The PACE trial. Are graded activity and cognitive-behavioural therapy really effective treatments for ME?

A few months ago, I read an article about a "landmark" study on myalgic encephalomyelitis (ME), also known as chronic fatigue syndrome (CFS). It described how gradually increasing activity levels (graded exercise therapy or GET), and encouraging positive thinking using cognitive behavioural therapy (CBT) "seemed to work". The headline even went so far as to suggest that "ME can be beaten by taking more exercise." Although the treatments didn't help every patient, the lead researcher described them as "the only game in town".

In the last paragraph of the article, the ME Association's medical advisor dismissed the claims as "bunkum" but it did not detail why. Here are some of the reasons why he, and other scientists, have a completely different view of the study in question: the PACE trial.

Diagnosis.

The participants in this trial were selected using the 'Oxford' criteria for CFS. This means that the patients in this study all reported having felt physically and mentally tired for at least six months. Which brings me to the first problem. Fatigue is a ubiquitous symptom and experienced by people suffering from a variety of conditions, both medical and psychiatric. This is why the guidelines require physicians to exclude all patients with another disorder that can explain the reported symptoms. From Sjogren's syndrome (SS) and a deficiency of vitamin D to Major Depressive Disorder (MDD) and chronic stress. In reality, most doctors do only a limited number of routine laboratory tests before diagnosing CFS and as studies have shown, may miss conditions such as those above. How many participants had evidence of ongoing disease? We don't know.

To be fair, the researchers tend not to make claims about the effectiveness of CBT or GET to treat ME. In their opinion, the illness described by experts such as Dr Ramsay ('classic ME') is very rare*. For those unfamiliar with classic ME, the key symptom is not fatigue but muscle fatiguability after minimal exertion plus a delay in the recovery of muscle strength after exertion ends. (In short, muscle weakness triggered by an activity that did not result in that symptom before, and which continues for at least 24 hours). The diagnosis also requires good evidence that the brain has been affected, resulting in problems such as poor memory and concentration, blurred vision etc, as well as signs of impaired circulation (e.g. cold hands or feet). ME usually follows an infection which like influenza, can result in outbreaks. Perhaps the most famous of these was the one which occurred in North London in 1955 and led to the temporary closure of the Royal Free Hospital.

The PACE trial researchers claimed to have used the London criteria (LC) for classic ME to establish if CBT and GET were also effective for this 'subgroup' but one of the authors of the LC checked the research manual and found that they had used a different case definition. So how many of the PACE trial participants had ME? How many had the core symptom of muscle weakness after trivial exertion? We don't know.

Assumptions about the cause.

Previous articles written by some of the PACE trial researchers suggest that ME and CFS resemble a psychiatric disorder called neurasthenia. However, I don't recall papers on outbreaks of neurasthenia during the last century. More importantly, their view of ME does not recognise the response to minimal exertion as anything other than a reflection of a patient's lack of fitness, compounded perhaps by stress and/or depression. Accordingly, they do not repeat tests after 24 hours and that's the time when, as far as ME and post-viral fatigue syndrome, are concerned, a lot of abnormalities show up. These include changes in brain function, metabolism and the immune system (see Goudsmit et al 2009 for details).

CBT and GET: The only game in town?

Given the close association between exertion and the symptoms of ME, I devised a strategy called pacing. Following feedback, it's now recommended by the ME Association and many other groups and it's also part of several multi-dimensional programmes offering medical care, counselling, advice etc. Controlled trials have shown some of these to be as helpful as CBT. In other words, when considering evidence-based treatments, CBT and GET are not the 'only game in town'. The PACE trial claimed to have assessed pacing but they didn't. It assessed a programme they named adaptive pacing therapy (APT).

The finding that APT was less effective than CBT and GET is interesting because all the published surveys conducted by or with help from support groups have rated pacing as one of the three most helpful strategies for ME and CFS. Groups recommend it because it makes sense and because it's a relatively easy way of avoiding exertion-related relapses. In psychological terms, it also increases the patient's sense of control. However, APT is not the same as pacing so the results of the trial do not undermine the survey results and more than 30 years of experience.

There is little published information on APT but from the original paper on the trial plus the manual, I learnt that the main aim of the programme was "to achieve optimum adaptation to the illness". The majority of the 14 therapy sessions were face-to-face but 14% were by telephone. Amongst the subjects covered were activity management, stress reduction and improving sleep and posture. Two aspects of the programme are worth flagging up. Firstly, periods of rest were planned up to a week in advance, so like GET, these were based, in part, on the clock and on estimates. Secondly, patients were advised not to undertake any activities that demanded more than 70% of their available energy (cf White et al, 2011. Why 70% and not 50%? I don't know. The manual justifies the 70% rule by suggesting that the extra rest promotes natural healing. However, I couldn't find a scientific reference to support this view.

Pacing as promoted by most of the support groups is less complicated. The main aim is to avoid over-exertion, hence patients are instructed to act on the warning signs that they have reached their limits. They can identify the latter by keeping a diary to determine what they can do per day which will not result in an exacerbation of symptoms during the next five. Then it's a question of being aware of one's body and responding to the onset or worsening of symptoms. For example, if a person has been walking for a while and suddenly notices that one or both legs feel weaker, they have the option to stop and rest or to engage in an activity that uses a different muscle group, e.g. reading or working on the computer. There is no advice on dealing with other aspects of the illness, no pre-determined schedule to adhere to

and no 70% rule. And it can be explained in a single session lasting less than 30 minutes. Given the differences between APT and pacing, one can't extrapolate the findings from the intervention assessed in the trial to the strategy I described.

The results.

Since the first publications on CBT and GET, many researchers have claimed that these are effective treatments for ME and CFS. However, the evidence suggests that such a view should be interpreted with care. Consider the two main outcome measures used to assess the interventions in the PACE trial: the levels of fatigue and physical functioning. At follow-up, the average scores for both were well below the means for healthy individuals, an indication that some patients were still severely disabled. Moreover, additional data revealed that a surprisingly large percentage of patients (mean age around 38 years) were in receipt of some kind of pension or benefit. So how many participants made clinically meaningful improvements? How many recorded scores well within the normal range at the last assessment (to be specific, how many had a score previously documented for healthy individuals)? How many patients were able to return to their pre-illness lives? The answer is that we don't know.

More missing data.

Most of the previous research on CBT and GET used actigraphy (sophisticated motion-sensing devices worn around waist, wrist or ankle) to confirm that the participants had increased their activity levels as instructed. However, the PACE trial did not use actigraphy after the treatment had finished so it's not possible to attribute the reported improvements to changes in activity. Indeed, there's still little evidence that ME or CFS can be beaten by doing more exercise. Also missing are data on symptoms other than fatigue and sleep. It's like testing a drug for cancer but only assessing the effect on the primary tumour.

CBT and GET for psychological problems: why the patients' impressions might be correct.

I've already noted that the PACE trial researchers tend to view CFS as a psychosomatic disorder, rather than a medical one. It should therefore not come as a surprise that the basis for the two treatments is a cognitive-behavioural theory. In a nutshell, this recognises infection as a possible trigger for the illness but assumes that like flu, the virus goes and leaves a patient feeling debilitated. The difference between the people who recover and those who don't is that the latter misinterpret their post-infectious malaise as an indication of ongoing disease. Consequently, they take it easy, rest when they feel unwell, and become increasingly unfit. When patients do attempt to return to their previous lifestyle, they experience feelings of exhaustion after minimal exertion so they limit their activities and end up in a 'vicious circle' which perpetuates their illness.

Many articles on CBT state quite clearly that a major aim is to reduce the fear of 'fatigue' and the avoidance behaviours (i.e. rest). GET is more focused on increasing the patients' activity levels, i.e. there is little discussion of a patient's beliefs. But there is more to the theory. Here is what recent descriptions of the basis for both treatments tend to exclude.

The version of CBT for CFS was influenced, in part, by an approach to a different symptom: chronic pain. During the 1950s, a number of doctors came up with a theory to promote a new

way of managing this symptom. The following is a very simplified summary. According to the theory, pain is perpetuated by rewards such as attention from significant others and disability benefits. The 'rewards' reinforce 'unhelpful' behaviours such as resting, which in turn reduce the patients' fitness and make them feel increasingly tired. In other words, resting when unwell after the acute phase is a conditioned response. In the 1990s, a number of British mental health professionals (not just psychiatrists) applied that theory to the problem of chronic fatigue and subsequently, to CFS.

The operant conditioning hypothesis as it's generally referred to, is just one element of the theory but as far as I can see, it's the main reason why people with CFS are discouraged from resting in response to symptoms. My impression is that a major aim of both CBT and GET is to extinguish the conditioned response. Hence the instructions to try and adhere to a pre-determined schedule where rest is not contingent on symptoms. This, it is argued, will break the link that perpetuates the illness. And the approach also explains why patients are encouraged to tolerate adverse reactions and not to attribute them to an underlying disease. The reasoning is that as rest becomes independent of symptoms and patients take control over their activities, they will improve. For the sake of accuracy, I must add that the theory recognises that inactivity and the stress of illness can result in physiological changes, which is why it's a psychosomatic model and not a psychological one.

Turning to the question of evidence, I have yet to identify a study supporting the view that rest is a conditioned response which perpetuates CFS. Indeed, most of the arguments in articles on the subject seem to rely largely on assumptions, generalisations and speculation. Also noteworthy is the very limited discussion of symptoms that cannot be easily explained in terms of fear of activity and lack of fitness, (e.g., bladder disturbances, vertigo and intolerance to alcohol).

Papers on the original operant conditioning theory described the phenomenon using studies on animals. One of the best known of these found that pigeons increased the number of times they peck at a coloured spot when they realised that doing so was rewarded by extra food. But human beings are not pigeons. They respond very differently to their circumstances. Just considering CFS, some may rest but as the psychiatrists keep pointing out, others try to do as much as they can until they crash (this is referred to in the medical texts as 'boom and bust'). As for 'gains', it's hard to obtain disability benefits and not all significant others respond to the individual's illness with sympathy and attention. More significantly, this theory can't explain the many losses reported by patients with ME, nor the evidence of ongoing disease.

One cannot deny that a percentage of the people who completed the trial recorded scores indicating improvements in fatigue and physical functioning. We also know that a majority were "satisfied" with their treatment. But did any of the patients who felt better after GET also have symptoms such as vertigo to deal with? We don't know. Could it be that the individuals who reported less fatigue had a condition such as stress or depression? Neither the Oxford nor for that matter, other often used criteria for CFS would have excluded them. We know that fatigue is a common symptom of stress and depression and that increasing activity levels not only helps, but that any adverse reactions associated with exercising are usually minimal and transient. This scenario is consistent with the findings of the PACE trial.

Had the patients suffered from ME or post-viral fatigue syndrome, the percentage who felt worse during and after GET should have been much higher.

The suggestion that the UK trials included people with conditions other than ME is not new. One of the first studies on CBT for CFS found that only those also suffering from depression improved. In addition, there are plenty of reports of a history of chronic stress in people who fulfil the criteria for CFS (but not ME). Alas, most trials have not assessed either chronic or current stress. Suffice to say, these, and other issues make it hard to interpret the main findings of the PACE trial.

The researchers' responses to the various criticisms have included suggestions that the therapist wasn't competent, that the patient wasn't motivated, and that some people with ME reject the treatments because they are unwilling to accept that their illness might be psychosomatic. In fact, the researchers have often alluded to the latter and denied that CBT and GET are focused on treating a psychological, as opposed to a medical disorder. But both are based on a theory which includes the hypothesis that that people rest to gain attention. And that patients are so afraid of post-exertional fatigue that they avoid most activities and end up struggling to get out of the house. Whichever way you present this, the rationale behind CBT and GET as tested in the PACE trial seems very psychological.

To sum up, the operant conditioning theory is out-dated and illogical, it relies on some highly questionable assumptions relating to gains, and it has little empirical support. Those who promote the complete cognitive-behavioural model have to ignore or dismiss evidence of ongoing pathology and limit the assessment of improvement to common and subjective symptoms such as fatigue and sleep disturbance.

CBT offered to patients with multiple sclerosis or cancer is different. I can see it helping many people with classic ME who become depressed or anxious. But the versions promoted by the PACE trial assume that the symptoms are largely the result of psychological problems. I can't interpret their arguments in any other way.

<u>Conclusion.</u>

In my view, the PACE trial is not controversial because of lay 'misunderstandings' or the rejection that stress might play a role, but because it is a poorly designed study with missing data, based on a narrow view of the illness with an emphasis on one symptom, and a lack of respect for alternative approaches. Science relies on attention to detail as well as accuracy. But the culture surrounding the PACE trial permits researchers to ignore evidence which undermines either the theory or the reports of improvement. There's also a bias and hostility that does not belong in science.

Dr Shepherd of the ME Association summarised his view of the results as 'bunkum'. Let me offer you my bite-sized response. A treatment like GET is simply not appropriate for a disease like ME which is linked to infection and metabolic abnormalities. Given the close relationship between exertion and symptoms, it follows that asking a patient to increase their activity levels is as logical as advising smokers with lung cancer to gradually increase the number of cigarettes they smoke. There's more to ME than fatigue, we don't have the

evidence to show that graded activity is effective, and finally, not all the critics of the PACE trial are prejudiced laymen who are unfamiliar with treatments such as CBT.

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*Footnote
If ME is rare and CFS is much more common (estimated to affect between 1 and 2.6% of the population), then it's hard to argue that the two conditions are the same. It follows that a treatment which is effective for one may not be as helpful for the other. Research criteria for classic ME are listed below.

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Fey, SG and Fordyce, WE. Behavioral rehabilitation of the chronic pain patient. Annual Review of Rehabilitation, 1983, 3, 32-63. See especially p. 38 (increases in affection and attention "when she complains of pain and discomfort"), and p.39 (financial gain, the influence of rest). This reference is included in the APT manuals.

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Gatzounis, R., Schrooten, MGS., Crombez, G and Vlaeyen, JWS. Operant learning theory in pain and chronic pain rehabilitation. Chronic Pain and Headache Reports, 2012, 16, 117-126. This also mentions CFS as well as graded activity plus activity pacing and notes the value of "predictable breaks". It is worth reading as it acknowledges that the earlier literature may have simplified the interactions between pain patients and their partners (p. 122).

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Dismissal of criticisms;
http://impact.ref.ac.uk/casestudies2/refservice.svc/GetCaseStudyPDF/18135 See p3. Section 4c.

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