Another "False Start" in ME/CFS Clinical Trials:

The GETSET Study

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I am a physical therapist, and movement is my medicine. Some people might need more movement, in the form of an exercise program, while some people might need less movement, in the form of a pacing program. I rely on scientific studies to help me decide who might benefit from which kind of treatment. Science helps me assign probabilities to outcomes, which I can then use to work with my patients collaboratively to establish the best possible treatment program to help them meet their goals. Reliable data from valid scientific studies can help me be more confident as a clinician that the decisions I make together with my patients actually will help them.

After starting my research career conducting clinical studies related to other fatiguing health conditions, I've now worked in the field of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) for over 10 years. During that time, I've been fortunate to work with a caring and dedicated group of scientists and advocates. To say that the body of intervention studies in ME/CFS has involved disappointingly (and sometimes breathtakingly!) poor science is an understatement. The trend of poorly designed intervention studies, most recently headlined by the PACE trial, has just led to reinforcement of erroneous perceptions about ME/CFS without providing the tools necessary for clinicians like me to help ameliorate the devastating impact of ME/CFS on real peoples' lives. So, it was with great interest that I read the GETSET study, which was recently published in the Lancet.

All the things that made me uneasy as a physical therapist about the PACE trial are back, now in the form of a study involving a slick self-help guide. It's the same confirmation bias of telling folks to move in the context of a graded exercise program, and then having them parrot back the study hypothesis on standardized questionnaires. It's the same absence of objective activity measures that result in the same self-fulfilling prophecy of telling people to move more, and then declaring victory when some of them are actually able to do it. It's the same disregard for foundational scientific evidence of aerobic system compromise, immune activation, and other forms of organic pathophysiology in favor of a behavioral approach to 'tell the tired people to move more.'

The subject selection criteria raise the first threat to study validity. Use of the NICE criteria, on its face, seems like a recruitment upgrade from the PACE trial because it mentions post-exertional malaise. However, post-exertional exacerbation of symptoms is not necessarily required for a diagnosis under the NICE criteria; instead, they are considered optional. Thus, it's unclear that the subset of participants in this study had post-exertional malaise in the way the National Academy of Medicine has characterized it (in part, based on Workwell Foundation research), as symptoms worsened by exertion and therefore potentially a uniquely distinctive feature of ME/CFS. Use of the NICE criteria still set up the possibility of heterogeneous etiologies of fatigue – and therefore heterogeneous expected responses to graded exercise – among study participants. As a side note, not all participants in the study who met the NICE criteria also met the Oxford criteria. If we think about NICE as identifying a more specific subset of people with fatigue, I'm not sure why all the subjects in this study wouldn't also meet older, more general criteria; this point was not discussed in the paper.

The graded exercise group reported exercising 1 hour per week less than the control group at baseline. This raises doubt whether the small observed effects of treatment still would be present if adequate statistical correction was undertaken for the sizable 65-minute per week difference in self-reported exercise time

between groups. It is possible that the exercise group had a greater potential for improvement than the control group, because the exercise group started off with lower self-reported exercise time. The authors controlled for International Physical Activity Questionnaire scores in the sensitivity analysis, but not physical activity time at intake, which is what was manipulated as the independent variable in the study.

The GETSET booklet describes a staged approach to 'reconditioning,' which repeats the false notion that ME/CFS is a problem of fatigue and can be solved with a 'mind over matter' approach. The early phases of the booklet involve pacing and an anaerobic approach to exercise, which is similar to one that we have advocated. However, rather than maintaining an approach of gradually increasing intensity of symptom-limited exercise after early-stage activity pacing and anaerobic conditioning, the latter stages of the GETSET treatment regimen involve a graded exercise protocol.

A giant, glowing, fluorescent red flag is that the number of subjects who completed the entire GETSET treatment was so low. According to the physiotherapist ratings (which are not the gold standard way to assess treatment adherence), only 42% of subjects in the graded exercise group even received a 'moderate' amount of the treatment. It would stand to reason that more compliant subjects ought to improve more, if the study-related treatment is really effective. An important secondary analysis should be whether this trend held in the study. Unfortunately, no analysis of treatment effect according to treatment adherence was conducted. This is remarkable because the fluctuating clinical course of ME/CFS creates a constantly moving baseline level of symptoms and function. This could account for small, measurable changes in a clinical trial, independent of the treatment itself which is especially concerning if fewer than half of the treatment group received all the intended treatment.

The authors of the GETSET study addressed adverse events, which I think was helpful. It's notable that the number of 'mild to moderate' adverse events didn't differ between groups. However, this may speak more to the fluctuating symptoms and disablement of ME/CFS than safety of graded exercise, because adherence to the graded exercise intervention was so low.

The authors found statistically significant decreases in Chalder Fatigue Scale (point estimate: -4.2) and increases in MOS SF-36 physical activity (point estimate +6.3). Although the mean differences were significant compared to the control group, it's hard to justify they are important beyond the relevance of 'decimal dust.' This concern is even more pressing when you consider from our own previous work that the MOS SF-36 may not be sensitive enough to detect change in people with ME/CFS to be used as an outcome measure for this type of work. They identified an 8 point change in SF-36 score as clinically important, but without a relevant citation to the literature. They also identified a 3-point change on the Chalder Fatigue Questionnaire as meaningful, but again without reference to the literature. To my knowledge, minimum clinically important change estimates haven't been specifically worked out for people with ME/CFS on the Chalder, so this level of analysis does not seem valid to me, either. For context, in people with lupus, a 7-point change in Chalder score is considered clinically important, and in people with rheumatoid arthritis, a 10-point change in Chalder score in considered clinically important. If minimum clinically important changes are within these ranges for people with ME/CFS, and we can't be sure that they are, it's pretty clear the authors set the bar artificially low.

People with ME/CFS and the clinicians who strive to help them need valid and reliable scientific data to make helpful decisions about diagnosis and treatment. Clinical trials could be the backbone of these decisions. Unfortunately, the GETSET study seems like another 'false start' for clinical trials in ME/CFS.