New NICE guideline on chronic fatigue syndrome: more ideology than science?

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The National Institute for Health and Care Excellence (NICE) in the UK published a new chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) guideline in October, 2021.[1] The previous NICE 2007 guideline recommended cognitive behavioural therapy (CBT) and graded exercise therapy (GET) for people with mild or moderate CFS/ME based on evidence from randomised trials.[2] Since then, more randomised trials and systematic reviews have provided additional evidence supporting these recommendations.[3-8] No new or more effective interventions have been identified. Although we applaud guideline efforts, it is remarkable that recommendations in the 2021 NICE guideline differ substantially from the previous one, and do not include CBT and GET as means to treat CFS/ME. The new guideline presents strengthened evidence, but a major shift in interpretation. How could this happen?

One reason for controversies in the field of CFS/ME is the unresolved puzzle regarding the relation between subjective symptoms and objective findings. Too many patients have felt rejected by health professionals and taken home the message that “we do not find anything wrong with you physically, so your symptoms are in your imagination”. However, symptoms are realities, although they can only be reported by those who experience them, and they always have a neurobiological correlate like all sensations and experiences. It is a common clinical experience that patients often respond to this ill-informed and stigmatising message by deciding that “I have bodily symptoms so there must be a bodily disease”. However, the relation between symptoms and disease is complex, as pain research showed decades ago: pain can be felt without any tissue damage, and tissue damage does not necessarily evoke pain.[9] Symptoms do not provide direct information on the nature of the underlying pathophysiology—eg, the sensation of fatigue is not necessarily related to immunological aberrations, but might be explained by functional alterations in the CNS.[10] This fact is not acknowledged by the new NICE guideline. It is uncontroversial that a diagnosis of CFS/ME rests upon subjective symptoms. But paradoxically NICE decided that evidence from clinical trials of CBT and GET showing improvement in subjective symptoms would be considered unreliable.[2–8] Given the first premise, subjective symptoms are the most valid endpoints, and interventions improving these symptoms are treatments, not only “symptom management”.

Nevertheless, the NICE guideline committee presented a new non-validated diagnostic definition of CFS/ME, making post-exertional malaise (PEM) a required criterion. This reliance on one subjective symptom for diagnostic purposes is inconsistent with the guideline committee’s downgrading of trials that use subjective symptoms as primary endpoints. This approach also overlooks research showing that changes in diagnostic criteria can lead to unintended consequences in the target population[11] and that PEM is unspecific (eg, it is prevalent among cancer survivors).[12] The guideline committee downgraded all studies not mandating PEM for indirectness, although data presented during the consultation process showed improvement of PEM and other symptoms in trials of CBT and GET, and also overlooked evidence that treatment effect is similar across different diagnostic criteria, including those with PEM.[6,13]

NICE has, rightly so, involved people with CFS/ME in the guideline process, yet in our view has given undue weight to one group of people and not taken sufficient account of those who have improved or recovered. The polemic unfortunately has become a battle. Seven medical leaders in Royal Colleges and faculties in the UK declared in a joint statement: “There is considerable disquiet in the medical profession and some patient groups about the way the data and evidence have been assessed”.[14] During the guideline process three professional members of the guideline committee stepped down.[15] The remaining committee did not accept the concerns from some leading medical organisations conveyed during the consultation phase, resulting in only minor adjustments in the final guideline.[1,14]

The guideline committee members declared conflicts of interests, but there are no statements regarding their prior beliefs.[16] We know from social media that some of the committee members and two of the three expert witnesses had negative opinions regarding the interventions considered.[17,18] Judgment has an unavoidable role in guideline development processes.[19] The guideline community might learn from qualitative researchers how to explore preconceptions and encourage reflexivity to address non-financial competing interests.[20–22]

The guideline committee gave instructions to the systematic reviewers that biased the evidence, and they misused the GRADE approach[23] to downgrade the certainty of evidence inappropriately.[24] Absence of blinding and subjective outcomes is common in studies of non-pharmacological interventions for conditions without objective criteria, but does not imply that all such studies are biased and should be downgraded. NICE ignored GRADE guidance on presenting and interpreting results of patient-reported outcomes, such as fatigue, pain, and quality of life.[25]

The guideline committee decided to consider trial outcomes at the furthest time away from recruitment, overlooking data on end of treatment and the trial primary endpoint in the largest trial of CBT and GET.[6] This omission contributed to downgrading for imprecision and the questionable conclusion in the new guideline that there was insufficient evidence for the efficacy of CBT and GET. Here, NICE did not account for cross-over between the intervention and the control group during long-term follow-up. Trials of COVID-19 vaccination might be illustrative: given the guideline committee's principle of using outcome measures "furthest time away", a long-term follow-up vaccination trial would probably show no beneficial effect of the vaccine because the control group would presumably have been immunised as well.

Unusually, the guideline committee decided not to include Cochrane reviews, because the review did not report one of the crucial outcomes determined by the committee, namely mortality. Mortality was not an outcome in any of the trials considered, however, because it is not relevant in studies of CBT and GET for CFS/ME. In addition to not including and updating Cochrane reviews, the committee did not conduct their own data synthesis of clinical trials; hence, the certainty of many primary outcomes was downgraded for imprecision.

NICE did not recommend GET, claiming this treatment is ineffective and harmful, based on anecdotal evidence from patient group surveys and qualitative studies, which it preferred to the systematically assessed trial safety data.[1,6,26] NICE ignored a summary provided to them in the consultation period of a now published meta-analysis of safety outcomes in the ten published trials of GET, suggesting that GET is safe so long as it is properly prescribed.[27]

These shortcomings in the guideline process suggest that it was not driven by science but by ideology—that is, socially determined perceptions of reality characterised by, for example, insufficient corrective effects from experiences and inherent defence mechanisms against criticism.[28,29] Whereas science aims to search the truth of something by adherence to jointly agreed standards, an ideological endeavour imposes the will of its proponents. By selective use of the evidence from randomised studies, cherry-picking statements from qualitative studies, and relying on the opinions of the committee, NICE disregarded the best available research evidence and tarnished the guideline process. In our view, this guideline denies patients treatments that could help them, undermines NICE as an international authority in guideline development, and jeopardises fundamental scientific principles by allowing some processes driven by ideology. We find these observations deeply concerning.

SAF reports that for about 20 years she has been involved in reviewing evidence on CFS/ME and taken part in debates in this field in Norway and is a member of the GRADE Working Group and of the GRADE Guidance Group. KGB reports that he is one of the authors of the Cochrane review about CFS/ME and exercise therapy and he is currently involved in the work with a review based on individual patient data that is about CFS/ME and exercise therapy. PF declares no competing interests. HK receives royalties for a treatment manual of CBT for CFS/ME and is currently preparing a review based on individual patient data of the outcomes of CBT for CFS/ME. VBBW reports that for two decades he has conducted research in the field of CFS/ME, and that he is chair of the international Collaborative on Fatigue Following Infection (COFFI); VBBW's research endeavours have been conducted within a biopsychosocial framework.

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Accelerating Indigenous health and wellbeing: the *Lancet* Commission on Arctic and Northern Health

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Arctic Indigenous communities and adjacent Indigenous peoples considered Northern or Circumpolar in distribution recognised the threat posed by COVID-19 to their communities. Despite inhabiting many of the world's most resourced countries, the health of Arctic Indigenous peoples lags behind their non-Indigenous counterparts across many indicators,[1,2] and many communities remember the devastating consequences of the 1918–19 influenza pandemic on their communities.[3] Swift action by Arctic Indigenous leaders limited COVID-19 cases in many communities, protecting their vulnerable groups from the worst outcomes seen in some other Indigenous communities globally.[4] The effectiveness of these early responses was shown in the initial low number of COVID-19 cases among Arctic Indigenous peoples[4,5] and highlights important lessons for other global regions. Yet there is an urgent need to address persistent health disparities in Arctic Indigenous communities.

These deep disparities reflect the destructive legacy of colonialism, forced displacement, inadequate health systems, systemic racism, and infrastructure deficits.[2,6] Compounded by inter-related and broad environmental deterioration, including temperatures rising at more than twice the global average in Arctic regions,[7] such conditions further threaten the health and wellbeing of Arctic Indigenous peoples. Despite the growing international acknowledgment of these crisis conditions, the health and wellbeing of Arctic Indigenous communities have been conspicuously absent from the global health agenda.

To address this concerning situation, *The Lancet* has convened a Commission on Arctic and Northern Health. This Commission is composed of a majority of Arctic