

## **A Comment on the Draft Statement from the NIH Workshop on ME/CFS, December 9–10, 2014**

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I am concerned about the claim on rows 113–114 in the draft statement that studies on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) demonstrate measurable improvement for patients with ME/CFS. There are two underlying biopsychosocial assumptions in these studies: firstly, that the illness is perpetuated by behavioral factors and deconditioning; and secondly, that behavioral intervention in combination with exercise can reverse the condition. There have been several studies of this kind during the last twenty years. Although some of them show small improvements, the only outcome measures that actually have improved are subjective. It is well known that there is a placebo response in subjective measures. This response is likely to cause large bias in studies on cognitive behavioral therapy and graded exercise therapy, as it is part of the protocol to convince patients that the treatment works.

To my knowledge, there are only two studies that have analyzed objective outcome measures. A Dutch group made a post-hoc analysis of actometer data from three of their own CBT studies and concluded that although the fatigue score was reduced in the subjective self reports, there was no objective improvement in the activity levels of the patients [1]. In another study, the same group showed that patients who reported reduced cognitive impairment after CBT did not improve their performance in neuropsychological tests [2].

In the British PACE study, patients made a six-minute walk test before, during and after intervention [3]. Such tests are regularly used to evaluate patients with heart or lung conditions. A healthy person covers about 600 m, whereas 400 m corresponds to severe disability and is suggested as a limit for lung patients when transplantation is justified. All four groups in the study showed small improvements, but the GET group improved slightly more than the others, from 312 to 379 m. This is, however, a poor measure of objective improvement. In contrast to cardiopulmonary exercise tests (CPET), there is no way to control what efforts the patient is making during the test. The performance of ME/CFS patients is affected by post-exertional malaise, and there was no follow-up on how the patients were doing the day after the test. Moreover, as actometers were not used, there is no way to determine how the general functionality of the patients was affected by the treatment.

It should also be emphasized that there is no theoretical foundation for the treatment strategies used in CBT and GET. The cognitive behavioral therapy in the PACE study, for example, was administered on the basis of the fear avoidance theory [3]. There are no supporting references cited in the paper, and the theory strikes a discordant note with our knowledge of ME/CFS. Many patients report crash periods caused by overexertion, which is inconsistent with fear of exercise. Moreover, it was shown in a prospective study that *increased* level of activity is a predictor for developing ME/CFS [4]. Participants who later developed ME/CFS continued to exercise more frequently even after they started to experience fatigue.

The statement on rows 113–114 in the draft completely ignores the evidence for adverse reactions due to graded exercise therapy. Patient associations in several countries have used surveys to compare the outcome of different therapies. There are now data from ten independent surveys in four different countries with more than 13700 participants. About 4600 patients had tried GET, and 52 % reported that they felt worse [5,6]. The largest survey was carried out by the ME Association in the UK [7]. More than 56 % of the participants said that they felt worse, and 33 % reported that they felt much worse. (The number of false negative reports in these surveys is expected to be low. For example, only 3 % of patients treated with homeopathy—which most scientists regard to be completely ineffectual—felt much worse [7].) This large body of evidence for the adverse effects of graded exercise therapy cannot be ignored.

There is also a growing amount of biomedical evidence for physical deterioration after exercise. Several independent groups have shown that ME/CFS patient are unable to reproduce physical measures in cardiopulmonary exercise tests, which are repeated after 24 h [8,9]. Studies have also demonstrated changes in the gene expression and increased pro-inflammatory cytokine levels after exercise [10,11].

There have been few reports of adverse reactions in the published studies on cognitive behavioral therapy and graded exercise therapy. It should be pointed out, however, that the dropout rate in many of these studies has been high, up to 42 % [12]. Patients may leave the program because they deteriorate, and adverse reactions are therefore likely to be underreported. Moreover, there rarely are any objective measures of adherence.

In the PACE study, there were comparatively few dropouts (8 %). The number of serious adverse events in the GET group was about the same as in other groups. The authors conclude that graded exercise therapy is safe if administered as described. However, no objective measure of adherence such as actometers was used. After following the program for one year, the patients in the GET group on average managed to cover 379 m in the six-minute walk test. The goal of the study was complete recovery, and although the authors were confident that the acceptance and adherence to manuals were high, the poor test performance and the lack of objective measures raise serious doubts about the adherence to the exercise protocol. The conclusion that graded exercise therapy is safe if administered as described therefore is dubious.

In conclusion, there is no objective evidence for the efficacy of cognitive behavioral therapy and graded exercise therapy based on a biopsychosocial model as a treatment for ME/CFS. The only available objective data suggest that the self-reported improvement in some of the studies is due to the placebo effect. Moreover, there is no theoretical support for the underlying hypothesis that behavioral factors and deconditioning perpetuate the condition. I suggest that this is clearly pointed out in the final report. This does not mean that all forms of cognitive behavioral therapy and exercise should be dismissed. CBT may help some patients to deal with a chronic debilitating disease, and many patients use pacing strategies to maintain the activity level that the disease permits.

There are numerous reports of adverse reactions after graded exercise therapy. Although controlled studies report fewer and less severe reactions than surveys from patient associations, high dropout rates and lack of objective measures of adherence in these studies make all claims of safe treatments unconvincing. As long as there is no credible explanation why adverse reactions are so common and no way to separate patients that are at risk from other patients, the use of graded exercise therapy should be discouraged and the risk for deterioration should be acknowledged.

The need for objective measures in future studies should be emphasized. Double blinding should be used whenever possible, and when this is not possible—for example in psychological interventions—actometers or other objective measures of functionality must be employed instead.

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