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Treatment Harms To Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

Despite evidence of physiological and cellular abnormalities in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), the dominant therapeutic approach has been cognitive behaviour therapy (CBT) and graded exercise therapy (GET). Patients report distress and dissatisfaction following healthcare encounters based on GET and CBT. A significant body of research suggests that CBT and GET are harmful for many patients with ME/CFS. These findings raise ethical concerns and suggest that more collaborative working between scientists, therapists and patients would be helpful in making scientific progress in this difficult field.

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Introduction

Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) are serious, unpredictable, complex, multisystem, chronic conditions that can profoundly limit the health, activities and psychosocial wellbeing of affected patients. The condition is estimated to affect approximately 70 million people worldwide with a prevalence of 0.89% according to the Centers for Disease Control-1994 case definition, with women approximately 1.5 to 2 times higher than men in all categories (Lim et al., 2020). Jason and Mirin (2021) updated the US prevalence and economic impact estimates of the 2015 National Academy of Medicine report on ME/CFS taking into account population growth, economic inflation, and inclusion of children. They reported a doubling of ME/CFS prevalence to 1.5 million (0.45%) and an economic impact in the US in the range of 36–51 billion dollars per year. The figures for PASC is a highly transmissible infectious respiratory disease exists in two main stages, acute and post-acute or chronic. The acute phase lasts between 7 and 28 days with an estimated 10% – 30% of patients developing PASC. It has been estimated that the global pooled prevalence of PASC is 0.43 (95% confidence interval, .39–.46) with women being around 1.3 times more likely than men to fall ill with PASC

(Chen et al., 2022). An estimated 200-250 million individuals are likely to be affected by PASC with high impact on health care systems worldwide. Combining the two populations together indicates that an estimated total of 270-320 million people could have ME/CFS or PASC, i.e., one in 33 of the world population.

There is converging evidence of similar symptomatology of ME/CFS and PASC (Marks, 2023). It seems highly possible that the same therapeutic approaches will be offered to patients with PASC as have already been tried with patients with ME/CFS (Yong and Liu, 2021). It is timely to review the evidence on the potential harms of such treatments, one of which is Graded Exercise Therapy (GET) and another that is often combined with GET, Cognitive Behaviour Therapy (CBT). Despite the evidence of physiological and cellular abnormalities in ME and CFS, these approaches follow the biopsychosocial model (BPSM) claimed by the discredited Psychosomatic School to legitimize the use of CBT and GET for patients with ME/CFS (Wessely, David, Butler & Chalder, 1989; White et al., 2011). A recent review concluded:

The evidence ... suggests that none of these psychosomatic hypotheses is empirically supported. The lack of robust supportive evidence together with the use of fallacious causal assumptions, inappropriate and harmful therapies, broken scientific principles, repeated methodological flaws and an unwillingness to share data all give the appearance of cargo cult science. The psychosomatic approach needs to be replaced by a scientific, biologically grounded approach to MUS/ME/CFS that can be expected to provide patients with appropriate care and treatments. Patients with MUS/ME/CFS and their families have not been treated with the dignity, respect and care that is their human right. Patients with MUS/ME/CFS and their families could consider a class action legal case against the injuring parties. (Marks, 2022).

Multiple patient reports and independent studies have indicated stigmatization, distress and dissatisfaction following GET and CBT. A significant body of research suggests that CBT and GET are not only ineffective, but harmful for many patients with ME/CFS. The following sections review the most recent studies of patient treatment harms following CBT and GET.

Twisk and Maes (2009)

A review of CBT and GET by Twisk and Maes (2009) found that CBT and GET are “not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS” (p. 284). Twisk and Maes (2009) suggested that CBT/GET are hardly more effective than non-interventions or standard medical care, but also that “many patients report that the therapy had affected them adversely, the majority of them even reporting substantial deterioration”. Exertion which is almost bound to occur with GET is most likely to have a negative impact on many ME/CFS patients. Exertion produces post-exertional malaise (PEM) which decreases aerobic capacity, increases musculoskeletal pain, neurocognitive impairment, “fatigue”, and weakness, and produces a slow recovery time. Twisk and Maes concluded that it is “unethical to treat patients with ME/CFS with ineffective, non-evidence-based and potentially harmful “rehabilitation therapies”, such as CBT/GET”.

Kindlon (2011) and (2017)

High rates of adverse effects have been reported with CBT and GET by ME/CFS patients. Kindlon (2011) reviewed 10 patient surveys from four countries found that 51 per cent of respondents (range = 28%–82%, $n = 4338$, eight surveys) reported GET worsened their health, whereas 20 per cent of respondents (range = 7%–38%, $n = 1808$, five surveys) reported similar results for CBT.

Kindlon (2017) also reviewed evidence that low-intensity exercise has the potential to exacerbate symptoms in CFS. The effects of exercise can persist for more than a week after exertion e.g. gentle exercise of less than 7-minute duration can lead to worsening of fatigue, pain, sore throat and/or general health (Nijs et al., 2008; Van Oosterwijck et al., 2010). Longer-term, the effects of exercise can persist beyond 24 hours (VanNess et al., 2010). Lapp (1997) followed 31 patients for 12 days after a maximal exercise test and found that the average relapse lasted 8.82 days with 22 per cent still in relapse at 12 days. Kindlon (2017) observed that: “interventions involving exercise could provoke a general and persistent worsening or exacerbation of symptoms in CFS. They also offer an explanation as to why it might be difficult for patients with CFS to adhere to graded activity/exercise interventions” (p. 1147). As noted, post-exertional malaise is a key symptom of ME/CFS. Numerous biological abnormalities have also been found following exertion (Lane et al., 2003; Light et al., 2009; Sorensen et al., 2009; Twisk and Maes, 2009).

Vink and Vink-Niese (2018)

The review by Vink and Vink-Niese (2018) focuses on the controversial Cochrane review of GET for CFS) that concluded that GET is effective and safe (Larun et al., 2017, 2019). Vink and Vink-Niese (2018) point out that Larun et al.

acknowledges that limited information makes it difficult to draw firm conclusions about the safety of exercise therapy yet claims no evidence to suggest exercise therapy may worsen outcomes. This conclusion relies on the fact that White et al. (2011) reported only two serious adverse reactions (SARs) possibly related to treatment, and Wearden et al. (2010b) reported no SARs due to therapy.

Vink and Vink-Niese (2018) discuss the many problems with the Cochrane review which included P-Hacking, extensive endpoint changes, overlap in entry/recovery criteria, selecting patients who do not have the disease, ignoring null effects, relying on subjective outcomes in unblinded trials and ignoring the absence of objective improvement. In regard to effectiveness, Vink and Vink-Niese (2018) concluded that GET is ineffective. If a treatment is potentially harmful yet ineffective, it should not be used, exactly as recommended by NICE (2020). As a consequence of the criticisms offered by the Vinks and others, Cochrane’s Editor-in-Chief, Dr Karla Soares-Weiser, required Larun et al.’s review to be redone, this time in consultation with an independent advisory group involving ME/CFS patients. The findings of the redone review appear to be little changed from those of the original version.

Geraghty and Blease (2019)

harm reported by patients:

1. difficulties in reaching an acceptable diagnosis;
2. misdiagnosis, including of other medical and psychological conditions;
3. difficulties in accessing the sick role, medical care and social support;
4. high levels of patient dissatisfaction with the quality of medical care;
5. negative responses to controversial therapies (cognitive behavioral therapy, CBT, and graded exercise therapy, GET);
6. challenges to the patient narrative and experience;
7. psychological harm (individual and collective distress).

Geraghty and Blease (2019) concluded that the *“biopsychosocial framework currently applied to ME/CFS is too narrow in focus and fails to adequately incorporate the patient narrative. Misdiagnosis, conflict, and harm are observable outcomes where doctors’ and patients’ perspectives remain incongruent. Biopsychosocial practices should be scrutinized for potential harms. Clinicians should consider adopting alternative patient-centred approaches.”*

McPhee, Baldwin, Kindlon and Hughes (2019)

McPhee et al. surveyed the National Health Service–affiliated ME/CFS specialist clinics in England to assess how harms following treatment are detected and to examine how patients are warned about the potential for harms. The researchers sent 57 clinics standardised information requests under the UK’s Freedom of Information Act. Data were received back from 38 clinics. Clinics were highly inconsistent in their approaches to the issue of treatment-related harm. Clinics placed little or no focus on the potential for treatment-related harm in their written information for patients and for staff.

Furthermore, no clinic reported any cases of treatment-related harm, despite acknowledging that many patients dropped out of treatment. McPhee et al. recommended that clinics need to “develop standardised protocols for anticipating, recording, and remedying harms, and that these protocols allow for therapies to be discontinued immediately whenever harm is identified”.

Friedberg, Sunnquist and Nacul (2020)

Friedberg, Sunnquist and Nacul (2020) also reviewed evidence suggesting that claims of safety of CBT and GET are “not adequately supported by the evidence and are contradicted by the experiences of clinicians and patients.” They quote the 2014 Agency for Healthcare Research and Quality (AHRQ) review that reported, *“Harms [worsening of symptoms and/or disability] were generally inadequately reported across trials”* (p. vi). The AHRQ report concluded that GET studies

reported more adverse events and withdrawals. As early as 2012, experienced clinicians were not recommending PACE-type GET or CBT as treatments (Friedberg et al., 2012). They also cite Kindlon's (2015) analysis of large international patient surveys in which more than 50% of pwME/CFS reported that CBT and GET fell short of delivering significant improvements and often led to worsened health due to ill-advised activity and exercise prescriptions.

NICE Draft Guidance (2020)

The NICE guideline released on 10 November 2020 stated:

- 1) NICE "recognises that ME/CFS, which is estimated to affect over 250,000 people in England and Wales, is a complex, multi-system, chronic medical condition where there is no 'one size fits all' approach to managing symptoms. It stresses the need for a tailored, individualised approach to care that allows joint decision making and informed choice."
- 2) "Because of the harms reported by people with ME/CFS, as well as the committee's own experience of the effects when people exceed their energy limits, the draft guideline says that any programme based on fixed incremental increases in physical activity or exercise, for example graded exercise therapy (GET) should not be offered for the treatment of ME/CFS."
- 3) "Instead, it highlights the importance of ensuring that people remain in their 'energy envelope' when undertaking activity of any kind and recommends that a physical activity programme, in particular, should only be considered for people with ME/CFS in specific circumstances."
- 4) "The draft guideline also emphasises that CBT it is not a treatment or cure for ME/CFS. However, as a supportive therapy which aims to improve wellbeing and quality of life, the draft guideline says CBT may be useful in supporting people who live with ME/CFS to manage their symptoms."

White and Etherington (2021)

Peter White (PW) has been a long-standing proponent of the BPSM and the use of GET as a treatment for ME/CFS. Although there is no empirical evidence to support the deconditioning hypothesis (Marks, 2023), PW has repeatedly stated it, and advocated GET as a treatment in numerous publications. PW was a principal investigator and first author of the discredited PACE trial (White et al., 2011). PW's declared conflicts of interest state that he was "co-author of three of the trials reviewed. He is also a member of the Independent Medical Experts Group, which advises the UK Ministry of Defence regarding its Armed Forces Compensation Scheme and provides paid consultancy to a re-insurance company." This paper with Etherington reviewed adverse outcomes in ten trials of graded exercise therapy for adult patients with chronic fatigue syndrome. However, these authors did not review any of the evidence described in the sections above. The results showed that drop-outs rates at trial follow up occurred in 74/679 (11%) participants after GET and in 41/600 (7%) participants after control interventions (RR (CI): 1.51 (1.03, 2.22)). Therefore, the drop-out rate was significantly higher by $11/7 = 57\%$ in the GET treatment groups than in the control groups.

The authors concluded:

[1] There was no evidence of excess harm with graded exercise therapy by either self-rated deterioration or by withdrawing from GET, in comparison to control interventions.

[2] More GET participants dropped out of trial follow up in comparison to control interventions.

Conclusion [2] contradicts conclusion [1]. This partial review covers only a thin part of the scientific evidence and appears inconclusive and unreliable.

Conclusions

1. It is self-evident that healthcare professionals must seek to avoid and minimize harms when assisting patients. As suggested by Geraghty and Blease (2019), a “concordant ‘patient-centred’ approach that give greater prominence to the patient narrative and experience of illness” is required.
2. In light of the findings on patient harms, extreme caution is required in offering patients with ME/CFS treatments such as CBT and GET which involve increased exercise or activity levels.
3. The findings on patient harms suggest that treatments using CBT and GET involve ethical dilemmas which practitioners can be helped to resolve by working with patients using a more collaborative approach.
4. Clinics should develop standardised protocols for anticipating, recording, and remedying harms, and these protocols should allow for therapies to be discontinued immediately whenever harm is identified.
5. Somewhat belatedly, the revised NICE guidance (2020) recognizes the evidence on harms to ME/CFS patients from the use of GET and, to a lesser extent, CBT. The change in guidance is in no small measure a tribute to the researchers and patients who are cited here.
6. The attempts by some practitioners to relabel GET in order to continue its use post-NICE-2020 is plainly unethical and must be vigorously resisted.
7. Physicians and others who are treating patients with PASC need to made aware of the possible risks and harms that may ensue from the use of GET with or without CBT.

Conflicts of interest

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