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LETTER TO THE EDITOR

GRADED EXERCISE FOR CHRONIC FATIGUE SYNDROME: TOO SOON TO DISMISS REPORTS OF ADVERSE REACTIONS

Sir,

Given there is no formal system to report adverse reactions to non-pharmacological interventions such as graded exercise therapy (GET) for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), other sources of data need to be considered when evaluating safety. As noted by Clark & White, a large survey conducted in 2001 by the charity Action for ME found that 50% of patients who received graded exercise felt worse (1, 2). They also referred to a subsequent study by the same group suggesting that many patients might not have been treated by experienced therapists (3). However, the sample was small and, as in all surveys, therapist competence was not assessed.

A review of all the surveys conducted to date not only supports the view that a significant proportion of patients experience adverse reactions following GET, but also that it is premature to attribute those reactions to practitioner inexperience or inadequate training (1, 4). For example, the results of a recent survey conducted by the ME Association showed that of the 906 individuals who had received GET, 33.1% felt "much worse" and 23.4% judged themselves to be "slightly worse" (4). Similarly, a survey of patients who had been treated in the previous 3 years, i.e. following the refinement of the protocol as discussed by Clark & White, revealed that 34% of the 722 who had tried GET perceived themselves to be worse (5).

Without details of the training of the therapist and their fidelity to the treatment manual, one can only speculate about the factors associated with poor outcome. Nijs et al. (6) discussed some of the possible reasons. However, there are additional factors that deserve consideration when evaluating the efficacy and safety of GET. Firstly, the survey results may reflect, at least in part, the experiences of patients receiving treatment in a clinical setting. As has been shown in studies on other interventions, the outcomes documented in routine practice may be more realistic than those obtained in randomized controlled trials (7). Secondly, many patients may not be able to complete graded activity schedules for various reasons, including ongoing pathology. For instance, Black & McCully (8) used an accelerometer to measure activity levels before, during and after a 4-week "training period" consistent with GET. They documented an increase in activity counts lasting between 4 and 10 days, and this was associated with higher scores for pain and fatigue. The inability to sustain target activity levels was also noted by Friedberg (9), who followed the progress of one patient during 26 sessions of GET. He recorded a 10.6% decrease in mean weekly step counts, leading Friedberg to speculate that the subjective measures of improvement might have been the result of activity substitution and a corresponding reduction in perceived stress.

Finally, we were surprised that neither of the letters cited the research by White et al. (10). This elegant study supports the growing evidence of abnormal metabolic and immunological reactions to exercise in subsets with CFS. Although their sample was small, White et al. found elevated concentrations of the pro-inflammatory cytokine tumour necrosis factor-alpha at time-points of 3 h and 3 days after exercise. In addition, they documented increased levels of the anti-inflammatory cytokine transforming growth factor-beta after normal exertion. We therefore concur with Nijs et al. (6) as well as other researchers, that GET may not be appropriate for all patients with CFS and that pacing may provide a useful, acceptable and safe alternative (6, 11, 12).

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RESPONSE 1 TO LETTER TO THE EDITOR BY KINDLON & GOUDSMIT

Sir,

The UK National Institute for Clinical Excellence (NICE) guidelines on the management of CFS/ME recommends that we should "offer cognitive behavioural therapy (CBT) and/or GET to people with mild or moderate CFS/ME, and provide them for those who choose them, because these are the interventions for which there is the clearest research evidence of benefit" (13). The full guidelines go on to state that "unsuccessful general exercise programmes, perhaps undertaken independently by the patient, or under brief advice from professionals

not adequately trained in the use of GET, are often begun at a high, unachievable level, with an inappropriately rapid rate of progression, or without adequate professional supervision or support. An unstructured and poorly monitored or progressed exercise programme can cause significant symptom exacerbation, and can arguably make CFS/ME worse" (13).

This view agrees with the one patient charity survey that attempted to explain the discrepancy in adverse effects of GET between published research and patient charity member surveys. "When those who had had GET in the last 3 years were examined in more depth, a high proportion had never in fact [received] GET as reported in research studies.... This appears to show that outside the major ME centres, who does it and to what standard is a lottery. Suggesting that the issue may not be the value of GET, but what type and the quality of the therapist. This would certainly support the evidence given to the Chief Medical Officer's (CMO) Report, and, if true, could explain why harm is not found through research trials (conducted in the best centres), but is found through surveys of people's experiences – few having had access to the best centres" (14).

Any effective medical intervention that is improperly given may cause harm. We believe the issue here is not the safety of GET, but its proper implementation and availability. The NICE guidelines provide an excellent description of how to carry out GET safely and effectively (13).

As to our own pilot study, suggesting that acute aerobic exercise (not GET) may be associated with elevated concentrations of certain cytokines (10), we are currently undertaking a proof of principle study. Finally, the PACE trial (www.pacetrial.org) is the largest ever trial of GET for patients with CFS/ME, and adaptive pacing therapy is one of the comparison treatments (15). We will soon have even more data that tests both the efficacy and safety of GET when compared with other non-pharmacological interventions; the main results are expected in 2010.

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RESPONSE 2 TO LETTER TO THE EDITOR BY KINDLON & GOUDSMIT: NEW INSIGHTS IN POST-EXERTIONAL MALAISE IN PATIENTS WITH MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME

Sir,

We are very pleased with the ongoing discussion following the publication of our special report in *Journal of Rehabilitation Medicine* (11). The major goal of that report was to encourage clinicians to plan treatment strategies to account for the biological as well the psychological aspect of CFS/ME, with special emphasis on post-exertional malaise as a unique feature of the illness. Kindlon & Goudsmit have correctly pointed out the clinical importance of studies examining the biological nature of post-exertional malaise in patients with CFS/ME. They correctly alerted readers to the interesting preliminary data reported in 2004 by White et al. (10). In line with that study, a number of recent research reports provide more consistent evidence favouring a biological nature of post-exertional malaise in patients with CFS/ME, which in turn supports the use of specific rehabilitation strategies that take account of these anomalies. Here we summarize these new and compelling findings.

Firstly, the previous findings addressing complement activation in response to exercise in patients with CFS/ME (16) were expanded by a study using quantitative reverse transcriptional polymerase chain reaction (PCR) to examine differential expression of genes in the classical and lectin pathways in peripheral blood mononuclear cells (PBMCs) (17). The data indicate increased expression of the lectin pathway (C4 and mannan-binding lectin serine protease 2) in PBMCs of CFS/ME patients in response to submaximal exercise, resulting in significant increase in C4a spilt product (16, 17). These findings suggest that the post-exercise increase in complement C4a split product represents a potential marker of post-exertional malaise in CFS/ME.

Secondly, another gene expression study highlighted the importance of pain in response to exercise in patients with CFS/ME (18). Real-time quantitative PCR was used to study gene expression in leukocytes prior to and following submaximal exercise in 19 patients with CFS/ME (the majority of whom also fulfilled the criteria for fibromyalgia) and 16 healthy control subjects. At rest, no differences in gene expression were observed. However, in response to exercise, marked differences in gene expression occurred between the 2 groups. In the CFS/ME group, the mRNA increased for genes that can detect increases in muscle produced metabolites, genes important for sympathetic nervous system processes, and immune function genes (18). No such changes occurred in the control group. Among the CFS/ME patients, the observed increases in gene expression were correlated with self-reported symptoms of fatigue and pain.

Thirdly, in an interesting study from Robinson et al. (19), 6 male patients with CFS/ME and 6 healthy controls were studied up to 24 h post-exercise. They found that neither interleukin-6, nor its soluble receptors responded to an exercise challenge to exhaustion. F_2-isoprostanes, an important marker of oxidative stress, were elevated in the CFS/ME group throughout the study (both prior to, immediately following, and 24 h post-

exercise). F_2-isoprostanes increased in response to exercise in both groups, but there was no group × time interaction (19).

Finally, a pilot study compared cerebral oxygenation during maximal exercise testing in 6 patients with CFS/ME with 8 healthy control subjects (20). Near infrared spectrophotometry was used to monitor cerebral oxygenation during exercise. A large between-groups difference was observed: patients with CFS/ME showed compromised blood flow and less oxygen transport and utilization by the brain during exercise. The authors linked these observations to the early onset of central fatigue during exercise in the CFS/ME group (20).

In conclusion, there is increasing evidence suggesting a biological nature for post-exertional malaise in patients with CFS/ME. Although the recent studies summarized above provide important new findings, their design precludes making definite (causal) conclusions. These studies used observational case control designs to monitor the changes in biological variables from baseline to post-exercise. This implies that other factors, such as the stress triggered by study participation or natural fluctuations, in part account for the findings. Future randomized, cross-over controlled studies comparing the exercise response with other experimental conditions should shed light on this issue. Still, we agree with Kindlon & Goudsmit, and conclude that clinicians using exercise therapy for patients with CFS/ME should take into consideration the biological nature of post-exertional malaise.

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