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Summary of Public Comments and PNW EPC response: Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): An Updated Systematic Evidence Review

The draft report was posted for public comment on the Federal Register website from May 17, 2021 to August 16, 2021. One hundred thirty-five respondents commented. Some of the comments were from organizations that represented a number of people. We sorted comments according to the most common themes, noting that many comments addressed more than one theme. In response to the comments, wording changes were made in the final report to clarify limitations in the published research and highlight need for more well- designed clinical trials.

Summary of Comments

Theme #1: Concerns with Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) We received many comments expressing concern with inclusion of the CBT and GET in the systematic review. Comments included personal testimony of harms experienced after attempting treatment with CBT or GET, critiques of the proposed mechanism (or lack of) of CBT or GET, suggested references for surveys and other publications regarding the harms of treatment with CBT or GET and addressing specific methodological concerns with the PACE and GETSET studies such as changes in the research protocol, conflicts of interest, and methodological limitations. Our EPC was aware of the criticisms of CBT and GET as treatments for ME/CFS. Our review adhered to standards for conducting systematic reviews, established a methodology, and adhered to the methodology throughout the review. We developed a scope for this review after consultation with key informants and CDC's ME/CFS program. The review addresses both benefits and harms of potential treatments for ME/CFS. Studies of CBT and GET were included because they met the inclusion and exclusion criteria described in the methods. The PACE and GETSET trials met our pre-defined inclusion criteria, and we did not think that exclusion was warranted. The UK Health Research Authority (UK HRA) reviewed PACE and found that the changes in protocol were appropriately reported and there was no evidence that they were done to favor a particular outcome (https://www.parliament.uk/globalassets/documents/commons-committees/science-technology/Correspondence/190129-Sir-Jonathan-Montgomery-Health-Research-Authority-to-Chair-re-PACE-trial.pdf). We performed sensitivity analyses using original (protocol) definitions for outcomes and results were similar. The UK HRA found that conflicts of interest were appropriately disclosed, and it was unclear how a particular outcome would financially benefit the investigators. PACE and GETSET applied alternative ME/CFS case definitions and reported similar findings, and issues related to the ME/CFS case definition are discussed in detail above. PACE and GETSET were assessed using standard criteria for assessing risk of bias in randomized clinical trials (RCTs). Both trials were assessed as medium risk of bias (due in part to open-label design); this was similar to other trials of GET and CBT.

The report also describes the limitations of the evidence on these therapies, including the PACE and GETSET trials. Because we are not proposing or conducting original research, we did not propose potential mechanisms for observed effects; rather, we summarized the effects on outcomes that have been observed in the published research literature. We reviewed suggested citations and references for potential inclusion against the pre-defined inclusion criteria for the report.

The review summarizes the evidence on benefits and harms of these treatments; it does not make treatment recommendations. Additional clinical context and expertise, including references presented in public comments that did not meet inclusion criteria for the review, will contribute to any future development of guidelines or recommendations.

Sample Comments:

The PACE trial has been debunked. Why didn't your literature review find this?
Please remove graded exercise from your site! Many studies have shown it is harmful to us. CBT doesn't help, we need medical solutions.
GET or CGT maybe work for CVS only. But is you have ME it's dangerous, you can get a PEM. This is outdated and has to stop spreading.
This latest review repeats the same methodological flaws of basing recommendations for people with ME on CBT and GET studies that have a range of methodological defects, including: subjective outcome measures in unblinded trials, outcome switching, problems tracking harms, and use of Oxford criteria, even though EPC had said that Oxford had a risk of including patients with other fatiguing conditions.
Experts have found GET and CBT to cause PEM and be ineffective in calming what most think is an immune system dysfunction and probably genetic factors. GET and CBT are archaic ideas in this field. It concerns me that if this review is published it may further the incorrect notion of already-confused PCPs that GET or CBT is not harmful or may be helpful.
Publishing anything that recommends treatments (GET or CBT) for ME/CFS patients is irresponsible, reckless, and will harm patients. Conversely, what would help ME/CFS patients is to provide funding for research being done to find a diagnostic test like Ron Davis is trying to do.
The inclusion of GET & CBT as a treatment option is at best disingenuous and at worst extremely harmful. The PACE trial which purportedly showed these as viable treatments has been discredited. GET is extremely damaging to ME/CFS patients as our fatigue is NOT related to deconditioning.
This treatment option leads to doctors dismissing patients and believing that ME/CFS is psychological disorder. When doctors believe it is a psychological disorder they stop listening and refer the patient out.

<u>Theme #2: Personal Testimonials</u>

The majority of comments included personal experiences with ME/CFS. These testimonials spoke to the sincere frustration and desperation experienced by many patients diagnosed with ME/CFS. Many patients shared experiences, including difficulty finding providers familiar with ME/CFS, struggles during and after attempted treatment with graded exercise therapy (GET) or cognitive behavioral therapy (CBT), and the impact of ME/CFS on their daily lives. Some patients shared success stories and suggested medications or treatments that had worked for them. We appreciate the commenters' courage in sharing their stories and acknowledge the struggles they face on a daily basis. Some patients felt that the systematic review was recommending treatment with GET or CBT. However, the purpose of the systematic review was to provide a summary of available published literature, including limitations; it **does not** make treatment recommendations, and therefore, does not recommend GET or CBT. A systematic review is one step required in the process of developing clinical management guidelines, including treatment recommendations. When the evidence is insufficient to support treatment recommendations, systematic reviews are also useful to identify research gaps and inform future research and funding priorities.

Sample Comments:

Aggressive REST is a large part of my recovery. I am also taking a variety of medications and doing a variety of other alternative therapies. None of which is graded exercise. I believe whole-heartedly that graded exercise would have made me much sicker.

The CBT was traumatic, and has left me with a lifelong fear of psychology. I was gaslit every session, told that I was doing this to myself, and blamed when I didn't get better.
I still struggle with this feeling that if I just pushed my kids to try GET again, they might get better, and there is such guilt there. While at the same time, I have followed that guidance and seen my kids get worse, and there is so much guilt there too. As a caregiver, trying to do what is best for my kids, I need our doctors and I need the CDC to support us and guide us to help our children with what is actually proven to prevent harm: REST and PACING
I have been fortunate to be treated by one of the Clinicians Coalition doctors skilled in treating immune dysfunction and infections, an autonomic neurologist, and a group of talented naturopathic and functional medicine doctors. Today, I regularly golf 18 holes, stand up paddle board, kayak, and can walk 6-8 miles. In 2016, I was sleeping 16 hours a day with significant brain fog.
Many of us are still around but stopped counting the times we seriously consider suicide as the only remaining option. We have lots to give back to society, if we just get the chance again.
As a sufferer with advanced Myalgic Encephalomyelitis (M.E.), I can tell you with certainty that Graded Exercise Therapy (GET) with the often suggested Cognitive Behavioral Therapy (CBT) *MADE ME WORSE!*
Being trained by a therapist to ignore my symptoms was one of the most damaging things anyone could have done to me. I should not be this disabled. There is no reason that anyone should experience what I experienced but the reality is that it happens all the time.
My illness has been entirely disregarded by a system which asks me to send 1/4 of my total Gross Domestic Product, to pay for insurance that provides no treatment for my illness.

Theme #3. Inclusion of Studies with High Risk of Bias

The comments express concern that unblinded trials and studies reporting participant-reported outcomes should have been rated high risk of bias. For interventions where blinding is not possible, we downgraded for open-label design, but did not necessarily downgrade to high risk of bias unless there were other methodological limitations. This is a standard approach used in many other systematic evidence reviews, including:

1. Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, Fu R, Brodt ED, Wasson N, Kantner S, Ferguson AJR. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER227
2. Chou R, Wagner J, Ahmed AY, Blazina I, Brodt E, Buckley DI, Cheney TP, Choo E, Dana T, Gordon D, Khandelwal S, Kantner S, McDonagh MS, Sedgley C, Skelly AC. Treatments for Acute Pain: A Systematic Review. Comparative Effectiveness Review No. 240. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20(21)-EHC006. Rockville, MD: Agency for Healthcare Research and Quality; December 2020. DOI: 10.23970/AHRQEPCCER240

Theme #4: Exclusion of non-RCT Studies on Harms Evidence

Commenters suggest that the EPC missed potentially relevant evidence on harms by excluding observational studies and patient surveys. We focused on randomized controlled trials for evaluation of benefits and harms of treatments because observational studies and non-RCTs are susceptible to bias and confounding, particularly for more subjective outcomes like those evaluated in this report.

Sample Comments:

The draft report on ME/CFS suffers from multiple flaws such as failure to include objective measurements and reports of harms from observational studies. The report also underestimates the risk of bias in non-blinded trials where subjective questionnaires are used, where the intervention influences how patients view their symptoms and where the control group receives no intervention. Such trials are at high risk of bias but this is not reflected in the draft report.
Unblinded trials using subjective outcome measures should be considered "high" risk of bias, especially considering the interventions themselves target perception. Objective outcome measures in unblinded trials are essential to draw any conclusions about efficacy.

Theme #5. Case Definitions and Impact on the Systematic Review

Some comments suggested the removal of studies that used older case definitions for participant inclusion. The available published evidence included studies that used a number of different case definitions of ME/CFS. Many of the trials varied in the ME/CFS case definitions, and few trials used more current ME/CFS case definitions; in addition, trials may have excluded patients with more severe ME/CFS, and most case definitions did not require presence of post-exertional malaise. Based on our methods, we required trials to diagnose ME/CFS using a published case definition but did not exclude specific case definitions given lack of consensus on a "gold standard" for diagnosis. In addition, excluding trials that used older case definitions or those that did not require post-exertional malaise would have resulted in exclusion of almost all trials. To address heterogeneity in case definitions, we stratified analyses according to the definition used; results were similar in trials that utilized different case definitions. We also evaluated within-study analyses from trials that evaluated subsets of patients who met alternative ME/CFS case definition criteria; though limited, these trials also found no differences in findings based on the case definition used. The report states that the applicability of findings to patients diagnosed using more current ME/CFS case definitions, those requiring post-exertional malaise as well as to patients with more severe ME/CFS by any definition is uncertain.

Sample Comments:

Use of the Oxford case definition is problematic as it has been found to diagnose 14 false-positive ME/CFS cases for every 15 individuals when compared with the CCC. Since GET as a form of physical exertion can incur a post-exertional malaise (PEM) response in ME/CFS patients, use of the Oxford definition is especially troublesome for GET studies since the definition does not require PEM for a diagnosis of ME/CFS. This is likely to lead to the underestimation of harms.
This review is not based on current definitions of ME/CFS and doesn't include the main criteria of Post-Exertional Malaise in the case definitions, so all studies included in their analyses have been flawed and included other patient populations beyond ME/CFS.
This review is fundamentally flawed, the criteria used to define ME/CFS patients was inconsistent, most of the treatment recommendations are based on the now retracted PACE study that was damaging to patients, your support for GET was based on patients without reports of Post Exertional Malaise despite that being the defining diagnostic criteria that separates ME/CFS from other similar illnesses.
I noticed you're including studies that rely on the Oxford Criteria such as the Powell 2001 (1) and the PACE trial (2). The Oxford Criteria does NOT include the defining symptom of Myalgic Encephalomyelitis, namely Post Exertional Malaise (PEM). This could be catastrophic if you intend to introduce GET as a primary treatment plan. James Baraniuk (3) has noted a vast overestimation of CFS (85% inappropriately classified) due to relying on the Oxford Criteria rather than other criteria that include PEM as a primary symptom like the International Consensus Criteria (4). Likewise, other reviews such as the Cochrane Review (5) have been met with serious criticism by reviews such as Mark Vink (6) due to a number of issues, including the Oxford Criteria.

In selecting which studies to review, the authors of this evidence review committed a error which renders their findings irretrievably flawed: they conflated idiopathic chronic fatigue with ME/CFS. The hallmark symptom of ME/CFS, as evidenced by the CDC's own definition, is post-exertional malaise (PEM). The review includes studies on chronic fatigue and studies which use a case definition which doesn't require PEM, such as Fukuda and Oxford criteria.
The GET and CBT studies included in the systematic review do not reference people with ME/CFS as defined by CDC, and therefore cannot apply to people with ME/CFS as defined by CDC.

Theme #6. Interpretation of Results

The comments question the use of meta-analysis in the systematic review, due to high heterogeneity, low strength of evidence, and high risk of bias studies. We pooled trials that evaluated similar interventions, comparisons, and outcomes. Due to anticipated heterogeneity, we used a random effects model to pool studies. In addition, the strength of evidence was downgraded if statistical heterogeneity was present and we performed stratified and sensitivity analyses to evaluate potential sources of heterogeneity (on factors such as ME/CFS criteria used, risk of bias, and control type). We include these issues in our descriptions of limitations of this systematic review.

Theme #7: CDC Programmatic Concerns and Recommendations, Future Research and Funding, Suggested Treatments for Consideration:

A number of comments included requests or recommendations to the CDC ME/CFS Program regarding future research and/or guidelines. We appreciated the comments, which are being taken into consideration. While these comments are helpful for informing future research and guideline development efforts, these comments were outside the scope of the evidence review. The findings of the systematic review support the need for additional clinical trials and research in ME/CFS.

Commenters specifically expressed concerns related to the need for additional patient and stakeholder engagement. These will be helpful to CDC in their continued planning for their ongoing work to improve the lives of those living with ME/CFS . In addition, they describe failure of this evidence review to counter inaccurate medical information and stigma. We agree that additional education about ME/CFS is needed for healthcare providers and the general public to improve care and reduce stigma associated with the diagnosis, but that is beyond the scope of the systematic review.

Sample Comments:

Ativan needs to be studied. It is unusually adaptogenic in people with ME/CFS. In very low, daily doses it can work wonders, though it by no means cures this wretched illness… Further ME/CFS research desperately needs a viable, likely blood based, diagnostic tool. As far as I know, there are SEVERAL in the works that are probably ready to go to market. WHAT ME/CFS RESEARCH NEEDS IS MONEY!!!!!!!!
Having been struggling with CFS for seven years, my exhaustion was finally eliminated with Cadmium Sulphuratum, a homeopathic remedy that is usually used to treat exhaustion accompanying chemo and radiation. It would make sense to commission a study on this
the CDC and Mr. Fauci in the NIH have ignored CFS and ME or SEID for over 35 years and refused to adequately fund scientific research into the illness for over 35 years. The statistics and funding figures prove this. When compared to similar illnesses and lesser illnesses in population terms and medical terms, CFS or ME has received too little funding or no funding for several decades and thus the science for this illness has not been fully developed.

Accept that there are currently NO treatments to recommend and start focusing on research to find the biomedical cause for mecfs so that you can eventually offer treatments based on a sound understanding of the actual cause of the condition and not on flaws psychosomatic reasoning.
These treatments put the patient at risk for a condition known as CRS (Ctyokine Release Syndrome) which causes a severe immune response, causing the body to attack healthy tissue and cells. ME/CFS carries this risk. Making someone with this condition exert themselves puts them right in the crosshairs of this dangerous reaction. So, please come up with safer methods to help someone live with this debilitating condition.
Patients with ME/CFS show measurable physiological changes compared to healthy controls. Unfortunately, because of the minute funding allocated to ME/CFS research, no one yet knows which of these changes might be the cause of ME/CFS and which are the effects. What the CDC should be doing is giving primary care physicians the information necessary to diagnose ME/CFS. Since there is no effective treatment for ME/CFS, it is impossible to do anything more than to say there is no treatment or cure for ME/CFS.
The researchers at Stanford are currently studying medications like Low Dose Naltrexone to blunt the response of Inflammatory Cytokines.
So we watch as billions goes to study in minute detail the scourge of Long COVID and everyone is warned about how terrible the effects. Meanwhile we struggle to stand up without our heart rate spiking, a doctor's visit leaves us suffering with myalgia and myoclonus for days, our vision suffers, migraines are a common occurrence, every food seems to irritate our system.

Theme #8: Recommended References:

Numerous comments included suggested additional information available on websites and in scientific publications. The EPC assessed each suggested reference with our pre-established inclusion/exclusion criteria. No new studies met inclusion criteria.