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Assessment of Individual PACE Trial Data: in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Cognitive Behavioral and Graded Exercise Therapy are Ineffective, Do Not Lead to Actual Recovery and Negative Outcomes may be Higher than Reported

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Abstract

The PACE trial concluded that Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) are moderately effective in managing Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and yielded a 22% recovery rate. Nonetheless, the recently released individual participant data shows that 13.3% of patients had already recovered, on one or both primary outcomes, upon entering the trial. Moreover, no one classified as recovered achieved the physical functioning, together with the fatigue scores, of the healthy sedentary controls from another trial by the PACE trial's lead principal investigator or achieved Kennedy's definition of recovery, whereby symptoms are eliminated and patients return to premorbid levels of functioning, due to CBT or GET (alone). Therefore, CBT and GET do not lead to actual recovery.

After CBT and GET therapy, 59% and 61% of participants, respectively were labeled as improvers in the original paper, which was lowered by the PACE trial authors to 20% and 21% in the newly released papers in which they used the original protocol; nevertheless, only 3.7% and 6.3% were objective improvers in the objective 6-minute walk test as defined by the same improvement of 50% or more, as used by the trial itself, to classify someone as an improver. If the effect of Specialist Medical Care had been removed from the analysis, then 0% and 1.3% of patients improved objectively with CBT and GET, respectively. Highlighting the fact that unblinded trials like the PACE trial, should not rely on subjective primary outcomes, but use either objective primary outcomes alone, or combined with subjective primary outcomes, as a methodological safeguard against the erroneous inference of efficacy in its absence. The objective individual participant data shows that in up to 82.2% and 79.8% of ME patients their health might have been negatively affected by CBT and GET, respectively. The independent PACE trial review had shown that this proportion was between 46% and 96%, and found to be between 63% and 74% by surveys involving more than 3000 patients by the Norwegian, British, and the Dutch ME Associations. These data confirm the conclusions of a number of studies that patient health was negatively affected by CBT and GET, including one that found that in 82% of patients with severe ME their symptoms were made worse by GET. Analysis of the individual participant PACE trial data has shown that CBT and GET are ineffective and (potentially) harmful, which invalidates the assumption and opinion-based biopsychosocial model. Consequently, we should stop using CBT and GET as (compulsory) treatments for ME/CFS to prevent further unnecessary suffering inflicted on patients by physicians, which is the worst of all harms, yet totally preventable.

Keywords: Chronic fatigue syndrome; CBT; Cognitive behavioral therapy; GET; Graded exercise therapy; Myalgic encephalomyelitis; PACE Trial; Pacing

Abbreviations: 6MWT: 6 Minute Walk Test; APT: Adaptive Pacing Therapy; BMJ: British Medical Journal; CBT: Cognitive Behavioral Therapy; CDC: Centers for Disease Control and Prevention; CFS: Chronic Fatigue Syndrome; CFQ: Chalder Fatigue Questionnaire; CMO: Chief Medical Officer (the UK government's principal medical adviser); GET: Graded Exercise Therapy; ME: Myalgic Encephalomyelitis; ME/CFS: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; SF-36: Short Form-36; SMC: Specialist Medical Care.

Introduction

The multicenter PACE trial involved 641 patients and was the largest Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) trial for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) conducted thus far. It was designed to be the decisive trial which compared "pacing, defined as adaptive pacing therapy (APT), CBT and GET, when added to specialist medical care (SMC) to SMC alone" [1], at a cost of 8 million USD [2].

The PACE trial's methodology and conclusions that CBT and GET are moderately effective, with 22% of patients recovering if they are treated with these therapies [3], have been questioned and criticized by patients (which the PACE trial authors have ignored thus far) and contradict the general experience of patients and the fundamental basis of ME/CFS. Specifically, if symptoms are ignored and exercise levels are increased, symptoms will be exacerbated and relapses are caused [4].

Freedom of information requests for raw data were rejected on the basis of being vexatious, with one exception [2], even though the UK Medical Research Council, which partly funded the trial, and the Queen Mary University of London (QMUL), the home of the PACE trial, have policies concerning research data sharing. These institutions state that publicly funded research data are a public good, produced in the public interest, and should be made openly available in a timely manner to the maximally possible extent [5]. And as concluded by the Nobel Prize winner Südhof, if science is publicly funded, which the PACE trial was, then "the public has a right to ask whether their funds are well spent. What's more, in a time when many publicly held and expressed opinions are patently false...

it is important for an engaged citizenry to demand evidence in support of claims" [6]. Moreover, Wicherts et al. [7], who explored "authors' reluctance to share data" in psychological studies, concluded that" "roughly 50% of published papers in psychology contain reporting errors" and "the unwillingness to share data was most pronounced when the errors concerned statistical significance" [7]. Lastly, Godlee, the Editor-in-chief of the *British Medical Journal* (BMJ), concluded that it is essential "that patients are properly involved, not just as participants" but also in trial conception, "analysis, reporting, and dissemination of results" [8].

Following a Freedom of Information Act request by Matthees which asked for an anonymous selection of trial data to analyze the study using its original standards for improvement and recovery, as mentioned in the PACE trial's protocol, an Information Tribunal ordered the release of the data after a 2-year court battle. As noted by Rehmeyer, the three PACE trial principal investigators, and QMUL "had refused the request, arguing that malicious patients would break the anonymization and publish the participants' names to discredit the trial. It again cited the death threats." Nonetheless, the court rejected these claims, deeming them "wild speculations" and "pointing out that the researchers themselves acknowledged in court that neither they nor PACE participants had received death threats" even though they had repeatedly said that they had [9].

On September 8, 2016, the day before QMUL released the requested data to Matthees (who has since made it available to others), the PACE trial authors published two articles on the QMUL's website. In these articles, they reanalyzed both primary outcomes, as outlined in the published protocol [10,11], instead of the outcomes to which an extensive number of changes had been made and were used in the original publication [1]. Yet, the authors derived an almost identical conclusion as that in the original publication even though the independent review of the PACE trial, published at the beginning of the year, showed that CBT and GET were not effective [5].

As a physician who has been bedridden with severe ME for a long period after GET caused a severe relapse from which I have not recovered, I can provide combinatorial perspectives from patients and physicians. I can ensure that patients are appropriately involved, not only as participants but also in the analysis, reporting, and dissemination of the results. To achieve this, I analyzed the outcomes of the individual participant data of the PACE trial to answer the following questions objectively:

- Are CBT and GET effective and safe treatments for ME/CFS?
- Do these treatments lead to actual recovery from ME/CFS?
- Were there any other important findings, and if so, what were they?

The Biopsychosocial Model and its Two Treatments, CBT and GET

The PACE trial's biopsychosocial model is based on the assumption that an initial viral infection leads to a vicious cycle, wherein the individual avoids activity for fear of deteriorating symptoms when the initial infection has long been cured by the body. In an effort to manage symptoms, people excessively focus on them and reduce their level of activity; this exacerbates symptoms and leads to fear-avoidance beliefs, resulting in more inactivity and subsequent deconditioning [1]. CBT and GET were designed to cure patients by encouraging an increase in activity by challenging fearful perceptions and instructing patients to ignore their symptoms, which are not symptoms of illness but merely symptoms of deconditioning [1]. It is important to note that CBT and GET are not the same as CBT for anxiety or depression, or exercise training in a local gym. They are based on the biopsychosocial model and developed specifically for ME/CFS [12]. This is despite the fact that White, the PACE trial's lead principal investigator, coauthored an article in 2005 in which the authors disproved fear avoidance beliefs when they concluded that, "CFS patients without a comorbid psychiatric disorder do not have an exercise phobia" [13]. Dutch proponents of this model had already disproved the deconditioning aspect of the model in 2001 when they concluded that "Physical deconditioning does not seem a perpetuating factor in CFS" [14]. These two studies disproved the biopsychosocial model as far back as 2005. Nonetheless, any evidence to the contrary, that this is a "medical" and "complex, multisystem, and often devastating disorder," and "not a psychiatric or psychological illness" as concluded by the Institute of Medicine after an extensive review of the literature [15], was simply ignored even though they produced the evidence themselves. Furthermore, objective evidence to support this model has never been presented perhaps because it doesn't exist [16,17]. Therefore, the biopsychosocial model is a prime example of assumption and opinion-based medicine at a time when medicine should be evidence-based.

New Analysis by the Pace Trial Authors using the Original Trial Protocol

In the two articles released on the QMUL website the day before releasing the data to Matthees, the authors reiterated that "PACE was a randomised controlled trial" [10,11], yet as found by the independent review of the trial, there was no blinding, masking, or placebo control group. Therefore, it was an unblinded trial that relied on two subjective self-report primary outcomes, fatigue, and physical function [1], together with a larger number of self-report and objective secondary outcome measures [5]. Nevertheless, as concluded by Lilienfeld et al., unblinded trials should not rely on subjective outcomes (but should use [a combination of subjective and] objective primary ones instead) [18], as they produce overoptimistic estimates of the effect of interventions or even the erroneous impression of therapeutic effectiveness in its absence [18]. However, almost all trials of CBT and GET in ME/CFS rely on subjective primary outcomes even though they are un-blinded by definition. Consequently, the history of medicine is full of ineffective and harmful treatments that have routinely been perceived and promoted as effective [18]. An analysis by Prasad et al. [19] estimated that 40% of today's medical practices are ineffective. Furthermore, a BMJ Clinical Evidence project, which reviewed 3000 current medical practices, concluded that up to 15% are harmful [20]. When medical practices are instituted erroneously, often based on inadequate and biased evidence, the cost to society, patients, and the medical system are immense [19], and as concluded by Prasad et al. [21], "patients who undergo the therapy during the years it is in favor receive all the risk of treatment and, ultimately, no…benefit".

Subjective Improvers

The PACE trial coded participants as improvers for physical functioning, "if they had either a score of 75 or more (out of 100) at 52 weeks post-randomisation, or a 50% increase from the baseline score at that time point"; improvers for fatigue had "either a score of 3 or less (out of 11) at 52 weeks post-randomization, or a 50% decrease from the baseline score on the bimodal scored Chalder fatigue scale at this time point" [11]. The percentage of overall improvers, those who improved on both physical functioning and fatigue [11], dropped from 59% and 61% as presented in the 2011 paper [1], to 20% and 21% when using the criteria from the original protocol for CBT and GET, respectively [11]. Since patients in all treatment groups were also receiving specialist medical care (SMC), the effect of SMC should be subtracted, resulting in overall improver rates in the CBT and GET groups of 10% and 11%, respectively. The figures published in the original PACE trial paper, which did not take the SMC effect into account, were six times higher [1]. Even if the effect of SMC was not subtracted, the effect of making an extensive number of endpoint changes during an unblinded trial would still increase the number of overall improvers threefold. Yet, the PACE trial authors came to the same

conclusion about CBT and GET as before, even though 59% and 61% are not the same as 20% and 21%, let alone to 10% and 11% if the effect of SMC had been subtracted.

Moreover, after receiving treatment deemed to be moderately effective, patients in all four treatment groups were still ill enough to reenter the trial based on both subjective primary outcomes [1,10]. In addition, the objective outcomes showed no significant improvement on any of their self-chosen objective measures, such as how many patients returned to work, or their level of fitness [9]. Lastly, in the review of the trial, the results of the 6-minute walk test showed that ME/CFS patients also remained ill enough to be on the waiting list for a lung transplant, 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 had actually doubled [5].

Objective Improvers

The PACE trial relied on two subjective outcomes to test for improvement [11]. As discussed previously, unblinded trials should use objective outcomes (as primary outcomes as well) as a methodological safeguard against the erroneous inference of efficacy in its absence [18]. Therefore, in this analysis, the individual data of the 6-minute walk test, the only objective individual data released by the PACE trial [22], was used to identify objective improvers. This analysis used the same improvement criterion, of 50% or more, as used by the trial itself [11], to classify someone as an objective improver.

As can be seen in table 1, the percentages of objective improvers were the following: 3.7% and 6.3% in the CBT and GET groups, respectively, and 5% in both the APT and SMC groups. Therefore, using subjective instead of objective outcomes, and making extensive endpoint changes during the trial, resulted in a 16- and 10-fold inflation of the improvers in the original paper for CBT and GET, respectively. The newly presented rates remained five and three times higher for CBT and GET, respectively. However, taken the effect of SMC into account, the percentage of objective improvers would be 0% and 1.3% for CBT and GET, respectively. Therefore, in the CBT group, there would have been no improvers instead of 59% and 20%. And the number of improvers for GET was 47 and 16 times higher than they should have been in the original [1] and the newly released article, respectively [11].

As also seen in table 1, the majority of improvers on the subjective outcomes did not improve objectively (93.7% and 89.7%; and 100% and 97.9%, if the SMC effect had been removed, in the original paper; and 81.5% and 70%; and 100% and 93.8%, if the SMC effect had been removed, in the new analysis by the PACE trial authors for CBT and GET, respectively). The lack of objective improvement in so many participants is likely due to a combination of the illusionary placebo effect (whereby participants have the illusion that they have improved which they have not, contrary to the normal placebo effect where change does happen [18]) and response-shift bias, which according to Lilienfeld et al. [18] occurs, when an intervention leads individuals to change "their evaluation standard with regard to the dimension measured" ... which is of particular concern for researchers or clinicians using self-report measures. "This is particularly noteworthy if the basis of the therapy in question, as is the case with CBT and GET for ME/CFS, is to change patient's perceptions of their symptoms [1], leading patients to overestimate the effect of the intervention [18].

The above is also a good illustration of the conclusion by Lilienfeld et al. [18] that unblinded trials should not rely on subjective primary outcomes to avoid erroneous inferences of improvement and efficacy in its absence and to avoid subjecting patients to ineffective and (potentially) harmful treatments. CBT and GET trials for ME/CFS, which are unblinded trials by definition, almost always rely on subjective primary outcomes, and in view of the very high number of subjective improvers in the PACE trial who did not improve objectively, it is very likely that the number of improvers in other trials who did not improve objectively, is equally very high. This suggests that CBT and GET have been promoted as effective without an objective evidence base.

Already Recovered at Baseline

Table 2 shows the proportion of participants classified as recovered on the physical functioning scale (SF-36 PF) and/or the Chalder Fatigue Questionnaire (CFQ), the two (subjective) primary outcomes of the trial, at trial entry. Due to the extensive number of endpoint changes made during the trial [5], the rate was 13.3% in a trial where the authors had concluded that 22% of patients had recovered after either CBT or GET [3]. Everyone will agree that a patient cannot be ill enough to participate in a trial and simultaneously be labeled as recovered at trial entry without having received any treatment and without a change in their medical situation.

A score of 60 or more, and a Likert score of 18 or less, represented recovery on the SF36 physical functioning scale and the Chalder Fatigue scale, respectively [3]. Nonetheless, a 2004 publication by White et al. [23], which was co-authored by White, the lead principal investigator of the PACE trial, that was published the year before the PACE trial started [5], found that healthy sedentary controls, with the same median age of 38 years as in the PACE trial, had a median physical functioning score of 100 and a bimodal Chalder Fatigue score of 0, which equates to a Likert Chalder Fatigue score of 0 or 1. This finding makes it difficult to understand how patients with a physical functioning score of less than 100 (as a matter of fact, 60 or more) and a Likert score of 18 or less, can be classed as recovered, in a trial run by the same author which started around the same time.

In the PACE trial, there was an overlap between recovery and being severely ill, as a physical functioning score of 60 or more represented recovery, even though the CDC's empiric case definition from 2005 had concluded that a score of 70 represented significant reductions in physical functioning [24]. Furthermore, Stulemeijer et al. concluded in 2005 that a score of 65 or less represented severe disability [25]. And on top of that, the PACE trial itself used a score of 65 or less to classify someone as ill enough to take part in the trial [1]. Yet Lewith, a professor of primary care at Southampton University, said "I've been appalled by what has happened. There's a small group of people with fixed and opposing views and they want to torture the data until it proves what they believe" [26]. Ignoring extensive endpoint changes made during an unblinded trial, which led to the above, would cast enough doubt about the conclusions of the PACE trial to warrant "an independent re-analysis and public access to anonymous data" which "should...be the rule, not the exception, whoever funds the trial" [27] concluded Godlee, the editor in chief of the BMJ in an editorial entitled "Data transparency is the only way" (which wasn't about the PACE trial), in which she also concluded that "Is it possible that some data are... "too important to share? I don't think so" [27]. Lastly, even though the independent review of the PACE trial published earlier this year showed that CBT and GET are not effective [5], the authors of the trial continue to ignore this. The reason for this, as noted by Ioannidis, is most likely that "investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a "null field"" [28]. And as noted by Edwards, University College London's Emeritus professor of Connective Tissue Medicine, "The only people with fixed views who tortured the data to prove what they believe were the PACE authors" [29].

Lewith (who published an article in August 2016, co-authored by White, and one of the other principal investigators of the PACE trial, in which they found that 70% of participants in the PACE trial used complementary and alternative medicine during the trial [30]) also ignored that if the authors

	CBT	APT	SMC	GET
White et al. 2011 [1]	59%	42%	45%	61%
Goldsmith et al. 2016 [11]	20%	9%	10%	21%
Objective improvers [22]	3.7%	5.0%	5.0%	6.3%
Objective improvers when the SMC effect was taken into account	0%	0%	5.0%	1.3%
False positives in White et al. 2011 [1]	(59 - 3.7): 59 x 100%=93.7%	(42 - 5) : 42 x 100%=88.1%	(45 - 5) : 45 x 100%=88.9%	(61 - 6.3) : 61 x 100%=89.7%
False positives in White et al. 2011 [1] **when the SMC effect was taken into account**	(59 - 0): 59 x 100%=100%	(42 - 0) : 42 x 100%=100%	(45 - 5) : 45 x 100%=88.9%	(61 - 1.3) : 61 x 100%=97.9%
False positives in Goldsmith et al. 2016 [11]	(20 - 3.7) : 20 x 100%=81.5%	(9 - 5) : 9 x 100%=44.4%	(10 -5) : 10 x 100%=50.0%	(21 - 6.3) : 21 x 100%=70.0%
False positives in Goldsmith et al. 2016 when the SMC effect was taken into account [11]	(20 - 0) : 20 x 100%=100%	(9 - 0) : 9 x 100%=100%	(10 -5) : 10 x 100%=50.0%	(21 - 1.3) : 21 x 100%=93.8%

Table 1: The proportion of improvers.
Sources: White et al. 2011 [1]; Goldsmith et al. 2016 [11]; Objective improvers [22].

	CBT	APT	SMC	GET	Total
SF-36 PF	21 (13.0%)	19 (11.9%)	24 (15.0%)	14 (8.8%)	78 (12.2%)
CFQ	0 (0%)	2 (1.3%)	0 (0%)	2 (1.3%)	4 (0.6%)
SF-36 PF & CFQ	0 (0%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.5%)
SF-36 PF and/or CFQ	21 (13.0%)	22 (13.8%)	25 (15.6%)	17 (10.6%)	85 (13.3%)
Number of participants	161	159	160	160	640

Table 2: Proportion of patients already recovered, on one or both primary outcomes, on entering the trial.
SF-36 PF: SF-36 Physical Functioning
CFQ: Chalder Fatigue Questionnaire
Source: Individual participant data [22].

had used their own definition of recovery, as specified in their own protocol, and used by Matthees et al. [31], then their conclusion should have been, as concluded by Matthees et al., "that the changes made to" the thresholds for recovery as specified in "the protocol were not minor or insignificant, as they have produced major differences" which "inflated the estimates of recovery by an average of approximately four-fold" [31]. They had found that the recovery rate, according to the protocol's definition of recovery, was 3.1% for SMC alone; for the adjunctive therapies, the rates were 6.8% for CBT, 4.4% for GET, and 1.9% for APT [31]. Matthees et al. concluded that "in contrast with the published paper by the trial investigators, the recovery rates in the cognitive behavioural therapy and graded exercise therapy groups are not significantly higher than with specialist medical care alone" [31]. Yet White, the lead principal investigator of the PACE trial, stated that "the argument was about the definition of recovery" and that Matthees et al. "used more conservative criteria" [26] even though they had simply used White et al.'s [32] own definition of recovery from the trial protocol defined by White et al. themselves. Furthermore, regardless of the definition of recovery, patients should not be labeled as recovered if they are still (severely) ill and patients should not already be classed as recovered, on one or both primary outcomes, the moment they enter a trial.

Recovery

On the 30th of September 2016, White wrote the following in his *Guardian blog* [33] in response to the analysis by Matthees et al. [31]: "One recent focus of criticism has been whether CBT and GET can actually bring about recovery or remission from the illness, not just reduce the symptoms. And by recovery we mean recovery from a patient's present episode of illness – which is not necessarily the same as being cured, as someone might fall ill again. To address this we did another test on the data, and found that 22% of people could be considered as recovered with either CBT or GET. Though not a large proportion it was about three times more than the recovery rates achieved by the other two treatments. Other studies showed similar proportions recovering after CBT" [33]. Yet, if 13.3% of the participants are already classified as recovered on one or both primary outcomes (two of the recovery criteria) the moment they entered the trial, and the definition of recovery also overlaps with being severely ill, then the figure of 22% is overly optimistic.

Instead of acknowledging this, White continues to write the following about the analysis by Matthees et al. [31] (whose authors also include two Professors of Statistics): "In the latest step in this saga, a blog that hasn't gone through the rigours of scientific peer-review, or being published in a journal claims that CBT and GET are not as effective as we reported. The authors got their figures by tweaks such as increasing the pass-grade for what counted as recovery, and excluding patients who had reported themselves as "much better"" [33]. Yet as noted by the independent review of the PACE trial (published earlier this year in a peer-reviewed medical journal), if you are "much better" you have improved, but you have not recovered yet [5] as anyone knows who has been ill with a flu like illness, for example. White had also stated in an article in *The Times* a few days earlier "it is very difficult to define recovery" [26]. Yet, if an ordinary person was asked the meaning of recovery, the answer would be that all problems have gone and that health has returned to how it was before the illness. This was worded by Kennedy in the following manner: recovery "is the elimination of...symptoms and a return to premorbid levels of functioning" [34].

The history of medicine and psychology demonstrates that subjective inferences of change and concluding that a treatment is effective in unblinded trials that rely on subjective outcomes, like the PACE trial, are often mistaken [18]. To minimize risk as much as possible, such trials should not rely on subjective outcomes but should use objective primary outcomes (as well) [18]. To settle the dispute of how many participants of the PACE trial had truly recovered, Kennedy's definition of recovery needed to be measured objectively. The best method to achieve this and avoid the erroneous inference of efficacy in its absence would be to use a

combination of subjective and objective individual outcome data of the trial itself. Therefore, to be classified as recovered, according to Kennedy's definition [34], patients needed to fulfill two criteria. The first criterion is a SF-36 physical functioning score (one of the two subjective primary outcomes) of a healthy 38-year old, which was the median age of the PACE trial participants. According to Bowling et al. [35] (which was also used by the PACE trial) this score is 100 and is the same score reported by White et al. [23] as the normal physical functioning score for healthy 38-year-old sedentary controls.

According to Bowling et al. [35], physical functioning scores for healthy 38-year-olds are not normally distributed but skewed to one side, with nearly everyone in the maximum range; and according to the BMJ's statistical resources for readers standard deviations will then be grossly inflated, are not a good measure of variability, and are therefore inappropriate for use [36].

The second criterion patients need to fulfill to be classified as recovered was a minimum of 600 m and 659 m, the normal distances for healthy women and men aged 38 years, respectively, on the 6-minute walk test [37], one of the objective secondary outcomes of the PACE trial. This test provides a good representation of a patient's ability to perform submaximal activities of daily living and is a reliable instrument to evaluate a patient's status and/or response to therapeutic interventions [38].

The Chalder Fatigue Questionnaire, one of the two subjective primary outcomes of the trial, was not used for Kennedy's definition of recovery, even though the individual data were released, as the scale does not provide a comprehensive reflection of functional disability, fatigue-related severity, and symptomology in ME/CFS [39]. Moreover, it also does not properly reflect deterioration in the health of patients with a debilitating neuroimmune disease, which is not surprising as this instrument was developed by mental health professionals [40]. Improvements on this scale could thus simply be improvements in the co-morbid psychiatric disorders, present in 47% of trial participants [1].

If we had used this scale, then as found by White et al. [23], the normal bimodal fatigue score for a healthy sedentary 38-year-old is 0 and the normal physical functioning score is 100 [23]. In the PACE trial, a bimodal score of 0 together with a physical functioning score of 100 was achieved by 3 patients each in the CBT, APT, and the SMC groups, and 2 patients in the GET group respectively. But, as can be seen in table 3, when the SMC effect was deducted, no one in the CBT and GET groups achieved these scores of the healthy sedentary controls from White et al. 2004 [23], hence no one in the PACE trial recovered due to CBT and GET.

Table 3 also shows that if the PACE trial had used Kennedy's definition of recovery [34] - which reflects actual recovery and was made measurable by this analysis using two of the outcomes of the PACE trial itself - only 3.7% and 2.5% of patients in the CBT and GET group, respectively, would have achieved a normal physical functioning score for a healthy 38-year-old. If the SMC effect would have been deducted, the rates would be 1.2% and 0%. In addition, only two patients possibly achieved the normal score for the 6-minute walk test as well. It is impossible to be more precise as the released individual participant data were made anonymous to the point that the sex of the participant was removed. If these two participants were women, (one in the CBT group and one in the APT group, with scores of 631 m and 610 m, respectively) then both would be classed as recovered as these are considered normal scores. If the two participants were men, then none of the patients in the trial would be classed as recovered because they didn't reach 659 m, the normal score for men [37]. (If we had also used the individual Chalder Fatigue Questionnaire scores, the other subjective primary outcome of the trial itself, then regardless of the sex of that participant in the CBT group, that participant would not be classified as recovered because its Likert and Bimodal Chalder Fatigue Questionnaire scores were 19 and 8, respectively [22]. And according to the PACE trial protocol, a Bimodal score of 3 or less (out of a maximum of 11) was needed to be classified as recovered and during the trial this was changed to a Likert score of 18 or less (out of a maximum of 33), as found by the independent review of the PACE trial [5]. And the normal score for a healthy sedentary control from the other trial by the lead principal investigator of the PACE trial, as mentioned before, was a Bimodal score of 0 [23], which equates to a Likert score of 0 or 1).

Using a combination of subjective and objective outcomes also highlights the fact that 44.4% of the patients that were recovered according to the physical functioning scale (a subjective outcome) did not achieve a statistically significant objective improvement in the 6-minute walk test (the objective outcome), for which an improvement of at least 86 m would be required according to Wise et al. [41].

In conclusion, CBT and GET do not lead to (actual) recovery, as patients have been saying for a long time which has been ignored by the proponents of the biopsychosocial model who use unblinded trials, rely on subjective outcomes, and use definitions of recovery which include the severely ill; consequently recovery in CBT and GET trials for ME/CFS simply means that patients have subjectively slightly improved. This has no resemblance to actual recovery, yet has led to the erroneous impression of recovery in its absence so that doctors, politicians, policymakers, and others globally believe that CBT and GET lead to recovery, when in fact, they do not. As stated by McGrath in his *BMJ blog*, "Like all patients, what I want most from clinical research is treatments that work, not ones that merely look good on paper" based on biased research towards positive results [42]. If you have been bedridden with ME/CFS for years or decades, you do not care about the name of the treatment, all you want is your health and independence back so that you return to work and a normal life. As worded by Radenkova: "If standing on one leg and singing the national anthem backward would cure this horrible, harrowing illness, then I would do it, and I know all the other sufferer's "(sic!)" feel the same way" [43].

The PACE trial, which set out to be the decisive trial [1], it has shown to be, has now confirmed what patients have been saying for a long time: that CBT and GET are ineffective, do not lead to recovery (as the biopsychosocial model said they would), and constitute a blind alley of ME/CFS research. The results also demonstrate that the proponents of the biopsychosocial model have now decisively disproven their own model again. This is similar to their report in 2005 when they disproved the fear avoidance aspect of their model [13], after already disproving the deconditioning aspect in 2001 [14], as discussed earlier.

Are CBT and GET safe?

For years, as noted by the authors in their protocol, there has been a discrepancy between patient organization reports of the safety of CBT and GET and the minimal risk associated with undergoing these treatments according to the proponents of the biopsychosocial model [32].

To settle this dispute, safety needed to be analyzed objectively by using the newly released individual participant data of the 6-minute walk test, the only objective outcome data released [22] that scientifically represents patient status and/or response to therapeutic intervention [38]. As seen in table 4, 23.0% and 13.8% had been negatively affected by CBT and GET, respectively.

Furthermore, 23.0% and 30.6% of patients in the CBT and GET groups respectively, did not take part in the 6-minute walk test at 52 weeks. Yet the PACE trial itself concluded that only 5% of patients had dropped out [1]. However, as concluded by Lilienfeld et al. [18], patients "who drop out of therapy are not a random subsample of all clients." Those who are not improving or suffer adverse reactions are the ones most likely

	CBT	APT	SMC	GET
White et al. 2013 [3]	22%	8%	7%	22%
Matthees et al. 2016 [31]	6.8%	1.9%	3.1%	4.4%
White et al. 2004 [23]	1.9%	1.9%	1.9%	1.3%
White et al. 2004 with the SMC effect deducted [23]	0%	0%	-	0%
Kennedy's definition: subjective (SF-36 PF) outcome	6 (3.7%)	4 (2.5%)	4 (2.5%)	4 (2.5%)
Kennedy's definition: subjective (SF-36 PF) outcome minus the SMC effect	1.2%	0%	-	0%
Kennedy's definition: objective (6-MWT) outcome	0 (0%) or 1 (0.6%)	0 (0%) or 1 (0.6%)	0 (0%) or 1 (0.6%)	0 (0%)
Kennedy's definition: meeting both criteria	0 (0%) or 1 (0.6%)	0 (0%) or 1 (0.6%)	0 (0%)	0 (0%)
Number of participants	161	159	160	160

Table 3: Proportions of participants recovered according to…
Sources: White et al. 2013 (PACE trial recovery paper with extensive endpoint changes) [3];
Matthees et al. 2016 (using protocol defined recovery) [31];
White et al. 2004 (using its healthy sedentary control scores: SF-36 physical functioning score of 100 + bimodal Chalder Fatigue Questionnaire score of 0) [23];
Actual recovery as defined by Kennedy [34] operationalised with a SF-36 physical functioning score of 100 [35] and a 6-MWT of at least 600 m and 659 m, the normal distances for 38-year-old healthy women and men, respectively [37].

	CBT	GET
Worse in 6-MWT at 52 weeks	37 (23.0%)	22 (13.8%)
Not taken part in 6-MWT at 52 weeks	37 (23.0%)	49 (30.6%)
Maximum number of participants negatively affected	74 (46.0%)	71 (44.4%)
Maximum number of participants negatively affected as a proportion of the London ME criteria	74 (82.2%)	71 (79.8%)
Number of participants fulfilling the London ME criteria	90	89
Number of participants	161	160

Table 4: Proportion of participants negatively affected by CBT and GET.
Sources: Individual participant's 6-minute walk test data (6-MWT) [22];
Number of participants fulfilling the London ME criteria [1].

to drop out of treatment. Yet many researchers and studies do not take this into account, and as a result, "may conclude erroneously that their treatments are effective merely because their remaining clients are those that have improved" [18].

Moreover, the PACE trial used the Oxford criteria [1], which do not require the main characteristic of ME (an abnormally delayed muscle recovery after doing trivial things [44]). As stated by David, one of the creators of the Oxford criteria (which was co-authored by White and one of the other principal investigators of the PACE trial), these criteria are a "less strict, operational definition which is essentially chronic…fatigue in the absence of neurological signs…with…psychiatric symptoms… as common associated features" [45]. The National Institute of Health concluded in 2015 therefore, that "The Oxford Criteria…are flawed and include people with other conditions, confounding the ability to interpret the science" and should not be used anymore [5].

White et al. [23], a study published the year before the PACE trial started and co-authored by White, stated that its patients were "diagnosed according to Fukuda et al. criteria...with the modification of having no co-morbid psychiatric disorder. All psychiatric disorders were excluded". Reeves et al. [46], again co-authored by White, concluded in 2003 that "the presence of a medical or psychiatric condition that may explain the chronic fatigue state excludes the classification as CFS in research studies because overlapping pathophysiology may confound findings specific to CFS".

Despite these findings, the PACE trial still used the Oxford criteria, ignoring their own recommendation. The London criteria were used as secondary criteria after the patients had been selected for the trial by using the Oxford criteria [1]. The PACE trial itself concluded that only 56% of patients selected had ME according to the London criteria [1]. Moreover, 47% of patients selected using the Oxford criteria had co-morbid depression or anxiety disorder [1], and these patients might actually benefit from exercise [16]. This in contrast to ME patients, who suffer from delayed recovery, worsening of symptoms, and relapses following exercise, as objective evidence provided by Paul et al. [47] and Black et al. [48] for example, showed. The White et al. [23] study, which was discussed earlier, "found that exercise induced a sustained elevation in the concentration of TNF-α, which was still present three days later, and this only occurred in CFS patients" (TNF-α as noted in White et al. 2004 [23], is a pro-inflammatory cytokine). And as noted by Edwards, University College London's Emeritus professor of Connective Tissue Medicine, who pioneered the use of Rituximab in Rheumatoid Arthritis (RA), "fatigue in RA is due to TNF alpha. If you take away the TNF there is no fatigue" [49]. Furthermore, the authors stated, "we found no differences in immune or muscle responses between a longer 70% sub-maximal exercise test and a shorter 100% maximal test of exercise endurance. Both of these exercise tests were sufficiently abnormal stressors, compared to usual activity in our patients" [23]. Specifically, exercise led to immunological abnormalities in patients with ME/CFS that, three days later, were still present and detectable in the blood. This was known before the PACE trial started, which included exercise therapy, even though this suggests that exercise is the problem, not the answer. It also indicates that White et al. [23] had shown once again that ME/CFS is a physical disease, disproving White's own biopsychosocial model as an explanation for this disease in the year before the PACE trial (which was based on this model) started [1].

Therefore, to assess the maximum number of patients with ME/CFS that had been negatively affected by CBT and GET in the PACE trial, the number of patients that deteriorated should be combined with the number of patients that dropped out and did not do the 6-minute walk test at 52 weeks, and then be divided by the number of patients in the trial that actually had ME (according to the London criteria) [1], and not "just" Oxford defined fatigue caused by a psychiatric disorder.

As can be seen in table 4, the individual data shows that up to 82.2% and 79.8% of ME patients could have been negatively affected by CBT and

GET, respectively. These rates are vastly different to the 1% and 2% for CBT and GET, respectively, based on the percentage of serious adverse events (which "involved death, hospital admission, increased severe and persistent disability,...were life-threatening or required an intervention to prevent one of these" [1]), that the trial used to declare these two treatments as safe [1], even though most of these problems are problems which patients do not complain about. Therefore the individual data show that CBT and GET could be harmful, in accordance with what patients have been saying for a long time, and with the above-mentioned 2004 study by White et al. [23], which found that exercise causes immunological damage in ME/CFS. It's also in accordance with the conclusion of a number of studies. For example, a review by Sabine et al. [50] of the Belgian CFS Reference Centres showed that after treatment with CBT and GET "Physical capacity did not change; employment status decreased" and "The percentage of patients living from a sickness allowance increased." The independent review of the PACE trial found that "46% of patients reported increases in their ME/CFS symptoms, 31% reported musculoskeletal, representing the M in ME, and 19% reported neurological adverse events, representing the E in ME. So that the proportion of participants negatively affected by CBT and GET is between 46% and 96%" [5], and most likely estimated between 63% and 74%, as reported by surveys conducted by the Norwegian (2014), the British (2015) and the Dutch ME Association (2016), involving more than 3,000 patients [51-53]. Twisk and Maes found that "many patients report that" CBT and GET "had affected them adversely, the majority of them even reporting substantial deterioration" [54]. Núñez et al. [55] found that treatment with CBT and GET led to "worse SF-36 physical function and bodily pain scores." Koolhaas et al. [56] found that 38% of patients had been affected adversely by CBT, "the majority of them even reporting substantial deterioration." And they also noted that "A striking outcome is that the number of those respondents who were in paid employment or who were studying while taking part in CBT was adversely affected" and they concluded that "Over all, CBT for ME/CFS does not improve patients' well-being: more patients report deterioration of their condition rather than improvement" [56]. And a review by Kindlon found that in 82% of patients with severe ME their symptoms were made worse by GET [57]. And treatments that are harmful, breach the Do No Harm Principle, one of the most important principles of medicine, and should not be used.

Discussion

The PACE trial was the largest CBT and GET trial conducted so far, established as a decisive means of testing their safety and efficacy in ME/CFS. It was based on the conclusions of the Medical Research Council's Research Advisory Group and the CMO's working group, that ME and CFS constitute the same illness [32], and the biopsychosocial model which posits: "that unhelpful interpretations of symptoms, fearful beliefs about engaging in activity, and excessive focus on symptoms are central in driving disability and symptom severity" [58] and that "both de-conditioning (loss of muscle strength and reduced exercise capacity) and avoidance of activity...maintain fatigue and disability" [58].

CBT and GET were designed to reverse these beliefs by getting the body used to activity again [5], and by doing so, cure ME/CFS. The trial itself concluded that these two treatments are moderately effective and that 22% of patients recover after CBT and GET [3]. The findings and methodology of the trial have been criticized by patients and others. Freedom of information requests for raw data, apart from one, were turned down on the basis of being vexatious. Yet a Tribunal recently dismissed these arguments and ordered the authors to release individual patient data to Matthees who has since made it available to others [22], and published a preliminary analysis himself [31]. Using the original trial protocol recovery criteria Matthees et al. [31] showed that the recovery rate was 3.1% for specialist medical care alone, 6.8% for CBT, 4.4% for GET, and 1.9% for APT, and "that the previously reported recovery rates were inflated by an average of four-fold. Furthermore, in contrast with the published paper by the trial investigators, the recovery rates" for CBT and GET "are not significantly higher than with specialist medical care alone."

The day before releasing the figures to Matthees, the PACE trial authors themselves published two new papers with a new interpretation of the figures using the original trial's protocol [10,11]. Even though the number of improvers fell from 59% and 61% to 20% and 21% for CBT and GET, respectively (so that it was 3 times higher in the original paper due to the extensive endpoint changes made during the trial), the authors still concluded that "these outcomes are very similar to those reported in the main PACE results paper" [11], even though 59% and 61% are not "very similar" to 20% and 21%. The current analysis found that the number of objective improvers was actually 3.7% and 6.3% for CBT and GET, respectively (and if the effect of SMC was deducted, the rates would be 0% and 1.3%). Therefore, it could be said that the initially presented figures for improvers were inflated 16 and 10 fold for CBT and GET, respectively. This was a consequence of using subjective instead of objective primary outcomes and making an extensive number of endpoints changes during an unblinded trial (without taking the SMC effect into account; if SMC was considered there would have been a 47-fold increase for GET and no one objectively improved due to CBT alone).

The PACE trial authors concluded in their newly published articles, "In summary, these results support our initial interpretation that "CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome"." [10,11]. However, the authors ignored the fact that, after moderately effective treatment, patients in all four treatment groups were still ill enough, according to both primary outcomes, to reenter the trial [1,10]. Furthermore, the main finding of the PACE trial's long-term follow-up study was that there was no difference in efficacy between the four treatments and none of them were effective as found by the independent review of the PACE, which also found that the objective outcomes showed that patients did not improve at all [5]. In addition, in July 2016, the American Federal Agency for Healthcare Research and Quality, removed its recommendation for CBT and GET, after concluding that there is no evidence that these treatments are effective [59].

The current analysis showed that 13.3% of patients were already classified as recovered, on one or both primary outcomes, the moment they entered the trial. Yet, if a definition of recovery had been used that resembles actual recovery, as defined by Kennedy [34], the percentage of patients recovered were not 22% for both CBT and GET as presented in the recovery paper [3], but were 0-0.6% in the CBT group and 0% in the GET group. If the normal physical functioning score of 100, together with the normal Chalder Fatigue score of 0 for healthy sedentary 38-year-olds, as found by White et al. [23], a study co-authored by the lead principal investigator of the PACE trial and published a year before the PACE trial started, had been used, then no one in the PACE trial would have been classed as recovered due to CBT or GET (alone). Confirming what patients have been saying for a very long time, that these treatments do not lead to (actual) recovery.

With regard to the safety of these treatments, the PACE trial concluded that CBT and GET are safe based on the very low percentage of serious adverse events, which "involved death, hospital admission" etc as discussed above [1], even though most of these problems are problems which patients do not complain about as patients have been saying for a long time that CBT and GET make symptoms worse and cause relapses. The independent review of the PACE trial found that 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 had

actually doubled following CBT and GET [5], which suggests that these two treatments had actually harmed patients. Furthermore, it also showed that "the proportion of participants negatively affected by CBT and GET is between 46% and 96%" [5]. And found to be between 63% and 74% by surveys conducted by the Norwegian (2014), the British (2015) and the Dutch ME Association (2016), involving more than 3,000 patients [51-53]. Moreover, Twisk and Maes concluded, "that it is unethical to treat patients with ME/CFS with ineffective, non-evidence-based and potentially harmful...CBT/GET" [54]. Núñez et al., Koolhaas et al., and Sabine et al. [50,55,56] who reviewed the effectiveness of CBT and GET in the Belgian CFS Reference Centers found that patient health was negatively affected by CBT and GET. Moreover, Koolhaas et al. [56], concluded about CBT "that the claims...about the effectiveness of this therapy...are...misleading" and as concluded by Helmfrid, using CBT and GET for ME/CFS is not evidence based and "graded exercise therapy often leads to deterioration" [16]. Moreover, the analysis of the objective individual PACE trial data, as can be seen in table 4, showed that the health of up to 82.2% and 79.8% of the ME patients treated with CBT and GET respectively, could have been negatively affected by these treatments.

The very low number of objective improvers, as found by this analysis (3.7% and 6.3%; and 0% and 1.3%, if the SMC effect had been removed, for CBT and GET, respectively) highlights the fact that a very high percentage of improvers did not improve objectively (93.7% and 89.7%; and 100% and 97.9%, if the SMC effect had been removed, in the initial PACE trial paper [1]; and 81.5% and 70.0%; and 100% and 93.8%, if the SMC effect had been removed, in the new analysis presented by the PACE trial authors itself, due to CBT and GET, respectively [11]). As mentioned above, and contrary to what the trial reported, CBT and GET do not lead to actual recovery. This confirms the conclusion by Lilienfeld et al. [18], that unblinded trials, like the PACE trial, should not rely on subjective outcomes but use objective primary outcomes (as well) as a methodological safeguard against the erroneous inference of efficacy in its absence. Not adhering to this simple fact has led to decades of subjecting patients with ME/CFS to ineffective and (potentially) harmful treatments, and in the process wasting a lot of money and resources, as the PACE trial has now decisively shown. This confirms that patients have been right all the time about the inefficacy and harmfulness of CBT and GET. It also highlights a major problem in the medical profession that for decades has ignored that patients have repeatedly said that these two treatments are not effective and are harmful. The medical profession needs to devise safeguards to protect patients against these practices. Even more importantly, we are not „just" talking about CBT and GET for ME/CFS; according to Prasad et al. [19], 40% of current medical practices are ineffective and up to 15% are actually harmful according to a BMJ clinical evidence project [20].

One way to safeguard patient health is that research articles about psychotherapy, CBT, GET, or other trials which (by definition) are unblinded (even if there are labeled as a randomized controlled trial which they are not) and which report that their treatments are effective based solely on subjective outcomes, should include a warning in the abstract and conclusion, from the authors or the journal, that these outcomes could be false positives, unless they are backed up objectively. This will prevent similar situations that have happened over the last few decades in ME/CFS research and treatment which were dictated by the biopsychosocial model, an assumption and opinion based model, which, as concluded by Helmfrid, "is at odds with physiological findings" [16], and lacks any objective evidence [17], in a time that medicine should be evidence-based.

In a recent editorial in the *International Journal of Care Coordination*, Vrijhoef and Steuten specifically mentioned the problems of the PACE trial, and conclude that, "journals should explicitly ask authors to describe the relevance of their study findings for patients" [60]. Therefore, from autumn 2016 onwards, authors must "insert a separate paragraph about the relevance of study findings from a patient's perspective. This necessitates authors to work with patients in order to get their publication accepted. The key argument here is that when research to inform evidence-based medicine is not relevant to patients, then it should not have been executed in the first place" [60]. If this policy had been in place with all medical journals, millions of dollars would not have been wasted for decades on ineffective and (potentially) harmful treatments, for example, CBT and GET for ME/CFS. Furthermore, patients would have had long effective treatments (which because of the above are still lacking) that restore health and independence, and enable patients to return to work, saving society billions of dollars [61].

Conclusions

The PACE trial concluded that CBT and GET are moderately effective and led to a 22% recovery rate. However, the recently released individual participant data [22] shows that 13.3% had already recovered, on one or both primary outcomes, upon entering the trial, as seen in table 2. Moreover, no one classified as recovered achieved the physical functioning, together with the fatigue scores, of the healthy sedentary controls from another trial by the PACE trial's lead principal investigator or achieved Kennedy's definition of recovery [34], whereby symptoms are eliminated and patients return to premorbid levels of functioning, due to CBT or GET (alone). Therefore CBT and GET do not lead to actual recovery.

For CBT and GET, 59% and 61% of participants were labeled as improvers in the original trial's paper, respectively. These rates were lowered by the PACE trial authors to 20% and 21% in the newly released papers in which they used the original protocol [11]. Nonetheless, only 3.7% and 6.3% were objective improvers. If the effect of SMC had been removed, then 0% and 1.3% improved objectively due to CBT and GET, respectively. This confirms the conclusion of a review by Lilienfeld et al. that unblinded trials like the PACE trial, should not rely on subjective primary outcomes, but either use objective primary outcomes alone or together with subjective ones, as a methodological safeguard against the erroneous inference of efficacy in its absence [18].

The objective individual participant data [22] showed that in up to 82.2% and 79.8% of the ME patients their health might have been negatively affected by CBT and GET, respectively. The independent PACE trial review had shown that that proportion was between 46% and 96% [5], whereas the rates were between 63% and 74% by surveys involving more than 3000 patients by the Norwegian, British, and the Dutch ME Associations [51-53]. These findings confirm the conclusions of a number of studies [16,50,55-57] that patient health was negatively affected by CBT and GET, including one that found that in 82% of patients with severe ME, symptoms were made worse by GET [57].

The analysis of the individual participant PACE trial data has shown that CBT and GET are ineffective and (potentially) harmful, which invalidates the assumption and opinion based biopsychosocial model [1,58]. Consequently, CBT and GET should not be used as (compulsory) treatments for ME/CFS. This will prevent further unnecessary suffering inflicted on patients by doctors, which is the worst of all harms, and as concluded by Spence, totally preventable [62].

Conflict of Interest

The author declares no conflicts of interest.

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