

# Checking our blind spots: current status of research evidence summaries in ME/CFS

Todd E Davenport,<sup>1,2</sup> Staci R Stevens,<sup>2</sup> J Mark VanNess,<sup>2,3</sup> Jared Stevens,<sup>2</sup> Christopher R Snell<sup>2</sup>

The evidence-based practice (EBP) model hierarchically organises scientific information by level, from lowly case studies to lofty systematic reviews and clinical trials. Clinical trials best influence recommendations because they putatively have the greatest internal validity.<sup>1</sup> This assumption is based on sound research ethics, such as scientific competence and good faith actors, as well as observed differences in outcomes. An EBP blind spot emerges when fundamental assumptions are unmet. Based on findings of a 2018 PEDro evidence summary in *BJSM*<sup>2</sup> and elsewhere,<sup>3</sup> it now seems clear that scientific research in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) resides in a blind spot.

## ME/CFS—A MULTISYSTEM CONDITION

ME/CFS is estimated to affect 836 000 to 2.5 million people in the USA.<sup>4</sup> Ninety per cent of cases are thought to go undiagnosed,<sup>4</sup> suggesting that people with ME/CFS are substantially undercounted, underdiagnosed and undertreated. Substantial literature exists to support that ME/CFS is a multisystem condition that appears associated with a combination of genetic, cellular and systemic metabolic deficits in aerobic metabolism. The hallmark clinical feature of ME/CFS is postexertional malaise (PEM), which involves a constellation of extensively disabling signs and symptoms in response to exertion. A number of diagnostic criteria exist, but the criteria including PEM appear to be most specific.<sup>4</sup> The pervasive nature of PEM in ME/CFS has led some working groups to revise diagnostic criteria for ME/CFS to highlight the multisystem deficits associated with exertional intolerance.<sup>4</sup> There is no known test, cure or a single drug for ME/CFS, highlighting a substantive need

for well-conceived and well-conducted clinical research in this area.

## EVALUATION OF THE UK PACE TRIAL—WHAT IS THE ROLE OF GRADED EXERCISE THERAPY (GET)?

The UK's Pacing, graded Activity and Cognitive behavioural therapy, a randomised Evaluation (UK PACE) compared the clinical outcomes of specialist medical care, adaptive pacing and GET in 641 people with idiopathic, disabling fatigue.<sup>5</sup> As published, symptomatic and functional outcome findings from the UK PACE trial did not reach clinical relevance. Perhaps the holy grail of ME/CFS research is objective evaluation of functional status, because the clinical presentation of fatigue can be deeply stigmatising. Many experts in the field of ME/CFS research contend that as published, the objective results of GET are marginal, probably not clinically relevant and unlikely to be of clinical benefit. For example, the statistically significant difference between the GET and control groups on the 6 min walk test was only 35.3 m. However, it is notable that results on subjective outcomes were not better than objective outcomes.

Among the many justifiable criticisms of how the UK PACE Trial was conducted is that criteria for recovery were revised downward after the study's inception. The extent of downward revision actually made it possible for a subject to be classified as 'recovered' on some criteria even if they worsened after enrolment into the trial.<sup>6</sup> Indeed, a secondary reanalysis of the trial data revealed recovery rates in the GET and CBT groups were low (4% and 7%, respectively), not significantly higher than in the control group (3%) and inflated by an average of 4-fold compared with predicted by baseline criteria.<sup>6</sup>

Despite the severe limitations of the UK PACE trial and its conceptual offspring, it continues to exert outsized influence on research evidence summaries as one of the few published randomised clinical trials in ME/CFS. It is important to note that the UK PACE trial is more than just a paper tiger: its dominance in the hierarchy of scientific evidence has led some countries with

planned health systems to develop treatment pathways based on flawed results.

## GRADED EXERCISE THERAPY MAY EXACERBATE POSTEXERCISE MALAISE

A major concern among patients is that GET may exacerbate the hallmark clinical symptom of ME/CFS—PEM.<sup>7</sup> Resulting treatment pathways involving GET may have exposed an untold number of patients with ME/CFS worldwide to GET that, at best, is marginally effective, and at worst, may be harmful. A disturbing corollary of this conundrum is that patients with ME/CFS are being harmed by a flawed standard of care, including forced separations of minor children from families and legal sanctions against parents.<sup>4</sup> Indeed, the UK PACE Trial has exposed some of the most important public health-related ethical and legal challenges of our time, which, as yet, remain largely under-reported and unknown to many clinicians.

EBP also includes patient perspectives. We should follow the example of engaged patient advocates and citizen scientists in ME/CFS by involving patients as advisory board members on trials and as reviewers on published evidence summaries. Community-based participatory research designs should be elevated to ensure information flows from bedside-to-lab bench, in addition to lab bench-to-bedside. By including evidence from patients in clinical decisions and research, we can begin to address the important blind spots in how we think about and implement EBP.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent** Not required.

**Provenance and peer review** Not commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2018. No commercial re-use. See rights and permissions. Published by BMJ.



**To cite** Davenport TE, Stevens SR, VanNess JM, et al. *Br J Sports Med* Epub ahead of print: [please include Day Month Year]. doi:10.1136/bjsports-2018-099553  
Accepted 27 June 2018

*Br J Sports Med* 2018;0:1–2.  
doi:10.1136/bjsports-2018-099553

## REFERENCES

- Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009 <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>
- Dannaway J, New CC, New CH, et al. Exercise therapy is a beneficial intervention for chronic

<sup>1</sup>Department of Physical Therapy, University of the Pacific, Stockton, California, USA

<sup>2</sup>Workwell Foundation, Ripon, California, USA

<sup>3</sup>Health and Exercise Science, University of the Pacific, Stockton, California, USA

**Correspondence to** Dr Todd E Davenport, Department of Physical Therapy, University of the Pacific, Stockton, CA 95211, USA; [tdavenport@pacific.edu](mailto:tdavenport@pacific.edu)

- fatigue syndrome (PEDro synthesis). *Br J Sports Med* 2018;52:542–3.
- 3 Larun L, Brurberg KG, Odgaard-Jensen J, *et al.* Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev* 2016;12:CD003200.
  - 4 IOM) IoM. *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness*. Washington, DC, USA: The National Academies Press, 2015.
  - 5 White PD, Goldsmith KA, Johnson AL, *et al.* Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011;377:823–36.
  - 6 Wilshire CE, Kindlon T, Courtney R, *et al.* Rethinking the treatment of chronic fatigue syndrome—a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. *BMC Psychol* 2018;6:66.
  - 7 Geraghty K, Hann M, Kurtev S. Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys. *J Health Psychol* 2017:135910531772615.