Clinical Guidance for ME: "Evidence-Based" Guidance Gone Awry

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This article is intended as a high-level summary of key issues in the conduct of reviews of the ME evidence-base that have resulted in flawed conclusions and recommendations in clinical guidance. This has misled medical providers on the nature of ME and its appropriate treatment and put people with ME at risk of harm. Comments can be sent to medimmock@gmail.com.

Summary

For many years, ME evidence-based reviews and clinical guidance globally, such as those from Cochrane, UpToDate, Mayo, NICE, and various medical journals and societies around the world have recommended cognitive behavioral therapy (CBT) and graded exercise therapy (GET) as effective and safe treatments for ME. Further, these sources have sometimes claimed that disease risk and poor prognosis is the result of behavioral and psychological factors such as maladaptive coping, a history of abuse, perfectionism, and the patient's belief that the disease is organic. In spite of patient surveys and ancedotal reports that these treatments were not only ineffective but harmful, these recommendations and statements have remained.

Since 2015, a growing chorus of international journalists and scientists, along with reports by the U.S. Health and Human Sevices have documented serious deficiencies in the supporting studies that call into question the validity of these recommendations. In parallel, the U.S. Institute of Medicine (IOM, now called the National Academy of Medicine) published a report that directly contradicts the disease theory underpinning these studies. These deficiencies and contradictions include the following (Further details in Appendix II):

1. **Lack of external validity:** According to the US Agency for Healthcare Research and Quality (AHRQ), the use of an overly broad definition (the Oxford definition) in many of these studies resulted in the inclusion of "patients who may have an alternate fatiguing illness." The 2016 AHRQ report also noted that studies using more specific definitions requiring hallmark symptoms of ME such as an abnormal response to exertion were "blatantly missing." After excluding Oxford studies from its analysis, AHRQ found no evidence of effectiveness for GET and barely any for CBT. This raises serious questions about the validity of applying CBT and GET recommendations to people with ME.

2. **Study design and conduct issues:** The CBT and GET evidence base is biased by unblinded studies that relied on subjective outcome measures, ignored or dismissed objective findings that contradicted subjective reports, switched outcomes, inflated claims of improvement and recovery, and contained other significant problems in the design and conduct of studies. The issues in these studies, including the UK's flagship £5 million PACE trial, call into question the quality and reliability of claims of CBT and GET effectiveness.

3. **Inadequate reporting of harms:** Conclusions that these therapies are safe are based on studies that inadequately reported adverse effects and did not monitor treatment

compliance. Further, neither the evidence reviews such as Cochrane nor the individual studies adequately account for patient survey reports of harm from these therapies. Nor do they account for the published biomedical evidence and the IOM report demonstrating the disease's abnormal physiological response to exertion, a response that supports concerns with the risk of harm from exertion. Claims of CBT and GET safety are not supported by the evidence.

4. **Flawed disease theory:** The disease theory underlying the use of CBT and GET in this disease is that the symptoms and the debility are not the result of an organic disease but rather the result of deconditioning which in turn is the result of false cognitions and a fear of activity. This disease theory also links a predisposition to the disease and poor prognosis with behavioral and psychological factors such as those described above. This theory is unproven and the studies cited to support it have most often used the overly broad Oxford definition which could include patients with a primary mental illness. But more importantly, this psychogenic theory cannot be reconciled with the 2015 Institute of Medicine report which found that ME is not psychological or a problem of deconditioning. Instead, the IOM found substantial evidence of neurological, immunological, autonomic, and energy metabolism impairment. In no other disease would such impairment be treated by talk therapy intended to convince the patients they are not really sick. The ethicality of doing do in this disease must be questioned.

In July 2017, the US Centers for Disease Control and Prevention (CDC) removed long-standing recommendations for CBT and GET from its website. Yet, today, the vast majority of providers for clinical guidance for ME globally still continue to use these flawed studies as the basis of CBT and GET recommendations and conclusions about poor prognosis. In Japan, recommendations for CBT and GET are scheduled to be published in a widely read medical journal in March. In the UK, NICE has agreed to review its guidelines but the current CBT and GET recommendations remain. In the US, even clinical guidance that has adopted the IOM criteria with its hallmark abnormal response to exertion still recommends CBT and GET. For instance, one medical education provider has adopted the IOM criteria and IOM-derived statements about neurological, immunological, and metabolism impairment but then goes on to recommend PACE-style CBT and GET and link poor prognosis to a patient's belief that the disease is physical. It is stunning that such highly regarded organizations continue to produce "evidence-based" guidance for ME using such poor-quality, contested, and inappropriate evidence. Doing so not only misleads medical providers on the nature of ME and its appropriate treatment but puts people with ME at direct risk of significant harm by their medical providers.

To best protect patients from further harm, it is essential that evidence review publishers such as Cochrane and providers of evidence-based clinical guidance such as Uptodate, Healthwise, Mayo, and various medical societies reevaluate the quality and validity of the evidence that they are using to support their conclusions and recommendations for ME. It is essential that these organizations update their reviews and guidance to remove the erroneous conclusions and recommendations based on poorly conducted, invalid studies and to incorporate what is known today about the biopathology of ME and its proper treatment.

Appendix 1: Key Events and References from recent debate on the use of CBT and GET

Aug 2017	The Journal of Health Psychology published a special issue on the PACE trial debate	http://journals.sagepub.com/toc/hpqa/22/9
Jul 2017	A petition, signed by over 15,000 people, was submitted to NICE calling, in part, for a reappraisal of the evidence supporting recommendations for CBT and GET	http://vadamagazine.com/news/no-confidence-charities-reject-nice-no-update-proposal-mecfs-guideline
Jul 2017	The US Centers for Disease Control and Prevention removed long-standing recommendations for CBT and GET from it's ME/CFS website, in part because of these issues	https://www.cdc.gov/me-cfs/treatment/index.html
Mar 2017	The New York Times published an editorial by Tuller and Rehmeyer highlighting the impact of PACE-based recommendations for CBT and GET on patients.	https://www.nytimes.com/2017/03/18/opinion/sunday/getting-it-wrong-on-chronic-fatigue-syndrome.html
Mar 2017	142 scientists, clinicians, other professionals, and patient organizations submitted a joint letter to Psychological Medicine calling for retraction of the 2013 PACE Recovery paper after reanalysis showed the claims of recovery were highly inflated	http://www.virology.ws/2017/03/23/an-open-letter-to-psychological-medicine-again/
Jul 2016	The US Agency for HealthCare Research and Quality (AHRQ) significantly downgraded their recommendations for CBT and GET in this disease after excluding studies using the overly broad Oxford definition from analysis. In 2014, AHRQ had called for the Oxford definition to be retired. In 2015, the US National Institutes of Health (NIH) called for Oxford to be retired because it could "impair progress and cause harm."	https://effectivehealthcare.ahrq.gov/ehc/products/586/2004/chronic-fatigue-report-160728.pdf and http://annals.org/aim/article/2322804/national-institutes-health-pathways-prevention-workshop-advancing-research-myalgic-encephalomyelitis
Aug 2016	A UK Tribunal ordered the release of a portion of the PACE data in response to an appeal of a rejected FOIA. This led to a reanalysis of the recovery data that showed recovery claims had been significantly inflated	http://informationrights.decisions.tribunals.gov.uk//DBFiles/Decision/i1854/Queen%20Mary%20University%20of%20London%20EA-2015-0269%20(12-8-16).PDF
Mar 2016	Professor Rebecca Goldin of George Mason University and Director of Stats.Org published an independent analysis of PACE that reached the same conclusions as Tuller.	http://senseaboutscienceusa.org/pace-research-sparked-patient-rebellion-challenged-medicine/
Feb 2016	Over three dozen scientists and clinicians submitted a joint letter to the Lancet calling for an independent reanalysis of PACE	http://www.virology.ws/2016/02/10/open-letter-lancet-again/
Oct 2015	Building on the years of analyses and published comments by patients in scientific journals, David Tuller published a three part series reporting his analysis of the PACE trial.	http://www.virology.ws/2015/10/21/trial-by-error-i/, http://www.virology.ws/2015/10/22/trial-by-error-ii/, http://www.virology.ws/2015/10/23/trial-by-error-iii/
Feb 2015	Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. U.S. Institute of Medicine Evidence Review and recommended clinical diagnostic criteria	http://www.nationalacademies.org/hmd/Reports/2015/ME-CFS.aspx

Appendix 2: Further Details on the Concerns Summarized Above

As discussed above, the Cochrane "CFS" evidence reviews and the clinical guidance recommendations for CBT and GET are based on a series of studies that were fundamentally flawed in design and conduct, failed to adequately evaluate harms or account for patient reports of harms, and were based on an unsupportable disease theory.

The size of UK's £5 million PACE and its ranking as a high quality trial in evidence reviews, such as Cochrane has given it significant weight in the conclusions of those reviews. But while PACE has received the most criticism, the problems with PACE are not limited to just the PACE trial or to just UK studies as demonstrated in a 2017 review of Dutch studies.[1] Many of the widely reported concerns with that trial apply to the whole body of CBT and GET studies and other studies using the "biopsychosocial" theory of CFS. These concerns included the following:

1. **Flawed Evidence Base – Lack of Both Internal and External Validity**

   A. Subjective Outcomes in Unblinded Studies

   As reported by Vink,[2] Lilienfield et al. recommended that unblinded trials use at least one objective outcome as a safeguard against erroneous conclusions of efficacy.[3]
   In peer reviewed commentary on the PACE trial, Edwards and Wilshire both noted the necessity of objective measures in unblinded studies to support claims of efficacy.[4]
   However, the studies for CBT and GET in CFS have been both unblinded and relied on subjective measures. As a result, the recommendations in evidence reviews and clinical guidance have also relied on subjective findings in unblinded trials.

   Objective measures could have been used but seldom were in the CBT and GET studies in this disease. When objective measures were used, they did not reflect the positive results reported for the subjective measures. For instance, Wilshire stated that CBT and GET had "modest, time-limited effects on self-report measures, but little effect on more objective measures" and noted that the effects that were seen "may reflect participant response bias."[5] In a review of CBT in those CFS studies that had included objective measures, McPhee also noted "a lack of evidence that cognitive behavioural therapy produces any improvement in a patient's physical capabilities or other objective measures such as return to work."[6]

   In response to published comments questioning why objective findings had not been included in the 2015 GET review, Larun's response was that the protocol had not included any objective measures.[7] But this only begs the question of why the protocol did not include objective measures. Methodological studies suggest that reporting biases are introduced when using subjective measures in open label studies. This is especially true if investigators give participants different expectations of the effectiveness of the treatments being investigated, as discussed further below. To overcome the potential of erroneous conclusions, these systematic reviews need to be redone, using whatever objective measures are available.

B. Use of overly broad definitions

The majority of these CBT and GET studies used the 1991 Oxford CFS definition which requires only 6 months of chronic medically unexplained fatigue and allows the inclusion of patients with various forms of mental illness who might be expected to respond positively to CBT and GET. The remainder used the 1994 Fukuda CFS definition which also allows the inclusion of some forms of mental illness.

It is important to note that neither Oxford or Fukuda CFS definitions require hallmark symptoms such as post-exertional malaise (PEM), defined as mandatory for a diagnosis of ME by the 2015 report of the Institute of Medicine (IOM, now called the National Academy of Medicine).[8] These hallmark criteria are also required by the 2003 Canadian Consensus Criteria and the 2011 ME International Consensus Criteria.

Based on these definitional differences, the 2015 IOM report concluded "a diagnosis of CFS is not equivalent to a diagnosis of ME."[9] As a result of these factors, both the Oxford and Fukuda CFS definitions, particularly Oxford, misclassify other conditions, including mental illness and other fatiguing conditions as ME. At the same time, these definitions have included co-morbid depression that could confound the interpretation of results. By introducing ambiguity in trial participant selection and what conditions were actually being studied, these definitions have confounded research findings and resulted in inappropriate treatment recommendations for clinical care.

The 2016 US Agency for HealthCare Research and Quality (AHRQ) Evidence Review concluded that studies of CBT and GET using more specific ME and ME/CFS definitions (those that require these hallmark symptoms) were "blatantly missing" from the evidence for CBT and GET.[10] Yet, despite the absence of these studies and the fundamental differences between the ME and CFS definitions, both the Cochrane 2008 CBT review and the 2015 Cochrane GET review included only Oxford and Fukuda CFS definitions but then stated that CFS is sometimes called ME, effectively treating CFS and ME patient cohorts and definitions as interchangeable. This has led to the conclusion that the findings of Oxford CFS studies are appropriately applied to patients who meet any ME or ME/CFS case definitions.

In 2014, the U.S. Agency for HealthCare Research and Quality (AHRQ) published an evidence review of ME/CFS treatments in which they concluded that CBT and GET were moderately effective and safe for ME/CFS.[11] Like Cochrane, AHRQ's 2014 conclusions were based largely on Oxford studies. Yet, that review also explicitly concluded that the results may not be applicable to those patients fulfilling stricter criteria for ME or ME/CFS (such as the Canadian Consensus Criteria). It also called for the Oxford criteria to be retired because Oxford creates "a high risk of including patients who may have an alternate fatiguing illness, or whose illness resolves spontaneously with time." A 2015 report by the US National Institutes of Health reiterated the call to retire Oxford, stating it could "impair progress and cause harm."[12]

In 2016, because of the concerns with the Oxford CFS definition, AHRQ reanalyzed the evidence for CBT and GET after excluding these studies. AHRQ's 2016 adddedum to its 2014 evidence review concluded there was insufficient evidence of effectiveness for GET and barely any for CBT once the Oxford studies were excluded.[13]

In response to criticism of their use of the Oxford definition, the PACE investigators have stated that they also subgrouped trial participants by the Fukuda CFS definition and by the London ME criteria and did not find a difference in treatment effectiveness between the definitions. Similarly, in response to September 2015 comments on the 2015 Cochrane GET review, Larun also stated that the Cochrane review found "no evidence for a difference" between Oxford and Fukuda studies,[14] based in part on findings reported by PACE.

But the statement that these definitions have similar responses is problematic for a number of reasons. First, the 2013 PACE Recovery publication stated that the Fukuda and London assessments were based on a combination of "self-ratings and research assistant assessment" and acknowledged this could have introduced bias in characterizing trial participants using these definitions.[15]

Compounding that problem, the 2013 PACE Recovery publication reported that the Fukuda criteria used by PACE had been modified to only require symptoms for one week, not the 6 months required by Fukuda.[16] The 2013 Recovery publication acknowledged that this could have affected the accuracy of trial participant identification, a problem apparently not reported in other PACE publications. PACE also used a modified version of the London criteria which could have similarly affected the accuracy of that trial participant characterization.[17] Finally, and most importantly, as reported by David Tuller in his series on PACE, Dr. Bruce Levin, a professor of biostatistics at Columbia University noted that PACE had selected Fukuda and London patients out of an already defined Oxford patient cohort and said that he "would not accept an extrapolation" from such a preselected subset to all Fukuda CFS or all London ME patients.[18]

More recently, the GETSET trial, a study of GET delivered as guided self-help, reported selecting participants with the NICE criteria, clinical criteria not intended for research.[19] The NICE criteria require "post-exertional malaise and/or fatigue" plus any one of ten other symptoms. As with PACE, the GETSET authors also subgrouped the already selected NICE patients - this time with Oxford and Fukuda - and concluded that this provided "confidence that our findings are generalisable" to patients meeting these other definitions. However, the same issues that Levin noted with PACE's approach to subgrouping preselected patient groups would also apply here. It is unclear whether GETSET also used a modified version of Fukuda as had been done with PACE. But even if it had, it's important to remember that neither Oxford or Fukuda require the symptoms that the 2015 IOM report said are required for a diagnosis of ME.

Compounding Levin's concerns, the NICE criteria states that it requires "post-exertional malaise and/or fatigue" but then states that the exacerbation of symptoms following physical

or mental exertion is considered optional. This post-exertional exacerbation of symptoms is one of the defining features of PEM as described by the Canadian Consensus Criteria and the Institute of Medicine. Thus, it appears unlikely that the NICE criteria is selecting the same group of patients as ME and ME/CFS definitions and it can not be considered a substitute for these definitions.

Collectively, these problems call into question what conditions have been studied in these CBT and GET studies for CFS. These problems also call into question the PACE investigator claims that the findings of PACE apply to all patients meeting definitions for ME and ME/CFS. In her 2016 independent analysis of the PACE trial, Rebecca Goldin, Professor of Mathematical Sciences at George Mason University and Director of Stats.Org, noted that the choices made in participant selection constitute a "selection bias [that] results in limited generalizability of any results" beyond the specific population studied.[20]

In its extensive review of the evidence base for ME, the 2015 Institute of Medicine report reported that the lack of external validity, in part as a result of inconsistent case definitions, was one of the most significant challenges in the field. Additionally, the IOM noted that the use of polythetic criteria such as Fukuda could result in patients with little similarity to each other all being given a diagnosis of ME/CFS. This concern with external validity reflects AHRQ's conclusions that Oxford definition studies include patients with other fatiguing conditions and that studies using ME and ME/CFS definitions are "blatantly missing" from the evidence base for CBT and GET. By conflating definitions that the IOM report said are not equivalent, evidence reviews such as Cochrane and "evidence-based" guidelines such as UpToDate perpetuate the risk of harm to patients who have ME.

C. Conduct and Design Flaws in the flagship PACE Trial

In addition to the use of broad criteria and subjective outcomes in unblinded trials, the influential PACE trial has other fundamental flaws, broadly documented by journalist Dr. David Tuller of Berkeley in 2015 and since then by a number of other researchers and academics, including those from outside the field.[21] The main flaws include:

a. Outcome switching: PACE changed the methods used to assess the primary trial outcomes of fatigue and physical function mid-trial in a way that reflected worse functioning than that required to enter the trial to begin with. PACE also loosened its criteria for improvement[22] and recovery mid-trial.[23] These changes, made without adequate justification or sensitivity analysis,[24] resulted in inflated estimates of both recovery and improvement.

   For instance, the scoring method for the Chalder Scale, used to assess fatigue, was changed from bimodel scoring to Likert scoring. When this was done, the threshold for the *normal range* for fatigue - used as one of the recovery criteria – was modified to be 18 or below.[25] As Tuller noted, this meant that a participant "could have started the trial with a revised fatigue score of 12, become more fatigued to score 18 at the end, and yet still been considered within the 'normal range'."[26]

Similarly, the SF-36, used to assess the primary outcome of physical function, was also changed mid-trial. The original protocol specified an SF-36 score of 85 or greater as one of the recovery criteria. But this was reduced to a threshold of 60 or greater mid-trial, a score lower than the SF-36 entry criterion of 65. Wilshire et al. noted that as a result of this change, thirteen percent of trial participants met this recovery criterion at the time they entered the trial.[27] Bruce Levin, a professor of biostatistics at Columbia University stated "I have never seen a trial design where eligibility requirements for a disease alone would qualify some patients for having had a successful treatment." He added, "It calls into question the diagnosis of an illness whose patients already rate as 'recovered' or 'within normal range.'"[28]

A recovery criterion of 60 on the SF-36 also calls into question whether PACE's definition of "recovery" is clinically appropriate. As Geraghty points out, a score of 60 on the SF-36 is roughly equivalent to a patient with congestive heart failure.[29]

Using these modified methods of assessing recovery and improvement, PACE reported that 60-61 percent of participants improved with CBT and GET and 22 percent of the participants recovered.[30] However, when data was reanalyzed by the PACE investigators using the protocol-defined method, the improvement rate dropped to 20 percent for CBT and 21 percent for GET.[31] The recovery rate dropped to 4-7 percent and showed no significant difference between these treatments and controls.[32] (Note: The recovery reanalysis was done by independent investigators after a UK tribunal ordered the release of PACE data following appeal of a denied FOIA request.[33] The PACE authors' reanalysis of improvement using the original protocol, noted above, was first released after this tribunal decision.)

Coyne notes the 2015 Cochrane GET review by Larun et al. similarly switched to Likert scoring for the Chalder scale for the FINE trial (Wearden 2010), even though the published FINE study report (Wearden 2010) had used bimodal scoring.[34] In response to comments made in published feedback on the review, Larun stated this change did not impact the conclusions but the results were not presented as originally reported.[35].

b. Dismissal of protocol-defined objective outcome measures: Objective outcomes included in the PACE protocol included a six minute walking test, a stepping test, and changes in employment and financial benefits.[36] In their 2015 response to Tuller, the authors reported statistically significant improvement in performance on the six minute walk test for the GET group but reported "no significant differences in fitness, employment or benefits between treatments," objective findings dismissed as clinically unimportant.[37]

But the claimed clinical significance of the reported improvement on the 6 minute walk test is questionable. Dr. Chris Snell told a 2013 FDA meeting that patients with

the level of performance reported by PACE are "unlikely to be eligible for heart transplant because they would not survive it."[38]

c. Conflicts of Interest: In the PACE trial protocol, the investigators had committed to comply with the Declaration of Helsinki, which requires informing trial participants of conflicts of interest. But investigators failed to disclose these conflicts of interest to the trial participants. As one example of these conflicts, Geraghty noted, "Both White and Sharpe have done paid consultancy work for re-insurance companies with an interest in ME/CFS claims exposure."[39] In their response to Dr. David Tuller's series on the PACE trial, the investigators said they reported the conflicts of interest in the publications of their study and also said they informed trial participants of the source of funding for the study.[40] But as Tuller noted, neither of these actions satisfied the commitment to explicitly inform trial participants of the investigators' conflicts of interest before participants enter the trial.

d. Provided positive reports of CBT and GET to participants mid-trial: Participants were sent a newsletter mid-trial which reported positive progress of the trial and also reported that the treatments were already endorsed by NICE.This type of influence is particularly problematic in unblinded studies with subjective outcomes. Dr. Bruce Levin, Columbia University, told Tuller, "To let participants know that interventions have been selected by a government committee 'based on the best available evidence' strikes me as the height of clinical trial amateurism."[41]

In her extensive assessment of PACE, Rebecca Goldin, Professor of Mathematical Sciences at George Mason University and director of STATS.org, concluded "the flaws in this design were enough to doom its results from the start."[42] An accompanying editorial on Sense About Science USA concluded that the fundamental issue "is that the way PACE was designed and redesigned means it cannot provide reliable answers to the questions it asked. There is really not a lot that can be said to mitigate that; it's a terminal prognosis."[43]

More recently, in the press release for the August 2017 special issue on the PACE controversies in the Journal of Health Psychology, the editor called PACE flawed and said "The results are, at best, unreliable, and, at worst, manipulated to produce a positive-looking result."[44]

2. Irreconcilable Disease Theory

As noted above, the PACE manual[45] and study publications and the publications of other trials of CBT and GET in CFS base the use of these therapies on a psychogenic disease theory most often referred to as the "biopsychosocial" theory.[46] This theory claims that the debility of the disease is due to deconditioning which in turn is the result of patients' false beliefs that they have a physical illness and their fear of symptoms and fear that activity will harm them. GET, used to reverse deconditioning, includes graded aerobic exercise such as walking and swimming.[47] Further, it's important to note that CBT, as defined and

recommended for CFS, is fundamentally different than the form of CBT used in other diseases such as multiple sclerosis and cancer where CBT is used to help patients cope. In the CFS studies, CBT is used to convince patients they are not really sick, that the symptoms they are experiencing are not the result of a physical disease, and that they should just ignore the symptoms they get when they exercise and push through it.

In addition to CBT and GET as treatments, biopsychosocial studies have also focused on the role of psychogenic factors in a "predisposition" to and "perpetuation" of this disease. These studies, which primarily used the Oxford definition, have claimed that psychological and behavioral factors, such as maladaptive coping, a history of abuse, perfectionism, and a patient's belief that the disease is organic create a predisposition to the disease and result in prolonged impairment and poor prognosis. For instance, the November 2017 version of UpToDate states "belief in a viral cause of the illness was associated with prolonged functional impairment." These statements do not reflect the nature of the disease and put patients at risk of harm from inappropriate clinical management.

There is little if any evidence to support this biopsychosocial theory.[48] At the same time, there is substantial evidence of multi-system impairments that directly refutes this theory. The 2015 IOM report stated that the disease is not psychological.[49] IOM defined PEM and its systemic intolerance to exertion as one of the key hallmarks of the disease and required it for a diagnosis in their recommended criteria. Supporting this finding, IOM reported studies of cardiopulmonary exercise testing (CPET) that showed objective evidence of aerobic metabolism impairment, including a lowered anaerobic threshold, following exertion.[50] Further, the IOM report, recent research,[51] and a 2017 article by the director of the National Institutes of Health[52] have highlighted a number of biological pathologies in ME, including neurological, immunological, autonomic, and energy metabolism impairment.

Unfortunately, neither the CBT and GET studies or the Cochrane reviews have accounted for the fundamental conflict presented by the broad biomedical evidence that ME is not the result of false cognitions and deconditioning. It seems likely that part of the explanation for this conflict is that some of the participants in the CBT and GET studies did not actually have ME, a conclusion reached in the 2016 AHRQ Addendum.

3. **Failure to Account for Evidence of Harms**

The 2008 Cochrane review for CBT by Price et al concluded that CBT was an effective treatment but the review did not state conclusions about the potential of harms from CBT.[53] The 2015 Cochrane review for GET by Larun et al. stated that few serious adverse reactions were reported. The review also noted that *few studies actually reported harms* but then concluded that "exercise therapy might be an effective *and safe* intervention for patients able to attend clinics as outpatients." [italics added]

Failure to report harms cannot be interpreted as evidence of safety.

The 2014 AHRQ Evidence Review noted that GET was "associated with higher numbers of reported adverse events compared with counseling therapies or controls" and that GET trials had more reports of withdrawals than other trials.[54] AHRQ also noted that "harms were generally inadequately reported across trials." AHRQ concluded that "evidence remains insufficient to determine harms of exercise therapies and whether subsets of patients may experience more or fewer harms."

PACE is one of the few trials of GET in CFS to report harms and adverse incidents. However, this was based primarily on reporting at follow up assessments and hence there are methodological issues in dealing with dropouts. Some measures rely on detecting deterioration due to self-reported measures which are subject to reporting biases. PACE also did not check on participant compliance to treatment nor did they check that participants increased their total activity rather than just switched from other activities to GET. Given the low-quality issues around safety data, it is difficult to draw conclusions about safety.

Countering claims of safety, a number of patient surveys have reported harm from these therapies. While patient surveys may not meet the standards typically required for evidence reviews, the sheer volume and severity of reports of harms warrant serious consideration. Kindlon reported that 51 percent of respondents across 8 surveys reported that GET worsened their health while 20 percent of respondents across 5 surveys said that CBT worsened their health.[55] One of these surveys, in severely ill patients, reported that 82 percent experienced harm due to GET. In 2014, U.K.'s ME Association reported that of 1428 respondents, 74 percent did worse following GET and 18 percent did worse following CBT.[56] A 2017 analysis of these patient surveys by Geraghty and published in the Journal of Health Psychology reported that GET "brings about large negative responses in patients," and CBT "had little impact on symptom improvement" and any benefit seen was associated with the therapists viewing ME as a physical illness.[57] Notably, Geraghty also reported that pacing "is the most favoured treatment with the lowest negative response rate and the highest reported benefit." The PACE trial had dismissed pacing as ineffective but it is important to note that PACE had used a modified version of pacing different than that used by patients.

This adverse reaction to GET could be predicted given the systemic intolerance to exertion that the Institute of Medicine defined as required for ME along with the objective findings of aerobic metabolism impairment in ME following exertion.[58] Further, using CBT to convince participants that they are not physically ill and should ignore their symptoms could be not only psychologically harmful[59] but also physically harmful as it could result in the exertion-induced relapse characteristic of PEM.

Given these issues and the additional evidence from the biomedical literature, it is essential that those publishing ME evidence reviews or clinical guidance recommendations evaluate any claims of safety in these studies and their own conclusions about the safety of CBT and GET for patients with ME.

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Goldin lists the following recovery definition as provided in the PACE 2007 protocol. A patient needed to meet all four
i. A Chalder Fatigue Questionnaire [bimodal] score of 3 or less
ii. SF-36 physical Function score of 85 or above,
iii. CGI [self-rated Clinical Global Impression] score of 1, and
iv. The participant no longer meets Oxford criteria for CFS, CDC criteria for CFS [n] or the London criteria for ME.
Goldin lists the *trial* criteria for recovery as provided the 2013 recovery paper:
i. A Chalder Fatigue Questionnaire [Likert] score of 18 or less (previously three or lower on the bimodal scale)
ii. SF-36 physical Function score of 60 or above, (previously 85 or above)
iii. CGI [Clinical Global Impression] score of 1 or 2, and (previously just one)
iv. The participant no longer meets Oxford case definition for CFS (the authors now change from Oxford criteria to Oxford *case* criteria, a less stringent definition of CFS)

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