

Literature Review on Exercise and ME/CFS

I frequently see people make passionate, well-intentioned statements about the research on exercise and ME/CFS. However, given the questionable scientific accuracy of their assertions, I am pretty sure they have not actually read the professional literature. For the sake of fairness and truth, I will summarize some of the findings and cite the relevant professional references. This can lead to a better discussion than resorting to emotional rhetoric. Please don't shoot the messenger!

I will begin with the infamous PACE Trials published in 2011. This study examined graduated exercise therapy (GET) and other treatment modalities. I would like to share some of the data, summarize the findings, and then add what reviewers who were critical of the study said in other journal articles. I will also share some general findings from scientific sources, as well as current recommendations about exercise and ME/CFS from the British National Institute for Health and Care Excellence (NICE). Because it is a few pages long, I put it in a link for interested parties.

The PACE Trial was a large scientific study funded by the UK Medical Research Council. It was impressive in scope. There were four treatment groups, each with about 160 subjects diagnosed with ME/CFS. Each group received at least 3 physician visits and up to 14 therapy sessions (except for the SMC group, which received only physician visits). One group received graduated exercise therapy (GET) provided by physiotherapists, another received cognitive-behavioral therapy (CBT) provided by psychologists or nurse therapists, one group was taught adaptive pacing (APT) by occupational therapists, and the final group received only specialist medical care (SMC) provided by a physician. The treatment phase lasted 24 weeks. Manuals were provided to participants, therapists, and doctors to standardize treatment.

Graded exercise (GET) was based on the theory that symptoms were caused by deconditioning and the avoidance of activity. The objective was to help participants overcome their fears and get back in shape by gradually increasing the duration and intensity of the activity. The goal was to coach people to do light exercise for 30 minutes, five times per week. Target heart rates were chosen to prevent overexertion. Once the 30-minute goal was achieved, participants would gradually increase the intensity. Walking was the main exercise the participants chose.

Cognitive behavior therapy (CBT) focused on the fear-avoidance theory of chronic fatigue syndrome. This theory holds that chronic fatigue syndrome is reversible and that cognitive responses (fear of engaging in activity) and behavioral responses (avoidance of activity) are linked and interact with physiological processes to perpetuate fatigue. The goal was to help people make gradual increases in cognitive and behavioral activity.

Adaptive pacing therapy (APT) was based on the envelope theory of chronic fatigue. The goal was to help participants plan and pace their activities to reduce or avoid fatigue, achieve prioritized activities, and provide the best conditions for natural recovery. They used a daily diary to help them plan activities. They were advised to avoid performing activities that would require more than 70 percent of their available energy.

Specialist medical care (SMC) was provided by doctors with specialist experience in chronic fatigue syndrome. All participants were given a leaflet explaining the illness and the nature of this treatment. Treatment consisted of an explanation of chronic fatigue syndrome, generic advice (such as avoiding extremes of activity and rest), specific advice on any self-help the participant chose, and symptomatic pharmacotherapy (especially for insomnia, pain, and mood).

Results were measured at the midpoint of treatment, at the end of the 24-week treatment period, and at the 52-week follow-up. Improvement at the one-year follow-up for the fatigue score change for both CBT and GET, compared to baseline, was about 25%. The physical functioning score for both CBT and GET improved by about 57% compared to baseline. These changes were described as a moderate improvement. There were smaller, but still significant changes, when GET and CBT were compared to the SMC only group, 15 % improvement for CBT in fatigue and 13 % improvement for GET in physical functioning; 15 % improvement for CBT in fatigue and 15 % improvement for GET in physical functioning. The only objective measure taken was walking distance, how far participants could walk in 5 minutes. Even after one year, the differences were slight; there was only a 31-meter, about 100-feet, difference between the SMC group and the GET group.

The GET group of 160 subjects had two people withdraw due to worsening symptoms, and two people reported serious adverse events. 88% of the GET group reported satisfaction with treatment. On the participant-rated Clinical Global Impression of Change scale, 62 of the 160 GET participants reported positive changes from treatment, 80 reported minimal change, and 10 reported negative changes.

Reference for PACE Trials: P D White, K A Goldsmith, A L Johnson, et. al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011; 377: 823–36 Published Online February 18, 2011 DOI:10.1016/S0140 6736(11)60096-2

Criticism of the PACE Trials

The PACE trials were a big deal. The research was impressive in its sample size of 641 participants and the organized approach to treatment. When the researchers claimed they had proved that CBT and GET could help people to recover from ME/CFS, people took notice. In 2011, the British National Institute for Health and Clinical Excellence (NICE) recommended GET and CBT as the main treatments of choice for ME/CFS.

The ME Association for individuals struggling with ME/CFS was unhappy with this study. They disliked the idea that people were being told that ME/CFS resulted from psychological problems and physical deconditioning. They also believed that the money spent on the PACE Trials could have been better spent looking for biological causes and treatments. They may also have heard complaints about the treatments from some of their members who participated in the trials.

A number of researchers were skeptical of the study for other reasons. Some scoring and measurement methods were changed from the original protocol. The standard they ultimately used to determine if any participants recovered seemed low and arbitrary. One of the main concerns was the weak design. If only subjective measures of the experimental variable are to be used, then the participants should be “blind” to the treatment to reduce bias. Subjective measures are known to be less accurate. Results were also thought to be contaminated by experimenter bias. **(Edwards, J. *Journal of Health Psychology* 2017, 02 (7); Shephard, C.B. *Journal of Health Psychology*, 2017, 22,9.)**

There is a difference between measuring how fast people run with a stopwatch (objective) and asking runners how fast they think they ran (subjective). In the PACE Trials, subjects were only asked to rate how much they believed they improved (subjective). That was even true when deciding which participants recovered. They could have easily used objective measures such as return to work or other normal functions, but chose not to. The critics concluded that the results of the PACE Trials were greatly exaggerated due to the subjective measures used. People tend to tell researchers what they want to hear. This is called *response bias*.

Probably the greatest concern was that the participants in the GET group may have actually felt that graded exercise therapy worsened their condition. There is a clash of statistics regarding this question. Only 2 of 160 participants in the GET group dropped out of the study due to their condition worsening. Ten out of 160 reported that GET made their condition worse, 6 percent. However, when the ME Association did a survey of people in their organization who had received GET as treatment from various sources (1428 respondents), 74 percent of them said GET made their condition worse. In a research study, looking at eleven different studies where some form of GET was used, 54% of those who participated concluded their health had worsened. **(Geraghty K. & Hann M. *Journal of Health Psychology*, 2019, vol. 24 ,10).**

Now, clearly, it is unethical to use a treatment where 54% may be harmed. This is why, in 2021, NICE changed its recommendations to say that GET was not acceptable as a treatment choice. **Unfortunately, many take this ruling to mean you should not consider any type of exercise as treatment, and that all exercise is dangerous for those with ME/CFS.** It is worth noting that despite recent findings of biological issues with this population, there is still no standard treatment for ME/CFS, so potentially helpful therapies should not be ignored. Exercise is not universally dangerous; looking at the Geraghty research, 46% of people who used GET in those 11 studies apparently had no serious complaints.

Exercise is actually the only treatment that has been empirically validated to help in the treatment of ME/CFS. A meta-analysis of the literature on treating ME/CFS with exercise was performed by De Vera Martin and Diaz Salazar in 2025. They found 44 eligible studies and chose 11 for quantitative review. Their conclusions were as follows: **“The recommendation for exercise-based interventions remains weak, but favorable, supporting exercise as a viable approach for improving physical function and fatigue in CFS patients.”** They also shared a biological explanation for why exercise may be helpful as a treatment:

The mechanistic underpinnings of exercise therapy in CFS are hypothesized to involve multiple physiological pathways. Exercise has been postulated to enhance mitochondrial bioenergetics, augmenting cellular ATP production and mitigating bioenergetic deficits commonly observed in CFS. 20-23 Additionally, it has been shown to attenuate systemic inflammation, thereby modulating chronic immune activation—a proposed

contributor to disease pathogenesis. Furthermore, exercise exerts a regulatory influence on autonomic nervous system function, optimizing stress resilience and cardiovascular homeostasis. From a neurophysiological standpoint, exercise has been demonstrated to suppress hyperactive nociceptive signaling via the endogenous analgesic system, facilitated by the release of β -endorphins and enkephalins, which inhibit nociceptive transmission at both spinal and supraspinal levels. Additionally, neuroplastic modifications within the descending pain modulatory network—particularly within the periaqueductal gray and rostroventral medulla—have been implicated in the enhancement of endogenous pain inhibition, thereby mitigating maladaptive nociceptive processing in CFS. These physiological adaptations collectively contribute to reductions in fatigue, improvements in functional capacity, and attenuation of hyperalgesia, thereby underscoring the therapeutic potential of exercise-based interventions.

De Vera Martin, A.; Diaz Salazar A.; Martin Perez, I.M.; & Martin Perez S.E. (2025) “Effectiveness of Exercise-Based Rehabilitation in Chronic Fatigue Syndrome: A Systematic Review and Meta-Analysis, “ *International Journal of Exercise Science*: Vol. 18: Issue 5, 495-530.

One positive thing that came out of the PACE Trials was that researchers better understand what went wrong with the GET exercise portion. In fact, the British National Institute for Health and Care Excellence (NICE) in 2021 did not recommend against exercise being prescribed; rather, they said that exercise programs that are “progressive and inflexible” should not be used as treatment with the ME/CFS population.

The following passage is taken directly from page 389 of the NICE recommendations:

The committee also outlined what a personalised physical activity or exercise programme should look like based on their experience. The programme included establishing the person’s physical activity baseline at a level that does not worsen their symptoms, starts by reducing the person’s activity to within their energy limit, can be maintained successfully before attempting to increase physical ability, uses flexible increments for people who want to focus on improving their physical abilities while remaining within their energy limit, recognises flare-ups and relapses early and outlines how to manage them and incorporates reviews regularly as well as whenever the person requests one. The committee stated the importance of flexible increments that were sensitive to the person’s energy limit and emphasised that fixed increments were not part of a programme. The committee recommended the plan should only be delivered or overseen by a physiotherapist who has training and expertise in ME/CFS.

It was the opinion of the committee that a physical activity or exercise programme can be beneficial for people who have chronic fatigue (not ME/CFS) and in a subset of people with ME/CFS who have already begun to improve and feel they want to do more. Due to some people with ME/CFS reporting harms in the qualitative review, as well as the committee’s experience of the effects of exceeding individual limitations in exercise capacity, the committee concluded that it would be misleading and potentially harmful to advise people with ME/CFS that a physical activity programme will be appropriate for them except in certain circumstances. They described this as people who are able and feel ready to progress their physical activity beyond their current activities of daily living, and as such would like to focus on their ME/CFS energy management around physical activity and exercise. The committee agreed the expertise of the person delivering the intervention is of high importance to prevent potential harm, they agreed that any physical activity or exercise programme should only be overseen under the supervision of a physiotherapist working in a ME/CFS specialist team.

<https://www.nice.org.uk/guidance/ng206/evidence/g-nonpharmacological-management-of-mecfs-pdf-9265183028>