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Special issue on the PACE Trial

Abstract

We are proud that this issue marks a special contribution by the Journal of Health Psychology to the literature concerning interventions to manage adaptation to chronic health problems. The PACE Trial debate reveals deeply embedded differences between critics and investigators. It reveals an unwillingness of the co-principal investigators of the PACE trial to engage in authentic discussion and debate. It leads one to question the wisdom of such a large investment from the public purse (£5million) on what is a textbook example of a poorly done trial.

Concept

The *Journal of Health Psychology* received a submission in the form of a critical review of one of the largest psychotherapy trials ever done, the PACE Trial. PACE was a trial of therapies for patients with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), a trial that has been associated with a great deal of controversy (Geraghty, 2016). Following publication of the critical paper by Keith Geraghty (2016), the PACE Trial investigators responded with an Open Peer Commentary paper (White et al., 2017). The review and response were sent to more than 40 experts on both sides of the debate for commentaries.

The resulting collection is rich and varied in the perspectives it offers from a neglected point of view. Many of the commentators should be applauded for their courage, resilience and 'insider' understanding of experience with ME/CFS.

The Editorial Board wants to go on record that the PACE Trial investigators and their supporters were given numerous opportunities to participate, even extending the possibility of appeals and re-reviews when they would not normally be offered. That they failed to respond appropriately is disappointing.

What transpired

Commentaries were invited from an equal number of individuals on both sides of the debate (about 20 from each side of the debate). Many more submissions arrived from the PACE Trial critics than from the pro-PACE side of the debate. All submissions were peer reviewed and judged on merit.

The PACE Trial investigators' defence of the trial was in a template format that failed to engage with critics. Before submitting their reply, Professors Peter White, Trudie Chalder and Michael Sharpe wrote to me as co-principal investigators of the PACE trial to seek a retraction of sections of Geraghty's paper, a declaration of conflicts of interest (COI) by Keith Geraghty on the grounds that he suffers from ME/CFS, and publication of their response without peer review (White et al., 4 November 2016, email to David F Marks). All three requests were refused.

On the question of COI, the PACE authors themselves appear to hold strong allegiances to cognitive behavioural therapy (CBT) and graded exercise therapy (GET) – treatments they developed for ME/CFS. Stark COI have been exposed by the commentaries including the PACE authors themselves who hold a double role as advisers to the UK Government

Department of Work and Pensions (DWP), a sponsor of PACE, while at the same time working as advisers to large insurance companies who have gone on record about the potential financial losses from ME/CFS being deemed a long-term physical illness. In a further twist to the debate, undeclared COI of Petrie and Weinman (2017) were alleged by two of the commentators (Agardy, 2017; Lubet, 2017). Professors Weinman and Petrie adamantly deny that their work as advisers to Atlantis Healthcare represents a COI:

> We are very clear that there is not a COI that we need to declare. We have had nothing to do with the PACE trial and neither of us work on CFS. Our Atlantis link does not provide any conflicts as Atlantis focuses on supporting patient adherence to medication for various long term conditions, and has not had any involvement with patients with CFS. (Weinman and Petrie, 9 May 2017, email to David F Marks)

After the online publication of several critical Commentaries, Professors White, Sharpe, Chalder and 16 co-authors were offered a further opportunity to respond to their critics in the round but they chose not to do so. They wrote: *As always, we would refer interested readers to our original publications and trial website where most, if not all, the issues brought up by commentators are addressed* (Chalder and Sharpe, 12 May 2017, email to David F Marks).

After peer review, authors were invited to revise their manuscripts in response to reviewer feedback and many made multiple drafts. The outcome is a set of robust papers that should stand the test of time and offer significant new light on what went wrong with the PACE Trial that has been of such high significance for the nature of treatment protocols. It is disappointing that what has been the more dominant other side refused to participate.

Unfortunately, across the pro-PACE group of authors there was a consistent pattern of resistance to the debate. After receiving critical reviews, the pro-PACE authors chose to make only cosmetic changes or not to revise their manuscripts in any way whatsoever. They appeared unwilling to enter into the spirit of scientific debate. They acted with a sense of entitlement not to have to respond to criticism. Two pro-PACE authors even showed disdain for ME/CFS patients, stating: *We have no wish to get into debates with patients.* In another instance, three pro-PACE authors attempted to subvert the journal's policy on COI by recommending reviewers who were strongly conflicted, forcing rejection of their paper.

The dearth of pro-PACE manuscripts to start off with (five submissions), the poor quality, the intransigence of authors to revise and the unavoidable rejection of three pro-PACE manuscripts led to an imbalance in papers between the two sides. However, this editor was loathe to compromise standards by publishing unsound pieces in spite of the pressure to go ahead and publish from people who should know better.

What next?

We are proud that this issue marks a special contribution by the *Journal of Health Psychology* to the literature concerning interventions to manage adaptation to chronic health problems. The PACE Trial debate reveals deeply embedded differences between critics and investigators. It also reveals an unwillingness of the co-principal investigators of the PACE trial to engage in discussion and debate. It leads one to question the wisdom of such a large investment from the public purse (£5 million) on what is a textbook example of a poorly done trial.

ME/CFS research has been poorly served by the PACE Trial and a fresh new approach to treatment is clearly warranted. On the basis of this Special Issue, readers can make up their own minds about the scientific merits and demerits of the PACE Trial. It is to be hoped that the debate will provide a more rational basis for evidence-based improvements to the care pathway for hundreds of thousands of patients.

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Editorial

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‘PACE-Gate’: When clinical trial evidence meets open data access

Keith J Geraghty

Abstract

Science is not always plain sailing and sometimes the voyage is across an angry sea. A recent clinical trial of treatments for chronic fatigue syndrome (the PACE trial) has whipped up a storm of controversy. Patients claim the lead authors overstated the effectiveness of cognitive behavioural therapy and graded exercise therapy by lowering the thresholds they used to determine improvement. In this extraordinary case, patients discovered that the treatments tested had much lower efficacy after an information tribunal ordered the release of data from the PACE trial to a patient who had requested access using a freedom of information request.

Keywords

chronic fatigue syndrome, clinical trials, cognitive behavioural therapy, psychotherapy, treatment

Introduction

The recent release of data from the largest clinical trial of psychotherapy treatments for chronic fatigue syndrome (CFS), the ‘PACE-Trial’, has triggered a perfect storm of patient anger and professional defensiveness. The data were only released after a protracted freedom of information case brought by a patient with CFS. A tribunal ordered the lead author’s institution to release their data. Upon release, re-analysis showed that the levels of improvement and recovery observed in the released data were much lower than the levels reported in the published report (White et al., 2011a) and other related publications. The released data showed that the effectiveness of cognitive behavioural therapy (CBT) and graded exercise therapy (GET), in comparison to standard medical care (SMC) and adaptive pacing therapy (APT), fell by almost two-thirds.

Patient groups and independent experts have remarked that without data access, the medical establishment would have been left to accept the outcomes from the PACE-Trial, as robust evidence that CBT and GET are effective treatments for CFS. Instead, patients are calling for the wider scientific community to investigate their claim that the PACE-Trial authors overstated the benefits of CBT and GET. This editorial considers the ramifications of this unfolding story for patients with CFS, and its impact on

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the science of clinical trials of psycho-behavioural therapies.

Background

In 2011, a group of UK researchers published results from the PACE-Trial, a large randomised controlled trial of treatments for CFS, with 641 participants (White et al., 2011a). This is the largest clinical trial ever conducted on therapies for CFS, with a combined cost of almost £5 million; funded by the Medical Research Council, the Department for Work and Pensions, the Department of Health for England and the Scottish Chief Scientist Office. The trial report carried the bold claim that 59 per cent of CFS patients receiving CBT and 61 per cent receiving GET had improved (White et al., 2011a). An accompanying editorial in *The Lancet* suggested a recovery rate of 30 per cent using CBT and GET in the PACE-Trial (Knoop and Bleijenberg, 2011). This figure was later lowered to a 22 per cent recovery rate in a follow-up paper by the PACE-Trial team (White et al., 2013). If credible, a 61 per cent improvement rate and a 22 per cent recovery rate would represent a significant breakthrough in the treatment of CFS; a serious condition affecting millions of patients worldwide.

Doctors and scientists have long struggled to understand the causes of CFS and have had little in the way of treatments to offer sufferers. Following the PACE-Trial, CBT and GET gained prominence as positive interventions. The National Health Service (NHS) has promoted CBT and GET as effective and safe treatments for CFS on their 'NHS Choices' website. The PACE-Trial also solidified the status of CBT and GET as 'evidence-based treatments' recommended by the National Institute for Health and Care Excellence (NICE, 2014).

While the health authorities accepted the findings from the PACE-Trial as *bona fide* and media outlets reported that CBT could cure CFS, patient groups raised concerns about the trial early on, particularly its methodology and findings. Individual patients and advocacy groups pointed to the fact that the trial investigators had altered assessment thresholds (primary outcome measures) after the start of the trial; had applied a broad inclusion criteria (the Oxford Criteria), rather than more strict sampling criteria; and had contaminated the trial by promoting the success of CBT and GET in newsletters to trial participants during the trial (Goldin, 2016; Newsletter available at Queen Mary University London (QMUL, 2016b: FAQ link). The President of the Royal College of Psychiatry, Professor Sir Simon Wessely, who had helped to recruit patients into the trial wrote, 'I think that we can have confidence in the principal findings of PACE' but referred to the controversy around the trial being like 'a ship voyage across a stormy sea' (Wessely, 2015).

A long and bitter battle ensued in the years following the end of the trial that pitted patients against the trial investigators (Chalder and Goldsmith, 2015). Patients and patient advocacy groups called for access to the trial data. They were not the only critics of the trial. *The Lancet* received two open letters from a list of distinguished academics, calling for the PACE-Trial to be independently analysed (Racaniello, 2016).

Patient scrutiny and data analysis

While patients and academics called for the release of the PACE-Trial dataset, the authors refused on the grounds that the data included sensitive patient information (QMUL, 2016b). In response, patients proceeded to submit freedom of information requests to the lead author, Professor Peter White at QMUL. However, QMUL turned down many of these requests. One patient, Mr Alem Matthees, took his case to appeal. QMUL lost, but appealed to seek to overturn this decision. The PACE-Trial lead authors submitted evidence to a subsequent information tribunal that they had already shared their trial data with the independent reviewers at the Cochrane Group (QMUL, 2016b), but also divulged that some of the PACE team were in fact the Cochrane reviewers (HMTS et al.,

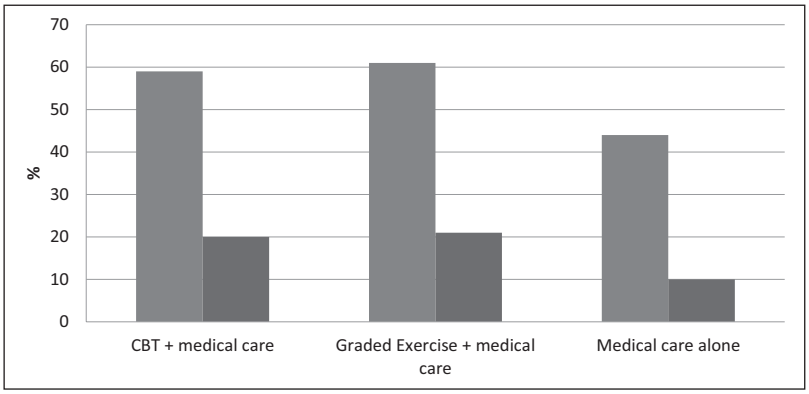

Figure 1. PACE trial improvers: published (blue) versus original protocol (red).
Source: White et al. (2011a; first published results); QMUL (2016b; re-analysed results).

2016). In August 2016, the tribunal dismissed the QMUL appeal and ordered the release of anonymised trial data. Immediately prior to the 1-month deadline, the PACE team published an analysis of the trial's original protocol and outcome measures, and QMUL released the requested data (QMUL, 2016a, 2016b).

Within days of the release, patients examined the authors' new data publication and the raw data found its way on to patient forums. It quickly became apparent that the improvements reported by White et al. (2011a) were much reduced when the original protocol thresholds (White et al., 2007) were applied. Using the trial's original markers for improvement, the effectiveness of CBT and GET fell from the reported 59 and 61 per cent, to just 20 and 21 per cent, respectively (Figure 1). Patients took to social media with statements that the PACE team had overstated claims of efficacy in their data analysis. Indeed, the Standard Medical Care group, which was the de facto control condition, had produced a 10 per cent improvement, meaning that CBT resulted in just a modest 10 per cent added benefit over usual medical care. In light of this revelation, there is little alternative but to conclude that the PACE team utilised methods that showed CBT and GET to be vastly more beneficial than would have been the case, if the authors used their original trial protocol. The impact of this troubling conclusion is made far worse by the fact that the PACE-Trial authors did not disclose these findings until after the information tribunal. The authors have steadfastly maintained that their changes to the thresholds were justified and approved by their oversight committees (Walwyn et al., 2013). However, figure 1 clearly shows that the size of the added benefit of CBT and GET falls to just 10–11 per cent applying the original trial protocol.

Over the past 5 years, the PACE team have published multiple follow-on papers from the trial, such as a long-term patient follow-up and an economic evaluation of the cost effectiveness of CBT and GET compared with APT and SMC (McCrone et al., 2012; Sharpe et al., 2015). Patients have scrutinised these outputs and highlighted some clear inconsistencies: specifically that the initial gains reported at trial end (52 weeks) mostly disappeared between groups at follow-up (2.5 years), with SMC and APT having improved to a similar degree to those in the CBT and GET groups (Sharpe et al., 2015). The trial authors have since argued that the SMC or APT patients probably went to get CBT or GET privately after the end of the formal trial (QMUL, 2016b). Patients also pointed to the fact that within the CBT and GET groups, the reported levels of improvement and recovery were not matched by clear reductions in secondary outcome measures; with levels of unemployment, health care usage and sickness benefit claims, remaining relatively unchanged

in all treatment groups (McCrone et al., 2012; White et al., 2013). The PACE authors have stated this was most likely the result of a harsh economic climate and patients being given welfare advice during the trial (QMUL, 2016b: FAQ).

Methodological concerns

Patients have pointed to several methodological concerns about the PACE-Trial. First, the trial authors had favoured subjective self-report measurement instruments over objective tests of physical function. For example, the PACE team used the Chalder Fatigue Scale and a quality-of-life survey (SF-36) to assess improvement, yet dropped plans to assess patients' activity levels using electronic activity monitors, reporting that such tests were too complex to undertake (QMUL, 2016b; Walwyn et al., 2013).

Critics have also pointed out a crucial methodological anomaly, that the PACE team had lowered the threshold for improvement and recovery from a score of 85 on SF-36, to a score of 60, at the analysis stage. This change meant that some trial participants had reached the level required to be classified as improved or recovered at trial entry, before they had even taken any treatment course (Walwyn et al., 2013; White et al., 2013). The trial authors have not offered a reasonable explanation for this observation. The other parameters rested on patients reporting feeling better using self-report measures and no longer meeting the Oxford Criteria (White et al., 2007).

Finally, it was noted that the PACE-Trial team derived a rather convoluted 'operational definition' of recovery using a mix of no longer meeting the criteria for CFS and a patient reporting feeling 'better' or 'much better', rather than objective markers of physical improvement. Much of the reported benefits in the PACE-Trial rested on patients' perceptions of mood and fatigue, rather than measurements of their physical improvement benchmarked against norms within a healthy population group. Despite the size and complexity of the PACE-Trial, the investigators did not explore whether participants were able to return to normal physical activities, such as walking outside, standing upright, doing shopping and socialising. Given CFS is a physically disabling condition, any assessment of recovery should have assessed these factors, particularly as 'self-reported improvements' in psychotherapy trials may be influenced by placebo and therapist effects (Geraghty and Blease, 2016).

The impact of the belated and enforced data release

The release of the PACE-Trial dataset was hard won. It took patients 5 years to win the right to obtain the data. Over this period there have been many discussions in academic circles about the need for open data access. As a backdrop, the most-read paper in *PLoS Medicine* claims that 'most research evidence in medicine is false' (Ioannidis, 2005). A major replication project in psychology could only reproduce 39 per cent of published results, suggesting as much as 61 per cent of studies are unreliable (Open Science Collaboration, 2015). These observations support the need for greater transparency in clinical trials. Ben Goldacre at the Evidence-Based Medicine DataLab in Oxford has dedicated much of his time to developing tools to register trials and promote open access (e.g. the Open Trials Initiative, Goldacre, 2010, 2014). However, not all scientists are in favour of sharing data. For example, Lewandowsky and Bishop (2016) wrote in *Nature Online* about how data access requests might be used as weapons of harassment by militants, specifically referring to CFS. Interestingly, the freedom of information tribunal heard from the PACE authors that they refused to release data partly on the grounds that they viewed requesters as vexatious patients who were using freedom of Information (FOI) for illegitimate reasons (HMTS et al., 2016).

The PACE-Trial stands out as a showcase example of why data transparency is needed in contemporary science. Patients suffering from health conditions like CFS, and independent scientists, should have the right to see the

evidence behind the claims of any scientific study, especially if this evidence is used to direct health policy or promote certain treatments – as was the case for the PACE-Trial.

The status of CBT and psychotherapy in CFS

There are other reasons why patients and independent critics challenged the PACE-Trial authors. Many CFS patients and advocacy groups reject the model that asserts that CFS is 'perpetuated' or 'maintained' by 'dysfunctional illness beliefs' (Moss-Morris et al., 2013). Many patients have raised concerns that CBT is being promoted as a cure for CFS, when there is little evidence to support this claim (Geraghty and Blease, 2016). The majority of patients are pragmatic. They are aware that there is currently no agreed cause for the condition, although an increasing amount of research points to immune and cellular alterations as important clues (Green et al., 2015). Many health professionals are in the dark about the condition, most likely the result of education programmes that do not adequately cover CFS. What patients appear to want is better recognition of the condition among all professionals, doctors, nurses and those in psychotherapy; deeper scientific enquiry that does not only focus on the social-psychology of CFS but explores potential biological aetiology and pathophysiology; and they also want better support within current health structures.

Many patients with CFS may need psychological support, particularly help with coping with the distress the condition can cause; but this is a far cry from a CBT-GET intervention regime that emerges from the fear avoidance model that seeks to convince a CFS patient that the pain or fatigue they are suffering, are dysfunctional cognitions that need to be altered (White et al., 2007, 2011b). Patients with CFS might value CBT more if it was offered as an adjunct support therapy, alongside good quality care from a knowledgeable physician. There is a role for psychologists to support patients with chronic health conditions that can include secondary depression, anxiety and vulnerability to suicide (Fuller-Thomson and Nimigon, 2008; Jason et al., 2006). The problem for many CFS patients has been that CBT is not offered as a support, but as a therapy to reframe illness beliefs. However, the re-analysis of the PACE-Trial data shows that CBT is largely ineffective at restoring physical function. Irrespective of the protocol changes, the majority of trial participants did not report benefit and the PACE team concede this, and they also agree that their trial was only applicable to milder cases of CFS, those fit enough to undertake the treatments (QMUL, 2016a).

The fall-out and the future

'PACE-Gate' stands as an example of how science is not always a simple process of discovery and reflects the ills of contemporary science in microcosm. As a result of the PACE-Trial saga, it is likely that patients with CFS will be less trusting of doctors, scientists and psychotherapy practitioners. To win this trust back, the medical-scientific community must learn lessons from PACE-Gate. First, was it wise to commission a small group of scientists that held very strong published views in favour of CBT/GET as treatments for CFS, to be the ones to test the efficacy of these treatments? Conflicts of interest have always been the thorn in the side of clinical trials and a major source of investigator bias (Goldacre, 2010, 2014; Marks, 2017). Funders of future trials must consider the independence of those entrusted to carry out clinical trials. Second, what role did the PACE-Trial steering committee and external adjudicators play in this saga? Why did it take patients to spot anomalies and irregularities in PACE-Trial publications? Third, we must question why the PACE authors were never required to publish the original trial protocol results alongside the results from the amended protocol? It appears that none of the funders, steering committees or peer reviewers called for this. *The Lancet* editor, Richard Horton, made a spirited defence of PACE in the media post publication, claiming critics were 'a small but highly vocal

minority' (ABC Radio, 2011). PACE-Gate has exposed how it may be too easy to rush to a judgement about critics. In the PACE tribunal hearing, we saw evidence that a team of distinguished professors based in elite institutions characterised critical patients as 'vexatious' (HMTS et al., 2016).

There are important lessons here: dissenting voices must be heard, clinical trials must be conducted by independent investigators (as much as is possible) and trial data must be publicly accessible. No scientific study should be immune from criticism. Without criticism, science will suffer and progress will arguably take longer. There is no utopia in research and no trial is free of all bias and error. However, there are accepted scientific procedures and standards that appear to have been neglected, or bypassed, by the PACE-Trial team. Their actions have arguably caused distress to patients, added a million pounds of additional costs to a publically funded trial and have left us with two versions of 'truth' concerning the trial's findings – the published analysis versus the recent re-analysis. It will be up with others and health authorities to decide which version to accept.

Conclusion

The PACE-Trial has been a controversial clinical trial for several reasons. First, CFS is a controversial and contested illness domain. Many CFS patients reject the theoretical rationale for the use of CBT and GET. PACE-Gate exposes the long-running acrimony between doctors and patient groups over the cause of the illness and the most appropriate approaches to treatment. Second, the lowering of improvement criteria after the trial had begun appears to have significantly inflated the benefits of CBT and GET. Third, patients had to engage in a long-drawn-out battle to gain access to the trial data. This exemplifies why data sharing standards are needed. The fact it took a tribunal to order the release of data has done much to damage the reputation of the trial and has added fuel to the fire concerning the conduct of the trial. Fourth, the release of the PACE-Trial data revealed a dramatic reduction in the benefit of CBT and GET as treatments for CFS, applying the original trial protocol. Collectively, PACE-Gate has damaged the trust CFS patients place in health professionals and science. It will now be up to health authorities to make a judgement on the revelations that CBT and GET may be less beneficial than first reported. If CBT and GET bring about improvement in self-reported mood and fatigue for just 10 per cent more patients than SMC, with little impact on restoring physical function, this indicates that these therapies are non-curative and should be downgraded to adjunct support-level status.

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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.

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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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Commentary

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Once again, the PACE authors respond to concerns with empty answers

David Tuller

Abstract

In their response to Geraghty, the PACE investigators state that they have "repeatedly addressed" the various methodological concerns raised about the trial. While this is true, these responses have repeatedly failed to provide satisfactory explanations for the trial's very serious flaws. This commentary examines how the current response once again demonstrates the ways in which the investigators avoid acknowledging the obvious problems with PACE and offer non-answers instead—arguments that fall apart quickly under scrutiny.

Keywords

chronic fatigue syndrome, cognitive behavior therapy, graded exercise therapy, illness perception

Other commentaries in this Special Section focus on specific methodological aspects of the PACE trial. (The study's full name: "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome: A randomised trial.") I would like to examine how the PACE investigators, in their response to the troubling questions about their research raised in Geraghty's editorial (Geraghty, 2016), have strategically avoided providing direct answers (White et al., 2017). Instead, they have provided non-answers—persuasive-sounding arguments that fall apart quickly under scrutiny. This approach is consistent with their earlier efforts to rebut legitimate criticism.

The PACE investigators note that they have "repeatedly addressed" the various concerns about the trial, citing journal correspondence as well as popular forums such as blog posts and news articles. A review of some of these publications confirms their point. But "addressing" concerns is not the same as offering credible explanations, and the investigators have failed this test each time they have responded. For example, they have acknowledged that some participants already qualified as "recovered" on primary outcomes at entry—even though these participants had been found on the same measures to be disabled enough for the study. But the investigators have not acknowledged the obvious—that this peculiar overlap in disability and recovery thresholds presents serious problems of interpretation. And they have not explained why people who were recovered

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on primary outcomes were included in the study to begin with.

In their trial protocol (White et al., 2007), the PACE investigators included four separate outcomes on which participants had to meet recovery criteria in order to be considered fully recovered. Two of them were the primary outcomes of physical function and fatigue. In the 2013 paper in *Psychological Medicine*, as has been reported previously, all four of the recovery criteria were watered-down versions of the criteria listed in the protocol (White et al., 2013; Wilshire et al., 2016). In essence, the investigators overhauled their definition of "recovery" in ways that boosted the trial's apparent success rate.

In responding to Geraghty, the investigators quote his editorial thus: "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." Yet in quoting Geraghty, the investigators have truncated his comments in a way that distorts his meaning. Geraghty was clearly referring to participants who were recovered at trial entry on a single recovery outcome—and in particular the physical function outcome. Unbiased readers could not reasonably interpret Geraghty's actual statement the way the PACE investigators have chosen to present it, as if he were referring to participants who were recovered at entry for all four criteria.

The PACE investigators next answer a question Geraghty did not ask. They provide assurances that no participants met the "full criteria for recovery" at trial entry—that is, none were recovered on all four criteria. This statement, while true, is a diversion, since neither Geraghty nor anyone else (to my knowledge) has argued that any participants met the "full criteria for recovery" at entry. And while making that point, the investigators decided not to explain why *anyone* was recovered on *any* of the four criteria at baseline—and especially on the two measures that were used to determine whether patients were sufficiently disabled to be in the trial. In short, the investigators refuse to grapple with the implications of this massive flaw at the core of their research. Instead, they appear to believe they deserve some credit because none of their participants entered the study having already met the "full criteria" for recovery.

The PACE investigators further state that only three participants, or less than 1 percent of the sample, met the recovery thresholds for both physical function and fatigue at baseline. Like their statement that no participants met all four of the recovery criteria, this point is also true, and also disingenuous. In fact, as was discovered after the trial through a freedom-of-information request, almost 13 percent of the sample—81 of 641 participants—met the recovery threshold for physical function at baseline. Seven participants met the fatigue recovery threshold at baseline; three members of this group also met the physical function recovery threshold. In all, 85 participants met at least one of these two recovery thresholds at baseline. Yet the investigators mention in their response only the three participants who met both thresholds, ignoring the many dozens of others who met at least one of them.

In not reporting these relevant facts in *Psychological Medicine*, the PACE investigators withheld important evidence from the scientific record. This omission should raise a host of difficult questions about the overall integrity of the study. It is self-evident that participants cannot logically be defined simultaneously as "disabled" and "recovered" on an indicator, even if it is only one of four indicators under investigation. Such an anomaly in a study of breast cancer, AIDS or any other illness would disqualify it from being published. Lack of approval from oversight committees for major changes in outcome measures would also be disqualifying; the PACE investigators do not reference any such approvals in *Psychological Medicine*.

Conscientious editors at journals that mistakenly published such flawed research would immediately move to correct or retract it. Yet those serving as gatekeepers and decision-makers at *Psychological Medicine* and other prestigious journals have yet to acknowledge the glaring and fundamental problems with the PACE trial. This editorial recalcitrance and

willful obtuseness harm the field of public health and undermine public belief in science. (One of the PACE investigators, Michael Sharpe, is on the *Psychological Medicine* editorial board.)

In their response to Geraghty, the PACE investigators also suggest that the improvement rates from cognitive behavior therapy (CBT) and graded exercise therapy (GET)—that is, the percentage of those found to have reached designated "improvement" thresholds for both physical function and fatigue—are irrelevant to their claims that the treatments work. What matters instead, they write, is the revised method they used to assess the effectiveness of the primary outcomes: a comparison of averages between the groups, which they reported in *The Lancet* (White et al., 2011). The PACE investigators explain, as they have previously, that their original method of measuring improvement rates was too complicated to interpret, so they substituted the comparison of averages.

Yet rates provide key information that averages, however useful, do not—namely, how many people in the different groups got better. This is information that patients and clinicians want, need, and deserve. Perhaps in response to potential criticism of their decision to scrap the protocol measure of improvement rates, the investigators reported in *The Lancet* a post hoc measure of improvement rates that was much more expansive than the protocol version. This revised method yielded improvement rates of 59 percent for CBT and 61 percent for GET. Last year, after a tribunal ordered the release of anonymized PACE data, the investigators published their own reanalysis of the data and reported that only 20 percent were defined as "improved" under the protocol methodology (Queen Mary University of London, 2016).

This big drop does not trouble the PACE investigators, nor does it alter their interpretation of the study. The issue, they write in their current response, has "nothing to do with efficacy."

It is true that the investigators found in their reanalysis of improvement rates that the extremely modest benefits for CBT and GET were nonetheless statistically significant. But the 59–61 percent improvement rates have been widely cited as a measure of the PACE trial's success. To insist now that anyone assessing the study should ignore the implications of the sharp decline in reported improvement rates is not a serious argument.

Indeed, the investigators appear perplexed that anyone would think of comparing the two sets of results. "It is no surprise," they write, "that fewer participants are regarded as improved if more stringent criteria are applied." By the same logic, it could have been "no surprise" to the PACE investigators themselves that more participants would be "regarded as improved"—and therefore reported as "improved" in their *Lancet* paper—if they substituted less stringent criteria to measure improvement rates in the trial.

If the investigators believed so strongly that their new improvement rate criteria were better than those in the protocol, they should have published both sets of findings or the appropriate sensitivity analyses. Then, they could have explained why the revised methods that produced the higher improvement rates were more valid and reliable than the original methods that produced the lower rates. That the investigators received oversight committee approval for the changes in primary outcome measures does not mitigate their responsibility to provide sufficient data for others to assess the results. That *The Lancet* did not require inclusion of this sort of information was a puzzling lapse in editorial judgment.

In addressing Geraghty's concerns, the PACE investigators refer readers seeking further explanations to previous correspondence and articles. Yet the claims in these publications also fall short in transparency and common sense. White, for example, wrote a *Guardian* commentary last fall after an independent group reanalyzed the recovery data and found null results (Matthees et al., 2016). In the commentary, White complained that the researchers had made "tweaks" to the outcome measures that made it harder for trial participants to achieve

recovery thresholds (White, 2016). White failed to mention that those "tweaks" were simply the stricter recovery methods he and his colleagues had themselves promised in their protocol, and later abandoned. In other words, the reanalysis did not "tweak" anything—rather, it corrected the scientific record by un-tweaking the investigators' own post hoc, unauthorized tweaks. These criteria changes had yielded 22 percent recovery rates for GET and CBT, rather than null results found in the reanalysis.

White also recently told *The BMJ* that it was unfair of critics to compare the high improvement rates from the *Lancet* paper with the lower improvement rates calculated from the protocol definition (Hawkes, 2016). "They're comparing one measure with a completely different one—it's apples and pears," White said. Indeed it is. White and his colleagues took 5 million pounds in government funds and promised to bring back apples from the market. Instead they brought back pears, refusing to show anyone the apples they had rejected. Given the resources involved, it should not be hard to understand why people would want to examine those apples for themselves, to make their own comparisons with the pears and draw their own conclusions about whether their 5 million pounds were spent wisely. The investigators appear to view this public interest in accountability for public money as confusing or even offensive.

For years, the PACE investigators have repeated their standard arguments while affirming their faith in the integrity of the study. They do not yet grasp that the ground has shifted, in ways that do not benefit this strategy. With the release of the trial data, it is no longer enough to have persuaded themselves, Sir Simon Wessely, and other adherents that their methods are sound and the findings robust. The larger scientific world is now scrutinizing both the study itself and the investigators' defense of their work and has found their reasoning problematic and their intellectual position unsustainable.

Rather than acknowledging the flaws that others now see clearly, the investigators appear determined to persist with their current approach and resist any concession of error. Given this ill-advised and anti-scientific stance, they should prepare themselves for an even greater onslaught of questions and challenges from leading researchers, clinicians, and other experts, not to mention myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients and advocates. Their inadequate and non-responsive responses to tough but fair criticism have apparently served the PACE investigators well in previous exchanges, when few but Sir Simon Wessely were paying attention. That time has passed.

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Commentary

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Investigator bias and the PACE trial

Steven Lubet

Abstract

The PACE investigators reject Geraghty's suggestion that the cognitive behavior therapy/graded exercise therapy trial could have been better left to researchers with no stake in the theories under study. The potential sources and standards for determining researcher bias are considered, concluding that the PACE investigators "impartiality might reasonably be questioned."

Keywords

chronic fatigue syndrome, cognitive behavior therapy, graded exercise therapy

After identifying a number of evident flaws in the non-blinded PACE trial, including a mid-course relaxation in certain measures for improvement and recovery, Geraghty (2016) posed a question: "Was it wise to commission a small group of scientists that held very strong published views in favour of CBT/GET as treatments for CFS, to be the ones to test the efficacy of these treatments?" It was a reasonable inquiry, given that investigator bias—due to conflicts of interest or for other reasons—presents a constant problem in clinical trials and in other sorts of trials as well. The specifics of the PACE trial, and its problematic history, are discussed in other contributions to this Special Section. In this commentary, I will focus on the general issue of latent or implicit bias among researchers, judges, and other decision makers.

Taking issue with Geraghty, the PACE investigators deny even the possibility that their results, methods, or choices might have been skewed by their preexisting commitment to cognitive behavior therapy and graded exercise therapy (CBT/GET):

> 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." … "[We are] obliged to conduct trials to test the effectiveness and cost-effectiveness of treatments that we use." (White et al., 2017)

It is understandable that the PACE investigators would defend the validity of their study, but they have understated their professional stake in the reported outcomes of the trial, which was framed from the outset as determining more than simply the effectiveness of the therapies. In fact, they were testing their own theories of the illness, as detailed in the *Lancet* paper in which they first announced their results:

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> CBT was done on the basis of the fear avoidance theory of chronic fatigue syndrome. This theory regards chronic fatigue syndrome as being reversible and that cognitive responses (fear of engaging in activity) and behavioural responses (avoidance of activity) are linked and interact with physiological processes to perpetuate fatigue. (White et al., 2011: 825)

> GET was done on the basis of deconditioning and exercise intolerance theories of chronic fatigue syndrome. These theories assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity. These changes result in the deconditioning being maintained and an increased perception of effort, leading to further inactivity. (White et al., 2011: 825)

The PACE investigators were deeply committed to the "unhelpful cognitions" theory of myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS), which they and other colleagues, most notably Simon Wessely, had originated and actively promoted for decades (King's College London, 2014; Queen Mary University of London, 2014; University of Oxford, 2014; Wessely, et al., 1989). If the PACE trial had failed to show significant "improvement" and "recovery" through CBT/GET, as now appears to be the case, that would have undermined the very theories of reversibility to which the investigators had "dedicated their careers" and the treatment of "thousands of patients" (White et al., 2017).

Consequently, the risk of latent bias was palpable from the outset, even if the investigators made no intentional effort to misrepresent or massage their results. As has been well established in the social science literature, physician behavior is often influenced by self-interest, even when the factors seem remote, trivial, or entirely extraneous. As Dana and Loewenstein (2003) have explained, bias is not exclusively the result of deliberate choice:

> Even when individuals try to be objective, their judgments are subject to an unconscious and unintentional self-serving bias. When individuals have a stake in reaching a particular conclusion, they weigh arguments in a biased fashion that favors a specific conclusion. (p. 252)

Thus, it has been shown that prescribing decisions may be influenced by seemingly inconsequential gifts such as pens, notepads, and inexpensive meals (Katz et al., 2010). One recent study, of over 125,000 physicians, "found that receipt of a single industry-sponsored meal, with a mean value of less than $20, was associated with prescription of the promoted brand-name drug at significantly higher rates to Medicare beneficiaries" (DeJong et al., 2016: E7). Tellingly, a survey of young physicians found that 61 percent believed they were not influenced by gifts from pharmaceutical representatives, while only 16 percent believed that their colleagues were equally unaffected (Steinman et al., 2001).

Virtually, all physicians and scientists value their reputations and hypotheses far more than a few negligible trinkets, or even a good meal, so it seems self-evident that researchers' intellectual allegiance to a favored theory could potentially influence the conduct, design, or interpretation of a randomized trial (Dragioti et al., 2015). This is the very definition of a conflict of interest, because the researchers' interest in—or hope for—a particular outcome is inherently in tension with the need for rigorously neutral metrics and observations. And this is true even in the complete absence of intentionality. "Conflicts of interest will inevitably bias physician behavior, however honorable and well-intentioned specific physicians may be." Furthermore, "bias may distort their choices, or they may look for and unconsciously emphasize data that support their personal interests." In other words, succumbing to conflicts of interest is not a matter of "conscious corruption." Instead, "unconscious bias is a far more serious problem" (Korn and Ehringhaus, 2007: 21).

Physicians and scientists are not immune to confirmation bias (Groopman, 2007: 65). "Like the rest of society, they are well able to ignore what they don't want to see and seek confirmation for what they do want to believe—with no conscious intention to deceive either themselves or anyone else" (Korn and Ehringhaus,

2007: 25). A recent review of clinical trials came to the unsurprising conclusion that "industry sponsored drug and device studies are more often favorable to the sponsor's products than non-industry sponsored drug and device studies due to biases that cannot be explained by standard 'risk of bias' assessment tools" (Lundh et al., 2013: 2). It is likewise unsurprising to observe that a preexisting belief in or adherence to a particular therapy or treatment may play a similar role in leading to more favorable results (Munder et al., 2013).

The latter phenomenon is known as researcher allegiance, which has been recognized in contexts including psychotherapy (Dragioti et al., 2015; Munder et al., 2012). Some degree of allegiance is to be expected in multi-investigator psychotherapy studies, which are necessarily non-blinded, but it was particularly pronounced among the PACE trial's co-principal investigators. As described by their own universities, Sharpe had been instrumental in the development of the "cognitive behavioral model" for ME/CFS treatment, White "designed graded exercise therapy (GET)," and Chalder had written a "CBT self-help booklet" for ME/CFS patients, among other contributions (King's College London, 2014; Queen Mary University of London, 2014; University of Oxford, 2014).

This brings us back to Geraghty's suggestion that CBT/GET could have been better evaluated by researchers other than the PACE team. Here, I would like to draw an analogy to judicial recusal, a field in which I have studied and written extensively. I recognize that the comparison is inexact; scientists are not judges. On the other hand, clinical investigators do conduct trials in which they examine evidence and, one hopes, reach impartial conclusions. Surely, no one would argue that a clinical investigator should be less objective—or allowed more bias—than a judge, so I believe that the judicial standard can shed some useful light on Geraghty's observation.

Under US law, a federal judge is disqualified ex ante from hearing any case in which his or her "impartiality might reasonably be questioned." This rule extends to any situation in which the judge appears to have an "interest that could be affected substantially by the outcome of the proceeding," whether financial or otherwise (Judicial Conference of the United States, Code of Conduct for United States Judges, Canon 3C(1), 2017; United States Code, Title 28 § 455(a), 2017).

Recusal under this rubric is prophylactic. Thus, the US Supreme Court has noted that a showing of actual or intentional bias is not required for the disqualification of a judge, so long as the possibility of bias is sufficiently apparent. Thus, a judge was held disqualified in *Williams v. Pennsylvania* because there was a "serious risk" that he "would be influenced by an improper, if inadvertent, motive to validate and preserve the result" that he had previously obtained when he was a prosecutor. It was the duty of the judge "to withdraw in order to ensure the neutrality of the judicial process in determining the consequences that his or her own earlier, critical decision may have set in motion" (United States Supreme Court, Williams v. Pennsylvania. 136 S.Ct 1899, 2016: 1902).

In *Caperton v. A.T. Massey Coal Co.*, the US Supreme Court addressed the problem of unconscious bias. Recognizing that few, if any, judges would intentionally exercise prejudice or prejudgment, the Court nonetheless observed that a judge's introspection is not sufficient to ensure that the balance is held "nice, clear, and true." Notwithstanding all good faith, there must be "adequate protection against a judge who simply misreads or misapprehends the real motives at work in deciding the case" (United States Supreme Court, Caperton v. A.T. Massey Coal Co., 556 U.S. 868, 2009: 883).

There are numerous cases that apply similar principles to US courts, requiring recusal to avoid "predisposition in decision-making," especially in circumstances where partiality has influenced "unconscious thought processes more than a judge may realize" (Geyh et al., 2013: 4–3). In addition, most American states have adopted the American Bar Association's Model Code of Judicial Conduct, which requires disqualification when a judge has made a public statement that "commits or appears to commit

the judge to reach a particular result" in a case or a category of cases (American Bar Association, Center for Professional Responsibility, 2016).

I do not mean that PACE team members were disqualified in the legal sense. There are no comparably strict rules of recusal for clinical trials, nor could there be. The PACE investigators state that they have "always wanted the best" for their patients, of which I have no doubt at all (White et al., 2017). The question, however, is whether their strongly held preconceptions of "the best" may have influenced the design, re-design, interpretation, and presentation of the trial and its results. Given their many years of advocacy for CBT/GET, dating at least to the early 1990s, in which they argued that ME/CFS is reversible through psychotherapy and exercise, it certainly seems that their "impartiality might reasonably be questioned."

Viewed in this light, Geraghty's proposal is persuasive. By virtue of their own experience, the PACE investigators were confident in the effectiveness of CBT and GET as ME/CFS treatments. Their earlier public statements—attributing ME/CFS symptoms to "false cognitions"—certainly appeared to dispose them toward a result. Coupled with their mid-trial revision of certain outcome measures—in a direction favorable to their own theories of improvement and recovery—it is reasonable to conclude that non-blinded trials of CBT/GET should be designed and overseen by investigators with no preexisting stake in the outcome.

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The problem of bias in behavioural intervention studies: Lessons from the PACE trial

Carolyn Wilshire

Abstract

Geraghty's recent editorial on the PACE trial for chronic fatigue syndrome has stimulated a lively discussion. Here, I consider whether the published claims are justified by the data. I also discuss wider issues concerning trial procedures, researcher allegiance and participant reporting bias. Cognitive behavioural therapy and graded exercise therapy had modest, time-limited effects on self-report measures, but little effect on more objective measures such as fitness and employment status. Given that the trial was non-blinded, and the favoured treatments were promoted to participants as 'highly effective', these effects may reflect participant response bias. In non-blinded trials, the issue of reporting biases deserves greater attention in future.

Keywords

chronic fatigue syndrome, cognitive behaviour therapy, graded exercise therapy, methodology

I read with interest Geraghty's (2016) editorial on the PACE trial for chronic fatigue syndorme (White et al., 2011) and also the PACE investigators' letter of response (White et al., 2017). Here, I will comment briefly on several issues raised in the response letter, all of which highlight important themes for future research into chronic fatigue syndrome (CFS) and/or clinical trial methodology more generally.

To summarise, the PACE trial investigated the effectiveness of three interventions for CFS: (1) graded exercise therapy (GET), which focused on gradually increasing patients' activity levels; (2) cognitive behavioural therapy (CBT), which addressed what were seen as patients' 'unhelpful cognitions' about their illness and their fears about exercise; and (3) a novel treatment, Adaptive Pacing therapy, which encouraged patients to restrict their activity levels (White et al., 2011). Participants were randomly assigned to one of these three treatments, or to a control, no therapy condition. Each participant also received at least three specialist medical care consultations. One year after treatment allocation, the primary outcome measures – self-rated fatigue and physical function – showed improvement in all groups, but significantly more so for the CBT and GET groups. Using a definition based largely on these primary measures, the investigators concluded that 22 per cent of patients in the CBT and the GET groups had 'recovered' following treatment, but only 7–8 per cent in the other two groups (White et al., 2013).

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At the outset, some clarification is needed on the current status of the PACE debate. The PACE researchers state they have, '… repeatedly addressed the criticisms made in the editorial of the methods and analyses used in the PACE trial' (White et al., 2017: 3). They then refer the reader to various letters to editors, commentaries and a website that provides answers to selected questions. However, in these documents, readers can neither raise new questions nor query any of the answers given. In short, they present only one side of the debate. The time has come for these researchers to engage in more direct academic dialogue with critics.

Scientific procedures and standards

Geraghty's editorial charged the PACE investigators with failing to adhere to 'accepted scientific procedures and standards'. In defending themselves against this charge, the investigators note their adherence to the CONSORT guidelines for conducting randomised trials (Schulz et al., 2010). They also note the various ethics reviews and procedures the project underwent, the high status of the journals they published in and the sheer number of papers that were published.

Some authors have raised concerns regarding PACE's ethics procedures, in particular about whether the participants were fully informed of the investigators' financial interests (see, for example, Tuller, 2015). However, here, I focus on one departure from protocol that may have significantly influenced conclusions about treatment effectiveness.

The authors emphasise that they published a trial protocol prior to data analysis (see White et al., 2007). A published protocol is desirable because it ensures that researchers do not alter their dependent measures after they have seen the data, in ways that might unduly favour the study hypotheses. However, to be of benefit in this way, the protocol must be followed. The investigators made several major ad hoc changes to their dependent measures – for example, they considerably altered the definition of 'recovery' (White et al., 2013). The CONSORT guidelines specify that authors should identify and explain any subsequent changes to outcome measures (Schulz et al., 2010). However, in a recent paper, we examined the explanations provided for these changes and found them to be either insufficient or based on inappropriate extrapolation from normative data (Wilshire et al., 2016). We also found that the changes operated to favour the study hypotheses: they served to increase the apparent rates of recovery by a factor of three and to yield a significant treatment effect where there would otherwise have been none. This is a significant cause for concern.

A more accurate statement is that *many* relevant procedures and standards were adhered to, but there were some significant departures, sufficient to undermine several key conclusions of the study.

Researchers' therapeutic allegiance

Another charge raised by Geraghty was that the researchers had significant professional and personal investment in two of the treatments: CBT and GET. Geraghty is referring to the 'researcher allegiance effect': the finding that, in studies examining more than one treatment approach, the treatment(s) favoured by the researchers tend to outperform other treatments (Luborsky et al., 1999, 2002; Munder et al., 2012; see also Wilson et al., 2012 for a discussion of this issue in relation to the Triple R parenting programme). Several factors may contribute to this effect, but one is likely to be the manner in which the non-favoured, 'comparison' treatment is conceptualised and implemented. Often, when a treatment is used as a comparison condition, it is implemented in a weaker form than when it is used clinically (Cuijpers et al., 2012; Munder et al., 2011). In the context of the PACE trial, the comparison treatment, Adaptive Pacing Therapy, was a novel intervention designed especially for the trial. None of the primary investigators believed in its effectiveness, and none had expertise in its

delivery, so its failure to yield successful outcomes is not particularly surprising.

The best way to address the researcher allegiance effect is to include primary investigators in the research team that specialise in the comparison treatment approach and to charge these persons with the design and supervision of those treatment sessions. However, there are also other much simpler steps that researchers can take. The first is to recognise the problem. The PACE researchers' defence against Geraghty's claim indicates that they believe themselves to be entirely impartial, which, of course, cannot be the case.

The next step is to ensure that therapists present all treatments to participants as equally likely to lead to improvement. This is especially important when the primary outcomes are self-report measures, since these measures can be strongly influenced by patients' expectations (Hróbjartsson et al., 2014). Unfortunately, in PACE, CBT and GET were promoted to patients during therapy as highly effective. For example, CBT participants were told that CBT was 'a powerful and safe treatment which has been shown to be effective in … CFS/ME' and that 'many people have successfully overcome CFS/ME using cognitive behaviour therapy, and have maintained and consolidated their improvement once treatment has ended' (Burgess and Chalder, 2004: 123). GET participants were told that 'in previous research studies, most people with CFS/ME felt either "much better" or "very much better" with GET' and that GET was 'one of the most effective therapy strategies currently known' (Bavinton et al., 2004: 28). No such information was given to the remaining two groups. In any rigorous trial, researchers need to at least acknowledge this potential confound and consider its possible impact on results.

Finally, one simple additional measure that can be taken is to share data as widely possible, so that researchers with different perspectives can examine it. I therefore urge the PACE researchers to share their (appropriately anonymised) data willingly and as widely as possible. This is the best way to demonstrate that they are aware of the issue of investigator bias and are willing to take steps to address it.

Our recent reanalysis of the PACE trial data on rates of recovery demonstrates just how powerful a data sharing approach can be. We were able to demonstrate that apparently minor, late changes to the definition of recovery impacted very substantially on the observed rates of recovery and on their final conclusions about the effectiveness of the different treatments (Wilshire et al., 2016). When we defined recovery according to the original protocol, we found that recovery rates were consistently low and not reliably different across treatment groups. The investigators appear to have been entirely unaware of the extent of this problem.

Specific problems and limitations

A researcher's enthusiasm for a particular treatment can also lead them to overinterpret their findings or overlook limitations. One limitation of the PACE trial – which has been pointed out by critics, but never fully acknowledged by the investigators – is that the treatment effects were almost entirely limited to self-report measures. Most of the objectively measurable outcomes did not yield significant treatment effects, for example, fitness and employment status did not differ across treatment groups when measured an entire year after trial commencement, and although mean walking distances were higher after treatment with GET than after medical care only, this difference was small (approximately 30 m, less than 10% of the baseline walking distance[1]), and no such benefit was observed for the CBT group.

Again, the problem here is that, in a non-blinded study, self-report measures are highly vulnerable to response bias. The size of this bias is not trivial. A recent meta-analysis of clinical trials for a range of disorders calculated that when participants were non-blinded to treatment allocation, self-reported improvements associated with treatment were inflated by an average of 0.56 standard deviations relative to comparable blinded trials. Importantly, no such inflation was observed when the outcomes involved objectively measurable indices (Hróbjartsson et al., 2014). Therefore, in order to securely

demonstrate the efficacy of any intervention within a non-blinded design, researchers need to show that self-reported improvements are supported by evidence based on more objectively measurable outcomes.

It would be unreasonable to expect the PACE investigators to solve the problem of participant response bias single-handedly. But in a trial of this size and importance, we can reasonably expect them to take some simple measures, such as balancing the information they provide to different participant groups about effectiveness. We can also reasonably expect them to minimise – or at the very least acknowledge – potential sources of bias. And we can reasonably expect researchers to acknowledge and discuss potential red flags, such as a lack of agreement between self-reported improvements and objectively measurable outcomes. Instead, the PACE investigators did not even report the most worrying results until several years after publication of the main findings, and when they did, they dismissed them as unimportant (see especially, Chalder et al., 2015; McCrone et al., 2012).

The critique by Geraghty also raises some concerns with the long-term follow-up assessment, which was undertaken at least 15 months after completion of the treatments (i.e. at least 2 years after trial commencement; Sharpe et al., 2015). About three quarters of participants completed this assessment, and at this stage, the differences between the treatment groups on self-report measures were no longer statistically reliable. The PACE investigators do not consider this to be a matter of concern, because many patients received supplementary CBT or GET after the main trial had been completed, and therefore the randomisation had not been maintained. They reasoned that, since the mean ratings in the CBT and GET groups did not significantly *drop* over the follow-up period, at least the treatment benefits were 'maintained'. Such a within-group comparison is of course meaningless, given that around one-quarter of participants were lost to follow-up, and these losses are unlikely to be random.

Recently, my colleagues and I calculated the long-term follow-up results for the sizeable number of patients who did *not* receive a substantial dose of CBT or GET after the trial. In this subsample, there were no significant differences between treatment groups at follow-up even on self-report measures (mean self-rated physical function scores for the CBT and GET groups were 64.2 and 62.5, and for medical care only, 62.6; for self-rated fatigue, the figures were 17.9 and 18.7, respectively, vs 18.7 for medical care only). This finding is not trivial. If patients who have received CBT and GET are indistinguishable from other patients when tested at least 15 months after treatment, the practical value of these treatments is limited. But more importantly, this finding raises further suspicions about the mechanisms underlying the self-reported effects obtained at the primary, 52-week endpoint. The limited duration of these self-report effects is fully consistent with an explanation in terms of participant reporting bias.

One might argue that the standards I describe here represent an ideal scenario and that many, if not most, behavioural studies fall short of them. However, few of those studies wield the power of the PACE trial when it comes to influencing policy and perceptions about this disabling illness. A false-positive conclusion in this context could significantly impact not only on patients' current treatment options but also on future research that could potentially yield better treatments. In sum, extra vigilance is required in this situation.

Conclusions from PACE and directions for future research

The PACE investigators conclude their recent published defence by expressing their hope that research of this nature will continue in the future, in spite of the criticisms. I am puzzled by this statement. The £5 million PACE trial, which assessed more than 600 participants, was designed to provide 'definitive' evidence of the effectiveness of CBT and GET for CFS (Walwyn et al., 2013: 2). Findings from the trial showed that CBT and GET – as delivered here – can have modest effects on patients' self-reports of

fatigue and/or physical functioning, at least if those reports are elicited within several months of trial conclusion. The size of these effects did not exceed what might be expected from reporting bias alone, and they were no longer evident at long-term follow-up. These treatments do not improve more objectively measurable aspects of functioning, such as physical fitness or employment status. Finally, there was no evidence from the trial that patients can recover from CFS as a result of either of these treatments.

In my view, the implications of these findings are quite clear: there is no need to pursue the question further. CBT and GET are simply not effective enough as treatments for CFS (if at all). We need to do better. It is time to begin the search for entirely new treatments.

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Note

1. These figures were calculated from the arithmetic mean walking distances for each treatment group. Individuals who did not complete both baseline and follow-up tests were excluded.

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Commentary

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PACE trial authors continue to ignore their own null effect

Mark Vink

Abstract

Protocols and outcomes for the PACE trial were changed after the start of the trial. These changes made substantial differences, leading to exaggerated claims for the efficacy of cognitive behavior therapy and graded exercise therapy in myalgic encephalomyelitis/chronic fatigue syndrome. The small, self-reported improvements in subjective measures cannot be used to say the interventions are effective, particularly in light of the absence of objective improvement. Geraghty's criticism of the trial was reasonable and supported by the evidence.

Keywords

cognitive behavior therapy, chronic fatigue syndrome, graded exercise therapy, myalgic encephalomyelitis

Introducing bias into the trial

In defending their work against Dr Geraghty's (2016) criticism, the PACE (Pacing, graded Activity, and Cognitive behaviour therapy: a randomised Evaluation) trial authors state that "The protocol was published some 3 years before the analysis began, and 4 years before the first outcome paper was published" (White et al., 2017). However, the protocol's "Final version 5.0" was submitted to the ISRCTN on 01 February 2006 (PACE trial protocol: Final version 5.0, 2006) even though the PACE trial started on 18 March 2005 (White et al., 2011). It was "updated from protocol 3.1, 11.02.2005" and incorporated two substantial amendments ("4.1, 05.08.2005" and "5.1, 01.02.2006"; PACE trial protocol: Final version 5.0, 2006). The final protocol was therefore not published before the trial started even though "A fundamental principle in the design of randomized trials involves setting out in advance the endpoints that will be assessed in the trial, as failure to prespecify endpoints can introduce bias into a trial and creates opportunities for manipulation" (Evans, 2007). Trial Participants received on average 16 (cognitive behavior therapy (CBT)) and 17 sessions (graded exercise therapy (GET); including 3 sessions of specialist medical care (SMC)) yet in the SMC group that was only 5 (White et al., 2011). This creates serious biases toward finding a positive effect for the intervention, regardless of whether it is effective or not (Coyne, 2016).

The PACE trial regarded myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) as the same disease based on the conclusions of the Medical Research Council's Research

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Advisory and the Chief Medical Officer's (CMO) working groups (White et al., 2007). ME is characterized by prolonged muscle weakness after trivial exertion (accompanied by muscle pain; Ramsay, 1988) and neurological symptoms indicative of cerebral dysfunction such as sleep disturbances, headaches, and cognitive problems, but not by (medically unexplained) chronic fatigue which is not a requirement for diagnosis (Carruthers et al., 2011) but it may accompany many chronic illnesses including ME. Chronic disabling fatigue is the only criterion of the Oxford criteria used by PACE. Only 56 percent of participants in the trial had ME according to the London criteria which do require the aforementioned main characteristic and 47 percent of participants had a comorbid depression or anxiety disorder (White et al., 2011). CBT is the most effective treatment for both (Lilienfeld, 2014). Therefore, improvement in PACE could simply be due to improvement in these comorbid psychiatric disorders.

Endpoint changes

When PACE was registered with the ISRCTN on 22 May 2003, participants needed a bimodal Chalder Fatigue score of 4 or more to be classed as ill enough to take part (ISRCTN54285094, 2003). Before the trial started, this was changed to a fatigue score of 6 or more (out of 11; White et al., 2011). During the trial, an extensive number of endpoint changes were made by the trial investigators (White et al., 2011; Vink, 2016). For example, the scoring of the Chalder Fatigue Questionnaire, one of its two (subjective) primary outcomes, was changed from Bimodal to Likert (White et al., 2011), which is more sensitive to change yet due to the ceiling effect is still too insensitive to deterioration (Stouten, 2005). After these changes, a Likert fatigue score of 18 or more (out of 33) was required to qualify for the trial, yet a patient with a score of 18 or less was deemed well enough to be considered recovered (White et al., 2011) even though Jackson concluded in his review of the Chalder Fatigue Questionnaire that a "binary fatigue score of 3 or less represents…not fatigued, with scores of 4 or more equating to 'severe fatigue'" (Jackson, 2014) and the PACE trial's original bimodal fatigue recovery criterion was 3 or less (White et al., 2011). A binary or bimodal fatigue score of 3 equates to a Likert score of 6–9 and a bimodal score of 4 to Likert 8–12. The consequence of this is that participants with a Likert score of 10–18 (inclusive) were severely fatigued and recovered at the same time.

At trial registration in 2003, patients with a 36-Item Short Form Health Survey (SF-36) physical function score of less than 75 were classed as ill enough to take part in the trial (ISRCTN54285094, 2003). Before the trial started, this was changed to 60 or less, and then, during the trial, this was changed to 65 or less, yet at the same time, the physical-functioning score needed to be classed as recovered was changed from 85 or more to 60 or more (out of 100; White et al., 2011) even though a score of 100 represents the "ability to do all activities" (Van Geelen et al., 2010). Healthy sedentary controls from another trial by the PACE lead principal investigator, with the same mean age of 38 years as in the PACE trial, had a physical-functioning score of 100 (and a bimodal fatigue score of 0; White et al., 2004). Additionally, in Deale et al. (2001; which included one of the principal investigators of the PACE trial), a physical-functioning "cutoff score of 83 was used" for participants with a mean age similar to Pace, "as it represents the ability to carry out moderate activities" which does not represent recovery in healthy 38-year-olds. A score of 70 represents significant reductions in physical functioning (Reeves et al., 2005), and a score of 65 or less represents an "abnormal level of physical function" according to PACE (White et al., 2013) and severe disability according to the literature (Stulemeijer et al., 2005). Participants with a score of 60–65 (inclusive) were thus considered to be ill enough to participate, to have abnormal level of physical functioning yet also to be recovered and severely disabled. Consequently, three PACE participants who saw their SF-36 score go down from 65 to 60 reflecting deterioration and three others who had unchanged SF-36 scores were all

(6/640 (0.9%)) still classed as recovered according to the physical-functioning recovery criterion (FOIA request to QMUL, 2016).

The extensive number of changes made to the recovery criteria during the trial broadened the definition of recovery, rendering it less accurate, and inflated the percentage of participants classed as recovered approximately four-fold (Wilshire et al., 2017). However, during a properly conducted (unblinded) trial, alterations should only be made by an independent trial steering committee without access to the data and only for compelling reasons as trial investigators may have impressions of the results to date, which might influence them (Evans, 2007) because outcome switching may, as Goldacre says, "exaggerate results (or even yield an outright false positive, showing a treatment to be superior when in reality it's not)." The wrong conclusion in medicine is "not a matter of academic sophistry—it causes avoidable suffering" (Belluz, 2015).

The PACE trial authors point out that scores within the normal population ranges for fatigue and physical function were not sufficient to be considered as recovered and that participants also had to meet additional criteria (White et al., 2017). But participants (85/640 (13.3%)) who are already classed as recovered on one or both primary outcomes the moment they entered the trial, before receiving any treatment and without a change to their medical situation (Vink, 2017) should be excluded as a patient cannot be both (partially) recovered and ill enough to participate in a trial.

Moreover, the trial defined recovery partially on the basis of patients rating their overall health as "much better" or "very much better" (White et al., 2017) which reflects improvement but not (full) recovery.

Safety of CBT and GET

In support of the conclusion that CBT and GET are safe, reference is made to a survey by Action for ME (White et al., 2017). Mention is not made, however, of another 2011 survey by the same charity which found that 60.2 percent of people with ME reported that GET had made their condition worse. In 44.1 percent of ME patients, GET had actually made it "much worse or very much worse" (Action for ME, 2011). The charity's chief executive officer (CEO), Sir Peter Spencer, reacting to the survey said, "Our findings are disturbing. They show… that GET in particular makes them worse" (Action for ME, 2011).

Claims that the interventions in PACE are safe are based on an unrealistic definition of harms: "Adverse events were considered serious when they involved death, hospital admission,… were life-threatening" (White et al., 2011). The claims must also be seen in the light of "a substantial body of evidence" which shows that clinicians and researchers "systematically downgrade the severity of patients' symptoms" and the "failure to note these symptoms results in the occurrence of preventable adverse events" (Basch, 2010). Research also shows that patients' self-reports frequently capture side effects clinicians and researchers miss and that studies of non-pharmacological interventions (such as CBT and GET) are more likely than pharmacological to fail to adequately report harms (Kindlon, 2011).

High rates of adverse reactions following CBT and GET have consistently been reported in large patient surveys in various countries over the last two decades (Kindlon, 2011), including by three recent surveys from the Norwegian, British, and Dutch ME Associations involving more than 3000 patients (Bringsli et al., 2014; De Kimpe et al., 2016 and ME Association, 2015). Paul et al. (1999) and Black and McCully (2005) provided objective evidence that ME/CFS patients suffer from delayed recovery and worsening of symptoms following exercise.

The individual participant data of the PACE trial showed that up to 82.2 and 79.8 percent of ME patients in the trial might have been negatively affected by CBT and GET, respectively (Vink, 2017), and in a trial by a leading proponent of the biopsychosocial model, 40 percent of ME patients reported deterioration of their health after GET (Moss-Morris et al., 2005).

Moreover, a review of the Belgium Government's CFS Centers showed that treatment with CBT and GET did not change the physical capacity of patients yet caused an increase in unemployment rate and also of patients needing sickness benefits (Stordeur et al., 2008). This means that both treatments were ineffective and suggests that patients' health deteriorated because of treatment with CBT and GET.

PACE trials' null effect

The trial classified 22 percent as recovered after CBT and GET, but assessment of the individual participant data found that none achieved the physical functioning, together with the fatigue scores, of the healthy sedentary controls from another trial by the PACE's lead principal investigator or achieved Kennedy's definition of recovery, where symptoms are eliminated and patients return to premorbid levels of functioning, which is the general public's understanding of the meaning of recovery (Vink, 2017). Therefore, CBT and GET do not lead to actual recovery.

Assessment of the individual participant data also showed that in the objective 6-minute walk test, only 3.7 percent (CBT) and 6.3 percent (GET) were objective improvers as defined by the same improvement of 50% or more, as used by the PACE trial itself, to classify someone as an improver (Vink, 2017). After removing the SMC effect, no participant improved objectively with CBT and only 1.3 percent (2/160) with GET yet 5 percent with SMC (Vink, 2017). This might indicate that CBT and GET impede the naturally occurring recovery process in ME/CFS.

Despite receiving treatment deemed to be "effective" (White et al., 2017), and stating that at long-term follow-up "the benefits of CBT and GET were maintained some 2 years after treatment" (White et al., 2017), patients in all four treatment groups remained ill enough to re-enter the trial based on both subjective primary outcomes (Vink, 2017; White et al., 2011). There was no significant improvement on any of the trial's objective measures, such as numbers returned to work or levels of fitness. The results of the 6-minute walk test showed that ME/CFS patients remained ill enough to be on the waiting list for a lung transplant (Vink, 2016). The number of patients claiming state sick pay and disability benefits increased and the number of patients in receipt of income protection or private pensions in the CBT and GET groups actually doubled (Vink, 2016). In reality, the main finding at long-term follow-up was that there was no difference in efficacy between the four treatments and none of them was effective (Vink, 2016). The actometer, an objective and reliable measure of activity, was not used at the end of the trial as it was deemed "too great a burden for patients." Even though the device is light and small and patients had consented to its use (Vink, 2016). Patients by this stage had also apparently completed effective treatment (White et al., 2017) and 22 percent of those in the CBT and GET groups had recovered (White et al., 2013). Therefore, using the actometer at the end of the trial should have been easier and less of a burden than at the beginning. Three other trials which reported CBT to be (subjectively) effective in ME/CFS used the actometer but did not report their results. A reanalysis showed no objective improvements according to the actometer results (Wiborg et al., 2010). The American Institute of Medicine concluded in February 2015 that there are no effective treatments for this disease (Institute of Medicine, 2015), and the Federal Agency for Healthcare Research and Quality (AHRQ) removed its recommendation for CBT and GET in July 2016 after concluding that there is no evidence that these treatments are effective (Smith et al., 2016).

Safeguards against erroneous inference of efficacy in its absence

Lilienfeld et al. (2014) concluded that unblinded trials should not rely on subjective primary outcomes, but use either objective primary outcomes alone, or combined with subjective ones, as a methodological safeguard against erroneous inference of efficacy in its absence. PACE

in contrast relied on two subjective primary outcomes (fatigue and physical functioning; White et al., 2011) even though it would have been easy to use (one of) their objective secondary outcomes (the step test, the actometer, or the 6-minute walk test) as primary ones (in combination with the SF-36 physical-functioning scale, as the Chalder Fatigue Questionnaire does not provide a comprehensive reflection of functional disability, fatigue-related severity, and symptomatology in ME/CFS (Haywood et al., 2012)).

The aforementioned study by the lead principal investigator of PACE, published in 2004, the year before the trial started, "found that exercise induced a sustained elevation in the concentration of TNF-α [a pro-inflammatory cytokine], which was still present three days later, and this only occurred in CFS patients" (White et al., 2004). In Rheumatoid Arthritis "fatigue…is due to TNF alpha. If you take away the TNF there is no fatigue" (Edwards, 2016). Why cytokines, including tumor necrosis factor-alpha (TNF-α; measured after exercise testing), were not a primary outcome is unclear as Kerr et al. (2003) demonstrated that recovery from ME/CFS led to normalization of cytokine levels.

Conclusion

Patients want their health and independence back so that they can come off benefits and go back to work, which is in everyone's interest. PACE showed that CBT and GET are ineffective in helping them achieve this.

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Commentary

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The PACE trial missteps on pacing and patient selection

Leonard A Jason

Abstract

As others have pointed out a variety of complicating factors with the PACE trial (e.g. changing outcome criteria), I will limit my remarks to issues that involve the composition of adaptive pacing therapy and issues involving patient selection. My key points are that the PACE trial investigators were not successful in designing and implementing a valid pacing intervention and patient selection ambiguity further compromised the study's outcomes.

Keywords

chronic fatigue syndrome, cognitive behavior therapy, diagnosis, PACE, pacing

This article examines two methodological issues: one involving ambiguity in the active components of the adaptive pacing therapy (APT) treatment and the other way that patients were selected; each of which itself could distort the findings, and when a study combines both of these possible complications, it is more difficult to interpret the outcomes. The PACE trial (White et al., 2011) concluded that APT along with specialist medical care was no more effective than specialist medical care alone and that both of these conditions were less effective than cognitive behavior therapy (CBT) and graded exercise therapy (GET). Patients, however, overwhelmingly endorse the strategies of pacing or learning to stay within their energy envelope, and patients report these interventions are the most effective strategies for coping with myalgic encephalomyelitis (ME; Goudsmit et al., 2012; Jason et al., 2013). So, the finding that the PACE trial's pacing intervention was no more effective than specialist medical care was both surprising and perplexing. In order to understand the possible reasons for this paradox, it is important to examine the APT used in the PACE trial.

Problems with APT

It is important to note that APT (Cox et al., 2004) also included advice on stress management, sleep, and so on, and this makes it difficult to determine what was effective or ineffective if one cannot separate the effects of advice on activity from the other components of the program. It could be argued that as translated to the public, and often in their own framing of the issue, there is an important distinction between APT and pacing as often practiced by patients. In other words, the authors evaluated APT, not solely pacing, but it has been interpreted by them, their colleagues, and media as "pacing."

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But even the way pacing was implemented could have compromised its effectiveness. More specifically, the APT intervention used by the investigators instructed patients to not go beyond 70 percent of their perceived energy limit. However, if expended energy is consistently lower than available energy, patients can become too inactive. In other words, the APT pacing intervention instructed patients to do less than their available energy might have allowed. By doing less than what patients have the energy to do, and the resulting pre-emptive rest, this intervention could even have the unwitting effects of increasing social isolation (Goudsmit et al., 2009).

In contrast, the Energy Envelope Theory is a form of pacing that was developed in the mid-1990s (Jason et al., 1999; King et al., 1997), which maintains there needs to be a balance between perceived and expended energy. In other words, a person could expend as much energy as they perceived that they had (Jason et al., 2013), rather than just 70 percent of perceived energy levels. If a person's perceived or available energy is at about 20 percent of what they once had, they can engage in or expend up to that 20 percent which is what they have in available energy. In this approach, the phrase, "staying within the envelope," is used to designate a comfortable range of energy expenditure, in which an individual avoids both overexertion and underexertion, maintaining an optimal level of activity over time. The Energy Envelope Theory would not endorse recommendations to either unilaterally increase or decrease activity. Some people with ME need to be encouraged to increase their activity, when they have the appropriate amount of perceived energy to do so (this is in contrast to APT that states staying at 70% of perceived energy). However, there are also people with ME that need to be encouraged to do less in order to decrease the discrepancy between available and expended energy. This theory emphasizes the need to understand the differential needs of subtypes of individuals with ME. The key is to not overexpend their energy supplies or consistently go outside their "envelope" of available energy, or underexpend energy supplies and go consistently under available energy. This theory postulates that by maintaining expended energy levels within the "envelope" of perceived available energy levels, patients are better able to sustain physical and mental functioning while reducing symptom severity and the frequency of relapses. Over time, patients may experience fewer crashes and even decreased fatigue and symptom severity.

There is evidence to support this Energy Envelope Theory (Brown, 2011; Jason et al., 2010; Taylor et al., 2006). As an example, in one trial of over 100 patients, patients who had been provided one of several non-pharmacological interventions were divided into two groups: those who were able to keep expended energy close to available energy and those who were not successful at this task. Those who were able to stay within their energy envelopes had significant improvements in physical functioning and fatigue severity (Jason et al., 2009). This type of pacing avoids the post-exertional exacerbations, a core symptom of ME, and thus keeps patients more stable. As they begin to feel better without the relapses, the envelope may expand and patients may be able to do more. These findings suggest that helping patients maintain appropriate energy expenditures in coordination with available energy reserves can help improve functioning over time.

In addition, it is important to note that the PACE trial's pacing intervention was provided by occupational therapists, whereas CBT was delivered mainly by clinical psychologists and nurse therapists, and GET was delivered by physiotherapists and one exercise physiologist. It would have been more methodologically rigorous to use professionals from one discipline (after careful training and monitoring) in all three interventions to reduce any possibility that differences among intervention could have been attributable to different types of professionals implementing the interventions. Furthermore, it is very likely that standard medical care contained pacing elements, as this condition included generic advice such as to avoid extremes of activity and rest, as well as specific advice on self-help. Certainly, in implementing

the interventions, it would have been preferable to keep the treatment strategies as separate as possible.

Finally, by the authors widely disseminating through the often-quoted *Lancet* publication that pacing was not effective, some health care providers, family members, and friends were discouraged from supporting what patients feel are their most effective coping strategy. These are iatrogenic effects that could have major consequences for further stigmatizing a vulnerable population.

The evidence for CBT

In contrast to positive reactions among patients for appropriate types of pacing, patient surveys suggest dissatisfaction with CBT and GET (Action for ME and Association of Young People with ME, 2008; Managing my M.E., 2010; ME Association, 2015). Moreover, Price et al. (2008) reviewed 15 studies of CBT with a total of 1043 patients with chronic fatigue syndrome (CFS) and found at treatment's end, 40 percent of people in the CBT group showed clinical improvement in contrast to only 26 percent in usual care. But changes were not maintained at 1- to 7-month follow-up when including patients who had dropped out (similar negative outcomes occurred in the PACE trial as pointed out by Geraghty, 2016). In addition to these outcome data in the literature, the CBT model is based on the assumption that activity level is a mediator between individuals' illness attribution (i.e. belief in a physical or psychological cause) and physical impairment, but Sunnquist and Jason (2016) found that only patients who met a less stringent Oxford case definition criteria demonstrated a strong relation between activity level and impairment. What this means is that using a broad or more restrictive case definition can have a large impact on what is found in CBT studies. Consequently, it is useful to closely inspect what patients were selected to be part of the PACE trial.

Patients were selected for the PACE trial who met the Oxford case definition criteria for CFS, which require fatigue to be the main symptom. Certainly, changing the cut off for the physical function subscale 11 months after the trial began, from a score of 60 to a score of 65 to increase recruitment, was a methodological flawed decision (as was changing the criteria of recovery as reviewed in Geraghty, 2016). The researchers also found that 67 percent of their patients met the Reeves et al. (2003) CFS case definition and 51 percent met the ME criteria (The London Criteria, 1994). Participant subgroups meeting the Reeves et al. CFS case definition, the ME criteria (The London Criteria, 1994), and depressive disorder criteria did not differ in the pattern of treatment effects, but there are difficulties in reliably operationalizing these criteria (particularly in dealing with exclusionary conditions), as will be explained below, and it is very possible that individuals without CFS were inadvertently included in the study.

It should be noted that 47 percent of the PACE sample had a psychiatric disorder (e.g. depression and anxiety), and the authors note that CBT provided the largest reduction in their depression. It is possible that individuals with a purely affective illness, such as major depressive disorder, were inadvertently included in their sample. A person with primary major depressive disorder can easily be misdiagnosed with CFS, as people with solely a major depressive disorder often experience chronic fatigue and several of the other Reeves et al. (2003) symptoms, such as unrefreshing sleep, joint pain, muscle pain, and impairment in concentration. Yet, with proper assessment methods, it is possible to separate with 100 percent accuracy those with CFS and major depressive disorder (Hawk et al., 2006). Any major chronic health condition, such as ME, can cause a depressive disorder, but this needs to be differentiated from those with a solely affective disorder. Some investigators do not understand or appreciate this important diagnostic issue. But including those with primary affective disorders makes it extremely difficult to interpret who is being helped in the clinical interventions, particularly as CBT is a proven effective treatment for those with a major depressive disorder. This problem provides complications for not only treatment studies but also in efforts to

estimate the prevalence of CFS. For example, in another study in Britain, Wessely et al. (1997) found a CFS prevalence rate of 2.6 percent, but if psychological disorders were excluded from the British study, the CFS prevalence rate drops to only 0.5 percent in this sample. Euba et al. (1996) compared those diagnosed with CFS in the Wessely et al. (1996) study to a CFS sample from a hospital unit. They found that 59 percent of the community sample reported thinking their illness might be due to psychological or psychosocial causes, whereas only 7 percent of the hospital sample expressed this view. Clearly, differentiating those with CFS versus those with illnesses due to psychological or psychosocial causes is critical in these treatment trials.

The possibility that the PACE trial included individuals without the illness is also supported by data regarding many within their sample who lacked core symptoms of CFS. For example, at baseline, only 72–77 percent had poor memory/concentration and only 82–87 percent had post-exertional malaise. These levels of key symptoms are low, suggesting the inclusion of a proportion of cases without CFS. A variety of factors, in addition to psychiatric issues, can result in CFS-like symptoms. These include poor sleep hygiene, poor diet, and deconditioning. It is critical to exclude people whose CFS-like symptoms and fatigue are due to these lifestyle factors as well as excessive exertion such as being over-committed. Given the PACE trial's position of adopting a broad case definition, such as the Oxford criteria, it is unclear if they excluded those whose fatigue and symptoms were due to these lifestyle factors.

Conclusion

When studies using broad criteria like Oxford were eliminated, the Agency for Healthcare Research and Quality (2016) downgraded their evaluation of CBT stating that given the inconsistent results and mixed quality of the studies made it impossible for them to determine if CBT was effective for those meeting the Fukuda et al. (1994) criteria. Individuals who meet very broad criteria, as well as those with solely affective disorders, would react much better to CBT and GET, thus complicating any interpretation of the treatment outcomes. This suggests that developing a consensus for a narrower case definition remains a critical task for investigators, as without a research case definition of ME, it continues to be unclear whether samples in different studies are comparable and have core symptoms of this illness.

There are many questions that remain unanswered, and it is possible that with encouragement of positive expectations and greater frequency and intensity in the cognitive therapy and graded exercise arms, nonspecific factors were influential in these treatments, and it is unclear if such factors were left out of the adaptive pacing arm. Other major problems for this study included using an APT intervention that had multiple components as well as recommendations that might have inappropriately limited activity. The problems with patient selection due to the use of broad case definitions that might not have excluded those not having this illness, along with the problematic implementation of the pacing arm, remain significant obstacles in interpreting the outcomes of this trial.

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Commentary

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Do graded activity therapies cause harm in chronic fatigue syndrome?

Tom Kindlon

Abstract

Reporting of harms was much better in the PACE (Pacing, graded Activity, and Cognitive behavioural therapy: a randomised Evaluation) trial than earlier chronic fatigue syndrome trials of graded exercise therapy and cognitive behavioural therapy. However, some issues remain. The trial's poor results on objective measures of fitness suggest a lack of adherence to the activity component of these therapies. Therefore, the safety findings may not apply in other clinical contexts. Outside of clinical trials, many patients report deterioration with cognitive behavioural therapy and particularly graded exercise therapy. Also, exercise physiology studies reveal abnormalities in chronic fatigue syndrome patients' responses to exertion. Given these considerations, one cannot conclude that these interventions are safe and risk-free.

Keywords

adherence, adverse events, cognitive behavioural therapy, chronic fatigue syndrome, graded activity, graded exercise, graded exercise therapy, harms, myalgic encephalomyelitis

In their response to Geraghty's editorial, White et al. (2017) claimed that the PACE (Pacing, graded Activity, and Cognitive behavioural therapy: a randomised Evaluation) trial, along with other studies, provide evidence that both cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are 'safe and effective treatments' for chronic fatigue syndrome (CFS). In this commentary, I consider some issues that deserve more attention regarding the safety and potential harms associated with CBT and GET, both within the PACE trial and also as they are used in clinical practice.

Historically, there has been more of a focus on efficacy measures than on the reporting of adverse events in clinical trials. This has led to specific Consolidated Standards of Reporting Trials (CONSORT) guidelines being developed for the reporting of harms (Ioannidis et al., 2004). However, there remains much scope for improvement in the reporting of harms in clinical trials, particularly with non-pharmacological interventions (Duggan et al., 2014; Meister et al., 2016). Compounding this issue is the fact that outside of clinical trials, systems for reporting adverse events associated with non-pharmacological interventions are more ad hoc and less well-developed than those for pharmacological interventions. This all means that signs of harm can be missed, leading to a false level of confidence that particular therapies are safe for all.

Exercise is a widely used intervention, providing benefit for people with many conditions.

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But it has the potential to cause harm (Barg et al., 2011; Cooper et al., 2007). As Cooper et al. highlight, 'like pharmaceutical therapies, prescribing exercise as therapy, an activity that is gaining in acceptance throughout the medical community, must be predicated on understanding the risks and benefits of exercise as thoroughly as possible' (p. 706). Some examples given by Cooper et al. (2007) of possible harms from exercise include exercise-associated allergic responses, overuse syndromes, exercise-induced bronchoconstriction and exacerbation of intercurrent acute and chronic illnesses.

Even low-intensity exercise has the potential to exacerbate symptoms in CFS, and the effects of exercise have been found to persist for more than a week after exertion. Single-trial studies have found that gentle exercise of less than an average of 7-minute duration can lead to a self-reported worsening of fatigue, pain, sore throat and/or general health (Nijs et al., 2008; Van Oosterwijck et al., 2010). Long-term studies show that the effects of exercise can persist well beyond 24 hours. One study followed 25 women with CFS and 23 age-matched sedentary controls for 7 days after a maximal cardiopulmonary exercise test (VanNess et al., 2010). In all, 85 per cent of the sedentary controls but none of the CFS patients had recovered based on questionnaire responses after 24 hours; the equivalent figures for 48 hours were 100 and 4 per cent. In total, 60 per cent of the CFS patients took more than 5 days to recover. Similarly, Lapp (1997) followed 31 of his patients for 12 days after a maximal exercise test. The average relapse lasted 8.82 days although 22 per cent were still in relapse when the study ended at 12 days. Some evidence suggests that there is an 'activity ceiling' in CFS above which patients cannot go without experiencing a worsening of symptoms (Black and McCully, 2005). These findings, taken together, suggest that interventions involving exercise could provoke a general and persistent worsening or exacerbation of symptoms in CFS. They also offer an explanation as to why it might be difficult for patients with CFS to adhere to graded activity/exercise interventions.

The PACE trial demonstrated many elements of good trial reporting including regarding harms. For example, they published the manuals for both therapist and participants, as recommended by the CONSORT extension for trials assessing non-pharmacologic treatments (Boutron et al., 2008). Trial outcomes included not just efficacy but also specific harms measures and the protocol included systems to track possible adverse events. This was a significant improvement over previous trials of CBT and GET, where the reporting of harms has been described as poor (Chambers et al., 2006; Marques et al., 2015; Price et al., 2008; Smith et al., 2015). Consequently, virtually, all the evidence we have about the harms associated with CBT and GET is derived from the PACE trial. This is unfortunate, because it applies only to the particular variants of CBT and GET that were used in the PACE trial: many differences can exist between behavioural interventions that appear superficially similar (Marks, 2009).

Reporting of adverse events and reactions in the PACE trial

The PACE trial researchers have been criticised for how some of the efficacy outcome measures were reported (Stouten et al., 2011; White et al., 2007; Wilshire et al., 2016). The changes to the composite recovery outcome are arguably the most notable: all four elements of the criteria were changed. Two of the criteria were relaxed so much that participants could deteriorate on the measures from baseline and still be counted as recovered. Some post-protocol changes were also made to the criteria for defining adverse events. Originally, adverse outcomes were defined as a score of 5–7 on the participant-rated Clinical Global Impression (PCGI) scale or a drop of 20 points on the 36-Item Short Form Survey (SF-36) physical function (PF) score from the prior measurement (White et al., 2007). But by the time the *Lancet* paper was published, 'serious deterioration in health' was defined as any of the following outcomes (bolding by the present author): (1) a decrease in

SF-36 PF score of 20 or more between baseline and any *two consecutive* assessment interviews, (2) scores of 'much worse' or 'very much worse' (6 or 7) on the PCGI scale at *two consecutive* assessment interviews, (3) withdrawal from treatment after 8 weeks because of a participant feeling worse or (4) a 'serious adverse reaction'. Data on those participants whose scores on the SF-36 PF scale dropped by 20 points or more at a single timepoint were never published nor were data on those who scored 5 on the PCGI. Also, the changes from the protocol were never highlighted explicitly to readers. Subsequently, data on post hoc measures of deterioration, 8 points on the SF-36 PF scale or 2 points on the Chalder fatigue questionnaire (Likert scoring), were published (Dougall et al., 2014).

In total, 3774 adverse events were recorded across the four arms of the PACE trial (White et al., 2011). In the final reports from the trial, the following categories were used to define severe adverse events (SAEs): (1) death; (2) life-threatening event; (3) hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included); (4) 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 4-week continuous duration; (5) any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; and (6) any episode of deliberate self-harm. Using this coding scheme, the researchers identified 48 SAEs during the trial, though without detailing which trial arm they occurred in. This seems unfortunate especially given that the authors stated that there was a statistically significant difference between the number of SAEs that occurred in the GET group (17) compared to the specialist medical care (SMC)-only group (7).

Severe adverse reactions (SARs) were defined as any of the SAEs that could be considered to be causally related to the interventions themselves. The PACE trial researchers further identified 10 events as SARs, and for these, we were given information about treatment condition. There were two SARs in the GET condition ('Deterioration in mobility and self-care' and 'Worse CFS symptoms and function') and four in the CBT condition ('Episode of self harm', 'Low mood and episode of self harm', 'Worsened mood and CFS symptoms' and 'Threatened self harm'). All of these were considered by an assessor to be 'possibly related' rather than 'probably related' or 'definitely related' to the intervention.

However, the trial's definitions of SAEs/SARs may not be sensitive enough to isolate some significant adverse events. Indeed, it was possible to have a 'non-serious adverse event' in the PACE trial that was classed as 'severe'. Adverse events can include those in the economic and social domains as well as those of a biological or psychological nature (Office for the Protection from Research Risks, NIH, PHS, DHHS, 1993). Deteriorations that lasted less than 4 weeks, particularly those that occurred more than once, could, for example, affect somebody's ability to maintain a job or keep up with an educational course: harms affecting major life goals.

In total, the non-serious adverse events were divided up as follows between the trial arms: adaptive pacing therapy (APT): 949, CBT: 848, GET: 992 and SMC alone: 977. Most participants reported at least one non-serious adverse event: APT: 152 (96% of the sample), CBT: 143 (89%), GET: 149 (93%) and SMC: 149 (93%). Data for the numbers and percentages of participants with one or more non-serious adverse events were categorised as follows: eyes and ENT, CFS/ME/PVFS, gastro-intestinal, psychol[ogical]/psychiatric, musculoskeletal, obs/gynae/urinary, respiratory, dermatological, neurological, stressful events, cardiovascular, nutrient and blood, allergies, endocrine and miscellaneous. There were no statistically significant differences in any of these categories (Dougall et al., 2014). A lot of information on harms was published in the two papers that dealt with these issues but it would have been interesting if additional data had been made available, particularly on 'non-serious' adverse reactions (as opposed to events) and on the 'non-serious adverse events' which had been classified as 'severe' (Dougall et al., 2014; White et al., 2011).

Both the forms of CBT and GET investigated were based on models that view inactivity and deconditioning as the major driver in perpetuating CFS symptoms (Burgess and Chalder, 2004b). Similarly, with both interventions, participants were encouraged to consider increased symptoms as a 'natural response to increased activity' (Burgess and Chalder, 2004b: 28). Such a view has the potential to bias the reporting of adverse events by participants and indeed professionals. For example, a participant in the CBT or GET group might not mention the occurrence or exacerbation of a particular symptom, because they may see it as a normal response to increased activity, while a participant in the other trial arms who had the very same experience might be more inclined to mention it. It is difficult to know how to definitively deal with such issues given the nature of the therapies. Hopefully, with further progress in understanding the pathophysiology of CFS, more objective tests will be developed to help identify the risk of harm with a particular dosage of activity and/or record when harm has actually occurred.

Adherence

Since there were few differences among the different trial arms in terms of adverse outcomes that were reported, the results appear reassuring. However, an important issue remains: the degree of adherence to the interventions. The CONSORT statement on harms notes that 'it is important to report participants who are non-adherent or lost to follow-up because their actions may reflect their inability to tolerate the intervention' (Ioannidis et al., 2004: 785). If participants do not take medication as prescribed, one is left with little useful information about harms associated with it. Similarly, with non-pharmacological interventions, one should look for evidence of adherence to the programmes before feeling reassured that they are safe. The principal measure reported in the PACE trial was attendance at appointments (either in person or by telephone; White et al., 2011). For some non-pharmacological interventions, this might be the most important measure of compliance. However, attendance at an appointment every 2 weeks or so seems unsatisfactory as the chief measure of compliance in a trial of GET where participants were encouraged to exercise several times a week. The same is true for the CBT intervention, since it also required participants to gradually increase both physical and mental activities (White et al., 2011). The form of CBT assessed regarded CFS as being 'reversible' (White et al., 2011: 825). Interestingly, there were minimal changes in fitness levels at 12 months for both the CBT and GET groups compared to baseline (Chalder et al., 2015). There was also no difference in the fitness outcome measure compared to the other two treatment arms neither of which encouraged participants to increase activity levels. This suggests a lack of compliance to the activity component of the CBT and GET interventions.

In terms of the 6-minute walking test, from a low baseline of 333 m, the CBT group only improved by an average of 21 m over the 12 months of the PACE trial, a similar amount to the APT and SMC-only groups (White et al., 2011). The GET group did have a statistically significant improvement reaching 379 m, 35 m more than the group that received SMC alone when baseline adjustments were applied (White et al., 2011). However, this remained a very poor result: less than, for example, the average for a sample of over 1000 cardiopulmonary patients reported in a review of 11 studies (Ross et al., 2010). Using a reference equation for the 6-minute walking test, the expected group average for a healthy cohort with a similar gender make-up (77% female) and average age to the PACE trial cohort is 719 m (Beekman et al., 2014). In fact, only two individual participants in the CBT arm, one in the SMC-only arm and no individuals in the GET arm of the PACE trial exceeded the expected lower bound of normal for individuals in such a group (589 m) (QMUL, 2016; Wilshire et al., 2016). It is also possible that a single exercise test may be insufficient to demonstrate the degree of functional impairment in CFS patients due to the abnormal response to exercise in the condition (Keller et al., 2014; VanNess et al., 2008). These results again suggest that the degree of adherence to the activity/exercise

components of the CBT and GET programmes may have been unsatisfactory.

Such poor results on objective measures were not fully unexpected. For example, a review of three trials of Dutch-graded, activity-oriented CBT interventions found that CFS participants did not increase their total activity level compared to the control groups as measured objectively with actometers, with activity levels remaining low (Wiborg et al., 2010), despite improvements being reported on some self-report measures. A similar result was found in a US study (Friedberg and Sohl, 2009). The PACE trial researchers initially planned to use actigraphy as an outcome measure in the PACE trial but 'decided that a test that required participants to wear an actometer around their ankle for a week was too great a burden at the end of the trial' (White et al., 2008). This decision is puzzling, given that the researchers required participants to wear an actometer for a week at baseline when they would have been expected to be less well than at the end of the trial. Information from actigraphy would have provided useful information on fidelity with the treatment protocols.

An alternative interpretation of the poor fitness and walking-distance results in the PACE trial is that instead of demonstrating a lack of adherence to the therapies, participants faithfully undertook the graded activity and exercise elements of the interventions but still only had very poor levels of improvement in the 6-minute walking test and in fitness post CBT and GET. This might be possible if there was an ongoing disease process in CFS. It would, however, seem to contradict the models proposed in the PACE trial's CBT and GET treatment manuals where the problems associated with CFS are seen as reversible using the interventions (Bavinton et al., 2004a, 2004b; Burgess and Chalder, 2004a, 2004b).

A review of patient surveys outside of clinical trials found pacing was associated with far fewer reports of deterioration than CBT and GET (Kindlon, 2011). If, as seems likely, there was some non-adherence in the PACE trial to the CBT and GET interventions, it would be interesting to have data on what form this non-adherence took. With GET in the PACE trial, what participants were asked to do was determined by 'their planned physical activity, and not their symptoms' (Bavinton et al., 2004a); similarly, 'a central concept of GET is to MAINTAIN exercise as much as possible during a CFS/ME setback' (p. 51) and 'if the participant reports an increase in fatigue as a response to a new level of exercise, they should be encouraged to remain at the same level for an extra week or more' (p. 66). A similar view was taken with CBT in the PACE trial where reducing activity based on increased symptoms was seen as a maintaining factor in the illness and part of a 'vicious circle of fatigue' (Burgess and Chalder, 2004b: 21). Conversely, in the APT arm in the PACE trial, 'activity is planned and then modified in the light of its effect on symptoms' (Bavinton et al., 2004a: 16). If participants in the GET and CBT arms of the trial reduced their activity levels based on symptoms, this could be described as treatment contamination with pacing.[1]

Data from patient surveys and exercise studies

Why is all this important? Because outside of the confines of clinical trials, high rates of adverse effects have been reported with CBT and particularly GET by myalgic encephalomyelitis (ME) and CFS patients. A review of 10 patient surveys from four countries found that 51 per cent of respondents (range = 28%–82%, $n = 4338$, eight surveys) reported that GET worsened their health, whereas 20 per cent of respondents (range = 7%–38%, $n = 1808$, five surveys) reported similar results for CBT (Kindlon, 2011). These results are consistent with a 2015 report which also included much qualitative data highlighting the sometimes long-term and severe nature of the deterioration following CBT and GET (ME Association, 2015). Clinical trials can represent artificial environments where clinicians may, for example, be more cautious with some interventions, given the closer monitoring they are under compared to when non-pharmacological

interventions are used in routine practice (Chou et al., 2008; Rawlins, 2008).

Post-exertional malaise is a key symptom of ME/CFS, and though it is not required for the Oxford criteria which were used to select participants in the PACE trial, it is an essential part of many criteria used by researchers (indeed it was proposed that the condition be renamed 'systemic exertion intolerance disease' in 2015) (Institute of Medicine (IOM), 2015; Jason and Fragale, 2016; Sharpe et al., 1991). It is not, therefore, that surprising that interventions aiming to increase levels of activity and exercise could cause adverse events in those affected by this symptom complex. In the PACE trial, which used the broad Oxford criteria, post-exertional malaise at baseline was reported by 84 per cent in the APT group, 85 per cent in the CBT group, 82 per cent in the GET group and 87 per cent in the control (SMC-only) group (White et al., 2011).

Numerous biological abnormalities have also been found following exertion in the condition (Lane et al., 2003; Light et al., 2009; Sorensen et al., 2009; Twisk and Maes, 2009). They have been categorised as follows: energetic abnormalities and reduced oxygen uptake amplified by exertion; muscular abnormalities related to exercise; long-lasting oxidative stress in response to exercise; increased pain sensitivity and lower pain thresholds during and after exercise; immunologic abnormalities in response to exertion; cardiovascular dysfunction related to exertion and orthostasis; autonomic abnormalities associated with exercise and orthostatic stress; and neurologic abnormalities in relation to physical and mental exertion (Twisk and Geraghty, 2015). These abnormalities again highlight the potential for harm from exercise in the illness.

Conclusion

Even if one assumes that there were no significant adverse events associated with CBT and GET in the PACE trial, it is unclear what healthcare staff, patients and others can read into such findings, given the question marks over compliance. What activity and exercise regimes are actually safe to use? Ones that do not increase fitness levels?

Future trials need to collect and report on objective data using devices, such as actometers and heart rate monitors, to help us establish what exactly is tested in trials of CBT and GET for CFS. Until that time and given the high rates of harm that have been reported outside clinical trials, caution needs to be used before proposing that any individual ME/CFS patient can safely increase their total exercise or activity levels using CBT or GET.

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Note

1. It is possible to devise a hybrid programme where symptom-contingent pacing can be combined with exercise (Goudsmit et al., 2012). For example, a group of Australians developed a programme of exercise in which 'on days when symptoms are worse, patients should either shorten the session to a time they consider manageable or, if feeling particularly unwell, abandon the session altogether' (Wallman et al., 2005). However, that should not be confused with the type of GET programme assessed in the PACE trial.

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Commentary

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PACE team response shows a disregard for the principles of science

Jonathan Edwards

Abstract

The PACE trial of cognitive behavioural therapy and graded exercise therapy for chronic fatigue syndrome/myalgic encephalomyelitis has raised serious questions about research methodology. An editorial article by Geraghty gives a fair account of the problems involved, if anything understating the case. The response by White et al. fails to address the key design flaw, of an unblinded study with subjective outcome measures, apparently demonstrating a lack of understanding of basic trial design requirements. The failure of the academic community to recognise the weakness of trials of this type suggests that a major overhaul of quality control is needed.

Keywords

chronic fatigue syndrome, cognitive behaviour therapy, methodology, PACE trial, reliability

Some years ago I was asked to advise on research strategies for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME), on the grounds of having expertise that might be relevant, although I never practiced in the field. I was introduced to the PACE study in 2014 by a presentation by Peter White that consisted of a cursory showing of one or two data images intended to assure the audience of robust evidence for efficacy of cognitive behavioural therapy (CBT) and graded exercise therapy (GET), followed by an extended series of unsupported statements directed at patient advocates who were accused of 'attacking science' by raising criticisms of the trial. Subsequent interaction with the patient community made it clear to me that the advocates' criticisms were, if anything, over-lenient and that if there was any threat to science it came from the poor quality of the study itself.

Debate about PACE has often focused on detail. Yet the trial has a central flaw that can be lost sight of: it is an unblinded trial with subjective outcome measures. That makes it a non-starter in the eyes of any physician or clinical pharmacologist familiar with problems of systematic bias in trial execution. In their article responding to a recent critical editorial by Geraghty (2016), White et al. (2017) write that '[Geraghty] has not said which [scientific] procedures and standards we neglected or bypassed'. In fact, Geraghty (2016) itemises these in detail. However, it is true that, perhaps because it seems

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too obvious, he does not spell out the central problem in full – the *combination* of lack of blinding *and* subjective outcome measures.

There is no way of addressing this flaw. The defence that the trial was peer reviewed by the Medical Research Council is no argument; it appears just to indicate that ignorance of methodological principles is widespread in the British medical establishment (not to mention the editor of a high-profile journal). Nevertheless, I have heard two arguments raised by the PACE authors and their colleagues (personal communications), which are worth at least mentioning.

First, it is argued that there are many good unblinded trials (surgery in oncology for example) and many good trials with subjective endpoints (drug studies in rheumatoid disease). That is undisputed, but misses the key point that there are essentially no good trials that have *both* features. Blinding is introduced specifically to address the potential for bias in the use of subjective outcome measures. It is not needed for objective outcomes and objective outcomes are not needed for fully blinded trials. It is hard to credit that anyone could miss this point, but if they do, it would at least explain how trials come to be designed without taking it into account.

Second, it has been suggested that if practical issues make robust methodology hard to set up then weaker methodology has to be used. That will sometimes be so. But it makes no sense to say that if you cannot work out how to do a reliable study then an unreliable study can be taken as reliable.

Apart from the apparent lack of understanding of trial design, the irony is that what appears least understood by the defenders of PACE is that its problems stem from what one might call human nature, or in jargon terms 'psychology'. If, as White et al. claim, the PACE team had done all in their power to minimise systematic bias due to human nature – loaded beliefs or motivations – this might have had some mitigating force. However, in contrast, as Geraghty indicates, material likely to lead to such bias, including the instruction manuals for patients and therapists and a subsequent newsletter, emphasising which treatments were expected to do best, seems to have been laid on with a trowel.

Reliable assessment of therapies delivered by dedicated therapists presents a serious methodological challenge. In rheumatology, the problem became familiar with physiotherapy techniques and joint protection programmes from occupational therapists. In the end, pretty much all evidence from studies of these modalities was discarded as unreliable. The central problem is that it is very difficult to find therapists who have no prior commitment to the validity of certain techniques. White et al. argue that it would be inappropriate for trials to be performed by disinterested parties. Geraghty's suggestion may be impractical, but I do not see it as misguided. White et al. argue that 'The clinicians amongst us have dedicated their careers to care for thousands of patients with CFS/ME and we always want the best for them'. It is precisely this sort of emotionally laden justification of 'those of us who know best' that needs to be removed from trial design. The way that human nature creeps into the research environment is something all too well known to physicians and pharmacologists. It seems strange that it should be unfamiliar in psychological medicine.

Another peculiar line of argument has been used to justify the claim that bias would not have been a problem in PACE. It has been claimed that there tends to be no significant placebo effect in CFS/ME; at the same time, it is pointed out that CBT operates through essentially the same mechanism as a placebo effect (Knoop et al., 2007) – by encouraging the patient to take a positive view of their progress through modifying perceptions rather than pharmacological means. The two premises would be compatible if the PACE trial had yielded a negative result for CBT. But if it is claimed that CBT was effective, then it is hard to maintain the first premise in the face of the second.

The problem highlighted here is that we have no real way of knowing what aspect of the modality called 'CBT' is responsible for any improvement, if indeed reported improvement reflects more than just a desire to meet a therapist's expectations. In pharmacology, some

form of quantitation is normally considered essential before evidence is considered reliable. This is often a dose–response curve, but there are other options. PACE provides nothing of this kind.

Moreover, the 'control' group does not meet reasonable criteria for an adequate control, which would require replicating all contextual aspects of treatment that might have a non-specific effect on reporting of outcome. The standard medical care arm apparently had no equivalent contact with professionals (White et al., 2011). Again, the PACE authors have failed to take the opportunity to mitigate the central flaw in the trial. In short, the trial was set up in such a way that the default assumption would be that systematic bias due to the usual factors associated with subjective outcomes in an unblinded setting would be operating full tilt. It would be quite surprising if the treatments advertised as best had not led to a better reported outcome.

It may be that it is easier for those of us involved in pharmacological interventions to recognise extraneous psychological influences on trial outcomes as extraneous. Systematic bias is rife within science wherever there is leeway in analysis of outcome. The scale and subtlety of the problem was brought home to me by a paper on the putative paranormal phenomenon of 'the [non-visual] sense of being stared at' (Radin, 2005). An inverted funnel plot of a set of studies of this effect subject to meta-analysis showed evidence for systematic bias towards a positive result, a familiar finding. More interestingly, the results were *too consistently only slightly positive*. If all studies were tracking the same effect, more of them should have been *more* positive, due to noise. The suspicion must be that more dramatic 'effects' were not reported since they might appear 'too big' and therefore implausible! Bias is not just common, but also often finely tuned, even if unwittingly. Judging from my own experience of both laboratory and clinical research, Murphy's Law applies. Whenever bias can creep in it will. The only solution is to design it out of the study from the outset.

More detailed criticisms of PACE in terms of shifting of recruitment and outcome criteria and implausible criteria for recovery have been covered by Geraghty, Tuller, Matthees, Wilshire, Kindlon, Rehmeyer and others (Geraghty, 2016; Rehmeyer, 2016; Tuller, 2015; Wilshire et al., 2016). As indicated, I see these problems chiefly in terms of failed opportunities to mitigate the basic design flaw. However, I think the claim that the effects of CBT and GET were maintained at two and a half years (Sharpe et al., 2015) is worth challenging again because it is not what any reasonably intelligent person would conclude. If there is no longer a difference in the level of improvement between treatment groups, then a preferential causal influence of one therapy or another cannot be claimed to be 'maintained'. It is conceivable that exposure of other patients to CBT allowed them to catch up, but there is no way that this can be used to shore up evidence that is otherwise entirely negative.

I think it is a matter of concern that White et al. (2017) reject out of hand the possibility that the 'actions [of the PACE authors] have arguably caused distress to patients'. They have. Distress is very evident among the patient community, as much as anything in terms of the insult to their intelligence made by insisting that seriously flawed research is in their interest. I have no doubt that most CFS/ME patients in the United Kingdom would want to campaign to preserve services, but it seems disingenuous to suggest that this is because they want more CBT and GET. If they are still ill, presumably these approaches have failed and the priority is to find something more effective.

I find it particularly disappointing that at the end of White et al.'s response there is an uncalled for innuendo that somehow in writing his editorial Geraghty might be inhibiting future high-quality research. I think Geraghty is to be congratulated for voicing a reasonable opinion with the admirable aim of inhibiting *poor* research and calling for something properly grounded. What the patients want most is confidence in the level of research and that will only come when the poverty of past attempts is fully appreciated.

White et al. conclude that they stand firmly by the findings of the PACE trial, presumably because of their inability to understand its basic flaws. As has been suggested by others, the flaws are so egregious that it would serve well in an undergraduate textbook as an object lesson in how not to design a trial. Its flaws may have only been widely appreciated recently simply because those involved in trial design in other disciplines were unaware of its existence. Now that they are aware, there appears to be near unanimity. The patients have been aware of the problems for several years, and all credit to them for their detailed analyses. In my experience, most of the people with a deep understanding of the scientific questions associated with CFS/ME are patients or carers. To suggest that when these people voice their opinions they are doing a disservice to their peers seems to me inexcusable.

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Commentary

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Bias, misleading information and lack of respect for alternative views have distorted perceptions of myalgic encephalomyelitis/chronic fatigue syndrome and its treatment

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Abstract

The PACE trial is one of the most recent studies evaluating cognitive behavioural therapy and graded exercise therapy for myalgic encephalomyelitis/chronic fatigue syndrome. These interventions are based on a model which assumes that symptoms are perpetuated by factors such as misguided beliefs and a lack of activity. Our analysis indicates that the researchers have shown significant bias in their accounts of the literature and may also have overstated the effectiveness of the above treatments. We submit that their approach to criticisms undermines the scientific process and is inconsistent with best practice.

Keywords

chronic fatigue syndrome, cognitive behavioural therapy, graded exercise therapy, myalgic encephalomyelitis, pacing

In his editorial, Geraghty (2016) reviewed some of the factors that have made it difficult to interpret the findings of the PACE trial. Given its flaws, we have been surprised that scientists familiar with this illness consider the trial to have been carefully designed, rigorously conducted and 'scrupulously analysed and reported' (British Association for CFS/ME (BACME), 2011; Crawley, 2013; Miller, 2011). Like Geraghty and others, we have noted the differences in outcomes when the analysis used the original criteria for recovery detailed in the protocol compared to the less stringent ones reported in the paper (White et al., 2013; Wilshire et al., 2016). Moreover, we are disappointed that the researchers have continued to ignore sound evidence in order to promote the view that fear plays a major role in the aetiology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and that increasing activity can lead to significant improvements (Spencer, 2015; White et al., 2011).

In this article, we focus on the researchers' bias and lack of respect for alternative approaches. We believe that this has led to a misrepresentation of the illness, the minimisation of the reported adverse reactions to graded exercise therapy (GET) and a less sympathetic attitude towards patients (Liddle, 2015).

Recent examples of the researchers' views can be found in the media coverage which followed the publication of the data collected

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more than 2 years after randomisation (Sharpe et al., 2015). Below a headline proclaiming that 'ME can be beaten by taking more exercise', one of the scientists involved in the trial was quoted as stating that 'patients become terrified of exercise and physical activity for fear that it will make their illness worse. These fears can be overcome by cognitive behavioural therapy or a gradual increase in exercise' (Spencer, 2015). He went on to say that these 'are not magic cures – but this is the only game in town in terms of evidence-based treatments'.[1]

We recognise that articles in the media are not subjected to peer review and that people can be misquoted, but in the case of the PACE trial, many healthcare professionals have echoed these opinions in the medical literature. The message since the first article in *The Lancet* has been that both cognitive behaviour therapy (CBT) and GET are 'safe and effective' (BACME, 2011; Sharpe et al., 2017) or at least more effective than specialised medical care and adaptive pacing therapy (APT; White et al., 2011, 2017).

Given that the results of the trial were published in one of the most prestigious journals in the world, readers will have assumed that the article had been subjected to rigorous peer review. We can therefore understand that many will have been mystified by the negative reactions of patients, support groups and a number of highly qualified health professionals (Davis et al., 2016; Shepherd, 2015). What most will not know is that for various reasons, scientists in the United Kingdom and the Netherlands have not been offered an objective and balanced view of the rationale behind the CBT and GET protocols for ME/CFS (Goudsmit, 2016; Sunnquist, 2016). Nor will they be aware of the flaws in the design of the various randomised controlled trials (RCTs), and the editorial policies which tend to relegate alternative views to the correspondence sections (Goudsmit and Stouten, 2004). Other commentaries on the PACE trial have focused on different aspects of the basis, design and reporting of results. We wish to draw attention to the approach adopted by a number of the researchers behind the promotion of CBT and GET which may help to explain some of the anger in the patient and scientific community.

How spin changed the view of ME/CFS in the United Kingdom

The scientific process requires that theories are amended if new evidence indicates that they are inaccurate or incomplete. However, the researchers who developed the fear-avoidance model underpinning the protocols for CBT and GET have shown a clear reluctance to acknowledge findings which undermine their theory, notably reports of abnormalities in brain, muscle and immune function (Costa et al., 2005; Goudsmit et al., 2009a; Lane et al., 2003; Shepherd and Chaudhuri, 2016). Moreover, the model posits that the core symptom of ME/CFS is fatigue and not what has become known as post-exertional malaise. Although recognised, a worsening of symptoms following minimal exertion is attributed to a lack of activity and fitness, plus the physiological effects of deconditioning and stress (Powell, 2005; Wessely et al., 1998; White et al., 2011). This view has changed very little, despite the growing evidence suggesting a more complex aetiology (Cook et al., 2017; Paul et al., 1999; Shepherd and Chaudhuri, 2016).

As well as the highly selective discussions of the literature, articles from those promoting CBT and GET have portrayed patients in a particularly negative way, proposing that almost all share the same misguided beliefs about aetiology and adopt the same maladaptive behaviours (Wessely et al., 1998; White et al., 2011). They rarely cite reports of realistic views of the illness and the use of more helpful strategies (Goudsmit et al., 2012; Lovell, 1999).

The researchers have also shown a great reluctance to address the key concerns raised by colleagues or to correct errors. For instance, while it was generally known that the strategy of pacing for ME/CFS was developed and evaluated by psychologists and physiologists, they tend not to cite the latest medical references and often infer, as others before them, that it is a construct lacking a sound scientific rationale

(Straus, 2002; White et al., 2011). Moreover, they continue to ignore the specialists in the field who have pointed out that APT is inconsistent with the Envelope Theory (Jason, 2017; Jason et al., 2013). At a time when the researchers must have been aware that the strategy of pacing as promoted by various support groups differed from the multi-component programme they refer to as APT, White (2016) claimed that 'patients get better results from CBT and GET – both confirmed as safe – than they do from pacing or medical care alone'. In our view, the differences between APT and pacing almost certainly explain the discrepancy between the results relating to the former, and the research as well as positive experiences of pacing reported by patients in surveys conducted by support groups (Jason et al., 2009; ME Association, 2015, Appendix 6).

We submit that overemphasis on psychological factors and the dismissal of evidence of pathology triggered the anger which motivated writers such as Marshall and Williams (1996). The announcement of the PACE trial increased the animosity, but the documented abuse and harassment of scientists (and some patients) should be seen as the product of a combination of factors, and not as a simple rejection of a specific theory or treatment (Hanlon, 2013; Hawkes, 2011; Jarrett, 2011). Most of the reports of the hostility can be found in the media and scientific publications but one activist who targeted a known critic of the trial was successfully prosecuted under the Protection from Harassment Act 1997 (Regina v Jane Bryant, 2011).

The misleading information about the illness and its treatment since the 1990s remains a significant impediment to progress in this field. It should be noted that there were attempts by patients to try and resolve differences (e.g. Lev and Goudsmit, 1990). However, nothing has resulted in more accurate descriptions of the illness or the recognition of the growing evidence of ongoing disease in a subset (Shepherd and Chaudhuri, 2016).

This impasse helps no one. It seems to us that in order to reduce the tension between the proponents of the fear-avoidance model and its critics, we need to examine and understand what lies behind the resistance of the former towards other hypotheses and interventions. Some have speculated about investigator bias and researcher allegiance, as most of those promoting CBT and GET were involved in the development of the therapies as well as the aetiological model on which they are based (Lieb et al., 2016). However, the errors and lack of balance should have been challenged during the peer review. This process may be 'poor at detecting gross defects and almost useless for detecting fraud, it is … highly subjective, … prone to bias, and easily abused' (Smith, 2006). With regard to British and Dutch trials of CBT and GET for ME/CFS, it has clearly failed.

Flaws could have also been identified and discussed in accompanying articles, but the editor of *The Lancet* invited two researchers with a similar view on aetiology and known advocates of CBT and graded activity to comment on the first report on the trial (Bleijenberg and Knoop, 2011). Similarly, *The Lancet Psychiatry* chose three authors who focused on the possible effect of 'exercise therapy' on 'neuronal function' and speculated about the potential efficacy of antioxidants and anti-inflammatory agents (Moylan et al., 2015). Neither addressed the flaws discussed above and summarised by Davis et al. (2016). In summary, it may be argued that editorial policies have favoured evidence supporting the fear-avoidance model and associated treatments, and added to the psychologisation of ME/CFS by publishing commentaries which did not challenge the message that CBT and GET are still 'the only game in town' (Spencer, 2015).

Responses to criticisms and possible counter-arguments

The chasm between those who promote CBT and GET and the critics will remain as long as investigators refuse to engage in a constructive debate. Having followed the developments for over 20 years, we have identified a number of arguments used by various scientists to defend the interventions as well as the rationale behind

them. It is our belief that this undermines the scientific process.

One common response to critics of the PACE trial is that they do not understand either the theoretical basis behind the two interventions and/or the statistical analysis (Sharpe et al., 2017; White et al., 2017). However, in terms of the fear-avoidance model, many of the criticisms are based on an analysis of the evidence and sound research (e.g. Goudsmit, 2016; Sunnquist, 2016). The same is true of the recent discussion of the change of criteria used to calculate recovery rates (Geraghty, 2016). While a few individuals without the relevant qualifications to interpret the data correctly may have misunderstood certain aspects of the trial, this argument does not apply to the majority of the scientists (Shepherd and Chaudhuri, 2016). Below are a number of other responses to criticisms, plus the evidence which can be used as counter-arguments.

The PACE trial is well-conducted and rigorous (Miller, 2011)

Our response: Other commentaries have discussed flaws such as the limited measures assessing symptoms, and the failure to use actigraphy to confirm fidelity to the protocol (Miller, 2011). The latter is particularly important given Dutch research found no significant increase in activity after treatment in three of their trials (Wiborg et al., 2010).

Research has shown that CBT and GET are more effective than specialist medical care or APT (White et al., 2011)

Our response: This depends on a very broad definition of effectiveness and recovery (White et al., 2011). Studies conducted outside the United Kingdom and the Netherlands, as well as audits within the National Health Service (NHS), have not been able to replicate the outcomes reported in the PACE trial (Jason et al., 2007; Quarmby et al., 2007; Shepherd and Chaudhuri, 2016). Moreover, surveys of patients conducted around the world since 1999 have indicated that a significant proportion judged CBT and GET to be unhelpful, and that the latter often resulted in adverse reactions that have not been fully acknowledged (e.g. Kindlon, 2017).

Based on the available evidence, we are still not able to ascertain how many participants in the trial met the generally accepted view of recovery, that is, the absence of symptoms that prevent patients leading the life they wish.

CBT and GET are 'the only game in town' (Spencer, 2015)

Our response: This is only accurate if one ignores all the literature on alternative interventions, for example, Goudsmit et al. (2009b) which evaluated a physician-led programme in an NHS setting (Spencer, 2015). In this study, 23 per cent of the patients were well enough to be discharged at 6 months and over 80 per cent reported feeling better or much better. Other pragmatic, multi-dimensional interventions have also been found to be helpful (Forrester-Jones et al., 2015; Taylor et al., 2006). However, these are rarely cited in the literature on CBT and GET which gives a limited view of the currently available therapeutic options.

CBT and GET are helpful for people with ME (White et al., 2011)

Our response: The PACE trial did not use the original London criteria for classic ME, based on the description of the condition by Ramsay (1988), but a less stringent version (White et al., 2011). The published data do not show that those with psychological disorders had been excluded, as the original criteria require (Dowsett et al., 1993). It is therefore possible that some of the participants selected using the broader criteria may not have had classic ME.

The fear-avoidance model does not imply that ME/CFS has a psychological cause (Chalder quoted by Siddique, 2015)

Our response: The literature on CBT and GET lists operant conditioning,[2] fear, misattribution

of symptoms, the avoidance of activity, lack of fitness and the physiological effects of stress as the main factors which perpetuate ME/CFS (Powell, 2005; Wessely et al., 1998: 278). These are primarily psychological. For a review, see Goudsmit (2016).

Other studies found similar results (Sharpe et al., 2017)

Our response: This is a fair point, but it should be noted that almost all the trials which have reported positive outcomes adopted the same design, with limited measures to evaluate symptoms and without stratification of subgroups, for example, those with a post-infectious onset (Sharpe et al., 2017). Jason et al. (2007), who used a different design, failed to replicate the results obtained in the United Kingdom and the Netherlands (summarised in Bagnall et al., 2007, Table 1). There are also other factors, notably the selection of patients using broadcase definitions, which may explain the similar results reported in the United Kingdom and the Netherlands (Malouff et al., 2008).

The PACE trial assessed an approach preferred by support groups, that is, pacing (White et al., 2011; Bleijenberg and Knoop, 2011)

Our response: We are not persuaded that the trial assessed pacing as described by all except two patient groups (Bleijenberg and Knoop, 2011; White et al., 2011). This was pointed out in various articles by both Goudsmit and Jason who developed this strategy (Goudsmit et al., 2012; Jason et al., 2013). The PACE trial assessed a programme called APT which includes advice about activity management and reducing stress, and also encourages the use of the 70 per cent rule. Simply put, this rule allows people to do less than they are able to. In contrast, pacing as recommended by most support groups is based on the Envelope Theory which requires patients to match expended energy with perceived energy (Jason, 2017). Thus the claim that the PACE trial evaluated pacing based on the Energy Envelope Theory is factually incorrect (Chalder et al., 2015; White et al., 2011).

CBT is also available to people with a number of medical conditions including multiple sclerosis and cancer. Why should it not be offered to patients with ME/CFS? (Campling and Sharpe, 2006)

Our response: The protocols for these conditions do not aim to cure or deal with somatic symptoms such as diplopia or incontinence (Campling and Sharpe, 2006). They tend to address adjustment, anxiety, depression and the effects of distress. They do not challenge the patients' view that they are suffering from a disease. See Goudsmit's (2001) factsheet written after the first time this argument was noted. The protocols for ME/CFS which have been assessed in RCTs focus on chronic fatigue and rarely discuss symptoms such as dizziness, blurred vision and bladder disturbances which are common in ME (Goudsmit et al., 2009a). These and other symptoms are invariably attributed to misattribution, a lack of fitness and the effects of 'worry'. For example, see articles by Powell (2005) and information on the King's College website (various years). In the case of disequilibrium, the presumed cause (e.g. inactivity and the 'mistaken' belief that the consequences reflect pathology) may be applicable to a proportion of patients who report chronic fatigue, but in disorders such as ME/CFS, evidence of central nervous system deficits suggests that interventions other than CBT and GET may be more appropriate (e.g. Ash-Bernal et al., 1995; Shepherd and Chaudhuri, 2016).

Conclusion

The bias and selective discussion of the literature as evident in articles and discussions on CBT and GET reflects a lack of respect for the scientific process in general, and for colleagues with a different view in particular. This disempowers clinicians and researchers and distorts our understanding of the illness-as-lived. More

rigorous peer review is essential, and the current editorial polices which operate in certain British journals must be challenged.

PACE-Gate is not just an example of flawed research. It is simply the latest in a series of studies which promotes one school of thought. We find this hard to reconcile with best practice and evidence-based medicine.

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Notes

1. In another publication, the latter part of the quote is attributed to Professor White talking on BBC radio 2.
2. The operant conditioning hypothesis was influenced by the literature on chronic pain. In short, it posits that when patients learn that rest alleviates fatigue, they become increasingly inactive. Excessive rest is deemed to be counter-productive as it undermines fitness, which in turn perpetuates the fatigue. The operant conditioning hypothesis is the reason why the protocol for GET requires patients to adhere to a predetermined schedule of rest and activity and why the researchers do not recommend symptom-contingent pacing.

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Commentary

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PACE investigators' response is misleading regarding patient survey results

Karen D Kirke

Abstract

The PACE investigators' citation of a patient survey might mislead readers into thinking that the experience of people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) supports PACE findings. In fact, patient survey evidence directly contradicts the results of the PACE trial. A review of survey data published between 2001 and 2015 reveals that for most patients, graded exercise therapy leads to worsening of symptoms, cognitive behavioural therapy leads to no change in symptoms, and pacing leads to improvement. The experience of people with ME/CFS as reflected in surveys is a rich source of information, made more compelling by the consistency of results. Consequently, patient survey evidence can be used to inform practice, research and guidelines. Misrepresentation of patient experience must be vigorously challenged, to ensure that patients and health professionals make decisions about therapies based on accurate information.

Keywords

Adaptive pacing therapy, chronic fatigue syndrome, cognitive behavioural therapy, graded exercise therapy, myalgic encephalomyelitis, pacing, patient survey evidence, systemic exertion intolerance disease

In 'Response to the editorial by Dr Geraghty' (White et al., 2017), the authors refer to a 2011 patient survey by Action for ME (2011a). They cite the survey as evidence that patients 'want treatments that help them to improve', including graded exercise therapy (GET) and cognitive behavioural therapy (CBT), and to refute Geraghty's suggestion that 'Their actions have arguably caused distress to patients' (White et al., 2017: point 2; Geraghty, 2016: 6). White et al.'s citation of the Action for ME (2011a) survey could suggest to readers that (a) patients want GET and CBT, (b) patients find GET and CBT to be effective treatments, and thus, (c) patient survey findings support PACE findings. This is not, however, what Action for ME (2011a) or other patient surveys show.

Patients support other therapies over GET and CBT

Action for ME (2011a, 2011b, 2011c) warned patients about widespread cuts to existing and future National Health Service (NHS) services for people with ME and asked patients which of six treatments/therapies they would like to be available on the NHS, regardless of whether they had experienced the therapies or not. Treatments deemed ineffective by the PACE trial (White et al., 2011), such as pacing (in the form of Adaptive Pacing Therapy, see further below) and Standard Medical Care, had markedly higher patient

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approval ratings for availability on the NHS than treatments deemed effective by PACE, namely, GET and CBT. GET was rated the lowest of all six therapies. 90–94 per cent of patients responded 'yes' to pacing, medications and fatigue/condition management being available on the NHS, compared to just 48 per cent responding 'yes' for GET and 66 per cent for CBT (Action for ME, 2011a: 5; Table 2). This is not the patient stamp of approval for PACE-approved GET and CBT that White et al.'s reference to the Action for ME (2011a) survey might suggest to readers. The survey supports the truism that patients 'want treatments', but did not assess which therapies 'help[ed] them to improve' (White et al., 2017: point 2) and demonstrates clearly that patients show considerably less support for GET and CBT's availability on the NHS than for other mainstream approaches, including pacing and medications.

A larger patient survey addressed the same topic; The ME Association's (2010) survey asked respondents which of six therapies they felt were 'helpful and acceptable' and thus would recommend 'for widespread use within the NHS' (The ME Association, 2010: 25). A total of 3099 patients responded to that question, compared to 977 total respondents to Action for ME (2011a). The results rank pacing first of the six therapies, CBT second last and GET last. 82 per cent of respondents wanted pacing to be used in the NHS, compared to 28 per cent who wanted CBT and 24 per cent who wanted GET. Thus, the same pattern was found in both Action for ME (2011a) and The ME Association (2010): pacing is consistently ranked as the most-wanted NHS therapy by patients and GET is consistently ranked as the least-wanted NHS therapy. In summary, patient survey evidence cannot be construed to show widespread support for GET and CBT relative to other therapies, since it consistently ranks them lower.

Patients find GET and CBT ineffective

A wide variety of management approaches have been explored in surveys, some of which do not fit easily into the categories of 'therapies' or 'treatments'. For example, pacing is generally not considered a treatment for ME/CFS (Goudsmit et al., 2012: 1141), rather a compensatory self-management strategy (see further below). For simplicity, however, in this article, the term 'therapy' will be used to refer to any management approach/strategy/technique/therapy/treatment explored in surveys. The terms 'effective' and 'efficacy' will be used when patients report that a therapy improved or helped their symptoms. The ME Association surveys (2010, 2015) used the term 'improve', while Action for ME surveys (2008, 2014) used the term 'helpful'. Similarly, 'harmful' and 'harm' will be used when patients report that a therapy led to worsening of their symptoms. Both ME Association and Action for ME surveys used the term 'worse'. Worsening of symptoms for a considerable proportion of patients will be interpreted as reflecting negatively on the 'safety' of a therapy.

Although the survey cited by White et al. (Action for ME, 2011a) did not address efficacy or safety of therapies, regular large patient surveys are conducted, asking patients who have used various therapies whether their symptoms improved, stayed the same or got worse, such as Action for ME (2014; $n=2081$), The ME Association (2010; $n=4217$) and Action for ME and Association of Young People with ME (2008; $n=2763$, henceforth referred to as Action for ME, 2008). These surveys are a valuable source of feedback from patients about the efficacy and safety of therapies that they have experienced, in larger numbers than those that can be feasibly enrolled in randomised trials.

When therapies are ranked in order of the percentage of patients who reported that their symptoms improved, GET ranks low, meaning that it is consistently identified as being one of the least effective therapies for ME/CFS. In three large surveys, GET ranked 19th of 20 therapies, 24th of 25 and joint last of 15 (Action for ME, 2014: 19; The ME Association, 2010: 9; Action for ME, 2008: 13, respectively). Most or all other therapies were thus more effective than GET in improving symptoms. Therapies ranking higher than GET for effectiveness include pacing, medication, meditation, dietary changes, reflexology, acupuncture and homoeopathy

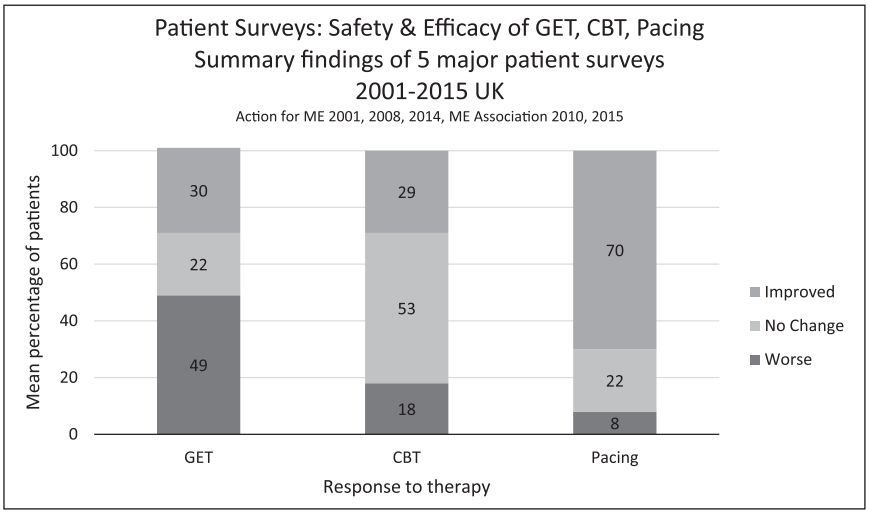

Figure 1. Summary of patient survey evidence on safety and efficacy of GET, CBT and pacing

(Action for ME, 2014: 19). In the same surveys, CBT ranked joint 15th of 20, 22nd of 25, and 13th of 15, making CBT one of the least effective therapies. Pacing, on the other hand, which the PACE trial deemed ineffective, ranked 2nd of 20, 1st of 25 and 2nd of 15 in the same surveys. Only rest was more helpful. In the largest of the three surveys, just 22 per cent reported improvement with GET and 26 per cent reported improvement with CBT, while 71 per cent reported improvement with pacing (The ME Association, 2010: 9). In summary, patient survey evidence consistently finds that GET and CBT are among the least effective therapies for ME/CFS, while pacing is effective, in direct contrast to PACE trial claims.

Patients find GET harmful

Since patient surveys ask whether symptoms got worse, therapies can also be ranked in terms of which cause the most harm. In three large surveys, GET consistently ranked highly for harm, meaning that a higher proportion of patients reported that their symptoms worsened with GET than with other approaches. GET ranked 2nd most harmful of 20 therapies, 1st of 25 and 1st of 15 (Action for ME, 2014: 19; The ME Association, 2010: 10; Action for ME, 2008: 13, respectively). CBT generally ranks towards the middle for harm in the same surveys: 7th of 20, 10th of 25 and 5th of 15. In the largest of the three surveys, 57 per cent reported worse symptoms from GET, 20 per cent reported worsening from CBT and 5 per cent reported worsening from pacing (The ME Association, 2010: 10). If PACE-approved GET and CBT were safe and effective, we would expect patient surveys to show GET and CBT resulting in a net decrease in patients on disability benefits. Instead, we see the opposite: a net increase in patients on disability benefits after GET courses (+13%) and CBT courses (+10%), compared to a net decrease in benefits (−1%) after pacing courses (The ME Association, 2015: 75). In summary, patient survey evidence consistently finds GET harmful and CBT to have a higher rate of harm than many more effective therapies, in contrast to PACE trial claims of both GET and CBT being safe.

Figure 1 summarises patient survey evidence on the safety and efficacy of GET, CBT and pacing. The results of five major patient surveys since 2001 by the two main ME patient organisations in the United Kingdom, Action for ME and The ME Association, are pooled to give an overview of patient response to each therapy. Data are further broken down by survey and therapy in Table 1. The Action for ME (2011a) survey cited by White et al. (2017) is not included

Table 1. Safety and efficacy of GET, CBT and pacing: patient survey evidence

Therapy	No. of respondents	Patient survey	Effect of therapy on symptoms		
			Improved/helpful	No change	Worse
GET	See note 5	Action for ME, 2014	35%	18%	47%
	233	ME Association, 2015: *course*	15%	21%	64%
	249	ME Association, 2015: *self*	28%	33%	39%
	906	ME Association, 2010	22%	21%	57%
	See note 5	Action for ME, 2008	45%	21%	34%
	Unknown	Action for ME, 2001	34%	16%	50%
		GET mean	**30%**	**22%**	**49%**
CBT	See note 5	Action for ME, 2014	54%	34%	12%
	493	ME Association, 2015: *course*	12%	65%	23%
	449	ME Association, 2015: *self*	26%	57%	17%
	997	ME Association, 2010	26%	55%	20%
	See note 5	Action for ME, 2008	50%	38%	12%
	Unknown	Action for ME, 2001	7%	67%	26%
		CBT mean	**29%**	**53%**	**18%**
Pacing	See note 5	Action for ME, 2014	85%	12%	4%
	226	ME Association, 2015: *course*	38%	42%	19%
	614	ME Association, 2015: *self*	56%	32%	12%
	2137	ME Association, 2010	71%	24%	5%
	See note 5	Action for ME, 2008	82%	15%	3%
	Unknown	Action for ME, 2001	89%	9%	2%
		Pacing mean	**70%**	**22%**	**8%**

1. Numbers have been rounded to nearest whole number.
2. Means shown in Table 1 were used for Figure 1.
3. Surveys are presented in order of recency of data collection. Data for The ME Association (2010) survey were collected in 2008. Data for The ME Association (2015) survey were collected in 2012.
4. The ME Association (2015) survey presented data for courses and self-management separately, shown in two separate rows in Table 1.
5. While Action for ME did not report the exact number of respondents to this question for each survey, they did report the percentage of overall survey respondents who did each therapy (Action for ME, 2014: 17). In 2014, of 2081 total respondents, 23 per cent did GET, 33 per cent did CBT and 67 per cent did pacing. In 2008, of 2763 total respondents, 26 per cent did GET, 26 per cent did CBT and 58 per cent did pacing.
6. The ME Association used the term 'improved'; Action for ME used the term 'helpful'.
7. Data from The ME Association (2015) shown in Table 1 are from Figure 3.4.1a (courses, p. 28) and from p. 73 and Figure 5.2 (p. 285; self-management). Page references for other data are as follows: Action for ME (2014: 19), The ME Association (2010: 9–10) and Action for ME (2008: 13). Results of Action for ME's 2001 survey are cited in Action for ME (2008: 13).

because it did not address the efficacy or safety of individual therapies. A traffic light colour coding system is used to highlight harm and benefit: red indicates that the patients' symptoms were worse after therapy, amber that the patients' symptoms remained unchanged after therapy and green that the patients' symptoms had improved after therapy. Data should be interpreted bearing limitations of surveys in mind (see Kindlon, 2011: 64–67).

A clear pattern can be seen from Figure 1 and Table 1: for most patients, GET results in worsening of symptoms (harm), CBT results in no change (ineffective) and pacing results in

improvement (effective). Patient survey findings are in direct contradiction of PACE findings of benefit from GET and CBT, no benefit from Adaptive Pacing Therapy (APT) and no harm from any therapy. Moreover, patient surveys support Kindlon's (2011) argument that harms associated with GET and CBT may be underreported in randomised trials including PACE (see also Vink, 2017). The consistency of results between surveys is striking, making patient survey evidence more compelling. Of particular note is that patient survey evidence shows that GET results in worsening of symptoms for more patients than it helps and patients find pacing effective.

Patients find pacing effective: why did PACE find APT ineffective?

As the data in Figure 1 and Table 1 demonstrate, patient surveys consistently show that patients find that pacing improves/helps their symptoms, with an average of 70 per cent reporting improvement in the surveys summarised. This is in keeping with research on pacing as a 'strategy which helps patients with ME/CFS limit exertion-related symptomatology' (Goudsmit et al., 2012: 1140). The efficacy of pacing is also consistent with the evidence on post-exertional malaise (Institute of Medicine, 2015: 78–86) and recent research on defective energy metabolism in ME/CFS (Fluge et al., 2016 and references therein).

The ME Association (2015: 19) defined pacing as 'an energy management strategy in which people with ME are encouraged to achieve an appropriate balance between activity and rest'. While rest is a key component of pacing, Clark and White (2008) refer to 'the many negative consequences of rest'. Patient survey data consistently indicate that rest makes just 1 per cent of patients worse and is helpful to more than 85 per cent of patients (Action for ME, 2008: 13; Action for ME, 2014: 19; Action for ME, 2001 cited in 2008: 13) compared to an average of 49 per cent worse with GET (Table 1). How do we explain the wide gulf between patient experience of pacing and rest in surveys and PACE claims?

The PACE trial purported to compare the efficacy of pacing with that of GET and CBT by devising a course called 'Adaptive Pacing Therapy' comprising 15 sessions with an Occupational Therapist and homework. White et al. (2011) concluded that APT was 'not an effective addition' to Standard Medical Care (p. 823) and that 'Our results do not support pacing, in the form of APT' (p. 834). The PACE trial APT manual, however, describes an extensive Occupational Therapy intervention that includes pacing, but also encompasses relaxation techniques, sleep management, body mechanics, ergonomics, problem-solving and advice for carers (Cox et al, 2004). It is this wide-ranging intervention devised for PACE, Adaptive Pacing Therapy, that was found ineffective in the PACE trial. Critics have pointed out differences between pacing and APT (Goudsmit et al., 2012: 1144; Jason, 2017: 1–3), which could account for APT having been found ineffective in PACE (White et al., 2011).

Patient survey evidence suggests that pacing is widely used by patients, with 67 per cent of respondents to the Action for ME (2014) survey using pacing, an increase from 58 per cent in 2008 (Action for ME, 2014: 17). Similarly, the ME Association's data from 2008 showed at least 51 per cent were practising pacing; 2137 of 4217 answered questions on pacing's effect on their symptoms (The ME Association, 2010: 9). The PACE trial, however, did not report the proportion of patients using pacing as a self-management strategy in each treatment arm either at onset or at conclusion of the trial. If a large proportion of patients randomised to APT in the PACE trial were already pacing prior to trial commencement, as patient surveys suggest might have been the case, then those patients may already have improved as much as they were going to from pacing. So, for many or perhaps most patients in the APT arm, the PACE trial may have been assessing the efficacy of the non-pacing elements of APT.

Interestingly, patients reported a higher rate of symptom improvement with self-managed

pacing than courses on pacing (56% vs 38%, The ME Association, 2015), a trend also seen for GET and CBT (see Table 1 above). Additionally, self-managed pacing is more widely used than courses on pacing; of 840 respondents to The ME Association's (2015) survey questions on pacing, 73 per cent reported using pacing as a self-management strategy, compared to 27 per cent who attended a course. These data could explain why PACE found APT, a course, ineffective, while patient surveys find pacing, mostly self-managed, effective. It also points to a potential issue with courses for people with ME/CFS. Perhaps the exertion of attending a course on pacing is negating some of the benefits experienced with self-managed pacing. Alternatively, patients who are self-managing may be mitigating some flaws in courses delivered by health professionals, by using different strategies or applying strategies differently.

Whatever the explanation(s) for APT being found ineffective in PACE, patient survey evidence highlights the importance of patients with ME/CFS using pacing and of health professionals continuing to encourage it.

Further evidence of harm from exercise therapies

Patient-reported harm from GET is echoed by high rates of reported harm from physical therapies in general. In The ME Association's (2010) survey, three of the four most harmful therapies were physical: GET, physiotherapy and yoga (p. 10). Action for ME (2011d) completed a smaller survey to look at physical rehabilitation therapies more closely, finding that physical rehabilitation therapies did more harm than good, with 60 per cent of those who did GET reporting worsening of their condition (compared to 22% reporting improvement), 52 per cent reporting worsening with exercise on prescription (compared to 26% reporting improvement), and 46 per cent worsening with other physical rehabilitation therapies (compared to 23% reporting improvement) (p. 12).

The ME Association's (2015) survey examined the effect of adding elements of GET to courses on CBT or pacing, that is, adding a physical rehabilitation element into an otherwise non-physical therapy. The data suggest that the addition of elements of GET increased the rate of harm (see Figures 3:4:2a, 3:4:3a and 3:4:4a, The ME Association, 2015: 29–31). For example, when patients did a CBT course with *no GET* elements, 18 per cent of patients reported worsening of symptoms, compared to 34 per cent reporting worsening from a CBT course *with GET* elements.

Patient survey evidence strongly suggests that far from being an effective therapy for ME/CFS, GET and other physical rehabilitation therapies actively harm patients with ME/CFS, meaning that they cause worsening of symptoms. This is in line with exertion intolerance being central to ME/CFS (Institute of Medicine, 2015) and accumulating biomedical research evidence that points to abnormal physiological response to exercise (see review by Twisk and Geraghty, 2015) and dysfunctional energy metabolism in ME/CFS (Fluge et al., 2016). Patient survey evidence is inconsistent with the PACE authors' beliefs in the deconditioning and fear avoidance models of ME/CFS (White et al., 2011: 825).

PACE-author White has previously argued that reported exacerbation of symptoms from GET in patient surveys is a 'mistaken criticism' (Clark and White, 2008), occurring not due to GET itself but due to improper implementation of GET (Clark and White, 2008, 2010), based on an interpretation of data from an Action for ME (2003) survey. In that survey, of 54 patients who did GET, 26 (48%) reported negative outcomes (Action for ME, 2003: 12). Clark and White (2008) argued that 'in many cases, exercise was being undertaken independently, without the supervision of a therapist trained to deliver GET to patients with CFS [Action for ME, 2003]. In other words, it was not GET'. The reader might interpret this to mean that those who did exercise independently reported negative outcomes, however, the data do not show this. For example, only 1 of 12 patients who did GET with 'no professional' reported a negative outcome, compared to 12 of 18 patients who did GET with the supervision of a physiotherapist (Action for ME, 2003: 12).

Further evidence that it is GET, rather than its implementation, that is most problematic comes from Action for ME's (2008) survey, where, as noted by Kindlon (2011: 65), there was

> no statistically significant difference in the rate of people saying they were made worse from engaging in GET under a 'NHS specialist' (31.27%, 111/355) compared to the rest of those reporting such an outcome from GET in another scenario (33.02%, 70/212).

The ME Association (2015) survey explored this issue in much greater detail, examining the effect of a number of variables affecting implementation of GET courses, including therapist specialism in ME/CFS, therapist beliefs about ME/CFS, individual versus group delivery, partial versus full course completion and whether elements of pacing and/or CBT were included. Regardless of how GET courses were implemented, the rate of harm from GET remained above 50 per cent in all conditions (range 51%–80%), and rate of improvement remained below 25 per cent across conditions (range 2%–24%; The ME Association, 2015: 28–41). This suggests that what causes harm is GET, contrary to Clark and White's (2010) claim. Poor implementation does amplify this harm, but well-implemented GET still causes worsening for most patients. GET courses implemented by therapists specialising in ME/CFS resulted in considerably more harm (57% of patients worsened) than good (20% improved; The ME Association, 2015: 32). A therapy doing markedly more harm than good to patients, even when implemented by specialists, is dangerous to patients. While survey limitations must be taken into account, these consistent findings should ring alarm bells for rehabilitation professionals and those in charge of clinical guidelines, to ensure that harmful therapies are withdrawn from use.

Discussion

The stark mismatch between patients' experience of GET/CBT/pacing as evidenced in patient surveys, and PACE trial investigators' claims regarding safety and efficacy of GET/CBT/APT, is at the heart of PACE-gate. White et al. (2017: 4) conclude their response by reiterating their claim that PACE 'provide[s] patients, healthcare professionals, and commissioners with the best evidence that both CBT and GET are safe and effective treatments' and as such are 'good news for patients who, in our experience, just want to get better'. However, patient survey data provide compellingly consistent evidence, from larger samples than PACE examined, that for most patients, GET results in worsening of symptoms, CBT is ineffective and as such, these two therapies are unhelpful for patients who want to get better. Additionally, pacing emerges as consistently helping patients to improve. Patient surveys thus contradict the PACE investigators' claim that 'CBT and GET can safely be added to [Standard Medical Care] to moderately improve outcomes for chronic fatigue syndrome, but [Adaptive Pacing Therapy] is not an effective addition' (White et al., 2017, 2011). Instead of supporting PACE findings, patient surveys are in line with critical reanalyses of the recently released subset of PACE trial data (Matthees et al., 2016; Vink, 2017; Wilshire et al., 2016).

Patient experience in the form of patient survey data is a rich source of information regarding the safety and effectiveness of treatments and therapies and must inform practice, research and guidelines. Readers who wish to judge whether PACE trial authors' 'actions have arguably caused distress to patients', as Geraghty (2016: 6) argued, and PACE trial authors rejected (White et al., 2017: point 2), or who wish to assess whether GET and CBT are safe or effective, would do well to examine patient survey data thoroughly. The ME Association's (2015) extensive report of patient experiences of GET, CBT and pacing, comprising both quantitative and qualitative data, is an excellent starting point and should be required reading for any clinician considering prescribing GET or CBT to patients with ME/CFS.

In spite of White et al.'s (2017) misleading citation of Action for ME (2011a), patient survey

findings cannot legitimately be cited as lending support to PACE findings, since they show the opposite. Misrepresentation of patient experience must be vigorously challenged to ensure that therapies experienced by most patients as causing worsening or no change in symptoms, such as GET and CBT, are not promoted as something that patients want or have found effective. While biomedical research advances are beginning to elucidate pathophysiology and will hopefully lead to effective treatments, in the meantime that treatment gap must not be filled by unhelpful therapies that worsen illness and cost money. Sometimes, nothing is better than something. Most importantly, when patients say 'This is harming us', health professionals must listen.

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Commentary

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Distress signals: Does cognitive behavioural therapy reduce or increase distress in chronic fatigue syndrome/myalgic encephalomyelitis?

Keith R Laws

Abstract

Reducing the psychological distress associated with chronic fatigue syndrome/myalgic encephalomyelitis is seen as a key aim of cognitive behavioural therapy. Although cognitive behavioural therapy is promoted precisely in this manner by the National Institute of Clinical Excellence, the evidence base on distress reduction from randomised controlled trials is limited, equivocal and poor quality. Crucially, data derived from multiple patient surveys point to worsening and increase distress; however, despite being invited, such data have been dismissed as second class by National Institute of Clinical Excellence. Crucially, the claim by National Institute of Clinical Excellence that cognitive behavioural therapy reduces distress in chronic fatigue syndrome/myalgic encephalomyelitis is not only at odds with what patients repeatedly report in surveys, but with their own gold-standard randomised controlled trial and meta-analytic data.

Keywords

adults, chronic fatigue syndrome, cognitive behaviour therapy, distress

The nebulous notion of *distress* is a key concern in the editorial and response debate articles by Geraghty (2016) and White et al. (2017). Geraghty states that '… patients with CFS may need psychological support, particularly help with coping with the distress the condition can cause …'; however, later, and more contentiously, adds that 'Their [the PACE authors] actions have arguably caused distress to patients'. White and colleagues rebut the implication asserting that 'We reject the accusation that our "actions have arguably caused distress to patients," for which Dr Geraghty offers no evidence'. I will restrict my comments here to the link between cognitive behavioural therapy (CBT) and distress in chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME).

Although *distress* is a many-headed hydra, we might expect it to be a vital target for a psychological intervention such as CBT. Indeed, the National Institute of Clinical Excellence (NICE; 2007) guideline (CFS/ME or encephalopathy: diagnosis and management – clinical guideline (CG53) presents a virtual panacean view where CBT is used '… to reduce the levels of symptoms, disability and distress associated with CFS/ME'. And interestingly, the NICE authors felt it necessary to add a Cartesian proviso 'CBT

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or psychological approaches to CFS/ME do not imply that symptoms are psychological, "made up" or in the patient's head' (p. 190). The targets would seem to include both the physical and the psychological, with distress falling within the realm of the latter and amenable to CBT.

The PACE trial monitored adverse events (Dougall et al., 2014; Sharpe et al., 2015; White et al., 2011), but did not measure 'distress' directly. The absence of evidence does not equate to evidence of absence, but PACE does provide some *indirect* evidence. The authors report that around 1 in 10 patients found CBT made them feel 'much worse' or 'very much worse' by follow-up – a not inconsiderable number of people who conceivably link the intervention to some increased experience of distress. Somewhat more *direct* evidence on distress (at least as rated on scales) can be garnered from the Cochrane review (Price et al., 2008) that was used to inform the NICE CG53 guide. Price et al. reported that in comparison to usual care, CBT failed to reduce distress at end of trial (three trials: −0.27 (95% confidence interval (95% CI): −0.56, 0.01)) or in the sole trial using a follow-up assessment (mean diff: −0.24 (95% CI: −28.85, 28.37)). Additional comparisons of CBT versus 'other psychological therapies' did, however, point to a significant end-of-trial distress reduction (3 trials and 90 people in total receiving CBT: −0.41 (95% CI: −0.71, −0.11)) and in a further analysis of a sole follow-up trial (43 people receiving CBT mean diff: −3.60 (95% CI: −7.07, −0.13)). That CBT seems efficacious in a *relative* (other psychological interventions) but not an *absolute* comparison (vs Treatment As Usual[TAU]) is unexpected. A closer look at the three studies in each meta-analysis reveals that two are common to both analyses (Barrett, 1992; O'Dowd, 2000), that is, they have CBT, TAU and a psychological intervention control; and a quick look at both trials reveals that distress was greater in the psychological intervention than the TAU control condition. This suggests not that CBT reduced distress so much as some psychological interventions increase distress.

These Cochrane findings, which played a pivotal role in NICE's development of CG53, are also fraught with interpretative impenetrability because of the often low quality of the trials, Price et al.'s widespread analysis of single trial data (e.g. a third of all analyses in their review were on *single* trials) and when they do analyse multiple trials, they are so *underpowered* that even adding the samples from every distress trials, the total remains insufficiently powered to detect the mean effect sizes they report.

No decision about me without me

The position(ing) of patients in this arena is noteworthy. The preface to NICE CG53 asserts how in developing the guideline an aim is to enable '… patients to receive therapy appropriate for, and acceptable to them' (p.7). *Acceptability* is similarly placed centre-stage by Price et al. in their Cochrane review when they state that 'Effective treatments are of little value to health services unless they are acceptable to the recipients – poor acceptability will reduce treatment uptake and adherence' (p. 21). They, however, go further and assert that 'CBT may be an acceptable form of treatment for CFS, although this evidence is currently based on a small number of individual studies' – possibly an overstated inference given that Price et al. failed to locate a single study measuring *acceptability* at end-of-trial and just one at follow-up.

Acceptability is naturally linked to whether people persist with interventions. The Cochrane meta-analyses (Price et al., 2008) revealed a significant – almost 50 per cent – greater drop-out rate for CBT compared to TAU in eight trials (20.6% vs 13.9%; odds ratio (OR): 1.70; 95% CI: 1.10 to 2.63). Similarly, four studies assessing short- to medium-term follow-up revealed a significantly larger attrition rate, which was 50 per cent greater for CBT than usual care (22.7% vs 14.8%; OR: 1.46; 95% CI: 0.52 to 4.10). Such findings point to an *acceptability problem* and are at least consistent with the idea

that a CBT-related increase in distress may have led more to leave the CBT arms of trials.

In this context, White et al. (2017) assert that 'People with CFS and/or ME want treatments that help them to improve' and cite a patient survey by *Action for ME* (2011) in support. The desire of patients to *improve* is unquestionable, but how do patients view CBT? If we turn to a more recent *Action for ME* (2014) survey of over 2000 ME/CFS sufferers in 2014, 12 per cent said that CBT had made their condition 'a bit or much worse'. Another recent survey by the *M.E. Association* (2015) is far more pessimistic, as among 35 per cent of respondents who had undertaken a course of CBT, 91 per cent stated that their 'symptoms were unaffected or made worse'.

The NICE CG53 guideline committee also invited survey data from stakeholder groups; the outcomes were, if anything, more damning than those outlined above. For example, the 25 Percent ME Group analysis (2004) reported that 93 per cent found CBT unhelpful. More important perhaps than bold numbers is the response of NICE to the stakeholder surveys that they had *invited* and deemed 'important as such surveys allow a more complete picture to be established concerning the effectiveness of, and satisfaction with, given aspects of patient care (for example, a therapeutic intervention)' (p. 77). Despite this, the authors of NICE CG53 felt it necessary to further assert that 'Randomised controlled trials (RCTs) are considered to be at the top of the hierarchy of evidence, with patient surveys found further down the hierarchy' (p. 78). This may be true, but it is notable that of 19 mentions of *bias* in the CG53, 13 are used to dismiss these survey data (the remaining six occasions are generic bias statements). By contrast, the NICE committee made little attempt to even mention the limitations and biases of randomised controlled trials (RCTs). To take just one example, although NICE remark on selection bias in surveys, they ignore the fact that more than half of the 'RCTs' in the Cochrane review failed to describe randomisation procedures, thus similarly making it impossible to assess the extent to which selection bias may have occurred.

Whether CBT reduces, increases or has no impact on distress is debatable. Although NICE advocate CBT to reduce distress in CFS/ME, their own evidence base – derived from the Cochrane meta-analyses of RCT data – reports no distress reduction for CBT over treatment as usual. Indeed, further analysis of the Cochrane data suggests that distress may even increase following some psychological interventions. We also know from the PACE trial itself that around 10 per cent of patients find that CBT makes their condition 'much worse' or 'very much worse'. Given the estimated 0.2–0.4 per cent prevalence of the disorder, advising a course of CBT could detrimentally impact the lives of a large number – especially as we cannot predict who will find CBT unacceptable or distressing. Patient surveys consistently paint a similar, albeit bleaker picture of worsening following CBT. NICE, however, display substantial bias in their dismissal of comparable methodological issues in RCT data. As far as distress in CFS/ME is concerned, CBT currently seems to promise no gain but the possibility of some pain.

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Commentary

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Cognitive behaviour therapy and objective assessments in chronic fatigue syndrome

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Abstract

Most evaluations of cognitive behavioural therapy to treat people with chronic fatigue syndrome/myalgic encephalomyelitis rely exclusively on subjective self-report outcomes to evaluate whether treatment is effective. Few studies have used measures appropriate to assessing whether cognitive behavioural therapy changes in more objective measures. A review of studies incorporating objective measures suggests that there is a lack of evidence that cognitive behavioural therapy produces any improvement in a patient's physical capabilities or other objective measures such as return to work. Future studies of chronic fatigue syndrome/myalgic encephalomyelitis should include some objective assessments as primary outcomes. If this is to include activity monitors, we first need a sound baseline dataset.

Keywords

chronic fatigue syndrome, cognitive behaviour therapy, effectiveness, qualitative methods, quantitative methods

The National Institute for Health and Care Excellence (NICE) recommends that an appropriate programme of cognitive behavioural therapy (CBT) should be offered to people with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). There may be a quarter of a million patients in the United Kingdom with such a diagnosis; many of these are sent to CFS/ME centres, most of which offer CBT as the principal treatment. Over the last 35 years, the total spending by the Medical Research Council and by the National Institute for Health Research on research into CFS/ME is around £10 million, but less than £2 million of this has been on biomedical research. The largest share of this spending has gone towards two trials: the PACE trial (White et al. 2011) which reported that CBT was effective, and its sister study, the FINE trial (Wearden et al. 2010), which reported that such therapies were not effective. Both relied upon the shifting sands of subjective responses as their primary assessments, which can be clearly seen from the responses by the PACE trial authors (White et al., 2017) to Geraghty's (2016) editorial piece on the independent analysis of a small subset of their data.

Virtually, all studies that claim that CBT is effective rely entirely upon subjective assessment. Any genuine improvement must be reflected in such reported levels of fatigue or of physical activity, but, as a patient from a mathematical background with CFS/ME, I want

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to know that a treatment will improve my day-to-day living and enable me to take a more active part in life. Consequently, I have been searching for evidence of practical improvement (objective assessments in areas such as walking and employment).

There are relatively few studies which look at the effectiveness of treating CFS/ME with CBT which use such objective assessments. O'Dowd et al. (2006), using an incremental shuttle walk, found a small improvement in the group given CBT, and a small deterioration in the group that had no intervention. A quarter of the patients in the CBT group dropped out of the trial, and five sets of values were discarded as being clear outliers. Only after excluding these outliers did the difference reach statistical significance, so it would not be appropriate to read anything into these small changes. Wiborg et al. (2010) looked at three trials using actigraphy (pedometers) and showed that CBT resulted in improvements in subjective measures but produced no meaningful corresponding improvement in activity levels.

Wearden and Emsley (2013), looking at the FINE trial which using a pragmatic form of therapy based on CBT, found that 'there were no between group differences in any of the timed step test measures at 20 or 70 weeks'.

The PACE trial (White et al., 2011) included a number of objective assessments: they were not considered as primary outcomes, nor did they form any part of the evaluation of *recovery*: the results are scattered through a number of reports, often in a very minor way. It is important that their objective assessments are considered as evidence.

It was also a complex trial: my analysis focuses on CBT, so for simplicity's sake, I will focus on just two of the four trial arms: the basic group which saw the specialist for a few sessions (the Specialist Medical Care (SMC) group) and the group that similarly saw the specialist for a few sessions but which had an additional dozen or so sessions of CBT. Each group had 160 patients. I will also only consider the assessments at baseline and at 52 weeks, the trial's primary endpoint. The trial was designed explicitly to compare such groups.

The six-minute walking test

The first intended objective assessment was to have been through the use of an actometer (a pedometer), but this was dropped part-way through the trial: in a question and answer document that they published online, the authors explained 'Before we started the trial, we were advised that the number and scope of the outcome measures were too great … Actigraphy was the obvious measure to reject because of its burden in time and effort required by participants' (PACE question and answer, n.d.). The reasoning is curious, as the researchers had previously added the six-minute walking test along with six more questionnaires, all to be completed at the centres, where clearly there was the greatest burden (in addition of course to the demands of travelling to the centres).

In their main paper, the first reported set of objective test results was that of the six-minute walking test. Patients were asked to walk along a level corridor, back and forth between two markers over a period of 6 minutes and were gently encouraged to walk as far as they could in the time: the total distance was measured. All distances in Table 1 are in metres: a healthy adult of working age would normally score 600+ metres (Goldman et al., 2008; Lipkin et al., 1986).

Table 1. The six-minute walking test: distances in metres.

	SMC 118 patients	SMC + CBT 123 patients
Baseline	326 (95)	333 (86)
52 weeks	348 (108)	354 (106)
Improvement	22	21

CBT: cognitive behavioural therapy;
SMC: specialist medical care.
Values given are mean (standard deviation).

It is very clear here that adding on the dozen sessions of CBT produced no additional benefit. The group that only saw the specialist improved their distance by 22 m, and the group that saw the specialist and had an additional dozen sessions of CBT improved their distance

by 21 m. The authors of the trial explained that the total distances covered were probably less than should be expected, as the end markers for the track length were set too close together, entailing too many *turnarounds*. This, of course, would have affected each group similarly.

Days lost from work

The next objective assessment, published in *PLoS One* (McCrone et al., 2012), concerned return to work, and claiming different forms of benefits. Table 2 shows the number of days lost from work on average per patient. In the original table, the data prior to entry covered a period of 6 months, and post entry covered 12 months, so I have reduced both of these to a 'per month' average for direct comparison.

Table 2. Number of days lost from work per patient per month.

	SMC 137/130 patients	SMC + CBT 135/122 patients
6 months prior to entry	12.6 (8.4)	14.2 (8.8)
12 months post entry period	11.8 (9.0)	12.6 (9.0)
Improvement	0.8	1.6

CBT: cognitive behavioural therapy;
SMC: specialist medical care.
N/*n* number of patients refers to 6 months/12 months.
Values given are mean (standard deviation).

Again, these differences are trivial in a statistical sense and minimal in a real-world sense (they are the improvements over the course of a year). Again, the additional CBT shows no significant advantage.

Proportion of patients receiving illness/disability benefits

Table 3 looks at benefits claimed. Here, the numbers in the table indicate the percentage of patients in each group that are involved.

This set of results is quite curious: at the end of the trial, the percentages were very close, and yet the SMC group started out with many fewer on disability benefits. In that sense, the increase in number of patients claiming illness benefits has increased three times more in the SMC group than in the CBT group. However, from details given in the original PACE paper (White et al., 2011), those in the SMC group had had the illness on average for 2 years, whereas the CBT group had had the illness for 3 years. Obtaining disability benefits is a slow process, and so this may well be the significant factor. Accompanying data on general income-related benefits and on income protection schemes or private pensions showed little difference between the two groups, so this would seem to be a valid interpretation.

Table 3. Proportion receiving illness/disability benefits.

	SMC 143 patients	SMC + CBT 138 patients
6 months prior to entry	21%	32%
12-month post-randomisation period	39%	38%
Deterioration	18	6

CBT: cognitive behavioural therapy;
SMC: specialist medical care.

Step test – fitness

The final set of objective assessments in the PACE trial were the two analyses of the step test, published in *The Lancet Psychiatry* (Chalder et al., 2015). Unfortunately, I have been unable to obtain the actual values of the plotted points, so I have had to calculate them from the graphs (my request for the data was labelled as vexatious).

Patients were asked to perform 20 step ups (and down) on standard 2 step equipment, at their own pace. The first set of calculations involved the increase in heart rate and effectively calculated each patient's actual power output (in watts) in comparison with how much harder their heart had to work at it. The larger the value the better (Table 4).

Table 4. Fitness.

	SMC 112 patients	SMC + CBT 113 patients
Baseline	1.83 (1.13)	1.76 (1.13)
52 weeks	1.99 (1.73)	1.84 (1.36)
Improvement	0.15	0.09

CBT: cognitive behavioural therapy;
SMC: specialist medical care.
Values given are mean (standard deviation), estimated from graphs.

Table 5. Borg/%max heart-rate reached.

	SMC 112 patients	SMC + CBT 113 patients
Baseline	0.205 (0.043)	0.195 (0.043)
52 weeks	0.197 (0.059)	0.184 (0.049)
Improvement	0.008	0.011

CBT: cognitive behavioural therapy;
SMC: specialist medical care.
Values given are mean (standard deviation), estimated from graphs.

It is difficult to obtain figures for healthy people for comparison; the figures from a study by Petrella et al. (2001) on patients with an average age of 72 years would give values of around 1.2. With the average age of the patients in the PACE trial being 39 years, little can be made of this: but the design of the PACE trial was to compare between groups, and here, once again, the difference in improvement between those that had CBT and those that did not is negligible. This test was included in the trial as it was considered an important test of fitness and conditioning. CBT was designed to improve hypothetical deconditioning in patients with CFS/ME. This measure should have provided clear evidence to support the idea that such patients are deconditioned and that CBT reverses deconditioning in CFS/ME: clearly it has not done so.

Step test – Borg scale

The other analysis of the step test involved the Borg scale of perceived effort: it compared how hard the patient thought they were working with their actual heart rate. Here, lower scores are better (Table 5).

Again, it is difficult to obtain figures for healthy people because those studies that use the Borg scale generally impose a speed, rather than, as here, allow it to be self-paced. But again, the comparison between the groups is negligible. CBT, as administered in the PACE trial, was intended to overcome patients' supposed fear of, or heightened awareness of the effects of exercise, but it seems that such a supposition is not supported either.

Subjective assessments

The improvements cited by the PACE reports focus on subjective assessments. When terms such as *within normal function* or *recovery* are used in a study on the effectiveness of treating CFS/ME with CBT, it would seem reasonable that any improvements assessed by questionnaires on physical functioning or fatigue should show some corresponding improvement in objective assessments. This disparity between such relatively small but statistically significant subjective improvements and the finding of no improvements in objective assessments has been found elsewhere, as mentioned earlier. Those subjective assessments for which data from the PACE trial has been given at baseline, 12 weeks, 24 weeks and 52 weeks show that most of any improvement occurs between baseline and 12 weeks: after that progress flattens out. Long-term follow-up confirms that trend and also shows that any perceived subjective improvement shown earlier by the group receiving CBT is subsequently matched by the SMC group (Sharpe et al., 2015).

Recently, following the release of a tiny subset of data from PACE by Queen Mary University after a tribunal ruling, it has been possible to analyse the claims of recovery according to the standards set in their original protocol (Wilshire et al., 2016): these were standards based on experience of both the methods and assessments used in the trial. The very much smaller success rates of the CBT group (dropping from 22% to 7%) became statistically insignificant, casting more doubt on the

advisability of relying entirely upon subjective assessment.

Concluding remarks

I find this apparent, consistent and unexplained disparity between subjective and objective outcomes unsatisfactory and can only come to one conclusion: a correct interpretation of the results lies between two possibilities – improvements in subjective scores on fatigue and physical conditioning do not reflect any real improvement in either, but simply reflect a re-scaling exercise by patients as a result of exhortations by the therapists, or there were improvements in fatigue and physical functioning, but these were too small to show up in any objective assessment. I would argue that continuing to rely on subjective measures is potentially misleading and is rather like using different sets of elastic tape-measures at a Weight-Watchers' meeting. It is vital that some consistent means of obtaining objective data is agreed.

In a fascinating study on patients with asthma, Wechsler et al. (2011) demonstrated very clearly that although placebo and sham acupuncture treatments 'did not differ significantly' in subjective reports of improvement, they failed to deliver the objective improvement that the albuterol inhaler produced. Similar problems with subjective assessments have been commented upon by Higgins et al. (2005) in their study on ulcerative colitis. As well as complaining about a lack of agreed scores for remission or for significant improvement in such assessments, they comment that 'Subjects in therapeutic trials both want to believe they are getting better and want to please the investigator, and are likely to over report improvement and remission in the setting of a clinical trial. Therefore it is important to derive objective measures that can identify patients in remission outside the context of a therapeutic trial'. This must be especially true in the case of CBT where the treatment in question is specifically designed to change patients' perceptions.

The recent and rapid development in personal physical activity monitors is worth investigation. Prior to any use in studies of treatments relevant to CFS/ME, there needs to be a long-term study of their use with patients in order to iron out any implementation problems, and, very importantly, to determine a respectable database mapping the variability of this condition and to determine suitable targets or levels to measure success – particularly when selection measures are used to restrict participation, which instantly introduces potential problems with reversion to the mean.

Of course, some patients may benefit from CBT: I know of a number of people with CFS/ME who have found that CBT helped them to adjust to the illness and to make the most of their situation. Clearly general practitioners (GPs) are able to diagnose when there is a specific need for that: but there is still no evidence that CBT has any real effect upon CFS/ME itself, nor is there any evidence to support the persistent beliefs that continuing symptoms are simply the results of fear and deconditioning. I believe that any form of CBT that is based on those beliefs is unsubstantiated and, based on the available evidence, is unable to improve physical capacity.

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Commentary

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PACE trial claims for recovery in myalgic encephalomyelitis/chronic fatigue syndrome – true or false? It's time for an independent review of the methodology and results

Charles Bernard Shepherd

Abstract

The PACE trial set out to discover whether cognitive behaviour therapy and graded exercise therapy are safe and effective forms of treatment for myalgic encephalomyelitis/chronic fatigue syndrome. It concluded that these interventions could even result in recovery. However, patient evidence has repeatedly found that cognitive behaviour therapy is ineffective and graded exercise therapy can make the condition worse. The PACE trial methodology has been heavily criticised by clinicians, academics and patients. A re-analysis of the data has cast serious doubts on the recovery rates being claimed. The trust of patients has been lost. The medical profession must start listening to people with myalgic encephalomyelitis/chronic fatigue syndrome if trust is going to be restored.

Keywords

activity, behavioural medicine, chronic fatigue syndrome, cognitive behaviour therapy, dissatisfaction, efficacy, exercise, graded exercise therapy

Keith Geraghty's (2016) editorial has identified and discussed most of the key reasons why both the PACE trial methodology and the results are not regarded as reliable. PACE – an acronym for **P**acing, graded **A**ctivity, and **C**ognitive behaviour therapy, a randomised **E**valuation – compared the effectiveness of four separate inteventions: specialist medical care (SMC) to SMC plus adaptive pacing therapy, cognitive behaviour therapy and graded exercise therapy in patients with myalgic encephalomyelitis/chronic fatigue syndrome. However, those involved in the PACE trial have responded by stating that these criticisms are based on misunderstandings and misrepresentations (White, 2017).

I would like to use this commentary to examine controversies surrounding how two of the PACE trial interventions – cognitive behaviour therapy (CBT) and graded exercise therapy (GET) – originated, why the PACE trial was bound to run into difficulties, and why the patient community is so at odds with the medical establishment over their promotion of CBT and GET.

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As a physician who has spent much of the past 35 years helping patients with myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), I have a strong desire to find safe, acceptable and effective forms of treatment that are aimed at the underlying disease process – rather than just trying to relieve some of the key symptoms. The same position is taken by most ME/CFS patients.

However, uncertainties and disagreements among doctors and patients as to how we should name, define and diagnose this illness, what causes it and how it should be managed make this a very challenging task.

The failure to accept that ME/CFS is a very heterogeneous condition in both clinical presentations and underlying disease mechanisms has meant that the two 'rehabilitative' approaches to management – CBT and GET – which were assessed in the PACE trial have become the only forms of treatment for ME/CFS recommended by NICE (National Institute for Health and Clinical Excellence, 2011). At the same time, CBT and GET are consistently rejected by a substantial proportion of people with ME/CFS for being either ineffective (in the case of CBT) or harmful (in the case of GET).

This conflict over the management of ME/CFS largely dates back to a decision taken in the 1980s to rename and redefine what had previously been known as ME as CFS. By relaxing the diagnostic criteria, CFS brought in a much wider group of people who had some form of undiagnosed chronic fatigue that, in some cases, primarily involved psychological or psychiatric factors.

Based on a new and seriously flawed hypothesis that CFS was largely being maintained by abnormal illness beliefs and behaviours, along with inactivity and deconditioning, CBT and GET became the two main recommended forms of treatment in both the United Kingdom and the United States.

Prior to publication of the PACE trial results, a small number of clinical trials had supported the use of CBT and GET, almost all of which had been carried out by health professionals who promoted a psychosomatic model of causation and management. However, patient survey evidence, as collected by the ME Association (ME Association, 2015) along with most other patient surveys (Kindlon and Baldwin, 2015), told a very different story. The majority of people with ME/CFS consistently reported that CBT was ineffective. And around 50 per cent consistently reported that GET had made their condition worse.

The largest and most recent ME Association survey (ME Association, 2015) of patient evidence on the acceptability, efficacy and safety of CBT, GET and Pacing involved 1428 respondents. In this case, 73 per cent of respondents reported that CBT had no effect on their symptoms and 74 per cent reported that their symptoms were made worse by GET.

Surveys carried out by patient support groups have a number of limitations and these are listed in detail in section 6 of The ME Association survey results. In particular, it should be noted that people who belong to patient support groups, or use their websites, are going to produce a bias towards those who have been ill for a longer period of time and/or have a more severe form of illness. At the same time, those who have recovered, or have largely recovered, are less likely to belong to a support group or take part in surveys. So the respondents in these sort of surveys are not necessarily a representative sample of the whole ME/CFS population who have tried these therapies.

And while entry to this survey was on the basis of having a diagnosis of ME/CFS, we did not collect any clinical details or contact the health professional involved for confirmation.

So the PACE trial was essentially set up to provide robust evidence of both safety and efficacy for graded activity (i.e. GET), CBT and a modified version of pacing known as adaptive pacing. But PACE was a study that selected patients using a flawed diagnostic criteria (i.e. Oxford) and only assessed a limited number of subjective outcome measures focusing on fatigue and disability – a design that required strict vigilance in order to prevent the possibility of bias. Not surprisingly, PACE met with widespread criticism right from the very start.

The MEA argued that PACE was not taking account of the clinical heterogeneity of the illness and was ignoring the complex interaction between central (brain) and peripheral (muscle) factors in the causation of fatigue in ME/CFS.

With specific reference to graded exercise, muscle performance and the observation that exercise often makes symptoms worse, Brown et al. (2015) have used magnetic resonance spectroscopy to demonstrate that there are at least two muscle phenotypes involved in ME/CFS. This finding, along with other research evidence on abnormal exercise physiology (VanNess et al., 2003), that is not consistent with a deconditioning/inactivity model of causation, emphasises the need to fully characterise muscle phenotypes, as well as muscle biochemical abnormalities, before generically prescribing exercise as an effective intervention.

The MEA therefore argued that PACE was unlikely to tell us anything we did not already know from previous clinical trials involving CBT and GET. The charity also argued that PACE was a colossal waste of money that should be far better spent on much needed biomedical research – which the main funder of PACE, the Medical Research Council, had always been reluctant to do.

When the first PACE trial results were published (White et al., 2011), they once again failed to convince people with ME/CFS that CBT and GET were the most effective ways of managing everyone with mild or moderate ME/CFS.

But it was the follow-up paper on recovery in *Psychological Medicine* (White et al., 2013) – where it was claimed that CBT and GET led to 'recovery' in 22 per cent – that really intensified the debate into the methodology of the trial, the way recovery had been defined, and the manner in which the results were portrayed to clinicians, patients and the media. Key criticisms included the following:

1. Recovery figures were based on a definition of recovery that differed from that specified in the trial protocol. In fact, the final definition of recovery was so lax that on some criteria it was possible to score below the level required for entry to the trial, yet still be counted as 'recovered'.
2. Participants were not even asked whether they had recovered in relation to normal aspects of daily living.
3. Information on overall receipt of state sickness or disability benefits failed to support a recovery – with the PACE trial cost analysis study (McCrone et al., 2012) reporting: 'Receipt of benefits due to illness or disability increased slightly from baseline to follow-up'.
4. Information on return to some form of meaningful employment or education status was never sought. This was dismissed by the investigators as not being relevant.
5. Information on ability to mobilise failed to support a recovery. Overall results for all treatments relating to changes in the 6-minute walking test from baseline to 52 weeks did not represent a return to normal levels of activity. In fact, data for all the treatment groups at 52 weeks indicated that they were below the 402 m achieved by patients with class three heart failure. In addition, rejecting the use of electronic activity monitors meant no objective assessment of mobility was carried out.

The term 'recovery' implies a sustained return towards symptom-free health along with the ability to repeatedly and reliably participate in all aspects of normal life – employment, education, social activities and so on. Without this information, it was impossible to conclude that any of the patients in the PACE trial had usefully recovered.

Not surprisingly, criticism of the PACE trial continued and intensified. There was a debate in the House of Lords (UK House of Lords, 2013) and 36 academics and clinicians signed an open letter to *The Lancet* (ME Association, 2016) calling for an independent re-analysis of the data.

Several requests by academics, clinicians and patients asked for unpublished data to be made available so that it could be subjected to independent analysis. These demands were consistent with the growing acceptance by the scientific community that there should be far more transparency in clinical trials, including the sharing of data. The investigators refused to give way even when asked to do so by the Information Commissioner. Queen Mary University of London, which oversaw the trial, then spent almost £250,000 of public money on legal fees by taking the case to an appeal tribunal – which they lost.

When the unpublished PACE trial data was re-analysed by Wilshire et al. (2017), the authors found that if recovery was defined according to the original trial protocol, recovery rates in the CBT and GET groups were low and not significantly higher than in the control group (4%, 7% and 3%, respectively). The authors concluded, *The claim that patients can recover as a result of CBT and GET is not justified by the data, and is highly misleading to clinicians and patients considering these treatments.*

I conclude with some observations on what we can learn from the mistakes of the PACE trial. Because if lessons are not learned, distrust of the medical and scientific community by the people with ME/CFS will only continue and intensify.

This is not an argument with psychiatry. Mental and physical illness are equally real and horrible. As with any long-term illness, some people with ME/CFS will develop comorbid depression and other mental health problems – where CBT can be of help alongside good quality general management. The argument here is with a flawed model of causation assuming efficacy for CBT and GET while taking no significant account of varying clinical presentations and disease pathways.

First, on behalf of all the journals that have so far published 16 papers from the trial, *The Lancet* must now set up an independent re-analysis of the PACE trial data, along with appropriate sensitivity analysis. This re-analysis should be carried out by well respected independent reviewers with expertise in statistics and study design. If any results are found to be significantly inaccurate or unreliable, the possibility of a retraction will have to be considered.

Second, if a drug treatment was found to be making a significant proportion of people worse, as is the case with patient evidence relating to the use of GET, the treatment would be withdrawn and would not form part of a NICE recommendation. As there is now both consistent and extensive patient evidence relating to the harmful effects of GET, the NICE guideline recommendation on GET must be reviewed as a matter of urgency. The generic prescribing of progressive and inflexible exercise programmes is not an acceptable form of treatment for people with ME/CFS.

Third, the enormous amount of public money spent by the Medical Research Council and Department of Work and Pensions on funding the PACE trial, along with legal costs met by Queen Mary University of London in appealing against the Freedom of Information requests, merits a formal inquiry, possibly at a parliamentary level.

Finally, there is a desperate need for clinical trials of activity management that examine the heterogeneity of ME/CFS, the fact that underlying disease processes involve both central and peripheral fatigue, and the consistent evidence from patients that inflexible or progressive exercise programmes aggravate symptoms in the majority of patients who come under the ME/CFS umbrella.

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Commentary

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PACE-GATE: An alternative view on a study with a poor trial protocol

Bart Stouten

Abstract

The controversies surrounding the effectiveness of cognitive behavioural therapy and graded exercise therapy for chronic fatigue syndrome are explained using Cohen's *d* effect sizes rather than arbitrary thresholds for 'success'. This article shows that the treatment effects vanish when switching to objective outcomes. The preference for subjective outcomes by the PACE trial team leads to false hope. This article provides a more realistic view, which will help patients and their doctors to evaluate the pros and cons.

Keywords

chronic fatigue syndrome, cognitive behaviour therapy, effectiveness, graded exercise therapy, randomized controlled trial, treatment

The 'PACE-gate' editorial by Geraghty and the subsequent response by White et al. (Geraghty, 2016; White et al., 2017) made me smile and shake my head at the same time. White et al. (2007, 2011) deviated substantially from the trial protocol of their randomized controlled study on treatments for chronic fatigue syndrome (CFS). Geraghty argued that therefore the effects of cognitive behavioural therapy (CBT) and graded exercise therapy (GET) were overstated by the authors and in the press. These therapies were not curative and should be downgraded to adjunct support-level status. White et al. (2017) responded that Geraghty's views are based on 'misunderstandings and misrepresentations', which they would 'correct'.

In my opinion, White et al. have failed to show that Geraghty is wrong. They provided additional information on their trial and decisions and repeated their findings that CBT and GET are more effective than specialist medical care (SMC). They defended the use of these therapies with arguments based on a series of false dilemmas: treatments are either effective or ineffective; the result is either black or white; the opponents are wrong and they are right. Unfortunately, they have not shown *how* effective CBT and GET are. I believe this is the crucial point in the debate between Geraghty and White et al. Let us consider the shades of grey by studying Cohen's *d* effect sizes.

Effect sizes

I was not able to find the statistics behind the effect sizes that White et al. (2017) have reported in their response to Geraghty. Therefore, I recomputed Cohen's *d* from data in their *Lancet*

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Table 1. Treatment effect size for CBT and GET versus SMC after 12 months.

	CBT	GET	SMC	Cohen's *d* treatment effect size	
				CBT versus SMC	GET versus SMC
Fatigue	20.3 (8.0); *n* = 148	20.6 (7.5); *n* = 154	23.8 (6.6); *n* = 152	0.48	0.45
Physical functioning	58.2 (24.1); *n* = 148	57.7 (26.5); *n* = 154	50.8 (24.7); *n* = 152	0.30	0.27
6-minute walking test	354 (106); *n* = 123	379 (100); *n* = 110	348 (108); *n* = 118	0.06	0.30

The treatment effect size is computed as the difference between treatments at 12 months, divided by their pooled standard deviation. See the Online Appendix for the calculations.

article, comparing CBT and GET versus SMC (White et al., 2011).

The first issue I addressed was whether to calculate the effect sizes from the primary outcome variables described in the trial protocol (White et al., 2007) or from the primary outcome variables published in the final article (White et al., 2011). The trial protocol has received criticism since its publication, for example, in the online comment section accompanying that document. Given that White et al. have abandoned it themselves, it appears that neither the authors nor others have shown faith in the primary outcome variables defined in the trial protocol. I believe that some commentators, such as Geraghty, considered the trial protocol not because they actually supported it, but because they wanted to show the consequences of White et al.'s faux-pas to redefine outcomes during the trial.

White et al.'s primary outcome variables were subjective fatigue and subjective physical functioning after 12 months. The trial protocol prescribed a 0011 coding scheme for the first primary outcome, which is the score on the Chalder fatigue scale, yet the authors switched to a 0123 coding scheme in the final article. My opinion is that, regardless of the coding scheme, the Chalder fatigue scale should be abandoned as a primary outcome. I refer the reader to my letter and its pre-publication history for more information (Stouten, 2005). For pragmatic reasons, I decided to use the 0123 coding scheme in my effect size analysis: the data are readily available from White et al., and it produces more precise results for fatigue than the 0011 scheme.

The other primary outcome, subjective physical functioning, was measured using the physical functioning subscale of the Short Form 36. For this scale, there was no difference in scoring method between the trial protocol and final publication.

Table 1 shows the effect of CBT and GET compared to SMC on the primary outcomes after 12 months. Cohen's *d* varies between 0.45 and 0.48 for subjective fatigue and between 0.27 and 0.30 for subjective physical functioning. This indicates that the additional benefits of CBT and GET over SMC vary between small and medium, which contrasts with the positive stories in the press.

The more objective the outcome, the worse the result for CBT and GET

Questionnaires that assess fatigue require the patient to rate subjective experiences, such as feeling tired, feeling weak and having not enough energy. In contrast, questionnaires assessing physical functioning ask the patient to estimate the ability to perform objective physical activities, such as dressing oneself, climbing the stairs and going for a walk. Consequently, the outcome of a questionnaire for physical functioning

represents a more objective quantity than the outcome of a questionnaire for fatigue. As Table 1 shows, CBT and GET resulted in smaller effect sizes for physical functioning than fatigue. This leads to the interesting hypothesis that the effect size of CBT and GET reduces as the objectiveness of the outcome increases.

To investigate this hypothesis, I added to the analysis the only objective test which I could find in White et al.'s study: the distance covered in a 6-minute walking test after 12 months. Table 1 shows the effect sizes. For GET, there was no difference in the results when using the data from the objective test of physical functioning. In other words, there was a small positive effect favouring GET over SMC. For CBT, the beneficial effect over SMC vanished when using the objective outcome measure. In other words, though patients *think* they are able to walk more after CBT, they *fail to actually do so*.

This is not the only case

The above analysis of the White et al. study shows that the effects of CBT and GET are affected by the objectiveness of the primary outcomes used in the trial protocol and in the final publication. To see how this relates to other CFS studies, I examined three other cases where the trial protocol has been questioned, namely, the randomized controlled trials by Prins et al. (2001), Stulemeijer et al. (2004) and Wearden et al. (2010a). The first was published in the *Lancet*, the latter two in the *British Medical Journal*.

Prins et al. initially proposed a multi-dimensional assessment system, including objective physical activity, as the primary outcome when they applied for funding (Van Essen and De Winter, 2002). Guided by the reviewers' comments of the funding source, they subsequently replaced the multi-dimensional assessment by measures for subjective fatigue and subjective physical functioning only, therefore omitting objective measurements as a primary outcome. This decision was made before the start of the trial. In their final article, Prins et al. showed that, after 14 months, CBT was significantly more effective than natural course (receiving treatment as usual without CBT) in improving subjective fatigue and subjective functional impairment. When they retrospectively analysed the data from the actometer, the device worn on the ankle to provide an objective measure for physical activity, the result after 14 months is not statistically significant (Wiborg et al., 2010).

Stulemeijer et al. studied the effects of CBT on subjective fatigue, subjective functional impairment and school attendance in young people with CFS. Their control group consisted of patients on a waiting list for receiving CBT. To deal with issues around missing data, they carried forward the last observations for all variables, except for school attendance. Their rapid response reveals that the final choice of the method for analysing school attendance was made after inspecting the trial data (Stulemeijer et al., 2005). This suggests that their analysis was not in line with the trial protocol. If they had carried forward the last observations for the missing school attendance data too, the results for CBT would have shown that it was not an effective treatment for this primary outcome (Stouten, 2004).

In contrast, Wearden et al. adhered to their trial protocol and used the 0011 coding scheme for the Chalder fatigue scale. They concluded that pragmatic rehabilitation delivered by trained nurses did not significantly improve subjective fatigue for adult CFS at 1-year follow-up compared to treatment as usual by the general practitioner (GP). After publication, the authors agreed that, according to my suggestion, recoding the Chalder fatigue scale from 0011 to 0123 gives more precise results (Stouten, 2010; Wearden et al., 2010b). Wearden et al. (2010b) subsequently demonstrated a modest improvement in fatigue that is statistically significant in favour of pragmatic rehabilitation.

To further investigate the hypothesis that objective data produce less favourable results for CBT, I computed the treatment effects for the aforementioned studies by Prins et al. (2001), Stulemeijer et al. (2004) and White et al. (2011), see the Online Appendix. The

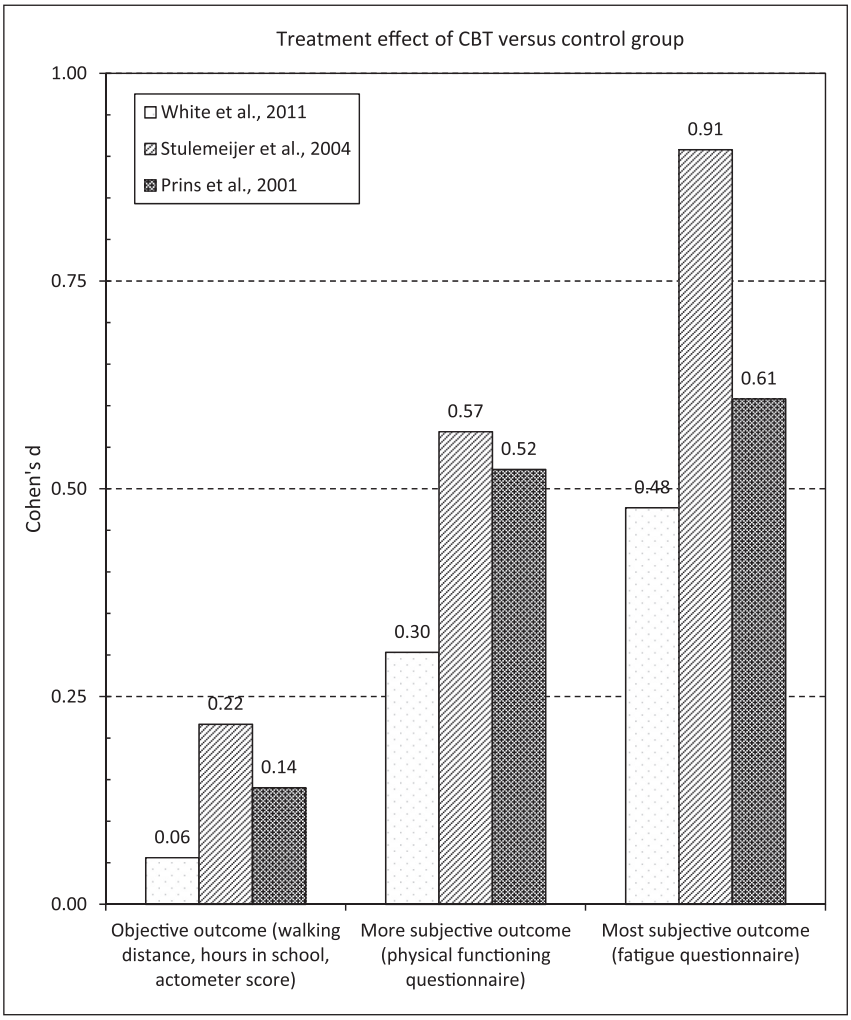

Figure 1. Effectiveness of CBT versus objectivity of the outcome measure.

results in Figure 1 show that the effect sizes of CBT with respect to the control groups are the smallest for objective measures of physical functioning. When the subjectiveness of the outcomes increase, the effect sizes increase to medium and even large.

Conclusion: where to go from here?

The results above lead me to conclude that White et al. systematically overestimate the effectiveness of CBT because they focus on subjective rather than objective outcomes. Their vigorous defence of their findings gives me the impression that they are not open to constructive criticism. This understanding is strengthened by their statement that Geraghty misunderstands and misrepresents their work, without providing sound evidence. I would appreciate a more constructive debate, where they attempt to understand why others do not share their views, and subsequently advance findings in this field in a more scientific way. Given the evidence that the objective improvements reported for CBT and GET are at most

modest, I agree with Geraghty that these should be downgraded to adjunct support-level status.

I presented three other cases where the trial protocols have been questioned. In the first example, the trial protocol was influenced by reviewers of the funding source. In the second example, the final analysis seems inconsistent with the trial protocol. In the third example, the authors agreed after publication of the final analysis that it would have been better to use a different coding scheme for the primary outcome. I believe that issues with a poor trial protocol cannot be solved within a study. Changing the protocol during the study is regarded as a faux-pas. On the other hand, continuing with a poor trial protocol is not helpful either. We have to await meta-studies for the final verdict, since these are allowed to deviate from the protocols of individual studies, and choose primary outcomes on their own.

We are living in the era of Internet and big data, where information is more accessible than ever before. It is refreshing to see patients asking critical questions and claim access to data that are generated by publicly funded studies. I hope they will use parts of my contribution to further investigate PACE-gate and other CFS studies. I admire their perseverance and look forward to see their upcoming publications.

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The PACE trial: It's time to broaden perceptions and move on

Keith J Petrie[1] and John Weinman[2]

Abstract

The continued critiques of the PACE trial highlight how differing beliefs about the causes of chronic fatigue syndrome still influence how scientific studies in this area are accepted and evaluated. Causal beliefs about chronic fatigue syndrome and a modern version of Cartesian dualism are important in understanding the reaction to the PACE trial. The continued debate on the PACE trial seems to miss the fact that science is incremental. An unfortunate outcome of the PACE controversy and intimidation of researchers may be less research in the area. It is time to move on from criticism and collect more data on effective treatments.

Keywords

cause, chronic fatigue syndrome, cognitive behaviour therapy, graded exercise therapy, illness perception

The controversy over the PACE trial (White et al., 2011) including the recent critique by Geraghty (2016) highlights how differing beliefs about the causes of chronic fatigue syndrome (CFS) still influence how scientific studies in this area are accepted and evaluated. The PACE trial was started in 2005 and the trial was published in *The Lancet* 6 years ago. The study's findings that cognitive behaviour therapy and graded exercise can moderately improve outcome in CFS created a storm of criticism led mainly from patient groups attacking the study's findings (*The Lancet*, 2011) and even the researchers themselves (Hawkes, 2011; *The Guardian*, 2011).

The criticism over the past 6 years has continued and include the recent critique by Geraghty (2016) who has strongly challenged the study's findings. He has criticised the PACE trial for their reporting of treatment effectiveness, the definition of recovery and for the fact that the data are not freely available. These issues and other points raised have been responded to by the PACE authors in detail in this journal (White et al., 2016). They have also previously answered a number of similar rounds of critiques (Sharpe et al., 2016; Wessely, 2015; White et al., 2016).

The reactions to a trial that identified helpful treatments for a chronic and severely disabling condition contrast markedly with other physical illnesses and highlight the suspicion of patients with CFS towards any psychological interventions for CFS. In our experience as health psychologists, patients with other illnesses such as cancer, renal disease, heart disease or chronic respiratory problems are usually very keen to adopt psychological interventions that can

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reduce fatigue, improve functioning and well-being. Indeed for these disorders a common complaint is that psychological support and interventions are not readily available.

Patient beliefs about CFS and in particular causal beliefs about the illness are clearly important in understanding the reaction to the PACE trial. As Geraghty (2016) states in the conclusion to his critique: 'Many CFS patients reject the theoretical rationale for the use of CBT and GET. PACE-Gate exposes the long-running acrimony between doctors and patient groups over the cause of the illness and the most appropriate approaches to treatment' (p. 6). This is really the key issue behind the criticisms of the PACE study and antagonism towards the study's authors. There is a strong resistance by some people who have CFS to any psychological interpretations or interventions, which are at variance with the way they view their illness.

Causal beliefs are an important factor in the way patients understand their illness. Causal beliefs provide a basis for patients to understand how their illness developed and, most importantly, these beliefs point towards treatments that make sense for controlling the condition (Petrie and Weinman, 2012). Common causal beliefs held by CFS patients highlight a viral explanation for the illness or personal susceptibility to developing CFS through a weakened immune system. These causal beliefs tend to point patients towards looking for biological therapies that can control the virus responsible or bolster personal immunity. Other forms of treatment do not fit so comfortably into the patient's view of their illness. Psychological interventions and graded exercise especially contrast with these beliefs. The use of exercise when someone feels fatigued is counterintuitive to the common sense model of CFS. Exercise and psychological therapies may also highlight for patients their experiences of stigma they have felt from other people's responses or explanations for their condition.

Another aspect of people's causal beliefs about illness is that they often demonstrate a modern-day version of Cartesian dualism and a rather crude division between mind and body. Thus, for the same illness, people may believe strongly in either a physical or a psychological cause, sometimes in a rather simplistic way. In reality, most diseases are caused and perpetuated by a complex mix of behavioural and physical factors and hence will be best managed by a range of treatments (e.g. lifestyle change, self-management and medication). A failure to appreciate this may inevitably result in sub-optimal management and poorer outcome.

Geraghty (2016) comments that the majority of patients with CFS are pragmatic and aware of the lack of an agreed cause for their condition but then cites Green et al. (2015) that 'an increasing amount of research points to immune and cellular alterations as important clues'. However, the Green et al. paper is not an overview of the evidence base but a set of recommendations from a working group on key directions for future research, including the need for biologically based studies as well as more treatment trials.

The continued debate on the PACE trial seems to miss the fact that science is incremental. One study rarely has all the answers, especially for a heterogeneous and complex condition such as CFS. Over time more research is published and greater clarity emerges from the evidence on whether there is support for these treatments. The important issue is whether CBT and graded exercise improve the lives of patients with CFS.

Currently, the weight of evidence would seem to support these treatments. A recent Cochrane review of exercise therapy for CFS, which included eight studies and data from 1581 participants, concluded that 'patients with CFS may generally benefit and feel less fatigue following exercise therapy and found no evidence that exercise therapy may worsen outcomes'. The PACE study provides important evidence that CBT may be a useful treatment option for patients with CFS but clearly more good quality research is needed. A recent review of cancer-related fatigue also found that exercise and psychological interventions, and both used in combination, were effective, and

recommended that clinicians should prescribe exercise and psychological therapy for cancer-related fatigue (Mustian et al., 2017).

The unfortunate outcome of the continued controversy about the PACE trial and intimidation of researchers in the CFS field has increased the likelihood of deterring quality researchers from working in the area. Who would want to set up a scientific base camp in an area where you will get continuously attacked should your research findings or clinical trials support an unpopular treatment? The opportunity cost of continuous criticism of the PACE trial over 6 years ago is likely to be a considerable reduction in researchers wanting to research to further understand CFS or do further treatment trials.

There is so much more research work to do in CFS. As well as finding out what treatments work best with what types of illness, how treatments are best delivered with new mobile technologies and via the Internet and how existing treatments can be improved to reduce the morbidity from this disabling condition. The PACE trial has made a start. It is time to move on and time for researchers to continue adding to the evidence base in order to increase our understanding of the condition and the most effective treatments.

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Defense of the PACE trial is based on argumentation fallacies

Steven Lubet

Abstract

In defense of the PACE trial, Petrie and Weinman employ a series of misleading or fallacious argumentation techniques, including circularity, blaming the victim, bait and switch, non-sequitur, setting up a straw person, guilt by association, red herring, and the parade of horribles. These are described and explained.

Keywords

beliefs, chronic fatigue syndrome, health beliefs, myalgic encephalomyelitis/chronic fatigue syndrome, PACE trial

Petrie and Weinman (2017) devote fewer than three pages to their defense of the PACE trial, but they nonetheless manage to employ a virtual catalog of misleading or fallacious argumentation techniques. These include circularity, blaming the victim, bait and switch, non-sequitur, setting up a straw person, guilt by association, red herring, and the parade of horribles. Sometimes they engage multiple fallacies in a single paragraph, as I shall explain seriatim.

Circularity

A circular argument assumes or incorporates the desired answer in the premise of the question itself. Petrie and Weinman engage in circular reasoning when they begin with the statement that "differing beliefs about the causes of chronic fatigue syndrome (CFS) still influence how scientific studies in this area are accepted and evaluated." They offer no proof for this assertion, although they revert to it repeatedly throughout the paper, claiming, for example, that "this is really the key issue behind the criticisms of the PACE study" and "causal beliefs are an important factor in the way patients understand their illness" (citing only themselves for the latter proposition). As with any study, the PACE trial can be made self-evidently impressive if one begins by assuming the validity of its conclusions. The very point of contention regarding the PACE trial, however, is whether or not myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) symptoms are the product of patients' "unhelpful" or "dysfunctional" illness beliefs. This is the longstanding theory of White, Chalder, and Wessely (Wessely et al., 1996, 1989; White et al., 2011), but it has been disputed by many others and it has been flatly rejected in a report by the US Institute of Medicine (IOM (now the Academy of Medicine), 2015). Disagreement is fair play in scholarly discussion, but eliding contrary research is not.

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Blaming the victim

Petrie and Weinman express puzzlement at patients' resistance to cognitive behavioral therapy (CBT) and graded exercise therapy (GET), noting that "In our experience as health psychologists, patients with other diseases such as cancer, renal disease, heart disease or chronic respiratory problems are usually very keen to adopt psychological interventions that can reduce fatigue, improve functioning and well-being." The implication is that there must be something wrong with ME/CFS patients, or some flaw in their belief systems, given their deviation from the behavior of patients with other illnesses. It must be their own fault if ME/CFS patients do not find CBT and GET beneficial, given how much the therapies are appreciated by everyone else. Entirely missing from the discussion is the reason that ME/CFS patients part ways from those with cancer or renal failure. Petrie and Weinman assert that the difference is solely attributable to correctable "beliefs," while failing to consider that it instead lies in the actual experience of ME/CFS patients.

Bait and switch

Continuing the cancer comparison, Petrie and Weinman also inform us that "A recent review of cancer-related fatigue also found that exercise and psychological interventions, and both used in combination, were effective and recommended that clinicians should prescribe exercise and psychological therapy for cancer related fatigue." This is an example of the bait and switch. The premise of the PACE trial, as Petrie and Weinman never acknowledge, was that ME/CFS is "reversible" through CBT and GET (White et al., 2011). In fact, the PACE investigators claimed that CBT and GET achieved ME/CFS "recovery" rates of 22 per cent (White et al., 2013). No reputable physician would claim that cancer is reversible through exercise and psychotherapy, much less boast about subsequent recovery rates. Thus, the experience of palliating cancer—or renal disease, or heart disease—with psychological interventions has no bearing on ME/CFS or the validity of the PACE trial (Wilshire, et al, 2016).

Non-sequitur

"Most diseases are caused and perpetuated by a complex mix of behavioural and physical factors," explain Petrie and Weinman, "and hence will be best managed by a range of treatments (e.g. lifestyle change, self-management and medication)." This statement is either trivial, in that all illnesses may benefit from a range of treatments, or a non-sequitur, in that it treats physical causation and behavioral perpetuation as though they are comparable when, in fact, they are often distinct phenomena. There is no doubt, for example, that the disability of a broken leg may be "perpetuated" by sub-optimal behavior and poor self-management, but that does not tell us anything about the underlying physical nature of the injury. In other words, the jump from perpetuation to causation is a non-sequitur.

Straw person

"The use of exercise when someone feels fatigued is counterintuitive to the common sense model of CFS," say Petrie and Weinman, suggesting that patient objections to GET are merely intuitive or perhaps even a "modern-day version of Cartesian dualism and a rather crude division between mind and body." Here, they are wrestling with a straw person, as they are setting up arguments—none of which have ever been made—solely for the purpose of refuting them. Critics of the PACE trial do not rely on intuition and do not indulge Cartesian dualism either crudely or otherwise. Rather, patients report having attempted exercise only to experience devastating relapses or crashes (Brea, 2017; Tuller, 2016). Although one would not know it from the Petrie and Weinman paper, the US Institute of Medicine (now the Academy of Medicine) has concluded that exertion intolerance is the defining characteristic of ME/CFS and has even proposed changing the name of the illness to Systemic Exertion Intolerance

Disease (Institute of Medicine, 2015). Needless to say, the IOM report was not based on intuition or mind-body dualism.

Guilt by association

The JHP special section on ME/CFS was initiated by Geraghty's (2016) very measured and thoughtful paper detailing the documented shortcomings of the PACE trial. Nonetheless, Petrie and Weinman seek to tarnish his (and others') criticism by invoking attacks on "the researchers themselves" and bemoaning the "intimidation of researchers in the CFS field." Geraghty and other PACE critics—such as the contributors to this special section—have neither attacked nor intimidated anyone. Although such deplorable behavior has evidently occurred (which I will address in the next section), it cannot be attributed to serious academic and professional critics of the PACE trial, who now number over 100 (Ablashi et al., 2017), and there is no point in bringing it up other than to impute guilt by association.

Red herring

In any case, the story of researcher intimidation is a red herring—an argument that serves only as a distraction from a relevant or important issue. In support of their claim, Petrie and Weinman cite two reports from 2011, both of which detail complaints of harassment by PACE and other ME/CFS researchers. I understand from other sources and private correspondence that certain ME/CFS researchers have been on the receiving end of extremely disturbing phone calls and emails, although not within the past several years. There is no excuse for such behavior, which must be condemned by all concerned. But what could be the point of raising it in a response to Geraghty's critique of PACE, which is completely unrelated to any sort of threats or provocations? Moreover, Petrie and Weinman do not tell us that the broadest allegations of harassment were rejected in a 2016 judicial ruling that ordered the PACE team to disclose their underlying research results pursuant to a Freedom of Information request. The First Tier Tribunal (2016) found that the stories of threats against the PACE investigators were "grossly exaggerated and the only actual evidence was that an individual at a seminar had heckled" one of them. Overstated reports of years-old events are a classic red herring that does nothing other than divert attention from serious criticism.

Parade of horribles

Following the overstated claim of attacks on the PACE investigators, Petrie and Weinman warn that "intimidation of researchers in the CFS field has increased the likelihood of deterring quality researchers from working in the area." What's more, "The opportunity cost of continuous criticism of the PACE trial over 6 years is likely to be a considerable reduction in researchers wanting to research to further understand CFS or do further treatment trials." These dire predictions would certainly be troubling if accurate. Fortunately, they are imaginary. First, as noted by the First Tier Tribunal, the PACE investigators and their supporters have themselves continued to research in the field, which alone brings Petrie and Weinberg's parade of horribles to a halt (e.g. Center for Child and Adolescent Health, 2017a, 2017b; Crawley, 2017; Herberholz et al., 2014; Janse et al., 2015; ME Research, 2016). More importantly, we are now in a virtual golden age of ME/CFS research. One can only wonder how Petrie and Weinman could be so unaware of the extensive biomedical research currently being conducted at Columbia University (e.g. Nagy-Szakal et al., 2017), Stanford University (e.g. Maxmen, 2017), and other medical schools in the United States (Naviaux, et al, 2016), as well as at research centers in Australia (e.g. Armstrong et al., 2017; Nguyen et al., 2016), Norway (e.g. Fluge et al., 2016), and Japan (e.g. Nakatomi et al., 2014). The truth is that criticism of the PACE trial has actually spurred research on potential biomarkers and biomedical causes of ME/CFS, which had previously been neglected for decades.

Conclusion

Petrie and Weinman are deeply committed to their "belief-driven" theory illness and recovery. Although not mentioned in their paper, Petrie and Weinman appear to be the only two members of the "health advisory team" of a company called Atlantic Healthcare, which promotes a "Belief-driven Behavior Change approach" that is marketed to "healthcare providers, public health systems, insurers and pharmaceutical companies." According to its website, the company works with "insurers to improve health and wellbeing and reduce the cost of care" (Atlantis Healthcare, 2017). While I do not question the sincerity of Petrie and Weinman's faith in their theory, and it is not unusual for academics to consult with industry, the relationship with Atlantis Healthcare is relevant to their paper and should have been included in their declaration of conflicting interests.

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Commentary

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Chronic fatigue syndrome patients have no reason to accept the PACE trial results: Response to Keith J Petrie and John Weinman

Susanna Agardy

Abstract

Petrie and Weinman urge chronic fatigue syndrome patients to move on from their beliefs about their illness and accept the findings of thePACE trial. This is unreasonable in view of the failure of PACE to achieve evidence of recovery through cognitive behaviour therapy and graded exercise therapy in either self-reports or the objective measure of the 6-minute walking test. Contrary to their suggestion, the Institute of Medicine describes chronic fatigue syndrome not as psychological but as a serious, chronic, systemic disease, with post-exertional malaise as its main feature which inhibits exercise. Linking debate about PACE with intimidation of researchers is unjustifiable and damaging to patients.

Keywords

beliefs, chronic fatigue syndrome, cognitive behaviour therapy, exercise behaviour, graded exercise, graded exercise therapy, myalgic encephalomyelitis, narratives, physical activity

Petrie and Weinman are much occupied with chronic fatigue syndrome (CFS) patients' beliefs about their illness and the PACE trial (White et al., 2011). Instead, they need to occupy themselves with evidence.

Release of the raw data used in the PACE trial showed that the proportions of patients that would qualify as 'recovered' on the investigators' revised definition was significantly higher than they would have been had they used the original definition of their protocol.(Wilshire et al., 2016) Using the original definition, Wilshire et al. (2016) found that recovery rates dropped from 22 to 7 per cent in the cognitive behaviour therapy (CBT) group, from 22 to 4 per cent in the graded exercise therapy (GET) group and 7 to 3 per cent in the Control (no therapy) group. These results are based on patient self-reports.

The findings of the objective measure of the 6-Minute Walking Test are not included in the definition of recovery. After 52 weeks of treatment, there was no improvement in the CBT group. GET produced a mean walking distance of 379 m, a gain of 67 m, 35 m more than the no special treatment group (White et al., 2011). This is less than the 402 m walked by older patients with Class III heart failure in another study (Lipkin et al., 1986). At the 52-week walking test, the investigators still had '… concerns about patients with CFS coping with physical exertion …', so that no encouragement

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was given to participants to walk faster, 'by contrast to the way this test is usually applied'. There is also an unexplained 28 per cent missing data for this part of the PACE trial (White et al., 2013a).

While claiming some success for the self-reported measures of recovery, the investigators state that 'Objective measures of physical activity have been found previously to correlate poorly with self-reported outcomes' (White et al., 2013b). Indeed, taking the lower bound of normal walking distance walked as 589 m, Wilshire et al. (2017) found that

> None of the patients in the CBT, GET or Control groups who qualified as 'recovered' achieved a walking distance that approached this lower bound even after a whole year – irrespective of whether the protocol-specified or the revised definition of recovery is used.

The CBT and GET treatments in PACE were based on the layered assumption that patients were merely deconditioned and that the deconditioning was due to assumed fear beliefs about exercise. It is implied that these beliefs are misguided (White et al., 2011). The investigators expected the reversal of the condition following CBT and GET treatments. The expected reversal did not eventuate (White et al., 2011). These results warrant the rejection of the hypothesis of deconditioning. They also demonstrate that the attempt to alter patient beliefs with CBT did not significantly improve physical function. Yet, these are the results patients are urged, unreasonably, to accept. They are urged to accept a psychological explanation of their condition and deny their own lived experience which often includes worsening of their condition following these treatments, as explained by Kindlon (2017: 5–6) and Vink (2017: 7).

While suggesting that CFS patients would benefit from psychological treatment, Petrie and Weinman (2017) ignore the conclusions of the Institute of Medicine (IOM) which '… stresses that SEID (Systemic Exertion Intolerance Disease) is a medical – not a psychiatric or psychological – illness' (Institute of Medicine (IOM), 2015a). The Institute further states that the condition '… is a serious, chronic, and systemic disease that frequently and dramatically limits the activities of affected patients' (IOM, 2015b: 5). As a result of the serious impact of activity on CFS patients, the Institute recommended renaming post-exertional malaise (PEM) to Systemic Exertion Intolerance Disease (IOM, 2015b: 11). It further concluded, 'There is sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS from other conditions' (IOM, 2015b: 86). Thus, it cannot be assumed that the recognised health benefits of physical activity for the general population and for other diseases such as cancer can be automatically applied to CFS patients.

The authors' claim in relation to the scientific value of PACE, that 'science is incremental' misses the requirement of rigour and quality in any study which is capable of adding to knowledge. The request for the retraction of the PACE report due to 'major flaws' by more than 100 scientists makes it clear that this trial is widely thought to be lacking in these requirements (Ablashi et al., 2017).

The most offensive claim of this article is, 'The unfortunate outcome of the continued controversy about the PACE trial and intimidation of researchers in the CFS field has increased the likelihood of deterring quality researchers from working in the area'. First, there is no justification for linking legitimate critical debate about PACE with 'intimidation of researchers'. Second, this claim is being repeated in spite of the fact that this issue has been addressed at the First Tier Tribunal appeal (HMTS et al., 2016) which directed the PACE investigators to release the raw data to the applicants. At that Tribunal, a statement by one witness about "…'young men, borderline sociopathic or psychopathic' attaching themselves to the PACE trial criticism" were considered to be 'wild speculations' which 'do him no credit'. In addition, when questioned about threats to researchers, Professor Chalder, a member of the PACE research team, accepted that while unpleasant things had been said, '… no threats have been made either to researchers or participants' (HMTS et al., 2016: 36).

This claim,. suggesting that research into CFS is fraught with intimidation, is being promulgated even though it has failed to withstand scrutiny in the legal setting of the Tribunal. It can have the effect of smearing and damaging CFS patients in general. Withdrawal of this claim and an apology to the patient community would be appropriate.

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Commentary

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Further commentary on the PACE trial: Biased methods and unreliable outcomes

Keith J Geraghty

Abstract

Geraghty in the year 2016, outlines a range of controversies surrounding publication of results from the PACE trial and discusses a freedom of information case brought by a patient refused access to data from the trial. The PACE authors offer a response, writing 'Dr Geraghty's views are based on misunderstandings and misrepresentations of the PACE trial'. This article draws on expert commentaries to further detail the critical methodological failures and biases identified in the PACE trial, which undermine the reliability and credibility of the major findings to emerge from this trial.

Keywords

clinical trial, cognitive behaviour therapy, evidence, myalgic encephalomyelitis/chronic fatigue syndrome, theory

Trial management

Edwards (2017) notes that PACE is an unblinded trial (for participants and perhaps researchers), each treatment did not have a comparable placebo/control and there are clear biases in how treatments were administered: for example, occupational therapists (OTs) provided an adapted pacing therapy (APT) that is not a formal treatment used by OTs, but a model of pacing crafted by PACE authors; while cognitive behavioural therapy (CBT) therapists provided a familiar therapy, CBT. Goudsmit et al. (2017) affirm that the version of 'pacing' administered in PACE does not reflect the type of pacing patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) undertake. This is a critical point. Participants in CBT, graded exercise therapy (GET), standard medical care (SMC) and APT were given starkly different treatments, not the same treatment compared with a blind 'sugar pill' placebo. Offering different treatments, and using different types of therapists, induces so much 'variability', it breaks a fundamental tenet of a randomised controlled trial (RCT), which is to standardise procedures and observe variance in outcomes between cases and controls. Contamination occurred in this trial by allowing therapists from all arms (APT, CBT, GET) to communicate with each other about how patients

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were doing in each group, in fact the trial manual encouraged it (PACE Trial APT Manual, Queen Mary University of London (QMUL), 2016), and the lead authors issued material to participants and therapists mid-trial hinting that the CBT and GET groups were doing better.

White et al. (2017) suggest Geraghty (2016) did not specify the trial procedures that were neglected or bypassed in PACE. For clarity, these are (1) altering outcome measures mid-trial with poor justification; (2) sending newsletters to participants mid-trial, reporting the positive progress of CBT and GET participants (contaminating the trial); (3) not altering the inclusion criteria for entry into the trial after the main outcomes measures were lowered – meaning 13 per cent met some of the criteria needed to be deemed recovered at trial entry point; and (4) not informing participants of certain conflicts of interest the lead authors hold (detailed below). The PACE authors point out that their trial had oversight from an ethics committee, an independent trial steering committee and data monitoring ethics committee; and all publications from the trial were peer reviewed. This begs the question how were such procedural anomalies accepted by these oversight bodies? The trial team have not supplied details of communications with each oversight body, thus some uncertainties remain about how and when changes were made and approved.

Data access case and patient community response

White et al. (2017) write, 'We reject the accusation that our "actions have arguably caused distress to patients," for which Dr Geraghty offers no evidence'. However, patients have expressed anger concerning the actions of the PACE trial team in relation to the trial and a freedom of information case brought by one patient (Mr Matthees) denied access to data from PACE. Peter White's (lead investigator) host, QMUL, assembled a legal team at a cost of over £220,000, to challenge Mr Matthees' right to access data from the trial. This action caused consternation among the patient community. The European ME Alliance called for release of data from PACE (ME Action, 2016), over 12,000 people signed a petition (ME Action, 2017) and a letter with over 120 signatures from scientists and patient organisations has called on a journal to retract a PACE recovery paper (Sharpe et al., 2015); while a similar letter has called on the *Lancet* to independently verify the PACE trial's evidence (Tuller, 2017).

The PACE authors assert that patients want CBT and GET, that 65 per cent of respondents want CBT and 45 per cent want GET available in the National Health Service (NHS; citing a patient survey, Action for ME, 2011). What the PACE authors do not quote from the same survey is that 93 per cent of respondents said they want fatigue or condition management, 94 per cent want medication for sleep and pain and 90 per cent want pacing treatments. Pacing, the approach the PACE authors suggest is an inferior treatment, actually has a much higher approval rating than CBT or GET. Kirke (2017) highlights a mass of patient survey evidence the PACE authors fail to reference. In a large survey conducted by the ME Association (MEA, 2015), 84 per cent of respondents rated pacing as appropriate to their needs, 44 per cent CBT and just 22 per cent GET. In the same survey, CBT resulted in 91 per cent of participants feeling their ME/CFS symptoms were unaffected or made worse and 74 per cent of patients reported that GET made their symptoms worse. Kindlon (2017) notes that outside the confines of highly controlled clinical trials, patients continually report significant negative outcomes after taking GET. Laws (2017) points out that evidence from clinical trials is given more credence than patient surveys, even if patients report negative outcomes, with harms inadequately studied in clinical trials and in clinical practice.

Conflicts of interest

Geraghty (2016) raises a view that in large clinical trials, such as the PACE trial, whereby millions of pounds of tax payers' money is being spent on testing the efficacy of treatments that could potentially shape health policy and clinical

practice, funders should look to involve the most 'independent-minded' assessors as is feasibly possible. The PACE authors write '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"' (White et al., 2017). Tuller (2017) and Edwards (2017) suggest that that the PACE trial team held a wide range of conflicts of interest that were not fully disclosed to trial participants. For instance, trial lead Peter White was an advisor to the Department of Work and Pensions (DWP) at the time the PACE authors applied for funding for the trial from the DWP (Faulkner, 2016). Both White and Sharpe have done paid consultancy work for re-insurance companies with an interest in ME/CFS claims exposure. Sharpe offers expert opinion in one insurance document describing the need to promote CBT in health care (UnUm, 2002). In addition, trial authors White and Chalder were registered as directors of a private company called 'One Health' (Companies House reg. 04364122) during the PACE trial – this company reportedly promoted the use of a biopsychosocial model with associated CBT and GET treatments. PACE leads White and Chalder have also published popular books promoting the benefits of CBT and GET. A null result in the PACE trial, that CBT or GET might not be effective treatments for CFS, would refute many of the claims the lead authors so strongly made in their academic and private sector work. We may only speculate how such clear treatment allegiances and investigator biases impacted the PACE trial (Lubet, 2017).

Suspect treatment effects

The trial authors stand by their claims that CBT and GET were more effective than APT or SMC alone and that this benefit sustained through the trial follow-up study. However, the between-group benefits reported in White et al. (2011) are not sustained at follow-up (Sharpe et al., 2015), as the SMC group and pacing therapy group improved to such a degree that there is only a negligible difference between CBT-GET and SMC-APT groups at 2.5 years. This finding is not unusual, in a Dutch RCT of CBT-GET, the initial trial results strongly favoured CBT and GET over SMC, yet at follow-up the control arm had also improved to a similar level (Nijhof et al., 2013). CBT and GET may bring about some short-term benefit for a minority of patients, but these benefits disappear over the medium to long term (Price et al., 2008; Wilshire, 2017). An explanation for this is offered in Geraghty and Blease (2016): that strong expectancy effects, placebo, and therapist effects, impact the way in which patients report 'subjective benefits' at the end of psycho-behavioural treatment.

The PACE authors state that 'The PACE trial simply confirmed what previous smaller trials had already found (Price et al., 2008): that patients are more likely to get better with either CBT or GET than with other treatments or usual care' (White et al., 2017). In fact, the Cochrane Review by Price et al. (2008) finds that roughly 40 per cent of patients had a clinical response (mild response) in CBT versus 26 per cent in usual care. This means only 14 per cent more patients report some benefit in subjective fatigue and mood compared with usual care (usual care means seeing a doctor as normal with no additional treatment). Price et al. (2008) also conclude that there is little evidence for long-term benefit using CBT. The PACE authors fail to cite the PACE sister trial, 'the FINE trial', conducted around the same time; a large RCT of CBT and GET treatments in a UK community setting (Wearden et al., 2010). FINE reported no substantial benefit across a range of measures of physical function, fatigue and well-being, at 70 weeks evaluation. The PACE authors neglect to reference such evidence.

Outcome switching

Vink (2017) details how the PACE authors changed their outcome measures mid-trial – a major blow to credibility in any clinical trial. After starting the trial, the authors lowered their Short Form (SF)-36 physical function subscale threshold for recovery from a score of 85 to a

score of 60 (a 25-point drop). The PACE authors state that they altered this measure of improvement and recovery as the original level chosen was 'too stringent' (QMUL, 2016; White et al., 2017, PACE). Yet, clinical trials are meant to have strict assessment criteria outlined prior to a trial starting. The recovery threshold the PACE authors originally decided upon (White et al., 2007), of 85 or more out of 100, is about the mean SF-36 PF score for the general population (Komaroff et al., 1996). Essentially, 90 per cent of healthy working-age persons would score above 85 (Wilshire et al., 2017) – not a stringent level, but a logical threshold. However, the PACE authors abandoned this mid-trial in favour of a SF-36 score of 60 – roughly around where a patient with congestive heart failure might fall (hardly a good marker of recovery). Tuller (2017) and Vink (2017) note that once they did this, 13 per cent (81 out of 641 patients) met a key condition of recovery at trial entry (as the trial entry score needed to join the trial was a score of 65 or less). We can speculate that many more patients were brought closer to the level needed to be deemed recovered by the PACE authors simply lowering this critical measurement threshold (and we see that clearly in recent reanalysis of data from PACE). It is worthwhile noting that in the FINE trial, to enter the trial (be deemed ill enough), CFS patients needed a score below 70 on SF-36 physical function. Here, we observe inconsistencies in methodologies used to assess benefit in psycho-behavioural trials.

Recent reanalysis of data from PACE trial (Goldin, 2016; Goldsmith et al., 2016), using the PACE protocol (White et al., 2007), result in reported improvement falling from 60 per cent for CBT and 61 per cent for GET, to just 20 and 21 per cent. A similar reanalysis by Wilshire et al. (2017) shows how the recovery rate of 22 per cent for CBT and GET falls to just 7 per cent for CBT and 4 per cent for GET using the trial's published protocol. After discounting the recovery rate in the SMC group, the added value of CBT or GET falls to a statistically insignificant level (Wilshire et al., 2017). Astonishingly, the PACE authors state such reanalysis '… made no difference to our interpretation' (White et al., 2017). It is difficult to comprehend how an improvement rate fall from 60 to 20 per cent and a recovery rate fall from 22 to 7 per cent, making no difference to the PACE authors' interpretation of outcomes.

Recovery measurement

PACE fails to demonstrate sizable improvements across objective tests of physical functioning (Kindlon, 2017; Shepherd, 2017; Tuller, 2017; Vink, 2017; Wilshire, 2017). Thus, what is 'recovery' if patients remain substantially functionally impaired? The PACE authors use an 'operational definition of recovery'. This involves complex four-strand criteria where participants have to (1) score 60 or above on an SF-36 function subscale, (2) score 18 or below on a fatigue scale, (3) report improvement in overall symptoms and (4) no longer meet the Oxford criteria for CFS (clinically assessed by PACE team members). Wilshire (2017) and Vink (2017) detail how such 'composite measures' may appear comprehensive, but largely rest on subjective accounts – ticking boxes on a survey instrument or Likert scale with limited choices (feeling better vs feeling very much better).

In PACE, modest improvements observed in the CBT and GET groups (contested by reanalysis) are not mirrored by substantive changes in objective measures of walking ability on a 6-minute walking test or step test (McPhee, 2017). Adding CBT to SMC did not substantially improve function from baseline (McPhee, 2017). In addition, the PACE authors dropped plans to assess patients' physical activity using electronic monitors (actometers) on the grounds they were too burdensome. Other measurements of physical function were not considered, such as measuring how many hours per day a participant spends upright, or in bed, or laying down (pre- and post-treatment). In addition, there is almost no change in secondary measures (employment or health care use) in CBT or GET groups (McCrone et al., 2012). Such data suggest recovery in PACE is more a design artefact than a clinical reality.

Stouten (2017) details how a reliance on subjective measures results in a confirmation bias in PACE: 'the more objective the measure, the worse results are for CBT and GET'. Confirmation biases spill over into reporting biases. An editorial by Bleijenberg and Knoop (2011) that accompanied PACE Lancet publication stated, '… the recovery rate of cognitive behaviour therapy and graded exercise therapy was about 30%'. In fact, the PACE authors reported a 22 per cent recovery rate 2 years later in 2013 (White et al., 2013). Media outlets picked up the PACE trial following press briefings by the PACE authors, with headlines that 'CFS sufferers can overcome symptoms of ME with positive thinking and exercise' (Knapton, 2015). It is arguable the PACE authors' use of the term 'recovery' contributed to a perception that CBT and GET are curative treatments (Goudsmit, 2017), yet the majority of participants within the 22 per cent PACE reported recovery rate did not reach a SF-36 physical function threshold of above 85 (the level of a healthy individual). Recovery in PACE rested on subjective self-report, in a study that sought to get patients to think 'more positively', with little improvement in objective measures or secondary outcomes.

Lessons versus moving on

Petrie and Weinmann (2017) claim the PACE authors have suffered unnecessary harassment and that a continual focus on the PACE trial is unfair, that 'it is time to move beyond PACE'. However, an Information Tribunal found little evidence of harassment and lead PACE author Trudie Chalder confirmed this. Petrie and Weinmann (2017) should be aware that science progresses from a recognition of error and failures. There are many valuable lessons to be learned from a review of the PACE trial. The PACE authors refusal to share data with requesters exemplifies a clear need for data-sharing rules. Only after a Tribunal ordered data to be released, were other researchers able to assess the PACE authors' improvement and recovery claims (e.g. Wilshire et al., 2017). It is important clinicians and health authorities are made aware of the biased methods, outcome switching, conflicts of interest, and fall in recovery and improvement rates following reanalysis, particularly if the PACE trial is to form part of the evidence-base that guides ME/CFS treatment recommendations (NICE or NHS).

Criticism versus validation

The PACE authors claim that they have adequately responded to criticisms about the PACE trial. It is important to remember that the last stop on a scientific papers' journey to 'acceptance' is the public and wider scientific community – here the PACE authors have failed to be convincing. The majority of invited expert commentaries in the *Journal of Health Psychology* echo the concerns raised in Geraghty (2016). The PACE authors suggest the National Institute of Clinical Excellence, NHS Choices and the Lancet, all agree that PACE offers the 'best evidence' that CBT and GET are safe and effective treatments for CFS (White et al., 2017). This claim demonstrates the import of this trial and consequently the import of reanalysis of trial outcomes and recent critiques of the trial. Most health authorities do not have time to scrutinise the methods and conduct of every clinical trial, this is a role the scientific community (and increasingly stakeholders) take on. The PACE authors suggest their findings are 'good news for patients'. However, recent reanalysis of findings, special commentaries and this article, arguably offer patients more accurate information about the limited benefits of CBT and GET as treatments for ME/CFS.

Data transparency

There is a contemporary movement for transparency in science, particularly in clinical trials. The PACE authors state they support this principle, yet they withheld data from interested parties for many years. They write, 'This is an ethical position, respecting patients' rights …' (White et al., 2017). However, did PACE trial participants really ask for scientific data not to be shared, or did participants simply ask that no

personal identifiable information (PIIs) be disclosed? – The latter seems more plausible. The Information Tribunal ruled that the sharing of data from PACE is in the public interest (HMTS, 2016). However, data from PACE continues to be withheld from requesters. To build trust in science and to enhance the power of data, it is important data from clinical trials are made more openly available. PACE is a publicly funded trial (almost £5 million); it would be unreasonable to require other researchers to replicate such a trial. Funding bodies must make data-sharing a requirement of any research grant in future.

Conclusion

Patients and clinicians deserve reliable information regarding 'best evidence'. PACE is a controversial trial that does not stand up well to close scrutiny. The majority of participants in the trial did not recover and the majority were not substantially functionally improved. Participants in PACE were drawn from milder cases, with more severe cases excluded. Reanalysis of part of the trial data suggests the benefits of CBT and GET were over-stated, the result of changes to the trial protocol. Most of the modest benefit reported in PACE rests on subjective accounts of improvement. Findings from the trial have been terminally damaged by the way in which the trial was conducted, with a lack of care for treatment fidelity and contamination – so much so, that doctors, commissioners and patients can have little faith in the outcomes reported. It may be that the best thing to emerge from the PACE trial will be an impetus to improve the way in which trials are funded, conducted, overseen and reported – with data being made available for reanalysis in future. Evidence from PACE suggests that CBT and GET are not curative treatments for CFS; recovery rates are low using these treatments. The PACE trial is a seminal contemporary example of how 'evidence' is a fluid construct – not an absolute. Trial outcomes are shaped by trial design choices, thus it is imperative 'evidence' is interpreted with appropriate caution and data from trials is accessible. There is a clear need for more research in ME/CFS, particularly better understanding of illness aetiology, pathogenesis and pathophysiology.

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