Commentary

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Do graded activity therapies cause harm in chronic fatigue syndrome?

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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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