

Call for Evidence – Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome

Please send the information before 04/10/19

- When submitting evidence that is published please provide reference details (which are to include author/s, title, date, journal or publication details including volume and issue number and page numbers)
- We are unable to accept forms with electronic attachments of published material (eg journal articles), or hard copies of published material. For copyright reasons, we cannot accept these copies. However, if you give us the full citation, we will obtain our own copy.
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Stakeholder Organisation	Evidence Submission (Details of evidence that relates to the questions. Please specify which question you are referring to)	Published / Unpublished material	How the evidence can be obtained (For published material, please include full reference details; author, date of publication, full title of paper/report and where can a copy be obtained from)
#MEAction	Question 1. Monitoring and/or reviewing. Question 1. Management strategies. Question 2. Interventions. The conclusions from the research based on 1900 respondents:	Published	Leary, S., Sylvester, J., Shorter, E., Moreno, E., (2019). Your experience of ME services. Survey Report by #MEAction UK. #MEAction. Retrieved from: https://www.meaction.net/wp-

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	<p>Management strategies during assessment for diagnosis:</p> <ul style="list-style-type: none"> • Results showed that healthcare professionals are commonly providing advice to maintain or increase activity during this period. Almost 9 out of 10 respondents deteriorated having followed this advice, compared to less than 1 in 10 who were told to rest. <p>Methods of monitoring and/or reviewing:</p> <ul style="list-style-type: none"> • Results identified that there was a failure of services to provide ongoing support or follow up which left respondents feeling abandoned and without help. • Respondents thought that services should be led by a consultant, with support from professionals trained in the causes and impact of ME. <p>People's experience of interventions for ME/CFS:</p> <ul style="list-style-type: none"> • The experience of respondents showed that many ME services are providing unsuitable advice and treatments that often have a negative impact on patients' health. • CBT was not helpful to a majority of respondents. • Advice on activity management was contrary to what respondents reported would have been most helpful in hindsight. • Respondents were commonly pressured to undergo treatments. • Overall, respondents wanted current services either to adapt or to be entirely rebuilt with patient input, confirming that current services are failing to meet the needs of patients. 		<p>content/uploads/2019/10/Your-experience-of-ME-services-Survey-report-by-MEAction-UK.pdf Raw data is also attached to this submission.</p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>25% Group review of severe M.E. sufferers who are and have been housebound and or bedbound for 2+ years. "When asked 'Do You Attribute Your Chronic Severe State To Anything Specific?' the most common responses were a virus, lack of info/overactivity and graded exercise. Furthermore of those who felt their health was improving, respondents most commonly attributed this to "Pacing Activity Programme & Rest".</p>	Published	<p>25% ME Group. (2000). M.E. Questionnaire Results. Retrieved from: https://25megroup.org/download/1819/?v=1828</p>

#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Survey of 162 members of 25% ME Group, including questions such as "If your condition deteriorated after referral, do you attribute this to anything specific?", to which respondents most commonly said "overdoing it/graded exercise". Further data investigates the experience of people with ME in different care settings.</p>	Published	<p>25% ME Group. (2002). M.E. Generic Members Survey Questionnaire Results. Retrieved from: https://25megroup.org/download/1819/?v=1826</p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Evidence that GET is harmful, and questionnaire responses on other interventions: "By far the most unhelpful form of treatment was considered to be Graded Exercise Therapy (GET). This is a finding that may surprise some readers, given the current medical popularity of this approach. However, these patients' perceptions are supported by data from previous experience: of the 39% of our members who had actually used Graded Exercise Therapy, a shocking 82% reported that their condition was made worse by this treatment."</p>	Published	<p>25% ME Group. (2004). Severely affected ME (myalgic encephalomyelitis) analysis report on questionnaire issued January 2004. Retrieved from: https://25megroup.org/download/1819/?v=1827</p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>This 2001 patient survey by Action for ME found that "Pacing and rest were reported to have been most beneficial and graded exercise was reported to be the treatment that had made most people worse." p.7</p> <p>50% of people reported they were made worse by GET, and 67% reported that CBT resulted in "No change".</p>	Published	<p>Action for ME. (2001). Severely Neglected. M.E. in the UK. [There isn't a link to retrieve online, therefore we have included a copy attached to this submission.]</p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Accessibility and appropriateness of interventions in severe ME: "Action for M.E.'s survey asked people with severe M.E. what would make a real difference to their healthcare: • 68% said a better informed GP</p>	Published	<p>Action for ME. (2014). Severe M.E. Time to Deliver report by Dr Andrew Pates. Retrieved from: https://www.actionforme.org.uk/uploads/pdfs/my-life-stopped-severe-ME-report.pdf</p>

	<ul style="list-style-type: none"> • 66% said more effective medication • 63% said home visits • 53% said joined-up health and social care • 36% said having more of a say in their treatment • 21% said telehealth." 		
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>"There are two groups of therapies which improve the situation for many and only make it worse for a very few:</p> <ul style="list-style-type: none"> - Pacing and various types of meditation and relaxation techniques including Qi-gong-training for ME patients have improved or even greatly improved the situation for two of three who have tested these therapies. They only made the situation worse for 1 in 10, or even less. - Therapy by Strømmen Medical Centre and its predecessor Lillestrøm Health Clinic, improved the situation for 2 out of 3 patients, and only made it worse for 1 out of 20. <p>At the other end of the scale we found two other therapies which improved the situation for a very few but made it worse or even considerably worse for many:</p> <ul style="list-style-type: none"> - Exercise training/ progressive physiotherapy and graded exercise therapy only improved the situation for around 1 out of 10 and made the situation worse for 2 out of 3, and seriously worse for half of these. - Lightning Process, which improved the situation for 1 out of 5, made the situation worse for half the patients, and seriously worse for 1 out of 4." 	Published	<p><i>Bringsli, G. J., Gilje, A., & Getz Wold, B. K. (2014). The Norwegian ME Association National Survey Abridged English Version. Norges Myalgisk Encefalopati Forening. Retrieved from: http://www.me-foreningen.info/wp-content/uploads/2016/09/ME-Nat-Norwegian-Survey-Abr-Eng-Ver.pdf</i></p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>This Dutch survey of 449 respondents looked at the effects of CBT alone and CBT combined with GET. The results state that:</p>	Published	<p><i>Corsius, L. A. M. M., Crijnen, B.G.P.J.M., Hogeweg, A.A., Kuijper, J.S.M. (2019). Zorg voor betere behandeling bij ME. Enquête onder ME-patiënten naar hun ervaringen met behandelingen bij ME. Retrieved from: <a 853="" 874"="" 905="" 923="" data-label="Page-Footer" href="https://www.me-</i></p> </td> </tr> </table> </div> <div data-bbox=">4</i></p>

	<p>"In the CBT group (n = 129), 61 respondents (47.29%) rate the effect of the treatment on their health status as 'negative' or 'very negative'. In the CBT / GET group (n = 142), 94 respondents (66.20%) gave the rating 'negative to very negative'. In the biomedical treatment group (n = 214), 25 responded (11.68%) 'negative to very negative'." p.31</p> <p>"In de CGT-groep (n=129) waarden 61 respondenten (47,29%) het effect van de behandeling op hun gezondheidstoestand als 'negatief' of 'zeer negatief'. Bij de CGT/GET-groep (n=142) geven 94 respondenten (66,20%) de waardering 'negatief tot zeer negatief'. Bij de biomedische behandeling (n=214) zijn 25 respondenten (11,68%) 'negatief tot zeer negatief'." p.31</p>		<p>cvsvereniging.nl/sites/default/files/documenten/Rapport%20Zorg%20voor%20betere%20behandeling.pdf</p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>A survey of severe ME patients in Norfolk and Suffolk, November, 2007. "From the survey, 90% of Norfolk and Suffolk severe ME patients reject GET. 72% of ME patients reject CBT."</p>	Published	<p><i>Crowhurst, G., Crowhurst, L., (2007). A survey of Severe ME patients in Norfolk and Suffolk, November 2007. East Anglia ME Patient's Partnership and the 25% Severe ME Group. Retrieved from: https://docs.google.com/document/d/1LUxpN2T5XO54uSuGmogp9TBhgPE7H4xr_4Vo-MqUZq4/edit?hl=en_GB</i></p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Qualitative research looking into the experience of people with ME accessing services, advice and treatment - including the additional stigma faced by minority groups: "Participants suffered from lack of control over choices of treatment for managing their illness, which they saw as due to both lack of resources in the National Health and social systems and relative lack of recognition or value given to their own experience with the illness. Where participants' and GPs' views differed on appropriate treatment, typically around graded exercises or antidepressants, a refusal to take antidepressant medication was often interpreted by the GP as a refusal of treatment."</p>	Published	<p><i>de Carvalho Leite, J. C., de L Drachler, M., Killeth, A., Kale, S., Nacul, L., McArthur, M., ... & Lacerda, E. (2011). Social support needs for equity in health and social care: a thematic analysis of experiences of people with chronic fatigue syndrome/myalgic encephalomyelitis. <i>International journal for equity in health</i>, 10(1), 46.</i></p>

<p>#MEAction</p>	<p>Question 2. Interventions. Survey meta-analysis.</p> <p>This article explores patients' symptom responses following these GET and CBT treatments versus pacing therapy, an approach favoured by many sufferers.</p> <p>"Findings from analysis of primary and secondary surveys suggest that cognitive behavioural therapy is of benefit to a small percentage of patients (8%-35%), graded exercise therapy brings about large negative responses in patients (54%-74%), while pacing is the most favoured treatment with the lowest negative response rate and the highest reported benefit (44%-82%)."</p>	<p>Published</p>	<p><i>Geraghty, K., Hann, M., & Kurtev, S. (2017). 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. Journal of health psychology, 1359105317726152.</i></p>
<p>#MEAction</p>	<p>Question 2. Interventions. Survey.</p> <p>Results from 2017 Healthwatch Lancashire survey, including questions looking at advice and interventions. E.g. "If you have used any of the following, did you find it made your ME/CFS more or less manageable?"</p> <p>Of those who had tried graded exercise therapy, a majority found it made their ME/CFS less manageable. Of those who had tried cognitive behavioural therapy, the most common response was that it made no difference to their ME/CFS.</p> <p>Other interventions are also reported on.</p>	<p>Published</p>	<p><i>Healthwatch Lancashire. (2017). ME/CFS Report June 2017. Retrieved from https://healthwatchlancashire.co.uk/wp-content/uploads/2014/06/REPORT_ME-CFS_June2017.pdf</i></p>
<p>#MEAction</p>	<p>Question 2. Interventions. Survey.</p> <p>Results from 2017 Healthwatch Trafford survey, including questions looking at advice and interventions. E.g. "If you have used any of the following, did you find it made your ME/CFS more or less manageable?"</p> <p>Out of 297 respondents who had tried graded exercise therapy for their ME/CFS, 203 (68.4%) found it made their illness less manageable. Out of 296 respondents who had tried cognitive behavioural therapy for their ME/CFS, 175 (59.1%) found it made no difference.</p>	<p>Published</p>	<p><i>Healthwatch Trafford. (2017). 'Tired of explaining' : ME/CFS Report by Healthwatch Trafford. Retrieved from https://healthwatchtrafford.co.uk/wp-content/uploads/2015/03/Tired-of-explaining-ME-CFS-Report-by-Healthwatch-Trafford.pdf</i></p>

	Other interventions are also reported on.		
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>"Patients with ME and CFS who reported experiencing a dismissive physician attitude were asked to detail the encounter via open-ended response on an international, online survey. Participant responses were thematically coded and analyzed using processes outlined by Patton. Emergent themes related to perceived physician attitudes and how they impact patient wellbeing are described and their implications discussed. Additionally, we highlight suggestions for how the health care system can effectively approach this often marginalized patient group."</p>	Published	<i>McManimen, S., McClellan, D., Stoothoff, J., Gleason, K., & Jason, L. A. (2019). Dismissing chronic illness: A qualitative analysis of negative health care experiences. Health care for women international, 1-18.</i>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>GET and CBT are not safe or effective treatments for people with ME. "In summary, the majority of individuals reported deterioration or no change in symptoms and health over the course of all treatment approaches."</p>	Published	<i>Oxford Clinical Allied Technology and Trials Services Unit (OxCATTS). (2019). Evaluation of a survey exploring the experiences of adults and children with ME/CFS who have participated in CBT and GET interventional programmes. Retrieved from: http://www.meaction.net/wp-content/uploads/2019/04/NICE-Patient-Survey-Outcomes-CBT-and-GET-Oxford-Brookes-Full-Report-03.04.19.pdf</i>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Survey showing high 'not helpful' response rates for CBT and GET, as well as importance of adequate testing to people with ME: "Of 168 to 171 respondents functional testing, e.g. sleep, immune system was rated as important.</p> <p>Over 160 respondents found pacing and rest the most helpful and least harmful</p>	Published	<i>Patient Representative Group, ME/CFS Service Design Project Group. (2009). Norfolk & Suffolk ME/CFS Service. 2009 Patient Survey. Retrieved from: https://drive.google.com/file/d/0B2eUb8PoOndFbXpWUC15aFc5Tik/view</i>

	<p>interventions, bringing about improvement for 77% and 76% of respondents respectively.</p> <p>Relaxation (118 respondents) and meditation (78 respondents) also had high beneficial.</p> <p>Of 85 respondents Cognitive Behavioural Therapy (CBT) helped only 20%.</p> <p>Of 86 respondents Graded Exercise Therapy (GET) helped only 13%. Both CBT and GET had high 'not helpful' ratings, 40% for CBT and 58% for GET."</p>		
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>Survey evidence of the harm of 'physical' interventions: "When looking at the techniques that made respondents slightly worse or much worse, Graded Exercise Therapy was specified by 56%, followed by physiotherapy, the drug modafinil, yoga and physiotherapy. It appears that any "physical" type of therapy has the potential to make many patients worse. Lightning Process made 20% worse. Cognitive Behaviour Therapy only made 19% worse, but it also produced 'no change' in 54%."</p>	Published	<p><i>The ME Association. (2010). Managing my M.E. What people with ME/CFS and their carers want from the UK's health and social services. The results of the ME Association's Major Survey of Illness Management Requirements. Retrieved from: https://www.meassociation.org.uk/wp-content/uploads/2010/09/2010-survey-report-lo-res10.pdf</i></p>
#MEAction	<p>Question 2. Interventions. Survey.</p> <p>"Where patients attended a CBT, GET or Pacing course which had no overlapping elements of the other two interventions, more reported an improvement in symptoms following their Pacing course than did those who attended either of the other courses. CBT resulted in 91% of participants feeling their ME/CFS symptoms were unaffected or made worse, GET 88%, and Pacing 55%."</p>	Published	<p><i>The ME Association. (2015). ME/CFS Illness Management Survey Results "No decisions about me without me". Retrieved from: https://www.meassociation.org.uk/wp-content/uploads/2015-ME-Association-Illness-Management-Report-No-decisions-about-me-without-me-30.05.15.pdf</i></p>
#MEAction	<p>Question 2. Interventions. Survey.</p>	Published	<p><i>The Neurological Alliance. (2019). Neuro Patience. Still waiting for improvements in treatment and care. The National Neurology Patient</i></p>

	<p>A 2018/2019 patient survey by The Neurological Alliance found that: “The table below therefore shows that respondents reported Myalgic encephalomyelitis (ME)/ chronic fatigue syndrome as having the most severe impact and Cavernoma as having the least severe impact” p.45. “this table shows that respondents with Myalgic encephalomyelitis (ME)/chronic fatigue syndrome and those with functional neurological disorder are least satisfied with the overall health care they receive”</p> <p>This adds further evidence that current treatment and care is failing people with ME.</p>		<p><i>Experience Survey 2018/2019: Technical Report. Retrieved from https://www.neural.org.uk/wp-content/uploads/2019/07/Neuro-Patience-Technical-Report.pdf</i></p>
#MEAction	<p>Question 1. Management strategies that are adopted while someone is being assessed for a diagnosis of ME/CFS.</p> <p>“Two-thirds of the respondents received treatment in the early stages of the illness (66.6% of mild cases, and 67.7% of severe cases). Among those subjects who did receive treatment in the early stages of the illness, 32.7% of mild cases (98 out of 300) found treatment in the early stages of the illness to be useful, compared with only 11.5% of severe cases (6 out of 52) (chi sq. = 8.52; p = 0.0035). By contrast, 73.1% of severe cases found it damaging, compared with only 30.0% of mild cases (chi sq. = 44.7; p <0.00001).”</p>	Published	<p><i>Pheby, D., & Saffron, L. (2009). Risk factors for severe ME/CFS. <i>Biology and Medicine</i>, 1(4), 50-74.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Children and adolescents.</p> <p>“An important aspect of the study methodology was that we included a comprehensive evaluation of orthostatic intolerance, incorporating the self-reported frequency of lightheadedness as well as a detailed clinical history and, where necessary, orthostatic testing. Although significantly more ME/CFS participants described lightheadedness several times per week or more compared to healthy controls [76 vs. 15%, P < 0.001], the prevalence of orthostatic intolerance increased to 84% when a history of recurrent syncope or prior positive orthostatic testing was included. A further 12% developed POTS or NMH in response to a 10-min passive standing test in clinic, all of whom reported provocation of their usual ME/CFS symptoms when standing.”</p>	Published	<p><i>Roma, M., Marden, C. L., Flaherty, M., Jasion, S. E., Cranston, E. M., & Rowe, P. C. (2019). Impaired health-related quality of life in adolescent myalgic encephalomyelitis/chronic fatigue syndrome: the impact of core symptoms. <i>Frontiers in pediatrics</i>, 7, 26.</i></p>
#MEAction	<p>Question 1. Monitoring and review. Children and adolescents.</p>	Published	<p><i>Josev, E. K., Malpas, C. B., Seal, M. L., Scheinberg, A., Lubitz, L., Rowe,</i></p>

	<p>"This study used resting-state functional MRI in a novel repeated-measures design to evaluate intrinsic connectivity, cognitive function, and subjective fatigue, before and after a period of cognitive exertion in 48 adolescents (25 CFS/ME, 23 healthy controls)."</p> <p>As a result: "Both groups demonstrated a similar rate of reduced intrinsic functional connectivity within the default mode network(DMN), reduced sustained attentional performance, slower processing speed, and increased subjective fatigue as a result of cognitive exertion. However, CFS/ME adolescents consistently displayed higher subjective fatigue, and controls out performed the CFS/ME group overall on cognitive measures of processing speed, sustained attention and new learning."</p>		<p><i>K., & Knight, S. J. (2019). Resting-state functional connectivity, cognition, and fatigue in response to cognitive exertion: a novel study in adolescents with chronic fatigue syndrome. Brain imaging and behavior, 1-16.</i></p>
#MEAction	<p>Question 2. Interventions. Children and adolescents.</p> <p>"Young people reported that management strategies that allowed them some control back over their lives, that reduced the uncertainty for families and ensured that they received the appropriate understanding and support were the most valuable intervention. Symptom management, especially sleep and headache were very helpful. There were many comments about needing to be believed and understood by the medical profession, teaching profession and family."</p>	Published	<p><i>Rowe, K. S. (2019). Long Term Follow up of Young People With Chronic Fatigue Syndrome Attending a Pediatric Outpatient Service. Frontiers in pediatrics, 7, 21.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Children and adolescents.</p> <p>Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. "Frequent monitoring of the patient once every 1–3 months, depending on the level of illness severity is important. Young patients who are ill appreciate continuing care. Functional improvement can be judged by determining how much activity generates post-exertional worsening of symptoms. Progress should be measured over time, rather than at a single clinic visit. In patients who are improving, fatigue is often the last symptom to resolve, since young patients often prefer to increase their activities and tolerate the resulting fatigue. The practitioner must be alert for the emergence of new symptoms. They might not be related to ME/CFS, but due to another illness."</p>	Published	<p><i>Rowe, P. C., Underhill, R. A., Friedman, K. J., Gurwitt, A., Medow, M. S., Schwartz, M. S., ... & Rowe, K. S. (2017). Myalgic encephalomyelitis/chronic fatigue syndrome diagnosis and management in young people: a primer. Frontiers in pediatrics, 5, 121.</i></p>

#MEAction	<p>Question 1. Monitoring and/or reviewing. Cognitive function.</p> <p>This is a comprehensive search of the PubMed and PsycINFO databases for studies that examined cognitive functioning in CFS between 1988 and 2008 identified 50 eligible studies. "The results state that persons with CFS demonstrate moderate to large impairments in simple and complex information processing speed and in tasks requiring working memory over a sustained period of time."</p>	Published	<i>Cockshell, S. J., & Mathias, J. L. (2010). Cognitive functioning in chronic fatigue syndrome: a meta-analysis. Psychological medicine, 40(8), 1253-1267.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Cognitive function.</p> <p>"The conclusion drawn is that cognitive impairments can be identified if appropriate measures are used. Furthermore, the authors have shown that performance changes in these measures have been used to assess both efficacy of a treatment regime and rates of recovery."</p> <p>Tests showing significant difference between subjects and controls included: free recall - CFS patients recalled significantly fewer words than the healthy controls indicating deficits in episodic memory in the patient group; simple reaction time tasks - longer mean reaction time; repeated digits vigilance task - slower reaction time; distraction from irrelevant stimuli (STROOP) - slower processing times.</p>	Published	<i>Thomas, M., & Smith, A. (2009). An investigation into the cognitive deficits associated with chronic fatigue syndrome. The open neurology journal, 3, 13.</i>
#MEAction	<p>Question 1. Monitoring and review. Cognitive function.</p> <p>"Seventy-eight participants were included in the study: 18 patients with CFS only (CFS group), 30 patients with CFS and comorbid fibromyalgia (CFS+FM group), and 30 individuals who were healthy and inactive (control group) were studied. Participants first completed 3 performance-based cognitive tests designed to assess selective and sustained attention, cognitive inhibition, and working memory capacity. Seven days later, they performed a fatiguing upper limb exercise test, with subsequent recovery measures."</p> <p>"Recovery of upper limb muscle function was found to be a significant predictor of cognitive performance in patients with CFS."</p>	Published	<i>Ickmans, K., Meeus, M., De Kooning, M., Lambrecht, L., Pattyn, N., & Nijs, J. (2014). Can recovery of peripheral muscle function predict cognitive task performance in chronic fatigue syndrome with and without fibromyalgia?. Physical therapy, 94(4), 511-522.</i>
#MEAction	<p>Question 1. Monitoring and review and question 2. Interventions. Cognitive function.</p>	Published	<i>LaManca, J. J., Sisto, S. A., DeLuca, J., Johnson, S. K., Lange, G., Pareja,</i>

	<p>Exercise as intervention leads to worse cognitive function in CFS subjects than sedentary control:</p> <p>"The purpose of this study was to determine the effect of exhaustive exercise on cognitive performance of patients with chronic fatigue syndrome (CFS) and sedentary healthy controls (CON). Subjects were 19 women with CFS and 20 CON. A test battery consisting of 4 cognitive tests (CTB) was given pre-, immediately post-, and 24 hours post-treadmill exercise to exhaustion. No differences were seen on the CTB pre-exercise. CFS patients improved at a slower rate than CON on the Symbol Digit Modalities Test (SDMT), Stroop Word Test (SWT), and Stroop Color Test (SCT). When compared with CON, a lower number of correct responses was seen for the CFS immediately postexercise on the SDMT (61 +/- 3 vs 66 +/- 2), SWT (137 +/- 6 vs 146 +/- 6), and SCT (99 +/- 4 vs 107 +/- 3), and 24 hours postexercise on the SDMT (64 +/- 3 vs 69 +/- 2), SWT (134 +/- 7 vs 148 +/- 5), and SCT (101 +/- 4 vs 106 +/- 3). We conclude that after physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals."</p>		<p><i>J., ... & Natelson, B. H. (1998). Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. The American journal of medicine, 105(3), 59S-65S.</i></p>
#MEAAction	<p>Question 1. Monitoring and review. Cognitive function.</p> <p>"Twenty-nine CFS participants without psychiatric comorbidity (CFS-noPsych) and 22 participants with an Axis I psychiatric diagnosis since CFS onset. Two control groups: 30 healthy persons and 19 participants with rheumatoid arthritis. Main Outcome Measures: After being equated for initial learning, recall and recognition were assessed after 30- and 90-min delays. Results: Both CFS groups required more trials to learn the word list than did healthy controls. The CFS-noPsych group performed significantly below healthy controls on recall but not on recognition. Learning/acquisition correlated with measures of complex information processing and not with depressive symptomatology or fatigue."</p>	Published	<p><i>DeLuca, J., Christodoulou, C., Diamond, B. J., Rosenstein, E. D., Kramer, N., Ricker, J. H., & Natelson, B. H. (2004). The Nature of Memory Impairment in Chronic Fatigue Syndrome. Rehabilitation Psychology, 49(1), 62.</i></p>
#MEAAction	<p>Question 1. Monitoring and review. Cognitive function.</p> <p>"[R]esearchers conducted a co-twin control study of 22 pairs of monozygotic twins, in which 1 twin met strict criteria for CFS and the co-twin was healthy. Twins underwent a structured psychiatric interview and comprehensive neuropsychological assessment evaluating 6 cognitive domains. Results</p>	Published	<p><i>Claypoole, K. H., Noonan, C., Mahurin, R. K., Goldberg, J., Erickson, T., & Buchwald, D. (2007). A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset.</i></p>

	indicated that twin groups had similar intellectual and visual memory functioning, but fatigued twins exhibited decreases in motor functions ($p = .05$), speed of information processing ($p = .02$), verbal memory ($p = .02$), and executive functioning ($p = .01$)."		<i>Neuropsychology, 21(4), 507.</i>
#MEAction	<p>Question 1. Monitoring and review. Cognitive function.</p> <p>"It has been shown that the time it takes to process a complex cognitive task, rather than error rate, may be the critical variable underlying CFS patients' cognitive complaints. The Attention Network Task (ANT) developed by Fan and colleagues may be of clinical utility to assess cognitive function in CFS, because it allows for simultaneous assessment of mental response speed, also called information processing speed, and error rate under three conditions challenging the attention system. Comparison of data from two groups of CFS patients (those with and without comorbid major depressive disorder; $n = 19$ and 22, respectively) to controls ($n = 29$) consistently showed that error rates did not differ among groups across conditions, but speed of information processing did. Processing time was prolonged in both CFS groups and most significantly affected in response to the most complex task conditions."</p>	Published	<i>Togo, F., Lange, G., Natelson, B. H., & Quigley, K. S. (2015). Attention network test: assessment of cognitive function in chronic fatigue syndrome. Journal of neuropsychology, 9(1), 1-9.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Comorbidities.</p> <p>Endometriosis (EM) is a recognized co-morbid condition in women with chronic fatigue syndrome (CFS). This 2019 analysis evaluates the impact of EM on the health of women with CFS. "We found more than a third of women with CFS reported endometriosis as a comorbid condition. The endometriosis comorbidity was associated with chronic pelvic pain, earlier menopause, hysterectomy, and more CFS-related symptoms." p1.As part of the results, it states that "further studies that include younger and more racially/ethnically diverse women are warranted."</p>	Published	<i>Boneva, R. S., Lin, J. M. S., Wieser, F., Nater, U. M., Ditzen, B., Taylor, R. N., & Unger, E. R. (2019). Endometriosis as a Comorbid Condition in Chronic Fatigue Syndrome (CFS): Secondary Analysis of Data From a CFS Case-Control Study. Frontiers in pediatrics, 7, 195.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Comorbidities.</p> <p>This 2012 study looks into the association of cancer between CFS. These were examined in a population-based case-control study among the US elderly. Its results state: "We observed an elevated risk of NHL overall and for two defined NHLsubtypes, MZL and DLBCL, following a CFS diagnosis. Chronic immune</p>	Published	<i>Chang, C. M., Warren, J. L., & Engels, E. A. (2012). Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults. Cancer, 118(23), 5929-5936.</i>

	activation or an infection may play a role in explaining the observed association between CFS and NHL.” p6		
#MEAction	<p>Question 1. Monitoring and/or reviewing. Comorbidities.</p> <p>The aim of this study is to determine prevalence of POTS inpatients with CFS/ME.</p> <p>Awareness of potential comorbid illnesses and appropriate investigation for these is vital.</p> <p>“POTS is a frequent finding in patients with CFS/ME. We suggest that clinical evaluation of patients with CFS/ME should include response to standing.”</p>	Published	<i>Hodges, L. D., Nielsen, T., & Baken, D. (2018). Physiological measures in participants with chronic fatigue syndrome, multiple sclerosis and healthy controls following repeated exercise: a pilot study. Clinical physiology and functional imaging, 38(4), 639-644.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Comorbidities.</p> <p>Awareness of potential comorbid illnesses and appropriate investigation for these is vital.</p> <p>“The presence of POTS marks a distinct clinical group of CFS patents, with phenotypic features differentiating them from those without POTS. A combination of validated clinical assessment tools can determine which CFS patients have POTS with a high degree of accuracy, and thus potentially identify those who require further investigation and consideration for therapy to control heart rate.”</p>	Published	<i>Lewis, I., Pairman, J., Spickett, G., & Newton, J. L. (2013). Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. Journal of internal medicine, 273(5), 501-510.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Comorbidities.</p> <p>“Haemodynamic and demographic differences between CFS-POTS and CFS-only patients suggest that the former group reflects a distinct subgroup of the CFS population. The findings highlight the utility of screening younger patients with fatigue for POTS, and identified heart rate variability as an important marker of fatigue for CFS patients in general.”</p>	Published	<i>Reynolds, G. K., Lewis, D. P., Richardson, A. M., & Lidbury, B. A. (2014). Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. Journal of internal medicine, 275(4), 409-417.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. And question 2. Interventions. CPET.</p> <p>Exercise as intervention leads to significant abnormal responses.</p> <p>“In the absence of a second exercise test, the lack of any significant differences for the first test would appear to suggest no functional impairment in CFS patients. However, the results from the second test indicate the presence of a</p>	Published	<i>VanNess, J. M., Snell, C. R., & Stevens, S. R. (2007). Diminished cardiopulmonary capacity during post-exertional malaise. Journal of Chronic Fatigue Syndrome, 14(2), 77-85.</i>

	<p>CFS related post-exertional malaise. It might be concluded then that a single exercise test is insufficient to demonstrate functional impairment in CFS patients. A second test may be necessary to document the atypical recovery response and protracted malaise unique to CFS.”</p> <p>2 day CPET testing is now regularly used to show functional impairment in people ME/CFS, and also as a diagnostic marker for ME/CFS.</p>		
#MEAAction	<p>Question 1. Monitoring and/or reviewing. CPET.</p> <p>Snell et al. found that, while a single exercise test showed no noticeable differences between CFS patients and controls, a second test performed 24 hours later showed significant abnormalities in oxygen use and how hard patients were able to work. This is known as a two-day CPET.</p>	Published	<p><i>Snell, C. R., Stevens, S. R., Davenport, T. E., & Van Ness, J. M. (2013). Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome. Physical therapy, 93(11), 1484-1492.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. and question 2. Interventions. CPET.</p> <p>22 subjects diagnosed with ME/CFS completed two repeat CPETs separated by 24 h.</p> <p>"ME/CFS participants were unable to reproduce most physiological measures at both maximal and ventilatory threshold intensities during a CPET performed 24 hours after a prior maximal exercise test".</p>	Published	<p><i>Keller, B. A., Pryor, J. L., & Giloteaux, L. (2014). Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO 2 peak indicates functional impairment. Journal of translational medicine, 12(1), 104.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. CPET.</p> <p>“Basic concepts of CPET are summarized, and special considerations for performing CPET on ME/CFS patients are detailed to ensure a valid outcome. The 2-day CPET methodology is outlined, and the utility of the procedure is discussed for assessment of functional capacity and exertion intolerance in ME/CFS.”</p>	Published	<p><i>Stevens, S., Snell, C., Stevens, J., & VanNess, J. M. (2018). Cardiopulmonary exercise test methodology for assessing exertion intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Frontiers in pediatrics, 6, 242.</i></p>
#MEAAction	<p>Question 2. Interventions. Vitamin B12.</p>	Published	<p><i>Regland, B., Forsmark, S., Halaouate, L., Matousek, M., Peilot, B., Zachrisson, O., & Gottfries, C. G.</i></p>

	<p>“Dose-response relationship and long-lasting effects of B12/folic acid support a true positive response in the studied group of patients with ME/fibromyalgia”</p>		<p>(2015). <i>Response to vitamin B12 and folic acid in myalgic encephalomyelitis and fibromyalgia</i>. <i>PLoS One</i>, 10(4), e0124648.</p>
#MEAAction	<p>Question 2. Interventions. Vitamin B12.</p> <p>“Nasal drop vitamin B12 administration resulted in a significant increase in vitamin B12 serum levels and therefore may be effective. This pilot study suggest that the nasal drops may be used as an alternative to injections because two thirds of ME/CFS patients reported a positive effect, accompanied by an increased number of steps, improvement of the RAND-36 physical functioning scale and the CIS20r fatigue scale, and a significant increase in serum vitamin B12 levels.”</p>	Published	<p>Van Campen, C. L., Riepma, K., & Visser, F. C. (2019). <i>Open trial of vitamin B12 nasal drops in adults with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: comparison of responders and non-responders</i>. <i>Frontiers in Pharmacology</i>, 10, 1102.</p>
#MEAAction	<p>Question 1. Monitoring and review and question 2. Interventions. Co-enzyme Q10.</p> <p>"Plasma CoQ10 has been assayed in 58 patients with ME/CFS and in 22 normal controls; the relationships between CoQ10 and the severity of ME/CFS as measured by means of the FibroFatigue (FF) scale were measured. RESULTS: Plasma CoQ10 was significantly ($p=0.00001$) lower in ME/CFS patients than in normal controls. Up to 44.8% of patients with ME/CFS had values beneath the lowest plasma CoQ10 value detected in the normal controls, i.e. 490 microg/L. In ME/CFS, there were significant and inverse relationships between CoQ10 and the total score on the FF scale, fatigue and autonomic symptoms. Patients with very low CoQ10 (<390 microg/L) suffered significantly more from concentration and memory disturbances."</p> <p>"Our results suggest that patients with ME/CFS would benefit from CoQ10 supplementation in order to normalize the low CoQ10 syndrome."</p>	Published	<p>Maes, M., Mihaylova, I., Kubera, M., Uytterhoeven, M., Vrydags, N., & Bosmans, E. (2009). <i>Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder</i>. <i>Neuro endocrinology letters</i>, 30(4), 470-476.</p>
#MEAAction	<p>Question 2. Interventions. Co-enzyme Q10.</p> <p>"A proof-of-concept, 8-week, randomized, controlled, double-blind trial was</p>	Published	<p>Castro-Marrero, J., Sáez-Francàs, N., Segundo, M. J., Calvo, N., Faro, M., Aliste, L., ... & Alegre, J. (2016). <i>Effect of coenzyme Q10 plus</i></p>

	<p>conducted in 80 CFS patients assigned to receive either CoQ10 plus NADH supplementation or matching placebo twice daily. Maximum HR was evaluated at baseline and at end of the run-in period using an exercise test. Fatigue, pain and sleep were evaluated at baseline, and then reassessed at 4- and 8-weeks through self-reported questionnaires."</p> <p>"Our results suggest that CoQ10 plus NADH supplementation for 8 weeks is safe and potentially effective in reducing max HR during a cycle ergometer test and also on fatigue in CFS."</p>		<p><i>nicotinamide adenine dinucleotide supplementation on maximum heart rate after exercise testing in chronic fatigue syndrome—A randomized, controlled, double-blind trial. Clinical nutrition, 35(4), 826-834.</i></p>
#MEAAction	<p>Question 2. Interventions. Erythromycin and probiotics.</p> <p>"The 4-week treatment protocol included alternate weeks of Erythromycin (400 mg of erythromycin as ethyl succinate salt) twice daily and probiotic (D-lactate free multistrain probiotic, 5 × 10¹⁰ cfu twice daily)."</p> <p>"Large treatment effects were observed for the intention-to-treat sample with a reduction in Streptococcus viable count and improvement on several clinical outcomes including total symptoms, some sleep (less awakenings, greater efficiency and quality) and cognitive symptoms (attention, processing speed, cognitive flexibility, story memory and verbal fluency). Mood, fatigue and urine D:L lactate ratio remained similar across time. Ancillary results infer that shifts in microbiota were associated with more of the variance in clinical changes for males compared with females."</p>	Published	<p><i>Wallis, A., Ball, M., Butt, H., Lewis, D. P., McKechnie, S., Paull, P., ... & Bruck, D. (2018). Open-label pilot for treatment targeting gut dysbiosis in myalgic encephalomyelitis/chronic fatigue syndrome: neuropsychological symptoms and sex comparisons. Journal of translational medicine, 16(1), 24.</i></p>
#MEAAction	<p>Question 1. Monitoring and review. Ferritin (iron).</p> <p>"In patients presenting with chronic fatigue and/or orthostatic intolerance, low ferritin levels and hypovitaminosis D are common, especially in patients with PT [postural tachycardia]."</p>	Published	<p><i>Antiel, R. M., Caudill, J. S., Burkhardt, B. E., Brands, C. K., & Fischer, P. R. (2011). Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance. Southern medical journal, 104(8), 609-611.</i></p>
#MEAAction	<p>Question 2. Interventions. KPAX002.</p>	Published	<p><i>Montoya, J. G., Anderson, J. N., Adolphs, D. L., Bateman, L., Klimas, N., Levine, S. M., ... & Kaiser, J. D.</i></p>

	<p>"This phase 2 randomized, double-blinded, placebo-controlled trial was conducted at 4 sites in the United States. A total of 135 subjects with ME/CFS were randomly assigned to either KPAX002 (n=67) or placebo (n=68) for 12 weeks of treatment."</p> <p>"The two groups demonstrating the most robust response to KPAX002 were subjects with more severe ME/CFS symptoms at baseline (P=0.086) and subjects suffering from both fatigue and pain (P=0.057)."</p>		<p>(2018). <i>KPAX002 as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a prospective, randomized trial. Int J Clin Exp Med</i>, 11(3), 2890-2900. Retrieved from: https://kpaxpharm.com/docs/research/Montoya-et-al-IJCEM-2018.pdf</p>
#MEAAction	<p>Question 2. Interventions. Rintatolimod.</p> <p>"After 24 weeks, patients receiving poly(I).poly(C12U) had higher scores for both global performance and perceived cognition than did patients receiving placebo. In particular, patients given poly(I).poly(C12U) had increased Karnofsky performance scores (P < .03), exhibited a greater ability to do work during exercise treadmill testing (P = .01), displayed an enhanced capacity to perform the activities of daily living (P < .04), had a reduced cognitive deficit (P = .05), and required less use of other medications (P < .05)"</p>	Published	<p>Stordeur, S., Thiry, N., & Eysen, M. (2008). <i>Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie. Health Services Research (HSR). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE), 2088.</i></p>
#MEAAction	<p>Question 2. Interventions. Rintatolimod.</p> <p>"Rintatolimod produced objective improvement in ET [exercise tolerance] and a reduction in CFS/ME related concomitant medication usage as well as other secondary outcomes."</p>	Published	<p>Strayer, D. R., Carter, W. A., Stouch, B. C., Stevens, S. R., Bateman, L., Cimoch, P. J., ... & Chronic Fatigue Syndrome AMP-516 Study Group. (2012). <i>A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. PLoS One</i>, 7(3), e31334.</p>
#MEAAction	<p>Question 2. Interventions. Rituximab.</p> <p>Evaluates the effect of the monoclonal anti-CD20 antibody rituximab versus placebo in patients with ME/CFS. B-cell depletion using several infusions of rituximab over 12 months was not associated with clinical improvement in patients with ME/CFS.</p>	Published	<p>Fluge, Ø., Rekeland, I. G., Lien, K., Thürmer, H., Borchgrevink, P. C., Schäfer, C., ... & Gotaas, M. E. (2019). <i>B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-</i></p>

	"B-cell depletion using several infusions of rituximab over 12 months was not associated with clinical improvement in patients with ME/CFS."		<i>Blind, Placebo-Controlled Trial. Annals of internal medicine.</i>
#MEAAction	<p>Question 2. Interventions. Rituximab.</p> <p>29 patients were included for treatment with rituximab (500 mg/m²) two infusions two weeks apart, followed by maintenance rituximab infusions after 3, 6, 10 and 15 months, and with follow-up for 36 months.</p> <p>"In a subgroup of ME/CFS patients, prolonged B-cell depletion with rituximab maintenance infusions was associated with sustained clinical responses."</p>	Published	<i>Fluge, Ø., Risa, K., Lunde, S., Alme, K., Rekeland, I. G., Sapkota, D., ... & Mella, O. (2015). B-lymphocyte depletion in myalgic encephalopathy/chronic fatigue syndrome. An open-label phase II study with rituximab maintenance treatment. PloS one, 10(7), e0129898.</i>
#MEAAction	<p>Question 2. Interventions. Sodium dichloroacetate.</p> <p>"Twenty-two consecutive patients suffering from refractory myalgic encephalitis/chronic fatigue syndrome (ME/CFS) were treated with an innovative nutraceutical containing sodium dichloroacetate in a proof-of-principle, pilot, open-label prospective cohort trial. Ten patients experienced significant improvement of their health condition with reduction to almost half of their score in the fatigue severity scale. In twelve patients treatment failed to exert any beneficial effect."</p>	Published	<i>Comhaire, F. (2018). Treating patients suffering from myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) with sodium dichloroacetate: An open-label, proof-of-principle pilot trial. Medical hypotheses, 114, 45-48.</i>
#MEAAction	<p>Question 2. Interventions. Valganciclovir.</p> <p>"VGCV [valganciclovir] may have clinical benefit in a subset of CFS patients independent of placebo effect, possibly mediated by immunomodulation and/or antiviral effect. Further investigation with longer treatment duration and a larger sample size is warranted."</p>	Published	<i>Montoya, J. G., Kogelnik, A. M., Bhangoo, M., Lunn, M. R., Flamand, L., Merrihew, L. E., ... & Desai, M. (2013). Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. Journal of medical virology, 85(12), 2101-2109.</i>
#MEAAction	<p>Question 2. Interventions. Valganciclovir.</p>	Published	<i>Watt, T., Oberfoell, S., Balise, R., Lunn, M. R., Kar, A. K., Merrihew, L.,</i>

	<p>“Valganciclovir treatment, independent of the baseline antibody titers, was associated with self-rated improvement in physical and cognitive functioning for CFS patients who had positive HHV-6 and/or EBV serologies. Longer valganciclovir treatment correlated with an improved response.”</p>		<p>... & Montoya, J. G. (2012). Response to valganciclovir in chronic fatigue syndrome patients with human herpesvirus 6 and Epstein–Barr virus IgG antibody titers. <i>Journal of medical virology</i>, 84(12), 1967-1974.</p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. Vitamin D.</p> <p>This study performs a retrospective survey of serum 25-OHvitamin D levels in 221 CFS patients. This is compared to a group of patients attending the hospital for other chronic conditions and to a large British longitudinal survey of 45-year old women, using a variety of appropriate statistical approaches. The results include: “25-OH vitamin D levels are moderately to severely suboptimal in CFS patients, with a mean of 44.4 nmol/L (optimal levels >75 nmol/L). These levels are lower and the difference is statistically significant ($p < 0.0004$) than those of the general British population from a recent national survey, but similar to those in patients with other chronic conditions.”</p>	Published	<p>Berkovitz, S., Ambler, G., Jenkins, M., & Thurgood, S. (2009). Serum 25-hydroxy vitamin D levels in chronic fatigue syndrome: a retrospective survey. <i>International journal for vitamin and nutrition research</i>, 79(4), 250-254.</p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing.</p> <p>Exercise as intervention leads to significant abnormal responses.</p> <p>The objective of the study was to determine the neural consequences of acute exercise using functional brain imaging. This study’s conclusions state: "This study’s findings emphasize the importance of symptom provocation in the study of ME/CFS by demonstrating significant and characteristically opposite brain and behavioral responses in patients compared to controls – providing evidence that acute exercise can negatively impact neurophysiological processes in ME/CFS. These findings also provide objective evidence for the subjective experience of cognitive symptoms (i.e. brain fog) reported by ME/CFS patients when they attempt to be physically active."</p>	Published	<p>Cook, D. B., Light, A. R., Light, K. C., Broderick, G., Shields, M. R., Dougherty, R. J., ... & Vernon, S. D. (2017). Neural consequences of post-exertion malaise in myalgic encephalomyelitis/chronic fatigue syndrome. <i>Brain, behavior, and immunity</i>, 62, 87-99.</p>
#MEAAction	<p>Question 2. Interventions.</p> <p>Exercise as intervention leads to significant abnormal responses.</p> <p>This study evaluates the magnitude of the difference in VO₂peak between patients with Chronic Fatigue Syndrome/ Myalgic Encephalo-myelitis (CFS/ME)</p>	Published	<p>Franklin, J. D., Atkinson, G., Atkinson, J. M., & Batterham, A. M. (2019). Peak oxygen uptake in chronic fatigue syndrome/myalgic encephalomyelitis: A meta-analysis.</p>

	<p>and apparently healthy controls.</p> <p>"Synthesis of the available evidence indicates that CFS/ME patients have a substantially reduced VO₂peak compared to controls."</p>		<p><i>International journal of sports medicine, 40(02), 77-87.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Exercise as intervention leads to significant abnormal responses.</p> <p>The purpose of this study is to compare physiological responses of chronic fatigue syndrome (CFS/ME), multiple sclerosis (MS) and healthy controls (HC) following a 24-h repeated exercise test</p> <p>"Differences in oxygen use (VO₂) on two-day cardiopulmonary exercise testing in people with multiple sclerosis, people with ME, and healthy controls." As a result: "These results suggest that exercise exhibits a different physiological response in MS and CFS/ME, demonstrating repeated cardiovascular exercise testing as a valid measure for differentiating between fatigue conditions."</p>	Published	<p><i>Hodges, L. D., Nielsen, T., & Baken, D. (2018). Physiological measures in participants with chronic fatigue syndrome, multiple sclerosis and healthy controls following repeated exercise: a pilot study. Clinical physiology and functional imaging, 38(4), 639-644.</i></p>
#MEAction	<p>Question 2. Interventions and question 1. Monitoring and review Exercise as intervention leads to significant abnormal responses.</p> <p>This study explores muscle bioenergetic function in response to three bouts of exercise. "When exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it."</p>	Published	<p><i>Jones, D. E., Hollingsworth, K. G., Jakovljevic, D. G., Fattakhova, G., Pairman, J., Blamire, A. M., ... & Newton, J. L. (2012). Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. European journal of clinical investigation, 42(2), 186-194.</i></p>
#MEAction	<p>Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>"In conclusion, previous exercise deteriorates physical performance and increases [Laa] (arterial lactate concentrations) during exercise in patients with ME/CFS while it lowers [Laa] in healthy subjects."</p>	Published	<p><i>Lien, K., Johansen, B., Veierød, M. B., Haslestad, A. S., Bøhn, S. K., Melsom, M. N., ... & Iversen, P. O. (2019). Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. Physiological reports, 7(11), e14138.</i></p>

#MEAAction	<p>Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>"Muscle fatigue and pain are major symptoms of CFS. After moderate exercise, CFS and CFS-FMS patients show enhanced gene expression for receptors detecting muscle metabolites and for SNS and IS, which correlate with these symptoms."</p>	Published	<p><i>Light, A. R., White, A. T., Huguen, R. W., & Light, K. C. (2009). Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. The Journal of Pain, 10(10), 1099-1112.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. Exercise as intervention.</p> <p>This study asks whether a submaximal exercise test would prove useful for identifying different patterns of tissue oxygen utilization in individuals with ME/CFS versus healthy subjects.</p> <p>"Relative to controls, participants with ME/CFS demonstrated higher RPE, lower TTI, and reduced dO₂Hb and dHHb during repetitive handgrip exercise"</p>	Published	<p><i>Miller, R. R., Reid, W. D., Mattman, A., Yamabayashi, C., Steiner, T., Parker, S., ... & Patrick, D. M. (2015). Submaximal exercise testing with near-infrared spectroscopy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients compared to healthy controls: a case-control study. Journal of translational medicine, 13(1), 159.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. Exercise as intervention.</p> <p>This study examined whether cytokine profiling or cardiovascular testing following exercise would differentiate patients with ME/CFS. Twenty-four ME/CFS patients were matched to 24 sedentary controls and underwent cardiovascular and circulating immune profiling.</p> <p>Decreased absolute heart rate recovery after single-day cardiopulmonary exercise testing was found in people with ME</p>	Published	<p><i>Moneghetti, K. J., Skhiri, M., Contrepois, K., Kobayashi, Y., Maecker, H., Davis, M., ... & Montoya, J. G. (2018). Value of circulating cytokine profiling during submaximal exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. Scientific reports, 8(1), 2779.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>"The CFS subjects exhibited significant exercise intolerance and reduced prefrontal oxygenation and tHb response when compared with CON subjects.</p>	Published	<p><i>Patrick Neary, J., Roberts, A. D., Leavins, N., Harrison, M. F., Croll, J. C., & Sexsmith, J. R. (2008). Prefrontal cortex oxygenation during incremental exercise in chronic</i></p>

	These data suggest that the altered cerebral oxygenation and blood volume may contribute to the reduced exercise load in CFS, and supports the contention that CFS, in part, is mediated centrally."		<i>fatigue syndrome. Clinical Physiology and Functional Imaging, 28(6), 364-372.</i>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. And question 2. Interventions. Exercise as intervention.</p> <p>Result of the study: "Although these findings were not significantly different from those in the control group, the effect of exercise on serum TGF-β and cerebral blood flow appeared magnified in the CFS patients."</p> <p>"Serum TGF-beta and cerebral blood flow abnormalities, detected by single-photon emission-computed tomographic scanning, were accentuated postexercise in the CFS group. Although these findings were not significantly different from those in the control group, the effect of exercise on serum TGF-beta and cerebral blood flow appeared magnified in the CFS patients."</p>	Published	<i>Peterson, P. K., Sirr, S. A., Grammith, F. C., Schenck, C. H., Pheley, A. M., Hu, S., & Chao, C. C. (1994). Effects of mild exercise on cytokines and cerebral blood flow in chronic fatigue syndrome patients. Clin. Diagn. Lab. Immunol., 1(2), 222-226.</i>
#MEAAction	<p>Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>"Upon exercise challenge, there were significant changes in the abundance of major bacterial phyla in the gut in ME/CFS patients not observed in healthy controls."</p>	Published	<i>Shukla, S. K., Cook, D., Meyer, J., Vernon, S. D., Le, T., Clevidence, D., ... & Frank, D. N. (2015). Changes in gut and plasma microbiome following exercise challenge in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PLoS One, 10(12), e0145453.</i>
#MEAAction	<p>Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>Staud (2018) found that, while people with ME showed no differences in cerebral perfusion (blood flow to the brain) from healthy controls at rest, they showed a significant decrease in perfusion following a strenuous task.</p>	Published	<i>Staud, R., Boissoneault, J., Craggs, J. G., Lai, S., & Robinson, M. E. (2018). Task related cerebral blood flow changes of patients with chronic fatigue syndrome: an arterial spin labeling study. Fatigue: biomedicine, health & behavior, 6(2), 63-79.</i>
#MEAAction	<p>Question 1. Monitoring and/or reviewing. Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p>	Published	<i>VanNess, J. M., Stevens, S. R., Bateman, L., Stiles, T. L., & Snell, C. R. (2010). Postexertional malaise in</i>

	<p>“Written questionnaires revealed that within 24 hours of the test, 85% of controls indicated full recovery, in contrast to 0 CFS patients. The remaining 15% of controls recovered within 48 hours of the test. In contrast, only 1 CFS patient recovered within 48 hours. Symptoms reported after the exercise test included fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia, and sore throat/glands. A significant multivariate effect for the SF-36 responses ($p < 0.001$) indicated lower functioning among the CFS patients, which was most pronounced for items measuring physiological function.”</p>		<p>women with chronic fatigue syndrome. <i>Journal of Women's Health</i>, 19(2), 239-244.</p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>“Low oxygen uptake by muscle cells causes exercise intolerance in a majority of CFS patients, indicating insufficient metabolic adaptation to incremental exercise. The high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients.”</p> <p>Oxygen extraction in people with ME was still found to be less than half that of these controls during activity. These differences are still present in minor-presenting people with ME who are as active as the average healthy individual but who manage the intensity and duration of activity carefully through pacing. If people with ME with an average activity level still experience debilitating symptoms, activity cannot be curative.</p> <p>Controls were sedentary, defined as active for less than 1 hour per week, and not on medication that could possibly influence the pulmonary, cardiovascular, immunologic system or cellular respiration.</p>	Published	<p>Vermeulen, R. C., & van Eck, I. W. V. (2014). Decreased oxygen extraction during cardiopulmonary exercise test in patients with chronic fatigue syndrome. <i>Journal of translational medicine</i>, 12(1), 20.</p>
#MEAction	<p>Question 2. Interventions. Exercise as intervention leads to significant abnormal responses.</p> <p>"The resting heart rate of the patient group was higher, but the maximal heart rate at exhaustion was lower, relative to the control subjects. The maximal workload and maximal oxygen uptake attained by the patients with CFS were almost half those achieved by the control subjects."</p>	Published	<p>De Becker, P., Roeykens, J., Reynders, M., McGregor, N., & De Meirleir, K. (2000). Exercise capacity in chronic fatigue syndrome. <i>Archives of internal medicine</i>, 160(21), 3270-3277.</p>

	<p>“This study clearly shows that patients with CFS are limited in their physical capacities. Based on the American Medical Association Guidelines for Impairment Rating, our 55.2% of patients who had a V.O2max of less than 20 mL/kg per minute correspond to class 3-4 on the disability scale, indicating moderate to severe impairment. Regardless of the cause and pathogenesis, the symptom complex labeled CFS can and does result in prolonged debilitation.”</p> <p>This study had a well characterised control group of sedentary subjects: "A group of 204 age-matched sedentary women served as a control population. We selected them from subjects who came for medical checkups. Only those who did sitting work and performed a maximum of 1 hour of sports per week were included. Control subjects were accepted into the study only if they denied having symptoms of chronic fatigue and did not suffer from any medical conditions known to cause chronic fatigue."</p>		
#MEAction	<p>Question 2. Interventions. Exercise as intervention.</p> <p>Found no objective improvements after CBT and GET using exercise testing (VO2 max). They also found that fewer people were able to work and more people were receiving illness benefits after undertaking these therapies, implying a loss of physical functioning.</p>	Published	<p><i>Stordeur, S., Thiry, N., & Eysen, M. (2008). Chronisch Vermoeidheidssyndroom: diagnose, behandeling en zorgorganisatie. Health Services Research (HSR). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE), 2088.</i></p>
#MEAction	<p>Question 2. Interventions. Exercise as intervention.</p> <p>"On the original protocol-specified primary outcome measure - overall improvement rates - there was a significant effect of treatment group. However, the groups receiving CBT or GET did not significantly outperform the Control group after correcting for the number of comparisons specified in the trial protocol. Also, rates of recovery were consistently low and not significantly different across treatment groups. Finally, on secondary measures, significant effects were almost entirely confined to self-report measures. These effects did not endure beyond two years."</p>	Published	<p><i>Wilshire, C. E., Kindlon, T., Courtney, R., Matthees, A., Tuller, D., Geraghty, K., & Levin, B. (2018). Rethinking the treatment of chronic fatigue syndrome—a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. BMC psychology, 6(1), 6.</i></p>

	<p>"Turning now to the recovery rates, the late changes to the definition of recovery made it much easier for a patient to qualify as recovered. These changes were quite substantial. For example, the minimum physical function score required to qualify as recovered was reduced from 85 to 60, which is close to the mean score for patients with Class II congestive heart failure (57/100 [21]), and lower than the score required for trial entry (65/100). Also, on the fatigue criterion, a patient could now count as "recovered" despite reporting continuing fatigue on as many as seven out of the 11 fatigue questionnaire items, a level that substantially overlaps with that required for trial entry."</p>		
#MEAction	<p>Question 1. Monitoring and/or reviewing.</p> <p>Currently clinics do not monitor for harm or record instances of deterioration following treatments. This prohibits any systematic appraisal of the impact of treatment approaches being utilised across the country.</p> <p>"Clinics were highly inconsistent in their approaches to the issue of treatment-related harm. They 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. In light of these findings, we recommend that clinics develop standardised protocols for anticipating, recording, and remedying harms, and that these protocols allow for therapies to be discontinued immediately whenever harm is identified."</p>	Published	<p><i>McPhee, G., Baldwin, A., Kindlon, T., & Hughes, B. M. (2019). Monitoring treatment harm in myalgic encephalomyelitis/chronic fatigue syndrome: A freedom-of-information study of National Health Service specialist centres in England. Journal of Health Psychology, 1359105319854532.</i></p>
#MEAction	<p>Question 2. Interventions.</p> <p>"Those who were able to stay within their energy envelope had significant improvements in physical functioning and fatigue severity. Findings suggest that helping patients with ME/CFS maintain appropriate energy expenditures in coordination with available energy reserves can help improve functioning over time."</p>	Published	<p><i>Jason, L., Benton, M., Torres-Harding, S., & Muldowney, K. (2009). The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient education and counseling, 77(2), 237-241.</i></p>
#MEAction	<p>Question 2. Interventions.</p> <p>Pragmatic rehabilitation for severe ME is ineffective:</p>	Published	<p><i>Wearden, A. J., Dowrick, C., Chew-Graham, C., Bentall, R. P., Morriss, R. K., Peters, S., ... & Dunn, G.</i></p>

	<p>"For patients with CFS/ME in primary care, pragmatic rehabilitation delivered by trained nurse therapists improves fatigue in the short term compared with unconstrained GP treatment as usual, but the effect is small and not statistically significant at one year follow-up. Supportive listening delivered by trained nurse therapists is not an effective treatment for CFS/ME."</p>		<p>(2010). <i>Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. Bmj, 340, c1777.</i></p>
#MEAction	<p>Question 2. Interventions.</p> <p>"Despite the growing evidence of physiological and cellular abnormalities in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS), there has been a strong impetus to tackle the illness utilizing a biopsychosocial model. However, many sufferers of this disabling condition report distress and dissatisfaction following medical encounters. This review seeks to account for this discord."</p> <p>"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."</p>	Published	<p>Geraghty, K. J., & Blease, C. (2018). <i>Myalgic encephalomyelitis/chronic fatigue syndrome and the biopsychosocial model: a review of patient harm and distress in the medical encounter. Disability and rehabilitation, 1-10.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing.</p> <p>Discusses the reporting of harms of graded activity-oriented therapies such as CBT and graded exercise therapy in the PACE Trial as well as in other trials and in clinical practice.</p> <p>"In total, 3774 adverse events were recorded across the four arms of the PACE trial (White et al., 2011). In the final reports from the trial, the following categories were used to define severe adverse events (SAEs): (1) death; (2) life-threatening event; (3) hospitalisation (hospitalisation for elective treatment of a pre-existing condition is not included); (4) increased severe and persistent disability, defined as a significant deterioration in the participant's ability to carry out their important activities of daily living of at least 4-week continuous duration; (5) any other important medical condition which may require medical or surgical intervention to prevent one of the other categories listed; and (6) any episode of deliberate self-</p>	Published	<p>Kindlon, T. (2017). <i>Do graded activity therapies cause harm in chronic fatigue syndrome?. Journal of health psychology, 22(9), 1146-1154.</i></p>

	<p>harm. Using this coding scheme, the researchers identified 48 SAEs during the trial, though without detailing which trial arm they occurred in. This seems unfortunate especially given that the authors stated that there was a statistically significant difference between the number of SAEs that occurred in the GET group (17) compared to the specialist medical care (SMC)-only group (7)."</p> <p>"Even if one assumes that there were no significant adverse events associated with CBT and GET in the PACE trial, it is unclear what healthcare staff, patients and others can read into such findings, given the question marks over compliance. What activity and exercise regimes are actually safe to use? Ones that do not increase fitness levels?"</p> <p>Future trials need to collect and report on objective data using devices, such as actometers and heart rate monitors, to help us establish what exactly is tested in trials of CBT and GET for CFS. Until that time and given the high rates of harm that have been reported outside clinical trials, caution needs to be used before proposing that any individual ME/CFS patient can safely increase their total exercise or activity levels using CBT or GET."</p>		
#MEAction	<p>Question 2. Interventions.</p> <p>This study looks into seven studies examining 159 people with ME/CFS/SEID met inclusion criteria, and 47 fatigue effects were derived.</p> <p>"Fatigue increases were larger for people with ME/CFS/SEID when fatigue was measured four or more hours after exercise ended rather than during or immediately after exercise ceased."</p>	Published	<p>Loy, B. D., O'Connor, P. J., & Dishman, R. K. (2016). <i>Effect of acute exercise on fatigue in people with ME/CFS/SEID: a meta-analysis. Medicine and science in sports and exercise, 48(10), 2003.</i></p>
#MEAction	<p>Question 2. Interventions.</p> <p>"Barriers to the effective clinical management of patients with irritable bowel syndrome and chronic fatigue syndrome are partly due to doctors' beliefs, which result in negative stereotyping of patients with chronic fatigue syndrome and the use of management strategies for both syndromes that may not take into account the best available evidence."</p>	Published	<p>Raine, R., Carter, S., Sensky, T., & Black, N. (2004). <i>General practitioners' perceptions of chronic fatigue syndrome and beliefs about its management, compared with irritable bowel syndrome: qualitative study. Bmj, 328(7452), 1354-1357.</i></p>
#MEAction	<p>Question 2. Interventions. CBT.</p>	Published	<p>Sunnquist, M. (2016). A</p>

	<p>"Findings suggest that individuals' activity level is unrelated to perceptions about illness etiology; rather, activity level is an indicator of general illness severity, along with impairment and fatigue. These findings are inconsistent with cognitive behavioral theories of [ME and] CFS that presume that individuals' symptoms stem from deconditioning and maladaptive illness beliefs. As these theories lack empirical support, and patients continue to express concerns about the efficacy of cognitive behavioral and graded exercise treatments, caution should be exercised in prescribing these treatments to patients."</p>		<p><i>reexamination of the cognitive behavioral model of chronic fatigue syndrome: Investigating the cogency of the model's behavioral pathway.</i> Retrieved from: https://via.library.depaul.edu/cgi/viewcontent.cgi?article=1200&context=csh_etd</p>
#MEAction	<p>Question 2. Interventions. GET.</p> <p>GET is neither effective or safe as a treatment for ME: "The analysis of the 2017 Cochrane review reveals flaws[...]. Because of the failure to report harms adequately in the trials covered by the review, it cannot be said that graded exercise therapy is safe. The analysis of the objective outcomes in the trials provides sufficient evidence to conclude that graded exercise therapy is an ineffective treatment for myalgic encephalomyelitis/chronic fatigue syndrome."</p>	Published	<p><i>Vink, M., & Vink-Niese, A. (2018). Graded exercise therapy for myalgic encephalomyelitis/chronic fatigue syndrome is not effective and unsafe. Re-analysis of a Cochrane review. Health psychology open, 5(2), 2055102918805187.</i></p>
#MEAction	<p>Question 2. Interventions. CBT.</p> <p>CBT is not an effective treatment for ME, nor is it proven safe: "Analysis of the 2008 Cochrane review of cognitive behavioural therapy for chronic fatigue syndrome shows that seven patients with mild chronic fatigue syndrome need to be treated for one to report a small, short-lived subjective improvement of fatigue. This is not matched by an objective improvement of physical fitness or employment and illness benefit status. Most studies in the Cochrane review failed to report on safety or adverse reactions. Patient evidence suggests adverse outcomes in 20 per cent of cases. If a trial of a drug or surgical procedure uncovered a similar high rate, it would be unlikely to be accepted as safe. It is time to downgrade cognitive behavioural therapy to an adjunct support-level therapy, rather than a treatment for chronic fatigue syndrome."</p>	Published	<p><i>Vink, M., & Vink-Niese, A. (2019). Cognitive behavioural therapy for myalgic encephalomyelitis/chronic fatigue syndrome is not effective. Re-analysis of a Cochrane review. Health psychology open, 6(1), 2055102919840614.</i></p>
#MEAction	<p>Question 2. Interventions. GET & CBT.</p> <p>Neither CBT nor GET improve employment status or illness benefit status: "These evaluations, just like the PACE trial itself, showed that CBT and GET do</p>	Published	<p><i>Vink, M., & Vink-Niese, F. (2019). Work Rehabilitation and Medical Retirement for Myalgic Encephalomyelitis/Chronic Fatigue</i></p>

	not improve employment and illness benefit status. As a matter of fact, both deteriorated. After treatment, more patients were unable to work and more were receiving illness benefits. Also, a systematic review by Ross et al. [59] concluded in 2004 that CBT and GET did not prove effective in restoring the ability to work. Chambers et al. and Castro-Marrero et al. [178,179] documented this conclusion by Ross et al. in their systematic reviews in 2006 and 2017, respectively."		<i>Syndrome Patients. A Review and Appraisal of Diagnostic Strategies. Diagnostics, 9(4), 124.</i>
#MEAAction	Question 2. Interventions. CBT. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. "Results show that CBT improved fatigue, but found that people with ME experienced no change in physical functioning after CBT."	Published	<i>Wiborg, J. F., Knoop, H., Stulemeijer, M., Prins, J. B., & Bleijenberg, G. (2010). How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. Psychological medicine, 40(8), 1281-1287.</i>
#MEAAction	Question 1. Monitoring and/or reviewing. Awareness of potential early death from comorbid illnesses and appropriate investigation for these is vital. "The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years, respectively, which is considerably younger than those who died from cancer and suicide in the general population."	Published	<i>Jason, L. A., Corradi, K., Gress, S., Williams, S., & Torres-Harding, S. (2006). Causes of death among patients with chronic fatigue syndrome. Health care for women international, 27(7), 615-626.</i>
#MEAAction	Question 1. Monitoring and/or reviewing. Awareness of potential early death from comorbid illnesses and appropriate investigation for these is vital. "The findings suggest patients in this sample are at a significantly increased risk of earlier all-cause (M = 55.9 years) and cardiovascular-related (M = 58.8 years) mortality, and they had a directionally lower mean age of death for suicide (M = 41.3 years) and cancer (M =66.3 years) compared to the overall U.S. population [M = 73.5 (all-cause), 77.7 (cardiovascular), 47.4 (suicide), and 71.1 (cancer) years of age]."	Published	<i>McManimen, S. L., Devendorf, A. R., Brown, A. A., Moore, B. C., Moore, J. H., & Jason, L. A. (2016). Mortality in patients with myalgic encephalomyelitis and chronic fatigue syndrome. Fatigue: biomedicine, health & behavior.</i>

#MEAction	<p>Question 1. Monitoring and/or reviewing. Orthostatic Intolerance.</p> <p>“Adults with ME/CFS had a significantly lower blood volume if they had a clinical suspicion of OI compared to those without a clinical suspicion of OI, as well as a significantly lower blood volume compared to the expected value. The data suggest that accounting for symptoms of OI could enhance the detection of the subset with reduced blood volume.”</p>	Published	<p><i>Van Campen, C. L., Rowe, P. C., & Visser, F. C. (2018). Blood Volume Status in ME/CFS Correlates With the Presence or Absence of Orthostatic Symptoms: Preliminary Results. Frontiers in pediatrics, 6, 352.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Orthostatic intolerance.</p> <p>“Dizziness and Lightheadedness symptoms while recumbent are an underreported finding in CFS and should be measured when doing a clinical evaluation to diagnose orthostatic intolerance.”</p>	Published	<p><i>Ocon, A. J., Messer, Z. R., Medow, M. S., & Stewart, J. M. (2012). Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome. Clinical science, 122(5), 227-238.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Post-exertional malaise.</p> <p>Understanding post exertional malaise is vital to the monitoring of ME/CFS and should be a part of training for all healthcare professionals working with people with ME/CFS. The study results state: “One hundred and twenty-nine subjects (90%) experienced PEM with both physical and cognitive exertion and emotional distress. Almost all were affected by exertion but 14 (10%) reported no effect with emotion. Fatigue was the most commonly exacerbated symptom but cognitive difficulties, sleep disturbances, headaches, muscle pain, and flu-like feelings were cited by over 30% of subjects. Sixty percent of subjects experienced at least one inflammatory/ immune-related symptom. Subjects also cited gastrointestinal, orthostatic, mood-related, neurologic and other symptoms. Exertion precipitated significantly more symptoms than emotional distress (7±2.8 vs. 5±3.3 symptoms (median, standard deviation), p<0.001). Onset and duration of PEM varied for most subjects. However, 11% reported a consistent post-trigger delay of at least 24 hours before onset and 84% endure PEM for 24 hours or more.”</p>	Published	<p><i>Chu, L., Valencia, I. J., Garvert, D. W., & Montoya, J. G. (2018). Deconstructing post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: A patient-centered, cross-sectional survey. PloS one, 13(6), e0197811.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Post-exertional malaise.</p> <p>“A survey was ultimately developed and was subsequently completed by 1534</p>	Published	<p><i>Holtzman, C. S., Bhatia, S., Cotler, J., & Jason, L. A. (2019). Assessment of Post-Exertional Malaise (PEM) in</i></p>

	members of the patient community. The findings of this survey suggest that there are key domains of this symptom, including triggers, symptom onset, and duration, which have often not been comprehensively assessed in a previous PEM instrument."		<i>Patients with Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS): A Patient-Driven Survey. Diagnostics, 9(1), 26.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Post-exertional malaise and orthostatic intolerance.</p> <p>Assessing orthostatic intolerance is an important part of reviewing people with ME, as is assessing PEM a major factor in monitoring severity. "The self-reported frequency of post-exertional malaise (PEM) was significantly associated with the severity of impaired HRQOL (P < 0.001). Cognitive impairment had a weaker association with the PedsQL score (P = 0.02). Orthostatic intolerance was present in 96% of the ME/CFS population."</p>	Published	<i>Roma, M., Marden, C. L., Flaherty, M., Jasion, S. E., Cranston, E. M., & Rowe, P. C. (2019). Impaired health-related quality of life in adolescent myalgic encephalomyelitis/chronic fatigue syndrome: the impact of core symptoms. Frontiers in pediatrics, 7, 26.</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Systematic Review.</p> <p>This systematic review from 2015 includes subsections on measuring PEM, neurocognitive dysfunction, sleep dysfunction, immune dysfunction, autonomic dysfunction, neuroendocrine dysfunction and pain. It states: "There is a clear need for more longitudinal studies in this area with larger data sets, which correct for multiple testing." p1. "Clearly, there is a need to adopt a common ME case definition, and then to use standardized measurement devices to collect both biological and self-report." p22</p>	Published	<i>A Jason, L., L Zinn, M., & A Zinn, M. (2015). Myalgic encephalomyelitis: symptoms and biomarkers. Current neuropharmacology, 13(5), 701-734.</i>
#MEAction	<p>Question 2. Interventions. Systematic Review.</p> <p>This detailed review of the cognitive behavioural model of ME/CFS and its evidence base concludes: "Our review exposes stark weaknesses, inconsistencies and contradictions, both in its theoretical underpinnings and the research said to prove model validity. Our findings suggest the CBM is not fit for purpose, as it poorly reflects the accounts given by patients and it ignores the wealth of evidence showing biological, immune and neurological dysfunction in ME/CFS."</p>	Published	<i>Geraghty, K., Jason, L., Sunnquist, M., Tuller, D., Blease, C., & Adeniji, C. (2019). The 'cognitive behavioural model' of chronic fatigue syndrome: Critique of a flawed model. Health Psychology Open, 6(1), 2055102919838907.</i>
#MEAction	Question 2. Interventions. Systematic Review.	Published	<i>Smith, M. B., Haney, E., McDonagh,</i>

	<p>“Among 35 treatment trials enrolling participants primarily meeting the 1994 Centers for Disease Control and Prevention and Oxford case definitions of CFS, the immune modulator rintatolimod improved some measures of exercise performance compared with placebo in 2 trials (low strength of evidence). Trials of galantamine, hydrocortisone, IgG, valganciclovir, isoprinosine, fluoxetine, and various complementary medicines were inconclusive (insufficient evidence). Counseling therapies and graded exercise therapy compared with no treatment, relaxation, or support improved fatigue, function, global improvement, and work impairment in some trials; counseling therapies also improved quality of life (low to moderate strength of evidence). Harms were rarely reported across studies (insufficient evidence).”</p>		<p><i>M., Pappas, M., Daeges, M., Wasson, N., ... & Nelson, H. D. (2015). Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Annals of internal medicine, 162(12), 841-850.</i></p>
#MEAction	<p>Question 2. Interventions. Systematic Review.</p> <p>"Of the 35 trials of treatment, rintatolimod compared with placebo improved measures of exercise performance; counseling therapies and graded exercise treatment (GET) compared with no treatment, relaxation, or support improved fatigue, function, and quality of life, and counseling therapies also improved employment outcomes. Other treatments either provided no benefit or results were insufficient to draw conclusions. GET was associated with higher numbers of reported adverse events compared with counseling therapies or controls. Harms were generally inadequately reported across trials."</p>	Published	<p><i>Smith, M. B., Nelson, H. D., Haney, E., Pappas, M., Daeges, M., Wasson, N., & McDonagh, M. (2014). Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Evidence report/technology assessment, (219), 1-433.</i></p>
#MEAction	<p>Question 2. Interventions. Systematic Review.</p> <p>Neither CBT nor GET can be said to improve functioning in those diagnoses with ME/CFS criteria other than the outdated Oxford criteria - it is especially of note that the treatments cannot be said to improve functioning in those experiencing post exertional malaise.</p> <p>"In removing the two Oxford case definition based studies, we are left with four fair-quality studies, two finding benefit (n=174), one finding no benefit (n=153), and one finding stable function in the CBT group but worsening function in the usual care group (n=65). Unlike the positive results of the Oxford based trials, the results of the trials fulfilling the CDC criteria are mixed and would provide</p>	Published	<p><i>Smith, M. B., Nelson, H. D., Haney, E., Pappas, M., Daeges, M., Wasson, N., & McDonagh, M. (2016). July 2016 Addendum. In Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Agency for Healthcare Research and Quality (US).</i></p>

	<p>insufficient evidence to determine the effectiveness of CBT on the outcome of function due to study limitations, inconsistency and imprecision of results."</p> <p>"By excluding the three trials using the Oxford (Sharpe, 1991) case definition for inclusion, there would be insufficient evidence of the effectiveness of GET on any outcome (1 trial, n=49)."</p>		
#MEAction	<p>Question 1. Monitoring and/or reviewing. Subjective scales.</p> <p>This study determines the validity and reliability of Short Form 36 Version 2 (SF36v2) in sub-groups of individuals with fatigue. As a result: "Individuals with CFS demonstrated significantly lower SF36v2 and MFI-20 sub-scale scores prior to CPET. Between-group differences remained significant post-CPET, however, there were no significant group by test interaction effects. Subjects with CFS reported significantly more total symptoms ($p < 0.001$), as well as reports of fatigue ($p < 0.001$), neuroendocrine ($p < 0.001$), immune ($p < 0.01$), pain ($p < 0.01$) and sleep disturbance ($p < 0.01$) symptoms than control subjects as a result of CPET. Many symptom counts demonstrated significant relationships with SF36v2 sub-scale scores ($p < 0.05$). SF36v2 and MFI-20 sub-scale scores demonstrated significant correlations ($p < 0.05$). Various SF36v2 sub-scale scores demonstrated significant predictive validity to identify subjects who recovered from CPET challenge within 1 day and 7 days ($p < 0.05$). Potential floor effects were observed for both questionnaires for individuals with CFS."</p>	Published	<p><i>Davenport, T. E., Stevens, S. R., Baroni, K., Mark Van Ness, J., & Snell, C. R. (2011). Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. Disability and rehabilitation, 33(25-26), 2596-2604.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Subjective scales.</p> <p>"The EQ-5D-3L-based HRQoL of ME/CFS is significantly lower than the population mean and the lowest of all the compared conditions. The adjusted analysis confirms that poor HRQoL of ME/CFS is distinctly different from and not a proxy of the other included conditions."</p>	Published	<p><i>Hvidberg, M. F., Brinth, L. S., Olesen, A. V., Petersen, K. D., & Ehlers, L. (2015). The health-related quality of life for patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). PloS one, 10(7), e0132421.</i></p>
#MEAction	<p>Question 1. Monitoring and review. Subjective scales.</p> <p>Validated questionnaires specific to people with ME are superior at measuring PEM: "Findings indicated that the majority of patients did support certain wordings of</p>	Published	<p><i>Jason, L. A., Mcmanimen, S. L., Sunnquist, M., & Holtzman, C. S. (2018). Patient perceptions of post exertional malaise. Fatigue: Biomedicine, Health & Behavior, 6(2),</i></p>

	both the precipitants and consequences of PEM. In addition, considerable approval was also found for a number of ways to phrase items assessing PEM."		92-105.
#MEAction	<p>Question 1. Monitoring and/or reviewing. Subjective scales.</p> <p>"The present study attempted to assess a comprehensive set of fatigue symptoms that have been commonly reported among patients with ME/CFS. A 22-item fatigue questionnaire was developed and administered to 130 persons diagnosed with ME/CFS and 251 controls. Adequate scale reliability was found."</p> <p>"Findings suggest that individuals with ME/CFS experience different types of fatigue than what are reported in the general populations."</p>	Published	<i>Jason, L., Jessen, T., Porter, N., Boulton, A., & Gloria-Njoku, M. (2009). Examining types of fatigue among individuals with ME/CFS. Disability Studies Quarterly, 29(3).</i>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Subjective scales.</p> <p>"The general and physical fatigue subscales on Multidimensional Fatigue Inventory-20, as well as the role of physical health on the RAND SF-36, demonstrated questionable or unacceptable internal consistency and problematic ceiling effects. The DePaul Symptom Questionnaire demonstrated excellent internal reliability, and less than 5% of participants were at the ceiling on each subscale. The post-exertional malaise subscale on the DePaul Symptom Questionnaire demonstrated excellent clinical utility as it was able to differentiate between ME/CFS patients and controls (OR = 1.23, p < .001), and predict ceiling effects on other patient reported outcome subscales. A score of 20 on the post-exertional malaise subscale of the DePaul Symptom Questionnaire optimally differentiated between patients and controls."</p>	Published	<i>Murdock, K. W., Wang, X. S., Shi, Q., Cleeland, C. S., Fagundes, C. P., & Vernon, S. D. (2017). The utility of patient-reported outcome measures among patients with myalgic encephalomyelitis/chronic fatigue syndrome. Quality of Life Research, 26(4), 913-921.</i>
#MEAction	<p>Question 1. Monitoring and review. Subjective scales.</p> <p>Generic tools can be used to assess functionality and change over time:"Generic instruments such as SF-36 and individual scales such as 'Role-Physical' may provide meaningful ways to assess the functional ability and wellness of people with ME, especially when combined with objective measures of functional status, thus enhancing the capacity to address the burden of disability experienced by patients and carers."</p>	Published	<i>Nacul, L. C., Lacerda, E. M., Campion, P., Pheby, D., de L Drachler, M., Leite, J. C., ... & Molokhia, M. (2011). The functional status and well being of people with myalgic encephalomyelitis/chronic fatigue syndrome and their carers. BMC public health, 11(1), 402.</i>
#MEAction	Question 1. Monitoring and/or reviewing. Subjective scales.	Published	<i>Roberts, D. (2018). Chronic fatigue</i>

	<p>"The WHOQoL-Bref26 has the potential to fill the gap identified in CFS/ME practice and capture change delivered through therapeutic interventions, being less resource-intensive and able to increase accuracy in reporting."</p>		<p><i>syndrome and quality of life. Patient related outcome measures, 9, 253.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Subjective scales.</p> <p>This systematic review aimed "to review the quality and acceptability of condition-specific, domain-specific and generic multi-item patient-reported outcome measures (PROMs) used in the assessment of adults with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)."</p> <p>"A total of 11 CFS/ME-specific, 55 domain-specific and 11 generic measures were reviewed. With the exception of the generic SF-36, all measures had mostly limited evidence of measurement and/or practical properties. Patient involvement was poorly reported and often cursory."</p> <p>"Evidence supports recommendation of the SF-36 as a generic measure of health status in CFS/ME; however, most evidence is limited to the PF domain. Although not yet widely evaluated in CFS/ME, the revised response options of the SF-36 (V2) PF [physical function] domain should improve data quality and enhance performance. There was limited evidence for the alternative generic measures, but the poor data quality of the EQ-5D suggests that it should be used with caution."</p>	Published	<p><i>Haywood, K. L., Staniszewska, S., & Chapman, S. (2012). Quality and acceptability of patient-reported outcome measures used in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. Quality of Life Research, 21(1), 35-52.</i></p>
#MEAction	<p>Question 1. Monitoring and/or reviewing. Biomarkers.</p> <p>"HGS [hand grip strength] is markedly reduced in ME/CFS, particularly in patients with more severe disease, and may indicate muscle and fatigue related symptoms. HGS is a potential diagnostic tool in ME/CFS, and could also be used to enhance patient phenotyping and as an outcome measure following interventions."</p>	Published	<p><i>Nacul, L. C., Mudie, K., Kingdon, C. C., Clark, T. G., & Lacerda, E. M. (2018). Hand grip strength as a clinical biomarker for ME/CFS and disease severity. Frontiers in neurology, 9, 992.</i></p>
#MEAction	<p>Question 1. monitoring and/or reviewing Question 2. Interventions.</p> <p>"These findings suggest that those who did not improve and those who did had</p>	Published	<p><i>Jason, L. A., Torres-Harding, S., Brown, M., Sorenson, M., Donalek, J., Corradi, K., ... & Fletcher, M. A. (2008). Predictors of change following</i></p>

	distinctly different patterns of lymphocyte subset distributions that predicted response to therapy. Past research has shown that CFS is associated with a shift toward a Type 2 immune response [51], and in the present study, those with this pattern tended not to improve. Other corroborating findings of this study indicate that those who improved versus those who did not were better able to stay awake and continue doing some type of work, and had more perceived energy at baseline."		<i>participation in non-pharmacologic interventions for CFS. Tropical Medicine and Health, 36(1), 23-32.</i>
#MEAction	Question 1. Monitoring and/or reviewing. "Our results indicate DNA methylation modifications in cellular metabolism in ME/CFS despite a heterogeneous patient population, implicating these processes in immune and HPA axis dysfunction in ME/CFS. Modifications to epigenetic loci associated with differences in glucocorticoid sensitivity may be important as biomarkers for future clinical testing. Overall, these findings align with recent ME/CFS work that point towards impairment in cellular energy production in this patient population."	Published	<i>de Vega, W. C., Herrera, S., Vernon, S. D., & McGowan, P. O. (2017). Epigenetic modifications and glucocorticoid sensitivity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). BMC medical genomics, 10(1), 11.</i>
#MEAction	Question 1. Monitoring and/or reviewing. In this study, "an analysis in 200 ME/CFS patients and 102 healthy individuals showed a specific reduction of amino acids that fuel oxidative metabolism via the TCA cycle, mainly in female ME/CFS patients." This study "found that the serum amino acid profile was changed in a large and well-characterized ME/CFS patient cohort, in a direction that suggests impaired mitochondrial pyruvate oxidation. This finding, in combination with increased mRNA expression of PDK1, PDK2, and PDK4, and of SIRT4, in PBMCs from patients, points to abnormalities in PDH regulation as a potential key factor in ME/CFS pathogenesis. Exposing cultured muscle cells to serum from ME/CFS patients indicated the presence of blood-borne substances affecting energy metabolism"	Published	<i>Fluge, Ø., Mella, O., Bruland, O., Risa, K., Dyrstad, S. E., Alme, K., ... & Ktoridou-Valen, I. (2016). Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. JCI insight, 1(21).</i>
#MEAction	Question 1. Monitoring and/or reviewing. "Mean lateral ventricular lactate concentrations measured by H MRSI in CFS were increased by 297% compared with those in GAD (P < 0.001) and by 348%	Published	<i>Mathew, S. J., Mao, X., Keegan, K. A., Levine, S. M., Smith, E. L., Heier, L. A., ... & Shungu, D. C. (2009). Ventricular cerebrospinal fluid lactate</i>

	<p>compared with those in healthy volunteers ($P < 0.001$), even after controlling for ventricular volume, which did not differ significantly between the groups. Regression analysis revealed that diagnosis accounted for 43% of the variance in ventricular lactate. CFS is associated with significantly raised concentrations of ventricular lactate, potentially consistent with recent evidence of decreased cortical blood flow, secondary mitochondrial dysfunction, and/or oxidative stress abnormalities in the disorder.”</p>		<p><i>is increased in chronic fatigue syndrome compared with generalized anxiety disorder: An in vivo 3.0 T 1H MRS imaging study. NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In vivo, 22(3), 251-258.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing.</p> <p>“These data suggest a correlation between low levels of NK cell activity and severity of CFIDS, which, if it is confirmed by additional studies of larger groups, might be useful for subgrouping patients and monitoring therapy and/or the progression of CFIDS.”</p>	Published	<p><i>Ojo-Amaize, E. A., Conley, E. J., & Peter, J. B. (1994). Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clinical Infectious Diseases, 18(Supplement_1), S157-S159.</i></p>
#MEAAction	<p>Question 1. Monitoring and/or reviewing.</p> <p>“The objective measures acquired by these methods should be used to accurately diagnose patients, to evaluate the severity and impact of the illness objectively and to assess the positive and negative effects of proposed therapies impartially.”</p> <p>See Table 4 for a list of "[s]ymptoms and tests to assess the disability in myalgic encephalomyelitis/chronic fatigue syndrome objectively": "Table 4 denominates tests that have demonstrated to yield aberrant results in ME/CFS. However, Table 4 should not consider to be exhaustive. Due to the heterogeneity of the ME/CFS patients population[1,34,88], not all patients will experience all symptoms, i.e., not all tests will show deviant results in all ME/CFS patients. Nevertheless, to assess the clinical status, the severity of the illness, and the disability of an individual patient impartially, patients should be subjected to the abovementioned and other objective tests as much is feasible."</p> <p>"The (long-lasting) physical effects of physical exertion (Figure 2A) can be evaluated objectively by subjecting a patient to two CPETs until exhaustion separated by 24 h[156]. The cognitive effects of physical exertion (Figure 2B)</p>	Published	<p><i>Twisk, F. N. (2015). Accurate diagnosis of myalgic encephalomyelitis and chronic fatigue syndrome based upon objective test methods for characteristic symptoms. World journal of methodology, 5(2), 68.</i></p>

	<p>can be assessed impartially by comparing the cognitive performance, e.g., simple and choice reaction times, before and immediately after a CPET, the cognitive effects of orthostatic stress (Figure 2C) can be established by subjecting patients to cognitive tests at various stages of a graded tilt table test, while the mental effects of cognitive exertion (Figure 2D) can be assessed objectively by exposing a patient twice to the same cognitive tests with several hours rest in-between."</p>		
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