

PE1690/F

Professor Jonathan CW Edwards submission of 29 June 2018

I am a professor of medicine at University College London, with no direct personal or professional interest in ME but a recent involvement in advising on research strategies.

Research Funding

I listened to Dr Chris Ponting's oral submission and agree that research into ME is seriously underfunded, largely because there have in the past been few, if any, useful leads in terms of hypotheses and technology. ME remains a very difficult problem but the development of dedicated Biobanks and molecular biological techniques now allows for meaningful strategies to be proposed. It would be proportionate for at least one centre in Scotland to have an annual research budget for ME of at least £500,000-£1M.

Service Provision Problems

The need for more research is also a useful starting point for filling in the wider background to current management of ME, where there are major problems. Because ME was so difficult to get to grips with scientifically, medical academics like myself tended to focus on conditions like rheumatoid arthritis and multiple sclerosis. ME became a backwater in terms of education, research and service development and drifted into rehabilitation medicine, clinical psychology, and the hands of alternative practitioners. Apart from some useful epidemiology much of the research published has been poor.

In this context an unhelpful polarised debate arose in relation to whether ME was a physical or a psychological disorder. Over a period of five years I have tried to assess all the relevant scientific literature and have come to the following conclusions (very much in agreement with Dr Ponting).

1. We still know almost nothing of the causes of ME other than gender/genetic risk and the apparent triggering effect of microbes such as EBV (glandular fever).
2. A number of drug or supplement treatments based on theories of infection or immune or metabolic disturbance have been tried but properly designed trials have so far been negative and these treatments have rightly remained outside mainstream healthcare.
3. A range of physical and psychological treatments, including graded exercise therapy (GET), cognitive behavioural therapy (CBT) and the 'Lightning Process', based on theories of psychological perpetuation of the illness, have been subjected to methodologically inadequate trials and have been introduced into mainstream healthcare based on uncritical interpretation of the results.

Specific Weaknesses in Clinical Trial Methodology

The details of my views, and those of others, on the problems of these therapist-delivered treatments are given in Journal of Health Psychology Vol 22, Issue 9, August 2017 (available online). There has been a focus on the PACE trial of CBT and GET but the problems affect the whole body of trials relating to these and similar treatments. There are several problems with these trials but I will stick to two key points that are reasonably easy to explain.

Firstly, all these studies were performed with both therapist and patient knowing whether they were supposed to be on the new 'good' treatment or the dummy (often no treatment at all). Improvement was then scored largely by subjective questionnaires. The reason why we have placebo-controlled trials (not just dummy-controlled) and normally blind both patient and investigator to which treatment is which is that unless you do this, if you use subjective outcomes you get uninterpretable results. In simple terms patients in trials always play their allotted role in a social game where they are expected to improve on the test treatment and not on the dummy. *No trial of a drug using the methods used in these trials would be acceptable for drug approval.* Authors of these trials have argued that it is hard to do trials of therapist-delivered treatments the way drug trials are done. But that makes no difference. If you are not able to obtain reliable evidence you cannot obtain unreliable evidence and treat it as reliable.

Secondly, the treatments used in these ME trials are uniquely susceptible to the above problem in the worst possible way. Both CBT and GET are based on the idea that the patient is not just encouraged to, but instructed to, take responsibility for taking on a frame of mind in which they see themselves as likely to improve. That is to say the treatment *deliberately* induces subjective bias of exactly the sort that proper trial design is designed to avoid. The role that in other trials is adopted by patients unwittingly is actively allocated to them by the therapist. So *we would expect an apparent positive result* with these treatments that is due merely to playing a role in a social interaction. The other two arms did not invoke this role.

The SMILE trial of the Lightning Process is of interest in that it effectively confirms the unsurprising prediction that any treatment that deliberately trains patients to think and say that they are better is likely to lead to patients saying that they are better. As for PACE it seems to show that it does not actually matter what the treatment modality is.

For these, and other, reasons, these trials generally tell us nothing useful. However, the PACE trial at least may tell us more – that the theory behind the treatment is actually wrong. The theory was that the persistence of *disability* (measurable as inactivity) in ME is due to unhelpful beliefs about inability to improve. What PACE seems to show is that it may be possible to change patients' beliefs, or at least to encourage reports of feeling better, but,

crucially, the *measures of disability* did not change¹. This suggests that even if unhelpful thoughts were present they were not the cause of the disability. Moreover, the long-term follow up data from PACE show no difference from control even in reported wellbeing in the CBT and GET groups.

Failure of Communication

It is reasonable to ask why these treatments have become routine practice despite the evidence base being valueless. These therapies have been promoted by a group of psychiatrists, neuro-rehabilitationists and therapists, but with other physicians largely unaware of what was going on until recently. (Few have read the trial reports.) The standard of assessment of evidence in psychological medicine appears to be well below other specialities. There is also a troubling hint that it is convenient both for general practitioners and for budget holders for patients to be shunted into standardised therapy protocols rather than given meaningful long term support.

The patient community has been publicly vilified by the trial authors and colleagues but they have turned out to be right. They have identified a serious weakness in the quality of both science and peer review in psychological medicine. It is now clear that this problem goes much wider than ME and applies to the Increasing Access to Psychological Therapies programme being advocated for a range of problems recently put under the heading of 'Medically Unexplained Symptoms'. IAPT appears to draw on ME (aka CFS) trials such as PACE as paradigms when in fact they are uninterpretable. The irony is that the problems with these trials do not arise from lack of understanding of statistics or even trial structure, but of psychology. Peer review in psychological medicine appears to be peculiarly unable to appreciate the problem of unwitting psychological bias that is recognised even in basic science laboratories.

Urgent Need to Address Legitimate Complaints

During the evidence session, the witnesses made two reasonable complaints. The first is that unproven treatments are being offered in place of meaningful care. The second is that these treatments cause distress and perhaps harm. CBT is demeaning because the patient works out that it presumes that their sense of being unwell is an illusion. Since very few recover it also offers false hope. GET makes no sense if the defining feature of ME is feeling ill after exertion. (The USA have suggested it be renamed systemic exertion intolerance disease.) Without evidence of any form of 'desensitisation', for which there is no known physiological basis in ME, the treatment can be expected to be worse than nothing. Patients report long-term deterioration after battling to achieve physical exercise goals. These reports are anecdotal but numerous and the *prima facie* case is that they should be taken seriously.

¹ It is now documented from trial committee minutes that detailed assessment of activity with actometers was abandoned because a previous study had already suggested no improvement would be seen – which would not have supported the preferred hypothesis.

The appreciation in the last two or three years that CBT and GET for ME have no sound evidence base leaves regional health services with difficult decisions. Where teams devoted to ME exist their presence at least provides a point of contact and very often some degree of support. Specialist services are needed for an illness that very few doctors have practical knowledge of. Management of intercurrent problems and diagnostic review are essential. On the other hand it is likely that significant sums of money are being wasted on treatments that are distracting health care professionals from useful care and causing unnecessary distress. The situation needs urgent review by, as the new NICE ME/CFS guideline committee vice-chair put it, 'people with an interest but not a vested interest'.