PERMISSION TO REPOST

Excerpt from chapter 6 of *Authors of our own Misfortune? The Problems with Psychogenic Explanations for Physical Illnesses* by Angela Kennedy, published by the Village Digital Press.

Pages 178 – 183:

"A study that is exemplary of how flawed CBT and GET trials can be is the PACE trial (White et al, 2011). The results of this study were published with a massive media campaign that saw newspaper headlines such as:

> Got ME? Fatigued patients who go out and exercise have best hope of recovery, finds study.[7]

An editorial in *the Lancet* accompanying the article claimed:

> Concerns about the safety of cognitive behaviour therapy and graded exercise therapy have been raised more than once by patients' advocacy groups. Few patients receiving cognitive behaviour therapy or graded exercise therapy in the PACE trial had serious adverse reactions and no more than those receiving adaptive pacing therapy or standard medical care, which for cognitive behavioural therapy has already been shown… This finding is important and should be communicated to patients to dispel unnecessary concerns about the possible detrimental effects of cognitive behaviour therapy and graded exercise therapy, which will hopefully be a useful reminder of the potential positive effects of both interventions. (Bleijenberg and Knoop, 2011)

The paper itself states:

> Trial findings show cognitive behaviour therapy (CBT) and graded exercise therapy (GET) can be effective treatments for chronic fatigue syndrome, but patients' organisations have reported that these treatments can be harmful and favour pacing and specialist health care. We aimed to assess effectiveness and safety of all four treatments.

But did the PACE trial adequately assess effectiveness and safety of CBT/GET, and did this study disprove patient (and medic and scientist) concerns re safety? The evidence below shows that it did not.

The trial itself was mostly funded by the Medical Research Council but also, possibly uniquely, partially funded by the UK Department of Work and Pensions. The trial cost several million pounds. It was subject to a large amount of concern and objection, from advocates for ME sufferers, from the beginning of the study in 2004. This author was one of those who outlined specific concerns at the beginning of the trial, and various concerns were also outlined in responses to the publication of the protocol mid-trial (White et al, 2007). [8]

It has already been discussed in chapter 4 how research cohorts for 'CFS' or 'CFS/ME', appear to be obtained (by those promoting psychogenic explanations for these conditions) by excluding patients with signs and symptoms (especially neurological) found in Myalgic Encephalomyelitis case descriptions, or indeed other organic diseases (the 'alternative diagnoses'). The PACE trial used, not just one case criteria to *exclude* patients with symptoms and signs of organic disease from the trial, but three: 'Oxford' (Sharpe et al, 1991); Reeves et al (2003), and those from the NICE guidelines (see White et al,
2011: 2).

Of 3158 patients who had been referred to "six specialist chronic fatigue syndrome

clinics in the UK National Health Service" (White et al, 2011: 2), 1187 patients (over a third) were excluded because they did not actually meet Oxford criteria for 'CFS'. Confusingly, no figures are given for those meeting Reeves et al (2003) and NICE exclusionary criteria, though these are claimed as part of the selection process. This is possibly because the Oxford criteria themselves efficiently exclude those with signs and symptoms of neurological myalgic encephalomyelitis, to the point that the Reeves and NICE exclusionary criteria may well have been superfluous.

There is a similarity of symptoms of neurological dysfunction found in specific case descriptions of myalgic encephalomyelitis (for example, Ramsay, 1988), or 'ME/CFS' (as defined by Carruthers et al, 2003), with other neurological conditions, for just one example, those found in multiple sclerosis.[9] Therefore, to have *included* patients with neurological symptoms and/or signs would have meant there was a risk of other neurological conditions being involved in the trial, which would have been a major flaw rendering the trial's findings unsafe. It is therefore likely that patients with signs and symptoms of neurological (and indeed other organic) dysfunction were excluded from the PACE trial. Ironically, if this premise is accurate, White et al cannot have substantiated their claims for the safety and efficacy of CBT/GET for the very patients they claim such treatments are safe and efficacious, those given an ME or CFS diagnosis who suffer physiological impairments including neurological deficits.

Indeed, it is notable that White et al, from the beginning of the trial and throughout, refused to use the criteria of Carruthers et al (2003)[10] to include people with symptoms (and possibly signs) of neurological dysfunction, although they used their own (customised) version of a set of criteria claimed to identify ME (the 'London' criteria), already controversial due to lack of peer reviewed publication, uncertainty in authorship, and the existence of different versions. [11] Indeed, as is evident from the PACE Trial protocol, the customized PACE version of the 'London' criteria for ME bore close similarities to the Oxford criteria for CFS, and were fundamentally different to the Carruthers et al criteria (2003).

That so many patients (nearly a third), of whom had been referred to a 'specialist chronic fatigue syndrome unit' by their GP, were actually *excluded* from the CFS diagnosis favoured by these authors, is extremely important, and leads to the question: what happens to such patients? When the patient exclusion process of another project (the negative 'XMRV' study by Erlwein et al, 2009) was clarified by co-authors (Wessely et al, 2010), some clinical patients who had attended chronic fatigue/CFS clinics commented in response that they had not been investigated thoroughly in the way the research cohorts appeared to be (in order to *exclude* organic disease), either at the clinic or by their GP. A study by Newton et al (2010) found that 40% of patients referred to a CFS did not have 'CFS', though, crucially, Newton was including, as 'CFS' patients, those with specific physiological conditions such as positional orthostatic tachycardia syndrome (POTS), which are associated with neurological dysfunction (Carruthers et al, 2003). If these patients had been also excluded from a diagnosis of CFS, the amount of patients referred to British CFS units (or, often, 'chronic fatigue units'), meeting the Oxford criteria for CFS and having no exclusionary conditions or organic dysfunction, would appear to be very small indeed.

This phenomenon supports the premise that, as discussed in chapter 2, general practitioners tend to adopt psychogenic explanations for somatic illnesses of uncertain aetiology (after very limited investigation), and refer patients to such units, where they are offered CBT/GET using a 'reattribution' model, informed by psychogenic explanations for their illnesses, and given little to no further investigation, or biomedical treatment, even though such clinical patients exhibit signs and symptoms of organic dysfunction. Significantly, various primary psychiatric conditions were *inclusive* for admission to the PACE trial, including but not limited to Major Depressive Disorder, lifetime psychosis, and post-traumatic stress disorder (see the PACE protocol included in White et al, 2007).

Another major problem in the PACE trial was that one of the treatments, 'Adaptive

Pacing Therapy', bore no resemblance to the strategy of 'pacing', specifically adopted by ME patients and reported as being helpful by them in charity surveys. 'Pacing' as reported in these surveys is merely an autonomous flexible management strategy utilised by patients with ME in order to cope with the limitations of the illness.[12] The PACE trial's 'Adaptive Pacing Therapy' was not autonomous, being therapist led, and imposed a regime upon the patient similar to the GET treatment. Even 'Specialist Medical Care', as defined by PACE, was subject to instability as an approach (in that the trial doctors could and did, for example, prescribe anti-depressants *ad hoc*), was given to all participants of the trial, and did not function as a placebo.

Like CBT/GET trials before, even with the inherent methodological problems engendering serious risks of inappropriate bias in claims of positive outcome, the 'positive' outcomes of the PACE trial themselves were weak. In particular, as discussed by Kindlon:

> The only objective outcome measure was the six-minute walk test, which only increased for CBT participants by 21m to 354m, a change that was actually slightly smaller than that of the control group. The GE T group increased by a bit more, to 379m after 12 months… However, this still is a very low absolute walking distance for a group with a mean age of 40. By comparison, a group of older adults (mean age: 65) covered an average distance of 631m… In addition, data was unavailable for 31 per cent of GET participants and 24 per cent of those who undertook CBT; it may be the case that sicker patients were less likely to try the test. [13]

Another issue arises regarding designated 'serious' adverse outcomes, which, after what appears to be an *ad hoc* analysis, were dismissed as not 'thought to be' related to treatment in the *Lancet* article. But the accompanying Web Appendix, published online by the *Lancet,* indicates that some serious adverse events were acknowledged as "possibly related" to treatments in one table (Web Appendix Table C), while Table D exhibited conditions which, to those familiar with the biomedical research around ME or CFS, for example, could well have been adverse results of treatment, including blackouts, drop attacks, cardiac problems, abdominal pain, and increase in disability/incapacity. In light of the apparent stringent attempts to exclude patients with organic dysfunction in this trial, the serious adverse events evidence points to two possibilities other than the 'not related to treatment' blithely claimed in the Lancet article: some patients with organic dysfunction were, by accident rather than design, included in the trial, and adverse events associated with the illness and the risks of exertion occurred; or, if the cohort did consist only of patients without organic dysfunction, increased incapacity nevertheless occurred in some patients, and this may mean even patients without organic illness do not benefit much from CBT or GET (or indeed the other treatments).

In the circumstances and bearing the above, extremely complex and serious problems of confounding inherent in this trial, it is of serious issue that unsafe claims of safety and efficacy of CBT/GET as treatments for ME or CFS were made by the PACE authors and supporters, to the point that iatrogenic harm could be caused to patients because of a lack of understanding of both the neurological and other physiological impairments in at least some patients given such diagnoses, and the abnormal physiological response to exertion that appears to be a key feature of those patients."