



# **Parliamentary briefing for Carol Monaghan MP's debate on Myalgic Encephalomyelitis Treatment and Research**

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**Westminster Hall**

by

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# Briefing for ‘Myalgic Encephalomyelitis: Treatment and Research’ Westminster Hall, 21<sup>st</sup> June 2018

## Contents

<a href="#">About ME</a>	3
<a href="#">The Debate</a>	3
<a href="#">Education of health professionals</a>	4
<a href="#">Review of the NICE guideline on ME/CFS</a>	5
<a href="#">NHS services</a>	6
<a href="#">Children and young people with ME</a>	7
<a href="#">Severe ME</a>	7
<a href="#">Biomedical research</a>	8
<a href="#">PACE trial</a>	10
<a href="#">ME and welfare benefits</a>	10
<a href="#">Social Care</a>	11
<a href="#">References</a>	13
<a href="#">Contact details</a>	15
<a href="#">Appendix: The PACE Trial Controversy</a>	16

This briefing has been produced jointly by [#MEAAction](#), [Action for M.E.](#), [ME Association](#) and the [ME Trust](#) (for contact details, see [page 15](#))

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## About ME

Myalgic Encephalomyelitis (ME) is a chronic, fluctuating, neurological condition that causes symptoms affecting many body systems, more commonly the nervous and immune systems. ME affects an estimated 250,000 adults and children in the UK, and around 17 million people worldwide.

People with ME experience severe, persistent fatigue associated with post-exertional malaise (PEM), their systems' inability to recover after expending even small amounts of energy, leading to a flare-up in symptoms. PEM means that simple mental or physical activities can leave people with ME debilitated, experiencing a range of symptoms that are not significantly relieved by resting. PEM is the hallmark symptom of ME, other symptoms can include muscle and joint pain, cognitive difficulties, noise and light sensitivities and digestive problems.

People with ME can vary enormously in their experience of the illness, and how their symptoms fluctuate. An estimated one in four children and adults with ME experience these symptoms severely (see 'Severe ME' on [page 7](#)).

Within the NHS, a diagnosis of chronic fatigue syndrome (CFS) or CFS/ME is often given. Research often shows variation across sub-groups of participants [Jason et al., 2010], indicating that these could be umbrella terms for what are in fact a number of illnesses. Therefore, it is critical that there is more biomedical research to further investigate and validate our understanding and increase knowledge of the different forms of ME (see 'Biomedical research' on [page 8](#)).

There is currently no cure and a majority of the people with the disease do not have access to adequate care and support (see 'NHS services' on [page 6](#)). There is an almost total lack of appropriate secondary services. Many primary care professionals receive minimal training on ME and may even be misinformed about the validity of the illness, which continues to be dismissed as 'medically unexplained' and has historically been disparaged as 'yuppie flu' (see 'Education of health professionals' on [page 4](#)). The NICE guideline on ME/CFS, which advises professionals on the diagnosis and management of ME, is currently under review. This presents an opportunity to secure a significant improvement in clinical policy and practice for ME (see 'Review of the NICE guideline' on [page 5](#)), and improve the lives of people with this condition.

The consequences of ME, and the lack of appropriate treatment for patients, are wide-reaching. Many adults are unable to maintain employment or relationships with family and friends, while children frequently fall behind in school (see 'Children and young people with ME' on [page 7](#)). The misunderstandings around the condition can make it harder for people with ME to access welfare benefits (see [page 10](#)). While recent studies show ME patients are no more likely to suffer from poor mental health or emotional problems than the general population [Unger et al., 2017; Cambras, 2018], adults with ME are six times more likely to die by suicide [Chang et al., 2016]. They may also be at an increased risk of earlier all-cause, cardiovascular, and cancer mortality [McManimen et al., 2016].

## The Debate

A 3 hour Westminster Hall Debate has been granted for Thursday 21<sup>st</sup> June, 2018 from 1:30 - 4:30pm. This briefing is intended as a comprehensive resource for MPs, to provide any extra information required to supplement the concerns raised by their constituents.

## Education of health professionals

The education of doctors about clinical assessment, diagnosis and basic management of people with ME is seriously lacking. Both undergraduate and postgraduate courses are still not providing any formal education on ME, nor experience with ME patients. Coverage of ME in many medical textbooks remains inadequate and can be misleading, or even non-existent.

This also occurs in the training of many nurses, occupational therapists and physiotherapists – all of whom could be playing an important role in the management of ME patients.

During 2017, the Forward-ME group of charities, chaired by the Countess of Mar, met with senior representatives from a number of professional organisations responsible for medical education, including the General Medical Council, Royal College of Paediatrics and Child Health, and the Royal College of General Practitioners (RCGP) [Forward-ME 2017]. We will be presenting a workshop at the RCGP conference later this year. However, much more needs to be done to ensure that healthcare professionals are adequately trained and able to offer patients with ME appropriate healthcare.

### How this impacts on people with ME

Lack of education, appropriate guidance and practical experience with patients mean doctors struggle with early and accurate diagnosis and with providing management advice and treatments. Delay in diagnosis or misdiagnosis, along with inappropriate or inadequate management, are significant risk factors for a more persistent and severe form of the illness (see [page 7](#) for more information on severe ME).

The Chief Medical Officer's Report into ME/CFS [CFS/ME Working Group, 2002], and the NICE guideline on ME/CFS [NICE, 2007], set out clear timeline markers for making an early and accurate diagnosis. Both recommended that adults should have normally had the diagnosis confirmed within 4 months from onset of symptoms and within 3 months for children and young people. Patient evidence collected by the ME Association indicates that only a small number are receiving a positive diagnosis within 6 months of onset [2016]. Our experience alongside people with the illness is that a majority have to wait for over a year, and a significant number for many years.

Misdiagnosis is also a significant problem – results from an analysis of GP referrals to a specialist ME service in Newcastle found that around 40% of those being referred did not have a diagnosis of ME [Newton et al., 2010]. Broad definitions of ME, such as the Oxford criteria, have been found to have an 85% error rate [Baraniuk, 2017], leading US agencies such as the Centers for Disease Control to no longer use studies with this broad criteria.

### Recommendations from ME charities

- The Chief Medical Officer and Department of Health and Social Care ensure that all professional bodies educate their members regarding the challenges for people living with ME or caring people with the illness.
- Medical schools, who do not share a centralised curriculum, cover ME in training and in their continuing professional development programmes.
- Health professionals are equipped with clear basic guidance on diagnosis of ME, the importance of early and accurate diagnosis, and appropriate basic management advice.



## Review of the NICE guideline on ME/CFS

After initially proposing retaining the 2007 guideline on ME/CFS, a robust response from the scientific, patient and clinical community has led NICE to commence a full review. Charities highlighted that international practice for ME has been changing, and that health authorities have an ethical obligation to ensure patient access to potentially beneficial healthcare is not restricted by their guidance.

There has recently been a sea-change in the attitudes towards ME internationally, with US agencies in particular removing their recommendations for behavioural treatments such as cognitive behavioural therapy (CBT) and Graded Exercise Therapy (GET) [Centers for Disease Control 2017]. A revised NICE guideline presents an opportunity for UK patients to secure the same recognition.

The current guideline does not reach a conclusion over the nature of ME, although it acknowledges that the World Health Organisation categorises ME as neurological in the International Classification of Diseases (G93.3), a classification UK authorities are legally required to follow. Since the development of the last guideline, the body of research revealing the biological and neurological markers of ME has been growing (see 'Biomedical research' on [page 8](#)).

The guideline recommends Graded Exercise Therapy and CBT for mildly- and moderately affected patients, although the strength of this evidence is poor: clinical trials have found only modest effects, the validity of which have been called into question owing to their reliance on subjective measures and non-blinded treatments [Geraghty, 2017; Wilshire, 2018] (see 'PACE trial' on [page 10](#)). In addition, new evidence of metabolic dysfunction [Armstrong et al., 2015; Fluge & Mella et al., 2016; Naviaux et al., 2016; Tomas et al., 2017; Lacourt et al., 2018] and the genetic and immune abnormalities provoked by exercise [Light et al., 2009] are inconsistent with the theory that patients with ME are deconditioned [Vermeulen & Vermeulen van Eck, 2014].

### How this impacts on people with ME

Graded Exercise Therapy is commonly offered to people with ME in the UK, despite patient surveys consistently finding that this can cause harm for patients with ME [Action for ME, 2014a; Geraghty, Hann and Kurtev, 2017]. These risks are not currently acknowledged in the guideline, undermining the capacity of patients to give informed consent. Patient experience is consistent with evidence that inappropriate exercise is detrimental for people with ME [Twisk, 2017].

While the guideline states that patients can refuse any treatment, in clinical practice this frequently does not happen. Treatments and management should be patient-centred, taking into account the level of severity and stage of the illness, and with potential risks recognised and managed. Furthermore, the guideline should not unduly restrict investigations that may reveal a differential diagnosis.

Additionally, there are only limited and inadequate recommendations for severely ill patients. Home visits are often refused, despite domiciliary care being included in the guideline. The guideline states that their care ought to be supervised or supported by a specialist in ME, but there are no recognised medical specialists or specialist training for doctors. More consideration needs to be given to ensure that this group receives appropriate care, and that more research is undertaken to develop improved understanding and treatment for severe ME.

### Recommendations from ME charities

- Recognise that ME is a biological disease in line with a growing international scientific consensus

- NICE to take patient concerns about treatments into account by immediately issuing a public statement about the harm that can be caused by the current guidelines for the period they remain active (i.e., until new guidelines are published October 2020) and ultimately, by removing Graded Exercise Therapy and CBT based on the biopsychosocial model in the new guidelines
- Enable patients to make fully-informed decisions about the healthcare they are offered and make them aware of their right to decline any treatments

## **NHS services**

Many people with ME do not have access to appropriate medical care, whether in a primary or secondary setting. In primary care, clinicians often have insufficient understanding of ME, or knowledge of appropriate management approaches, to adequately diagnose and support patients. Additionally, a majority of severely affected patients are unable to access these services but are not offered domiciliary visits or specialist inpatient care.

Patients are also increasingly labelled under medically unexplained symptoms (MUS), and are routed to inappropriate psychological services that do not recognise the specific characteristics of ME. It is vital that patients receive improved diagnoses of ME and obtain access to clinicians who understand their condition.

Very few of the hospital-based ME services provide a domiciliary (home visiting) service for people who are unable to attend an out-patient department - there is now only one hospital service that has dedicated in-patient beds for the assessment and management of people who require a hospital admission to a ward where the staff have experience in dealing with this condition.

### **How this impacts on people with ME**

We acknowledge the pressures on the NHS and its hard-working professionals, but specialist services for ME are scarce and under-resourced. The situation is worse in the devolved nations, with no services in Northern Ireland and Wales, and only three (with limited capacity) in Scotland. Services for children and young people with ME, or for severely affected patients, are scant.

Services offer a variety of different treatments, highlighting that patients are often subject to a postcode lottery due to the absence of a consistent referral pathway and treatments [Action for ME 2017c]. This means that a patient in one locality will be offered one treatment, while somewhere else they would receive another, without due consideration given to their particular circumstance or preference. This lack of consistency stems from a failure to recognise appropriate treatments for people with ME.

There is a challenge in treating this disease, with its broad spectrum of patients, but many patients find that the treatments on offer through the NHS do not help, or are detrimental to their condition.

### **Recommendations from ME charities**

It is essential that people with ME receive appropriate and timely healthcare. While there are no cures for ME or treatments that work for everyone, patients can be assisted with management techniques and pharmacological treatments to alleviate their symptoms. The treatment needs of 250,000 adults and children with ME must not be ignored while health bodies are updating guidance.

- Patients receive a timely diagnosis of ME, not MUS or other broad categories, to ensure that their specific health and care needs are recognised and met.

- Clinical Commissioning Groups and Health Boards to meet the need in their locality, collect data on prevalence and ensure funding for this patient group is commensurate to the disease burden.
- There needs to be a defined referral pathway, to ensure that all ME patients consistently receive the same standard of care.
- Development of services specifically for people who are severely affected including home visits, consultation by video or phone call, and specialist inpatient services.

## Children and young people with ME

ME is estimated to affect 0.1 to 0.5% of children and young people [Rowe et al., 2017]. They are affected by many of the issues that adults face: lack of healthcare, misunderstanding from the medical profession, and isolation from peers.

Additionally, ME has been found to be the leading cause of long-term school absence [Dowsett and Colby 1997]. While symptom severity mainly prevents their participation in education, professionals' lack of understanding can further limit their ability to take part. Too often schools do not make the necessary adjustments that could enable children to continue with their education either part-time or by completing tasks at home.

A significant proportion of families caring for a child with ME have been referred for child protection proceedings. This is often related to school absence, and the professionals not understanding what ME is and how it affects a child's ability to attend school. As well as school staff, a large proportion of these referrals were made by health professionals. Charities have advised hundreds of families in this situation, and none of them have had the case against them upheld [Colby, 2014]. An Action for ME survey found that 22% of respondents had a safeguarding/child protection referral made against them, with the vast majority of cases dropped within a year. Most families are affected by the wider issue of professionals not having sufficient awareness of ME: 96% of respondents felt that a lack of understanding of ME impacted on the support their family received [Action for ME, 2017a].

Children and young people may experience significant distress at being disbelieved by medical and teaching staff. Social isolation and exclusion from social or educational activities at key stages of development, which impacts on their sense of self [Parslow et al., 2017].

## Severe ME

Around 25% of people with ME are severely affected by the illness, leaving them extremely debilitated. They are house- or bed bound, unable to properly care for themselves, sometimes for many years or decades at a time. They are dependent on carers for their everyday needs, with some requiring tube feeding and some unable to speak. Very little research has looked at severe ME.

People with severe ME face extra challenges in accessing services. They are not able to travel to out-patient services, and domiciliary and specialist inpatient services are scant. Often the services do not meet their accessibility requirements, such as reducing exposure to noise and light, and other sensory inputs. One person with ME said:

"I had been bedbound at home with ME/CFS for 18 years. After pleading with my doctor for hospital care, I was told there was nothing available to help me."

People who are severely affected also face extra challenges in obtaining social care assessments (see [page 11](#)). When they are able to access support, many of the services available are not

suitable for patients who are severely affected. The lack of training for carers results in a huge strain on people who are severely affected, who struggle to explain their needs and limitations whilst barely able to communicate. For example, many have been provided with social care that aims for re-ablement. This fails to take into account the long-term nature of the condition, and pressurises individuals into completing homecare tasks that they may not be able to sustain, especially in the short period of time in which the carer is present. One person said:

“I’ve tried to explain that severe ME doesn’t work like that, I often have paralysis, I’ve orthostatic intolerance, physically can’t turn in bed etc. Managing personal care and giving me meal replacements isn’t promoting dependence as these are things I physically cannot do.” [Action for ME, 2015]

ME can be fatal in severe cases. Autopsy studies have found dorsal root ganglionitis -- an inflammation of the nerves at the spine -- which may account for the fatigue, pain, and sensory symptoms of ME. In the UK, there have been two patients – Sophia Mirza and Merryn Crofts – whose deaths have been attributed by coroners to ME. However, the actual number of deaths due to ME may be much higher. People with ME die of infection, heart failure, or neurological issues such as stroke far earlier than those without ME [McManimen et al., 2016].

## Biomedical research

ME is estimated to affect 250,000 people in the UK, with an annual cost to the economy of £3.3billion [2020health and Optimum Health Clinic Foundation, 2017]. ME receives far less research funding than other neurological conditions of similar prevalence or disease burden. For example, recently published research concludes that people with ME are “measurably more disabled” than those with Multiple Sclerosis (MS), which is estimated to affect less than half as many people [Kingdon, 2018; Komaroff et al., 1996]. And yet, MS receives at least 20 times more research funding than ME [Chowdhury et al., 2016].

Other research shows that people with ME score lower on health-related quality of life scores than people with most other chronic illnesses, including lung disease, depression, heart disease and diabetes [Hvidberg et al., 2015; Nacul et al., 2011a].

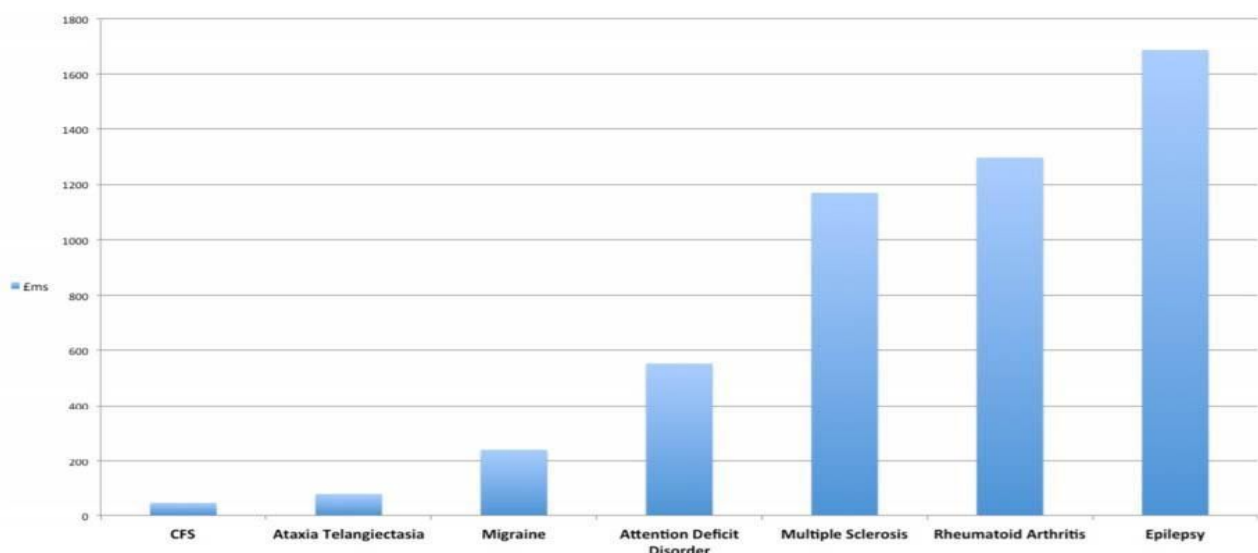


Figure 1. ME/CFS funding compared with other neurological disorders (worldwide funding). Source: CMRC Report [5]



In 2015 the US Institute of Medicine published a report which analysed over 9,000 scientific articles about ME. “The primary message of this report,” it concluded, “is that ME/CFS is a serious, chronic, complex and systemic disease” [Institute of Medicine, 2015]. Since then a number of biomedical studies have been published which have led to new insights into the metabolic, immunological and neurological abnormalities of ME [Twisk 2017; Solve ME/CFS Initiative, 2017]. In contrast to the PACE trial, this research offers patients real hope of diagnostic tests and effective treatments. It is also notable how little of this research has been funded by the UK government.

Since then, the National Institutes for Health (NIH) in the US has set aside \$35m for the development three biomedical ME research centres and one data centre. Having invited bids for the allocated funds, it received ten high quality research proposals [National Institutes of Health, 2017]. Despite the level of funding still being far below what is needed, it provides good evidence of what can be achieved when funds are made available for a specific purpose.

### **How this impacts on people with ME**

Despite its WHO classification as a neurological condition [International Classification of Diseases, 2016], and the growing evidence of its physiological nature [Institute of Medicine, 2015; Twisk, 2017], the vast majority of UK public funding for research into ME has been awarded to psychological and behavioural studies [Chowdhury et al., 2016], which have been criticised for multiple flaws [Wilshire et al., 2018; Journal of Health Psychology, 2017] and left many patients feeling mistreated, neglected and abused [Geraghty, Hann and Kurtev, 2017].

The Medical Research Council (MRC), National Institute for Health Research and Department for Health and Social Care have repeatedly cited a lack of high quality research proposals for the lack of investment in biomedical ME research. Yet biopsychosocial studies, which suffer from methodological flaws (see ‘PACE trial’ below), have received generous funding.

The only year that the MRC invested any significant sum in biomedical ME research was in 2012 when £1.5m of funds were ring-fenced, with a resulting investment of £1.6m. However, no funds have been ring-fenced for biomedical ME research since then.

Consequently, most of the biomedical research that takes place in the UK has been funded by the ME charity sector. One important example is the ME Biobank, a vital part of the ME research infrastructure which has achieved an international reputation. All start-up costs were funded by the charity sector, and on-going costs are being met by the ME Association Ramsay Research Fund.

### **Recommendations from ME charities**

- Funding for research to reflect the disease burden of this condition, both in its severity and prevalence throughout the UK. The ME community experience a considerable disease burden, and for decades have faced underinvestment, mistreatment and neglect. The need for biomedical ME research is urgent and long overdue.
- Development of a clear strategy for research on this condition, which could include government-funded biomedical ME research centres and encouraging interest from leading researchers and scientists.

## PACE trial

In 2007, the National Institute for Health and Care Excellence (NICE) recommended Graded Exercise Therapy and CBT for patients with ME. This guideline was based on weak evidence from small trials and so the much larger PACE trial was designed as a definitive test of these therapies. The PACE trial cost over £5 million, funded mostly by the Medical Research Council, with uniquely some funding from the Department for Work and Pensions.

PACE researchers reported that with Cognitive Behavioural Therapy and Graded Exercise Therapy approximately 60% of patients 'improved' and 22% 'recovered'. The treatments were claimed to be moderately effective, and safe.

PACE's claims ran counter to patients' knowledge and lived experience, leading some to examine the trial's methods. Those who did found two considerable problems:

- Objective results were poor. After a year of therapy, the Graded Exercise Therapy group's increase in walking speed was less than half that achieved in three weeks in a sample of Class II chronic heart failure patients receiving graded exercise.
- After the trial had finished, the PACE authors lowered the threshold they used as the definition of improvement. This inflated the number of participants classed as either 'recovered' or 'improved', in some cases even patients whose condition had deteriorated during the trial were classed as 'recovered'.

After spending over £200,000 fighting a Freedom of Information request, Queen Mary University London (QMUL), PACE's data custodian, had to share access to the data. Subsequent re-analyses have shown changes to the criteria for 'recovery' and improvement distorted the results.

For more information on PACE, see the [briefing](#) produced by members of patient forum Science for ME.

## ME and welfare benefits

Individual assessors frequently do not have sufficient understanding of ME and do not properly apply the assessment criteria. They frequently display a lack of understanding of the condition, and sometimes show outright disbelief of the patient. 79% of survey respondents disagreed that their assessor had sufficient expertise of their condition to effectively and appropriately conduct the assessment [Action for ME, 2017b]. This problem can be exacerbated by assessors' failure to take into account whether the claimant can complete a task 'reliably': safely, repeatedly, in a timely manner and to an acceptable standard.

Additionally, the method of assessment does not accurately capture the impact of ME on an individual. One reason for this is that the assessor makes informal observations at the assessment, of what the claimant looks able, or unable, to do. However, the symptoms of ME can be invisible and therefore cannot be observed.

The assessment taking place on one day can also prevent assessors getting an overall picture of a person's health. For example, someone with ME may attend an assessment and display a certain level of functionality on that day. What the assessor does not observe is that the person may have managed their symptoms by resting for days before the assessment, and also avoiding any mental or physical exertion for days after the assessment. By doing so, they are comparatively well on the

day of the assessment, but as the symptoms of ME fluctuate, they could at other times be much more severely impacted.

### **How this impacts on people with ME**

People with ME face a number of unique barriers to accessing welfare benefits. These benefits can be vital in helping them to meet basic living costs as well as the additional costs of their disability. Often the onerous and ill-conceived assessment process results in an inaccurate award. It can also lead to an exacerbation of ME symptoms which can result in a long-term deterioration of the individual's health.

The symptoms of ME can be cumulative. By looking at individual activities in isolation, the current benefit assessments do not capture this overall impact of doing several activities on the capability of people with ME. For example, whilst an individual may be able to walk 20m, and prepare a meal, they may not be able to do these tasks in close succession or even on the same day. Additionally, the hallmark symptom of post-exertional malaise means that the activities at the assessment could trigger a worsening of symptoms that is not seen until up to 3 days later.

The benefit assessment process can be inaccessible for people with ME. Due to a lack of ME services and low engagement with primary care due to few treatment options, people with ME often do not have medical evidence to contribute to the assessment. Therefore it is vital that the assessor takes any familial or carer evidence into account, and the patient's own account of their illness.

### **Recommendations from ME charities**

- Assessors listen to claimants and respect the patient's account of their experience.
- More robust consideration of the 'reliability' criteria in PIP assessments.
- Written evidence, particularly from family or carers, to be given due weight in decision-making.
- Assessments need to be accessible for people with ME. Potential adjustments include taking rest breaks, minimising travel, and ensuring sufficient time for collecting evidence.

## **Social care**

The process for securing care and support is complex, and people with ME frequently struggle to navigate this. In a 2015 survey on access to social care, 97% of respondents experienced difficulties with two or more difficulties listed in the Care Act 2014 for England - the threshold for receipt of care - yet only 16% had been assessed for care and only 6% then received a care package [Action for ME, 2015].

Social care provision is often provided using a 'time and task' approach, where several daily living activities need to be completed in a short time slot. However, many people with ME pace their activities to preserve their energy in order to manage their symptoms. Completing activities in short period of intense activity is not achievable.

Social care approaches can also be inappropriate for ME, where they focus on promoting independence rather than providing the basic daily needs that a patient with ME may not be able to do for themselves.

Good quality, personalised care provision is essential to ensure the wellbeing of people with ME, and to prevent the exacerbation of their health and an increase in their social care needs.

The failures in social care mean that people with ME are being left without vital support to wash or feed themselves adequately, or get to hospital appointments.

### **How this impacts people with ME**

Post-exertional malaise is a key symptom of ME, meaning symptoms worsen unduly following exertion. This symptom is not well-recognised by social care providers. For example, using the 'time and task' approach mentioned above means that patients can over-exert themselves to complete activities while the social carer is present, triggering this symptom. This is particularly acute for those with severe ME, who can have difficulty with small daily tasks such as brushing teeth or holding a short conversation.

People with ME can be pushed to do even more activities when they are granted social care based on a re-ablement approach. This is designed to rehabilitate patients and improve their condition over time, but it is inappropriate for ME. ME responds negatively to rehabilitation approaches and cannot be treated in the same way as an injury or post-operative condition.

Additionally, patients often struggle to navigate the assessment, or to get social care providers to listen to why such care approaches are not suitable for ME. Direct payments facilitate greater control over the individual's care, but due to cognitive difficulties people with ME often require more support from Local Authorities to manage this payment.

### **Recommendations from ME charities**

- People with ME need better access to advocacy to help them secure necessary social care support, which could be equipped through enabling mainstream advocacy services to better understand ME.
- Re-ablement should not be used for people with ME: it is not appropriate for a fluctuating condition, and unduly increasing an individual's levels of activity could worsen their symptoms.
- People with ME require more support in using Direct Payments, which enable them to plan their care arrangements as appropriate for them.

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## **Appendix: The PACE Trial Controversy**

The following is an independent briefing produced by members of patient forum Science for ME and provides more detailed information on the PACE trial. It can also be downloaded from:

<https://www.s4me.info/docs/PaceBriefing3.pdf>

## The PACE Trial Controversy: A Summary

This briefing was prepared by a Science for ME working group of patients, most with a background in science and mathematics. The authors, including Tom Kindlon, Sean Kirby and Graham McPhee, have published over twenty papers and letters of expert commentary on the PACE trial and related matters in peer-reviewed journals such as The Lancet and the British Medical Journal.

*White et al. conclude that they stand firmly by the findings of the PACE trial, presumably because of their inability to understand its basic flaws. As has been suggested by others, the flaws are so egregious that it would serve well in an undergraduate textbook as an object lesson in how not to design a trial.*

**Emeritus Professor of Medicine Jonathan Edwards<sup>1</sup>**

### Background

In 2007, NICE recommended graded exercise therapy (GET) and cognitive behavioural therapy (CBT) for patients with chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME).<sup>2</sup> But this guideline was based on weak evidence from small trials and so the much larger PACE trial was designed as a definitive test of these therapies.<sup>3</sup>

PACE had over 600 patients, cost £5 million,<sup>4</sup> and was taxpayer-funded, mostly by the Medical Research Council. Uniquely for a clinical trial, the Department of Work and Pensions also contributed to it.<sup>3</sup>

PACE used subjective outcomes as its primary measures, but also included objective outcomes such as aerobic fitness. In clinical trials, subjective measures – patients' self-ratings of symptoms – are influenced not only by how they actually feel but by their expectations of the treatment and their wish to please the experimenter. This is why drug trials use identical-looking pills to keep patients 'blind to' (ignorant of) whether they are receiving the new drug or the old one (or a placebo). In PACE, this 'blinding' was not possible because of the nature of the treatments, and so the objective measures were crucial.

Another important feature of the trial was that the researchers prespecified how they would analyse its data – an established method to avoid the later 'cherrypicking' of favourable results.

During the year-long trial, all of the patients received standard medical care. They were randomly split into four groups. Three of the groups received an additional therapy – GET, CBT or 'adaptive pacing therapy' – and the fourth, a comparison group, received none.

From 2011 onward, PACE's findings appeared in The Lancet and other journals.<sup>3</sup> The researchers reported that in the CBT and GET groups, approximately 60% of patients 'improved' and 22% 'recovered' – more than for the comparison groups.<sup>3,5</sup> The treatments were said to be moderately effective, and safe.<sup>3</sup>

These claims had two consequences. First, NICE left its recommendations for CBT and GET in place.<sup>6</sup> Second, widespread promotion of the trial's success to the public, clinicians and academics<sup>7,8,9</sup> led to uncritical acceptance of the explicit assumption behind PACE's CBT and GET: that CFS patients are just deconditioned and fearful of exertion, and can recover if they increase their activity and focus less on their symptoms.<sup>3</sup>

## Why has PACE been criticised?

*'I'm shocked that the Lancet published it...The PACE study has so many flaws and there are so many questions you'd want to ask about it that I don't understand how it got through any kind of peer review.'*

**Ronald W. Davis, Professor of Biochemistry and Genetics at Stanford University<sup>10</sup>**

ME/CFS has been shown to be at least as disabling as multiple sclerosis,<sup>11</sup> with roughly a quarter of patients bedbound or housebound<sup>12</sup> – many for decades – and an estimated recovery rate in adults of only 5%.<sup>13</sup> Recent, major research reviews of the biomedical literature commissioned by the US government have emphasised that ME/CFS is not psychological, but is a severely debilitating, multi-system, physical disease.<sup>14,15</sup>

PACE's claims ran counter to patients' knowledge and lived experience, leading some to examine the trial's methods. Those who did found two main problems, both serious.

### **1. The objective results contradicted the subjective results**

Objective results were poor.<sup>16</sup> The GET group outperformed the no-therapy comparison group on a six-minute walking test<sup>3</sup> but PACE's authors did not make clear what a bad result this was: after a year of therapy, the GET group's increase in walking speed was less than half that achieved in *three weeks* in a sample of Class II chronic heart failure patients receiving graded exercise.<sup>17</sup> In fact, the GET group's walking speed was only about half that of a healthy age-matched sample.<sup>18</sup>

In PACE, aerobic fitness – and therefore probably also activity levels – did not improve in any group, but these results were not published until four years after the main paper.<sup>19</sup> Other objective outcomes, whose publication was also delayed, showed that the therapies did not return patients to work or reduce their uptake of sickness benefits.<sup>20</sup>

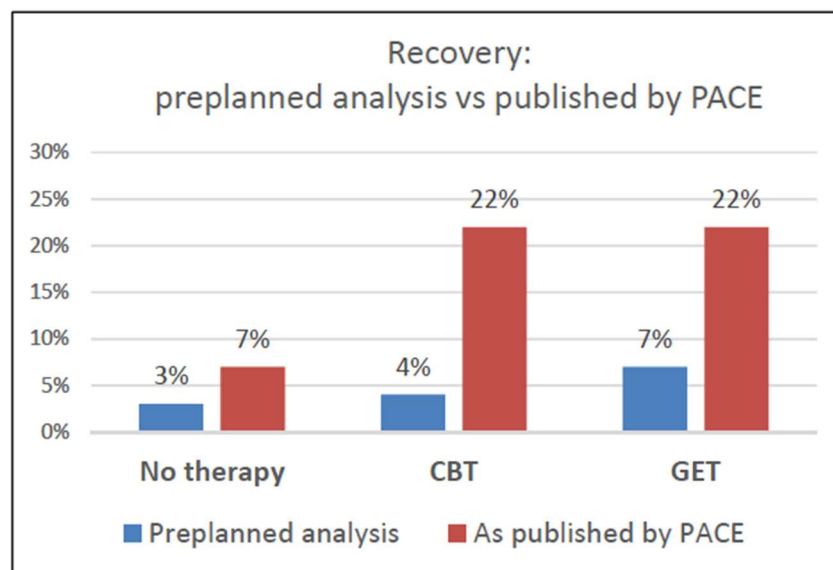


## 2. The planned analyses for improvement and recovery had been abandoned

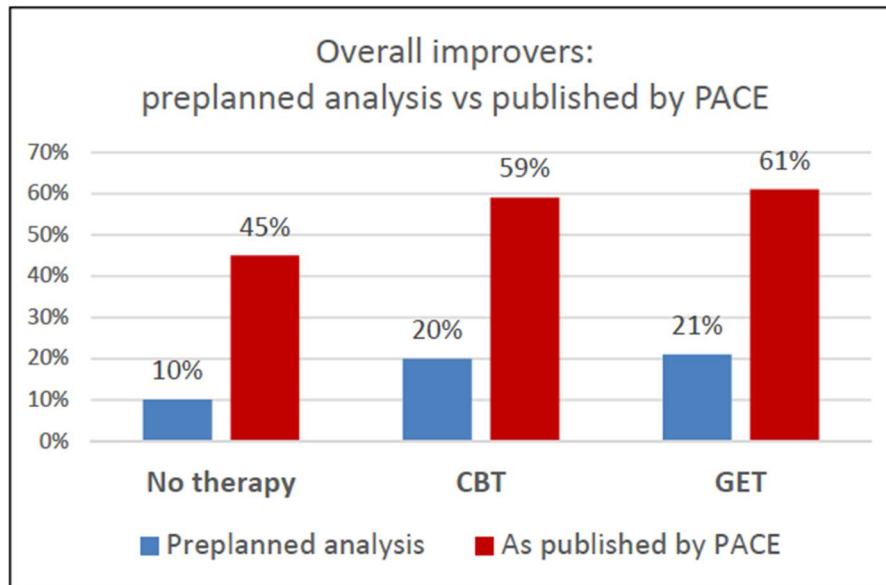
After the trial had finished, the PACE authors discarded their originally planned definitions for improvement and recovery and replaced them with laxer ones that would inevitably inflate those figures.<sup>3,5</sup> The new thresholds were so low that *patients could get worse on a scale of fatigue or activity levels than when they entered the trial and yet be considered to have entered a 'normal range' and to have recovered.*<sup>21</sup>

Queen Mary University London (QMUL), PACE's data custodian, refused to provide critics with either the study's pre-planned outcomes or the relevant raw data to calculate the figures themselves.<sup>22</sup> QMUL spent over £200,000<sup>23</sup> unsuccessfully fighting a Freedom of Information Act request to provide the data.<sup>24</sup>

Despite the limited data finally released by QMUL, independent researchers were able to carry out statistical analyses almost identical to those prespecified by PACE.<sup>16</sup> The percentage of patients who 'recovered' fell from 22% for CBT and GET to 7% or below in each group, and showed no statistically meaningful difference between groups: that is, CBT and GET did not help patients recover.



The 'improvement' results were also far less impressive. 'Overall improvement' rates (requiring specific levels of improvement on both fatigue and physical function) fell from roughly 60% for CBT and GET to roughly 20%, compared to 10% for the no-therapy group – again, not a statistically meaningful difference and so a 'null' result, indicating that the treatments had no effect.<sup>16</sup> For fatigue on its own, only the CBT group did better than the no-therapy group; and for physical function on its own, only the GET group did so. But the results only just scraped into being statistically meaningful in each case.



If these weak and null results had been published in 2011, it seems likely that NICE would have withdrawn its recommendation of the use of CBT and GET for ME/CFS.

### Why was PACE's failure not acknowledged?

PACE was a nonblinded trial with unimpressive or null results on its subjective measures, when analysed according to its prespecified methods. Its objective measures showed that CBT and GET did not improve patients' fitness or ability to work. PACE's long-term follow-up results were also null.<sup>16,25</sup>

The trial has, however, been defended vigorously by its researchers and their supporters.<sup>26,27</sup> Crucially, they do not accept the key criticism that the nonblinded design of the trial favoured CBT and GET. They argue that patients' pre-trial expectations of success did not particularly favour those two therapies.<sup>3</sup> However, any undue influence on self-ratings would have arisen *during* the many treatment sessions in the trial, in which CBT and GET patients alone were told that their treatments were 'powerful' and 'effective' and that there was nothing to stop them getting well.<sup>28,29</sup>

The PACE authors have claimed that reviews by the Cochrane organisation of other CBT and GET studies confirm PACE's results<sup>30</sup> – but the studies in those reviews are also nonblinded trials with subjective primary measures.<sup>31, 32</sup>

## What patients need now

PACE's serious flaws are increasingly widely recognised;<sup>33,34</sup> it is even being used as a teaching example of bad scientific practice in a number of universities.<sup>35,36</sup> In addition to a petition from more than 12,000 individuals – mostly patients<sup>37</sup> – over 90 scientists and clinicians and more than 50 patients' groups worldwide have written to Psychological Medicine demanding retraction of the misleading 'recovery' results,<sup>38</sup> and The Lancet has been asked to correct the 'normal range' results.<sup>39</sup> The controversy has reached the British and international press.<sup>40-44</sup>

Patients want this recognition of PACE's failure to turn into action, and their immediate concern is that GET is actively dangerous. PACE reported no more harm to patients in the CBT or GET groups than in the comparison groups,<sup>3</sup> but the lack of increase in fitness in any group in the trial suggests that most patients may not have increased their activity enough to trigger a reaction.<sup>18</sup> If patients in a drug trial do not achieve the required dose, the results do not help to evaluate drug safety: PACE's safety data are similarly uninterpretable.

But ME/CFS's cardinal symptom is that patients get worse with exercise.<sup>14</sup> Physiology researchers warn that graded exercise would be expected to harm ME/CFS patients, regardless of the skill of the therapist.<sup>45</sup> In surveys, more than 2,000 out of 4,000 patients, including children, reported being made worse by GET.<sup>46</sup> Some patients tell of being made bedbound.<sup>47</sup> On a national scale, the level of harm is likely to be considerable.

*Robert was 12 when he first started [NHS] graded exercise therapy. His mother [explained]: 'Robert was moderately ill when the physio began but became severely ill and required a wheelchair after a few months... After just a few months, he lost the ability to walk... The physiotherapist wouldn't accept they were causing the harm and blamed my son for not trying hard enough, saying he didn't want to get better; they would not accept that there was anything physically wrong with him... He had a fit in the pool where they were doing the exercises, which the neurologist later said was caused by extreme pain. Eventually, we had to get a charity to intervene so that we could stop the graded exercise. My son is now 21 and is still severely ill and housebound.'*

**Report in The Independent<sup>48</sup>**

Contrary to the claims of the PACE researchers and their supporters, PACE's results show that CBT and GET do not work for this disease. In the US, the Centers for Disease Control recently withdrew its recommendation of these therapies for ME/CFS.<sup>49</sup> Patients urgently want NICE to do the same, before more harm is caused.<sup>50</sup>

This would leave patients without any recommended treatments, due to a longstanding failure of government bodies in the UK and abroad to fund biomedical research at meaningful levels.<sup>51</sup> Patients need the British government to now fund a proactive, coordinated, urgent biomedical research strategy for ME/CFS in line with the scale and seriousness of the problem.

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