Is the RACGP HANDI recommendation of incremental physical activity for chronic fatigue syndrome/myalgic encephalomyelitis harming patients?

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In April 2024, The Royal Australian College of General Practitioners (RACGP) Handbook of Non-Drug Interventions (HANDI)committee published a guideline: Incremental physical activity for chronic fatigue syndrome/myalgic encephalomyelitis.[1] The HANDI committee claims to recommend interventions that are based on 'solid evidence'.[2] But is this always the case?

An evaluation under the AGREE II instrument for assessing guidelines scored the RACGP guideline at only 2% for rigour of development.[3] Alarmingly, the guideline provides no evidence of a systematic review of the literature, nor an analysis of the strengths and limitations of the three cited papers: the PACE trial; the Cochrane review, Exercise therapy for chronic fatigue syndrome; and Fawzy et al's systematic review of treatments for post-acute COVID-19 syndrome [PACS]).[1,4,5,6] Indeed, the PACE trial has been heavily criticised for outcome switching and bias.[7–9] If the PACE trial had adhered to the original definition of recovery laid out at the beginning of the study, only 4% of graded exercise therapy participants would have been classified as recovered, and the effect would not have been statistically significant.[9] After participants had completed therapy, the study's authors weakened the definition of recovery to encompass values that fall far below healthy norms. In fact, many 'recovered' participants were still sick enough to meet the entry requirements to the study.[8] Worse, some participants were classified as recovered or improved before undertaking any treatment.[10]

Similarly, the Cochrane review has been criticised for failing to consider reports of harm or to downgrade the reviewed studies for their use of outdated diagnostic criteria that lacked specificity.[11,12] In the majority of the reviewed trials, around 90% of participants are likely to have had general fatigue, not myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[11–13] Additionally, all of the Cochrane-reviewed trials were unblinded and at high risk of bias.[5] Note that the Cochrane review has updated the date on their 2017 and 2019 studies to 2024 without altering the contents. All criticisms of the 2017 and 2019 Cochrane reviews still apply.[14,15]

The third reference, Fawzy et al's systematic review, concluded that the evidence supporting PACS treatments is weak.[6] It is unclear why the RACGP guideline cites a paper that does not support exercise therapy and does not mention ME/CFS.

Furthermore, the RACGP guideline lists the benefits of exercise therapy.[1] However, these benefits have been demonstrated in other fatiguing conditions, not in ME/CFS. This is concerning, because the research consensus now recognises post-exertional symptom exacerbation (PESE) as the defining feature of ME/CFS (Box 1).[16,17] The RACGP guideline acknowledges PESE and the consequent reports of harm from patients with ME/CFS undergoing exercise therapy.[1] However, the guideline dismisses the reports of harm without providing evidence for the dismissal.[1] The document admits that the recommendations may not apply to people diagnosed with ME/CFS under stricter criteria or those who have severe PESE, but it does not explain how to differentiate between those who might be harmed and those who might benefit.[1] Consequently, the AGREE II assessment concluded that the guideline has very serious limitations and is not fit for purpose.[3]

Graded exercise therapy establishes an achievable baseline of physical activity or exercise.[1] Patients then increase their activity at fixed increments.[1] Graded exercise therapy misconstrues ME/CFS as deconditioning combined with a psychological fear of exercise.[18] Therefore, therapists actively suppress reports of harm, and worsening symptoms are not recorded.[18] However, independent surveys indicate

Box 1. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

ME/CFS is a neurological disease characterised by cognitive deficits, unrefreshing sleep and debilitating fatigue that is not relieved by rest.[17,20] Patients may experience gastrointestinal, immunological and autonomic dysfunctions, including orthostatic intolerance, flu-like symptoms, sensory sensitivities, alcohol intolerance, food sensitivities, chemical sensitivities, pain and neuromuscular symptoms.[16,17]

The defining feature of ME/CFS is post-exertional symptom exacerbation (PESE), otherwise known as 'post-exertional malaise' – a prolonged, system-wide flare of symptoms following minimal physical, cognitive or social exertion.[17] PESE is associated with cardiovascular, immunological, metabolic, gastrointestinal, autonomic, sleep and cognitive abnormalities in response to exercise.[16] The onset of PESE may be delayed by up to 2 days and the recovery period is prolonged, lasting from days to weeks, depending on disease severity.[17]

that graded exercise therapy intensifies ME/CFS symptoms in 54–74% of patients.[18] If therapies were subject to the same requirement to report adverse reactions as medications, it is likely that graded exercise therapy would have been contraindicated for ME/CFS in Australia, as it has been in the UK[17] and the US.[19]

Anecdotally, people with mild to moderate ME/CFS may tolerate non-aerobic exercise, such as careful strength-building, stretching or Dru relaxation yoga. However, the purpose is to maintain function and prevent deconditioning; exercise does not cure ME/CFS.[17] All forms of exercise should be guided by an exercise physiologist, physiotherapist or occupational therapist with training in ME/CFS, who can help the patient to avoid PESE.[17]

The UK's National Institute for Health and Care Excellence (NICE) followed a rigorous development process for their ME/CFS guideline, Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: Diagnosis and management.[11] An AGREE II evaluation of the NICE ME/CFS guideline scored the guideline at 92%.[3] The NICE guideline contraindicates exercise therapy for ME/CFS,[17] and this is reflected in the British Medical Journal (BMJ) Best Practice guideline for ME/CFS, which also contraindicates graded exercise therapy.[20] Similarly, after careful consideration, the US Centers for Disease Control and Prevention has also withdrawn its recommendation of graded exercise therapy for ME/CFS.[19]

Given the lack of sound research support for graded exercise therapy in ME/CFS, the contraindication of graded exercise therapy by best practice guidelines in the US and the UK, and patient reports of iatrogenic harm, the RACGP guideline, Incremental physical activity for chronic fatigue syndrome/myalgic encephalomyelitis, should be withdrawn immediately. Furthermore, graded exercise therapy should be contraindicated as per the BMJ Best Practice guideline until the National Health and Medical Research Council (NHMRC) has completed its review of ME/CFS guidelines in 3 years' time.[17–20] In the meantime, for evidence-based recommendations regarding the management of ME/CFS, general practitioners can refer to the UK's NICE and BMJ Best Practice guidelines.[17,20]

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Invited response to viewpoint article ‘Is the RACGP HANDI recommendation of incremental physical activity for chronic fatigue syndrome/myalgic encephalomyelitis harming patients?’

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) remains a poorly diagnosed yet debilitating condition. The Handbook of Non-Drug Interventions (HANDI) aims to make evidence-based non-drug interventions accessible and easier for clinicians to use where appropriate.

HANDI’s development and review processes are detailed on the website:[1] best evidence is reviewed and summarised, and tips are provided for implementation by a multidisciplinary editorial committee with a wealth of clinical and epidemiology experience. HANDI is not a guideline as it does not compare the treatments in entries to other treatment options, nor make recommendations. Hence assessment using the AGREE II instrument is inappropriate. HANDI interventions are graded using the National Health and Medical Research Council (NHMRC) standards, or the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) process for quality of evidence (not strength of recommendation).

Clinicians should note that some patient support groups have rejected the evidence of benefit from appropriately graded exercise, which has fractured the healthcare for CFS/ME, pre-dating the significant PACE trial 2008.[2] Debate on methodological quality of the PACE trial is addressed in *The Lancet*.[3] Several randomised controlled trials (RCTs) examining graded exercise for CFS/ME are provided in the supportive Cochrane review.[4] While Cochrane reviewers (2019) do account for study limitations, there is still moderate-strength GRADE evidence, for some patients, for a benefit of graded exercise over passive control groups or usual care with fatigue as the primary outcome.

For CFS/ME, all the studies reviewed by the HANDI editorial committee (and Cochrane review) are RCTs or systematic reviews of RCTs. The evidence offered for harm from exercise is from surveys at high risk of bias. Clinicians should be aware that some patients with CFS/ME cannot tolerate graded activity, but some may have been poorly guided in correct exercise implementation, triggering exacerbation of symptoms. HANDI provides some detail about the importance of patient selection and correct implementation.

HANDI recognises the underlying pathophysiology of CFS/ME is not known, and there are few proven treatment options. Current evidence supports appropriately graded incremental physical activity to manage symptoms.

The 2023 NICE guideline retraction was highly controversial and not aligned with research evidence, resulting in members of its writing group resigning. Details of the aberrant interpretation of evidence are outlined elsewhere.[5,6]

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