

Reply to ‘Graded exercise therapy should not be recommended for patients with post-exertional malaise’



We thank van Rhijn-Brouwer and colleagues for responding to our Review (A. Fedorowski et al. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. *Nat. Rev. Cardiol.* <https://doi.org/10.1038/s41569-023-00962-3> (2024))¹ with their Correspondence (F.C.C.-C. van Rhijn-Brouwer et al. Graded exercise therapy should not be recommended for patients with post-exertional malaise. *Nat. Rev. Cardiol.* <https://doi.org/10.1038/s41569-024-00992-5> (2024))². They expressed concerns about our statement that the “[a]pplication of graded exercise therapy is especially important in the setting of coexistent ME/CFS [myalgic encephalomyelitis/chronic fatigue syndrome] to reduce the effects of the highly expected post-exertional malaise”. Although discussing the benefits of aerobic reconditioning in patients with postural orthostatic tachycardia syndrome (POTS) and other forms of cardiovascular autonomic dysfunction, we factually meant that a more cautious approach is required in patients who present with signs of ME/CFS. We did not advocate generic advice to ‘do exercise’, but were calling for a more nuanced, individualized and supervised approach to exercise in these patients, as recommended by the UK National Institute for Health and Care Excellence (NICE)³. In this spirit, we recommended a graded approach to exercise therapy. Although a graded approach can have many meanings, we see that some authors use the term ‘graded exercise therapy’ to advocate a more standardized and less individualized approach to physiotherapy. Our understanding is that, in some cases, a standard approach to physical exercise might potentially harm patients with a still poorly defined susceptibility to post-exercise energy depletion⁴. We apologize for our lack of clarity. Our intention was to raise awareness of this special subgroup of patients among those who have post-COVID-19 cardiovascular dysautonomia, rather than to promote the training programme in an indiscriminate way.

The issue of post-exertional malaise after different types of exercise is intriguing and

hitherto not extensively studied^{4,5}. Patients with post-exertional malaise undoubtedly feel substantially worse immediately, and in the short-term, after exercise. However, clinical observations demonstrate that, over time, exercise can be beneficial in many patients with POTS^{6,7}, including those with post-COVID-19 syndrome⁸. Although post-exertional malaise was not formally assessed in these studies, some patients are likely to have had post-exertional malaise. We, the authors of the Review, see many patients with POTS in our clinical practices, and each of us has seen patients who had initial worsening at the onset of an individual training programme, but who improved during follow-up under careful supervision by professional staff. Importantly, this approach is supported by the NICE guidelines³. We undoubtedly agree with van Rhijn-Brouwer and colleagues that further research is needed to understand how best to care for patients with cardiovascular autonomic dysfunction in post-COVID-19 syndrome. New evidence based on well-designed trials will be crucial, as demonstrated by the list of ongoing projects in our Review¹. Until then, the jury is still out; we should wait for the verdict and respect it when it comes.

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References

1. Fedorowski, A. et al. Cardiovascular autonomic dysfunction in post-COVID-19 syndrome: a major health-care burden. *Nat. Rev. Cardiol.* <https://doi.org/10.1038/s41569-023-00962-3> (2024).
2. van Rhijn-Brouwer, F. C. C.-C. et al. Graded exercise therapy should not be recommended for patients with post-exertional malaise. *Nat. Rev. Cardiol.* <https://doi.org/10.1038/s41569-024-00992-5> (2024).
3. National Institute for Health and Care Excellence. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. *NICE* <https://www.nice.org.uk/guidance/ng206> (2021).
4. Komaroff, A. L. Advances in understanding the pathophysiology of chronic fatigue syndrome. *J. Am. Med. Assoc.* **322**, 499–500 (2019).
5. Komaroff, A. L. & Lipkin, W. I. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. *Front. Med.* **10**, 1187163 (2023).
6. Shibata, S. et al. Short-term exercise training improves the cardiovascular response to exercise in the postural orthostatic tachycardia syndrome. *J. Physiol.* **590**, 3495–3505 (2012).
7. Wheatley-Guy, C. M. et al. Semi-supervised exercise training program more effective for individuals with postural orthostatic tachycardia syndrome in randomized controlled trial. *Clin. Auton. Res.* **33**, 659–672 (2023).
8. Svensson, A. et al. Individual tailored physical training in patients with postural orthostatic tachycardia syndrome associated with post-acute COVID-19 syndrome — a feasibility study [abstract]. *EP Europace* **25** (Suppl. 1), euaad122.673 (2023).

Competing interests

A. Fedorowski has received speaker fees from Bristol-Myers Squibb, Finapres Medical Systems and Medtronic, and is a consultant to Argencx and Medtronic in the field of syncope, cardiovascular autonomic dysfunction and postural orthostatic tachycardia syndrome. A. Fanciulli has received royalties from Springer Verlag, and speaker fees and honoraria from the Austrian Autonomic Society, Broadview Ventures, Elsevier, GE Healthcare, Stopp-HSP and Theravance Biopharma. S.R.R. has served as a consultant for Amneal Pharmaceuticals, Antag Therapeutics, Argencx BV, Regeneron and Theravance Biopharma, and receives an honorarium from Elsevier for being Associate Editor of *Autonomic Neuroscience*. C.A.S. has received speaker fees and honoraria from Argencx and Theravance Biopharma, and is a consultant for Antag Therapeutics and Theravance Biopharma. R. Sutton has received consulting fees from Medtronic and payment for expert testimony in medicolegal cases in the UK; was a member of the clinical events committee for the BioSync study; and is secretary to the Executive Board of the World Society of Arrhythmias. R. Sheldon declares no competing interests.