very much better' counted towards being considered recovered on this measure.

6. Dr Geraghty is also incorrect in his comments about the repeated use of the Freedom of Information Act (FOIA) to obtain trial information – 'the PACE authors … refused to release

data partly on the grounds that they viewed requesters as vexatious patients …'. Of the 46 FOIA requests that Queen Mary University of London have received, only 2 requests (not the requesters) were considered vexatious by the University; this view was confirmed by the Information Commissioner on appeal (Information Commissioner Office, 2016a, 2016b).

7. We have repeatedly addressed the criticisms made in the editorial of the methods and analyses used in the PACE trial. These can be found in blogs (Wessely, 2015; White, 2016), journal correspondence and as answers to frequently asked questions on the PACE trial website (http://www.wolfson.qmul.ac.uk/current-projects/pace-trial#patients).

8. In the editorial, Dr Geraghty makes two criticisms which we have not previously addressed. In the first one, he states that 'the effectiveness of cognitive behaviour therapy (CBT) and graded exercise therapy (GET), …, fell by two thirds' in a reanalysis of some of the trial data and concludes that these 'have left us with two versions of "truth" concerning the trial's findings – the published analysis versus the recent analysis'. This is incorrect. Effectiveness was measured by comparing the mean scores for each of the two primary outcomes between treatment groups; the effect sizes varied between 0.5 and 0.8 (moderate effect sizes), depending on the different comparisons (White et al., 2011). In his editorial, Dr Geraghty has compared two different things: one is a secondary post hoc analysis from the main paper, in which we reported the proportions of participants who improved by a clinically useful amount in both the primary outcomes (an improvement of 8 or more points for physical function and 2 points for fatigue), which equated to 61 per cent for CBT and 59 per cent for GET (White et al., 2011). The other is our reanalysis of some of the trial data comparing the proportions of participants who met a composite threshold for improvement (either improving by 50% on the primary outcomes or meeting a threshold for improvement) (Goldsmith et al., 2016). Using this composite outcome, 21 per cent improved with GET and 20 per cent with CBT; significantly more than with adaptive pacing therapy (APT) (9%) or specialist medical care (SMC) alone (10%) (Goldsmith et al, 2016). Dr Geraghty suggests that the effectiveness fell from 61 per cent by one analysis method to 20 per cent when using another method. It is no surprise that fewer participants are regarded as improved if more stringent criteria are applied. Since this has nothing to do with efficacy, it made no difference to our 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). The later analysis mentioned by Dr Geraghty was described in our original protocol and then abandoned for the definitive analysis plan after statistical advice (Walwyn et al., 2013). This was because we accepted that using composite outcomes was complex, difficult to interpret and incongruent with expert views (Senn and Julious, 2009). We changed this analysis with oversight committee approvals and before outcome data were examined (Walwyn et al., 2013; White et al., 2011).

9. The second criticism concerned our secondary analysis paper about recovery (White et al., 2013). Dr Geraghty states that '… some trial participants had reached the level required to be classified as improved or recovered at trial entry'. This is incorrect; 3/640 (<1%) of participants had scores within the normal population ranges for both fatigue and physical function at trial entry, which was only one of the criteria necessary to be considered as recovered. To meet the criteria for recovery, a participant also had to have met additional criteria: no longer be considered a case of CFS (using the trial definition of CFS) and rated their overall health as 'much' or 'very much' better compared to trial entry. No participants met the full criteria for recovery at trial entry.

10. Regarding comments on the release of trial data, we wish to clarify that one of the main reasons for our refusal to provide individual patient data to members of the public (following a FOIA request) was that we did not have the consent of our participants to make their data publicly available. We were also concerned that patients might be personally identified by releasing their data. We support sharing data for the benefit of medical research and ultimately of patients (White et al., 2016), as long as it is subject to certain guarantees – principally concerning confidentiality and an agreement not to attempt to identify participants. This is an ethical position, respecting patients' rights, as we are required to do by research governance and the data protection act, and has been repeatedly supported by the Information Commissioner and Information Tribunal on all but one occasion.

We stand firmly by the findings of the PACE trial, which, along with other studies, provide patients, healthcare professionals, and commissioners with the best evidence that both CBT and GET are safe and effective treatments for this chronic and disabling illness. Others share this view (National Institute for Health and Clinical Excellence, 2011; NHS Choices, 2011; The Lancet, 2011, 2015). These findings are good news for patients who, in our experience, just want to get better. Of course, we need further trials, not only of CBT and GET but also other treatments. To this end, we hope that editorials such as that by Dr Geraghty do not discourage others from doing such research.

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