Evidence Report/Technology Assessment

Number 219

Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

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Evidence Report/Technology Assessment

Number 219

Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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The information in this report is intended to inform a National Institutes of Health Pathways to Prevention Workshop on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The purpose of the Workshop is to develop a research agenda. AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Institutes of Health requested and provided funding for this report to inform their Pathways to Prevention Workshop.

The reports and assessments provide comprehensive, evidence-based information on common, medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

This topic was nominated to AHRQ by NIH. Therefore, in place of Key Informants, an NIH Working Group Planning Meeting was conducted to design the Key Questions and the scope of the report.

Technical Expert Panel

In considering the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Two patient advocates were also members of the Technical Expert Panel.

Peer Reviewers

Prior to publication of the final evidence report, the EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Structured Abstract

Objectives. This systematic review summarizes research on methods of diagnosing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and benefits and harms of multiple medical and nonmedical treatments. It identifies evidence gaps and limitations to inform future research.

Data sources. Searches of electronic databases included MEDLINE® (1988 to September 2014), PsycINFO® (1988 to September 2014), and the Cochrane Library (through the third quarter of 2014). The searches were supplemented by reviewing reference lists, seeking suggestions from reviewers, and requesting scientific information from drug and device manufacturers.

Review methods. Two investigators reviewed abstracts and full-text articles for inclusion based on predefined criteria. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision.

Results. We identified 6,175 potentially relevant articles, selected 1,069 for full-text review, and included 71 studies in 81 publications (36 observational studies on diagnosis and 35 trials of treatments). Eight case definitions have been used to define ME/CFS; those for ME, requiring the presence of postexertional malaise, represent a more symptomatic subset of the broader ME/CFS population. Researchers are unable to determine differences in accuracy between case definitions because there is no universally accepted reference standard for diagnosing ME/CFS. The Oxford criteria are the least specific and include patients who would not otherwise meet criteria for ME/CFS. Self-reported symptom scales may differentiate ME/CFS patients from healthy controls but have not been adequately evaluated to determine validity and generalizability in large populations with diagnostic uncertainty. Fourteen studies reported on the consequences of diagnosis, including perceived stigma and the burden of misdiagnosis, while feelings of legitimacy upon receiving the diagnosis of ME/CFS were also reported.

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 a higher number of reported harms and withdrawal rates compared with counseling therapies or controls. Harms were generally inadequately reported across trials.

Limitations. Diagnostic methods were studied only in highly selected patient populations. Treatment trials were limited in number and had small sample sizes and methodological shortcomings.

Conclusions. None of the current diagnostic methods have been adequately tested to identify patients with ME/CFS when diagnostic uncertainty exists. Rintatolimod improves exercise performance in some patients (low strength of evidence), while counseling therapies and GET

have broader benefit but have not been adequately tested in more disabled populations (low to moderate strength of evidence). Other treatments and harms have been inadequately studied (insufficient evidence). More definitive studies are needed to fill the many research gaps in diagnosing and treating ME/CFS.

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Executive Summary

This systematic review was commissioned by the Office of Disease Prevention at the National Institutes of Health (NIH), sponsored by the NIH Office of Research on Women's Health, and cosponsored by the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group to inform the NIH 2014 Pathways to Prevention Workshop, an evidence-based methodology workshop. The purpose of the workshop is to develop a research agenda. Accordingly, this review evaluates and summarizes research on methods for diagnosis of ME/CFS and the benefits and harms of treatments, and identifies gaps and limitations of current studies and needs for future research in these areas.

Background

ME/CFS is a condition characterized by chronic and disabling fatigue, as well as various additional manifestations, including neurological and cognitive changes, motor impairment, pain, sleep disturbance, and altered immune and autonomic responses.[1-4] Experts consider postexertional malaise and impairment of memory or concentration as critical components.[5-7] Consistent with the NIH Workshop, this review uses the combined term ME/CFS to describe the condition.

The etiology of ME/CFS is not known, and there is uncertainty whether the condition reflects a single pathologically discrete syndrome, whether ME and CFS are subsets of the same illness, and whether ME/CFS is a nonspecific condition shared by other disease entities. Numerous studies have attempted to identify risk factors for developing ME/CFS, but none are definitive.

The diagnosis of ME/CFS relies on the use of clinical criteria to distinguish it from other conditions that may also present with fatigue. There are currently eight published case definitions with clinical criteria.[1-3,8-12] All include persistent fatigue not attributable to a known underlying medical condition, as well as additional clinical signs and symptoms. Depending on the case definition, prevalence rates of ME/CFS in the United States range from 0.3 percent to 2.5 percent.[13-15] Currently, no medications have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of ME/CFS, but several have been used "off label." In practice, there are wide variations in the clinical management of patients, and many patients receive a multifaceted approach to treatment.

Scope of Review

This review includes studies of adults with symptoms related to ME/CFS. Outcomes from treatment trials include improved function, fatigue, quality of life, and involvement in daily activities. Included studies were conducted in clinical settings relevant to health care practices in the United States. Scientists from the NIH and Agency for Healthcare Research and Quality (AHRQ) and a panel of experts and patients worked with the systematic review investigators to consider the context and studies related to the Key Questions that guided the review. These are—

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

(a) What are the accuracy and concordance of methods used to diagnose ME/CFS?

(b) How does the use of these methods vary by patient subgroups?

(c) What harms are associated with diagnosing ME/CFS?

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

(c) What are the characteristics of responders and nonresponders to interventions?

Methods

This systematic review follows established methods of AHRQ's Effective Health Care Program.[16] A research librarian conducted electronic database searches identifying articles published between 1988 and September 2014. Searches were supplemented by references identified from additional sources, including suggestions from panel members and reviewers of the draft report. Criteria for including studies were developed based on relevance to the Key Questions. Two investigators independently reviewed all potential articles for eligibility, and discrepancies were resolved through discussion and consensus, with a third investigator making the final decision as needed. Only English-language articles were included.

For questions regarding diagnostic methods, studies were included that compared case definitions, outlined in the Results section under Diagnosis (e.g., Fukuda/Centers for Disease Control and Prevention [CDC], Canadian, International), and provided measures of agreement, or tested the ability of the method to identify ME/CFS patients using one of the case definitions as a reference. Studies of potential harms from diagnosis were also included, such as psychological harms, labeling, risk from diagnostic tests, and misdiagnosis.

For questions regarding treatment, studies were included that enrolled patients diagnosed with ME, CFS, or both by fulfilling criteria from at least one case definition. We included randomized controlled trials of at least 12 weeks in duration that compared medications, complementary and alternative medicine approaches, counseling and behavior therapies, and exercise therapies versus no treatment or other types of treatment. For completeness, additional trials of medications that were designed for shorter durations of treatment were separately summarized. Treatment outcomes included improved function, fatigue, quality of life, and involvement in daily activities. Studies of the results of laboratory tests or studies focusing on individual symptoms were not included.

Two investigators extracted data from each included study, and they independently rated the quality of the methods of each study based on predefined criteria. Results of some of the treatment trials were statistically combined using meta-analysis. The overall strength of evidence was assessed for each Key Question and outcome in accordance with established methods. Experts in ME/CFS, individuals representing interest groups, and the expert and patient members of the panel were invited to review the draft report. The draft report was also posted for public comment during September and October 2014.

Results

Diagnosis

Thirty-six observational studies of methods to diagnose ME/CFS were included. Most studies enrolled predominantly female patients, had small sample sizes, and were conducted in the United States and Western Europe.

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

Eight case definitions that include clinical criteria have been developed to identify patients with ME/CFS and are used by clinicians to distinguish ME/CFS from other conditions that also present with fatigue (Table A).[1-3,8-12] One study considered the comparison based on age variance and is discussed under Key Question 1b.[17] Although most case definitions require that other conditions be excluded prior to assigning a diagnosis of ME/CFS, no studies compared strategies for ruling out alternative diagnoses. The Oxford (Sharpe, 1991) case definition incorporates the smallest number of symptoms (new onset of fatigue with impairment of physical and mental function), suggesting less specificity for ME/CFS.[12]

Table A. Case definitions

Symptoms	London ME[8]	Canadian ME/CFS[1]	Revised Canadian ME/CFS[10]	Inter-national ME[2]	CDC – CFS, Holmes[9]	Oxford CFS[12]	CDC – CFS, Fukuda[3]	CDC – CFS, Reeves[11]
General physical	X	X	X		X	X	X	X
Neurological; neurocognitive	X	X	X	X	X	X	X	X
Postexertional malaise	X	X	X	X	X		X	X
Neuroendocrine; immune		X	X	X	X		X	X
Other system involvement				X				

Notes: CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis.

Key Question 1a. What are the accuracy and concordance of methods used to diagnose ME/CFS?

Diagnostic methods were evaluated in eight descriptive studies comparing case definitions, although the accuracy of each method could not be determined because there is no established reference standard. Patients diagnosed using clinical criteria for ME or ME/CFS had more severe symptoms or impairment than those diagnosed using criteria for CFS alone. The Oxford CFS (Sharpe, 1991) and the London ME (Dowsett, 1994) case definitions were not compared in studies, leaving uncertainty as to whether these represent similar or discordant representations of ME/CFS.[5,14,18-22]

Three studies that compared CFS patients diagnosed using the CDC (Holmes, 1988, or Fukuda, 1994) case definitions versus patients with other diseases identified differences in reported symptoms using various self-reported symptom scales.[18,23,24] These results suggest that some scales could be reasonable candidates for further evaluation as diagnostic tests (Fatigue Impact Scale, Chalder Fatigue Scale, Hospital Anxiety and Depression scale, and certain subscales or combinations of the 36-Item Short Form survey [SF-36] with the Zung Depression Scale). However, these measures have not yet been evaluated for this purpose. No studies evaluated whether diagnostic methods could adequately identify clinical subgroups of patients.

Eleven studies evaluated other types of methods to diagnose ME/CFS, but results were inconclusive. These included studies using self-reported symptom scales (the artificial neural

network test, the Schedule of Fatigue and Anergia for CFS scale, subscales of the SF-36, and other scales) and various serum biomarkers.[25-36] The artificial neural network test was able to differentiate ME/CFS patients from healthy controls; however, no studies evaluated this method or other methods using an adequate sample size and spectrum of patients. No studies demonstrated an accurate and reliable method for identifying patients or subgroups of patients with ME/CFS in comparison with other patients, with diagnostic uncertainty as to whether they have ME/CFS or another condition in which fatigue is a prominent symptom.

Key Question 1b. How does the use of these methods vary by patient subgroups?

Three studies described how methods for diagnosis may differ for patient subgroups.[17,33,34] One study reported that older patients were more impaired, but it did not consider how symptom evaluation might vary with age. Two studies found that cardiopulmonary exercise tests were different for ME/CFS patients and for healthy controls, and that certain subscales of the SF-36 were associated with slow recovery after exercise. No studies evaluated differences in the performance of case definitions among patients with specific sets of symptoms (autonomic/neuroendocrine, neurological/neurocognitive, immunological/infectious).

Key Question 1c. What harms are associated with diagnosing ME/CFS?

Fourteen studies evaluated harms of the diagnostic process or diagnosis of ME/CFS, including the perceived harms (or benefits) of receiving a diagnosis of ME/CFS, as well as missed/alternative diagnoses.[13,37-49] Five studies found that patients with CFS feel stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their characters, social isolation, and interactions with the health care system.[38,39,41-43] Two studies indicated that medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and what treatment is being given.[37,44] A substantial burden of misdiagnosis was found in the ME/CFS population.[13,37,40,45,46,48]

Treatment

Thirty-five randomized trials of the benefits and harms of treatments for ME/CFS were included. Most had fair- or poor-quality research methods, enrolled predominantly female patients from ME/CFS specialty clinics based on the CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) case definitions, had small sample sizes, and were conducted in the United States and Western Europe.

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

Nine trials compared medical treatment of ME/CFS with placebo, although none of these medications have been approved by FDA for this indication.[50-58] Results are summarized in Table B**.** Studies primarily included patients meeting CDC case definitions for ME/CFS (Fukuda, 1994, and/or Holmes, 1988), which identify less debilitated patients than those meeting ME case definitions. The immune modulator rintatolimod improved some measures of exercise performance compared with placebo in two trials (low strength of evidence), while trials of

galantamine, hydrocortisone, immunoglobulin G, valganciclovir, isoprinosine, and fluoxetine were inconclusive (insufficient evidence). Additional trials with durations less than 12 weeks indicated no differences versus placebo for acyclovir[59] and improved scores for physical health and function with rituximab,[60] although both studies enrolled 30 or fewer participants and the clinical implications of these results are not clear.

Harms of medications included suppression of adrenal glucocorticoid responsiveness, increased appetite, weight gain, and difficulty sleeping with hydrocortisone; flulike syndrome, chills, vasodilation, dyspnea, and dry skin with rintatolimod; headaches with immunoglobulin G; discontinuation of treatment with fluoxetine; and nephrotoxicity with acyclovir.

Table B. Trials of medications

Treatment	Number of Trials (Participants)	Results (Treatment Vs. Placebo)*
Galantamine (acetyl-cholinesterase inhibitor)	1 (423)	No differences. (Insufficient evidence)
Hydrocortisone (corticosteroid)	1 (68)	No differences. (Insufficient evidence)
Hydrocortisone + fludrocortisone (corticosteroid)	1 (80)	No differences. (Insufficient evidence)
Immunoglobulin G (antibody)	1 (28)	Better scores on social functioning scale for placebo group; no difference on physical functioning scale. (Insufficient evidence)
Rintatolimod (immune modulator)	2 (324)	Increased activities of daily living. Improved exercise duration, exercise work, and cardiopulmonary exercise tolerance. (Low strength of evidence)
Valganciclovir (antiviral agent)	1 (30)	Decreased fatigue scores; no differences in overall function. (Insufficient evidence)
Isoprinosine (immune modulator)	1 (15)	No differences. (Insufficient evidence)
Fluoxetine (selective serotonin reuptake inhibitor)	1 (68)	No differences. (Insufficient evidence)
Acyclovir (antiviral)†	1 (30)	No differences. (Insufficient evidence)
Rituximab (monoclonal antibody)†	1 (27)	Improved physical health and function scores, but not other outcomes. (Insufficient evidence)

*Statistically significant differences between treatment and placebo groups.
†Trial less than 12 weeks in duration

Seven trials compared complementary and alternative medicine approaches versus usual care, placebo, or alternative therapies (Table C) in ME/CFS patients diagnosed by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions.[61-67] Therapies included dietary supplements, distant healing, homeopathy, melatonin, and phototherapy. Although studies of homeopathy, pollen extracts, and L-carnitine preparations reported benefit for some outcomes, these findings are inconclusive because of methodological limitations and small sample sizes (insufficient evidence). Harms were not reported in the studies.

Table C. Trials of complementary and alternative medicine therapies

Treatment	Number of Trials (Participants)	Results (Treatment Vs. Control)*
Acclydine vs. placebo	1 (57)	No differences. (Insufficient evidence)
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination	1 (89)	Lower fatigue scores with acetyl-L-carnitine, but more improvement from baseline with propionyl-L-carnitine and the combination. Better global improvement with propionyl-L-carnitine and acetyl-L-carnitine compared with the combination. (Insufficient evidence)
Pollen extract vs. placebo	1 (22)	Improved fatigue and quality-of-life scores. (Insufficient evidence)
Low sugar/low yeast diet vs. healthy eating	1 (39)	No differences. (Insufficient evidence)
Distant healing vs. no treatment	1 (409)	No differences. (Insufficient evidence)
Homeopathy vs. placebo	1 (89)	Improved fatigue scores for placebo. (Insufficient evidence)
Melatonin vs. phototherapy	1 (30)	No differences. (Insufficient evidence)
Home orthostatic training vs. sham home orthostatic training	1 (36)	No differences. (Insufficient evidence)

*Statistically significant differences between treatment and control groups.

Fourteen trials compared counseling or behavioral therapy versus usual care, no treatment, or other types of counseling or behavioral therapy (Table D) in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions.[68-89] Results were mixed for most outcomes, but when considering all studies comparing any type of counseling with a control, counseling improved fatigue (7 of 11 trials showed positive effect), measures of functioning (4 of 11 trials showed positive effect; 2 of 11 showed mixed results on different measures), quality of life (2 of 4 trials showed positive effect), and global improvement (2 of 2 trials showed positive effect). Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME). Harms of counseling and behavioral therapies were rarely reported by the studies, but when they were reported, harms were fewer with counseling compared with usual care, support, or adaptive pacing.

Table D. Trials of counseling or behavioral therapy

Treatment	Number of Trials (Participants)	Results (Treatment Vs. Control)*
Counseling and behavioral therapy vs. no treatment, support, relaxation, or adaptive pacing	13 (1,648)	Higher function scores; weighted mean difference, 7.73 (95% CI, 3.58 to 11.87; 8 trials). (Low strength of evidence) Improved fatigue in 7 trials; no differences in 4 trials. (Low strength of evidence) Improved quality of life in 2 trials; no differences in 2 trials. (Low strength of evidence) More hours worked per week (mean 36 vs. 24; p<0.04) in 1 trial; no differences in 1 trial. (Low strength of evidence) Improvement on work and social adjustment scales in 2 trials. (Low strength of evidence) Better global improvement in 2 trials. (Moderate strength of evidence)
Face-to-face vs. telephone cognitive behavioral therapy	1 (43)	Better clinical global improvement with face-to-face therapy; no differences in overall function. (Insufficient evidence)

*Statistically significant differences between treatment and control groups.
Abbreviation: CI = confidence interval.

Six trials evaluated exercise therapies, including graded exercise therapy (GET), qigong, and home orthostatic training, compared with no treatment or several other types of therapies in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions (Table E).[57,89-93] GET improved measures of fatigue, function, and clinical global impression of change compared with controls. Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME). Harms were not well reported, although in one trial patients receiving GET reported more adverse events compared with those receiving cognitive behavior therapy (CBT), adaptive pacing, or usual care; one trial reported more withdrawals of patients receiving GET, one trial had a high percentage of patients refusing repeat exercise testing, and several other trials reported more withdrawals of patients receiving GET, all compared with controls.

Table E. Trials of exercise therapy

Treatment	Number of Trials (Participants)	Results (Treatment Vs. Control)*
Graded exercise therapy vs. no treatment, flexibility/relaxation therapy, or adaptive pacing	4 (619)	Better overall function scores; weighted mean difference, 10.29 (95% CI, 6.71 to 13.86; 3 trials). (Moderate strength of evidence) Decreased fatigue in 3 trials; no differences in 1 trial. (Low strength of evidence) More working 1 year after treatment (66% vs. 39%). (Insufficient evidence) Improved scores on work and social adjustment scales compared with adaptive pacing and no treatment. (Low strength of evidence) Better global improvement; changes in clinical global improvement, 1.26 (95% CI, 1.26 to 1.89; 3 trials). (Moderate strength of evidence)
Qigong exercise vs. no qigong exercise	1 (52)	Better physical function and fatigue scores. (Insufficient evidence)
Home orthostatic training vs. sham home orthostatic training	1 (36)	No differences. (Insufficient evidence)

* Statistically significant differences between treatment and control groups.
Abbreviation: CI = confidence interval

Four trials compared either head-to-head interventions or combinations of two interventions (Table F). GET and CBT had similar improvement in measures of function but mixed results on other outcomes.[57,73,74,76,79,89] When reported, harms of CBT appear to be less than those with GET. GET appears to improve fatigue and function when compared with fluoxetine, which was found to be ineffective.

Table F. Head-to-head and comparison trials

Treatment	Number of Trials (Participants)	Results*
Cognitive behavioral therapy vs. cognitive therapy vs. anaerobic therapy	1 (114)	Improved function with cognitive behavioral therapy or cognitive therapy vs. anaerobic therapy. (Insufficient evidence)
Graded exercise therapy ± fluoxetine vs. fluoxetine ± placebo	1 (136)	Improved functional work capacity with exercise alone or combined with fluoxetine. Improved fatigue with exercise alone or combined with fluoxetine. (Insufficient evidence)
Cognitive behavioral therapy vs. graded exercise therapy	1 (314)	No differences. (Insufficient evidence)
Cognitive behavioral therapy + graded exercise therapy vs. usual care	1 (115)	No differences. (Insufficient evidence)

* Statistically significant differences between treatment and control groups.

Key Question 2c. What are the characteristics of responders and nonresponders to interventions?

Four trials describe characteristics of patients more likely to respond to therapies for ME/CFS. Younger patients with less impairment and less focus on symptoms who are adherent

to therapy (e.g., readings, sleep diaries, activity goals, relaxation) are more likely to improve on some measures of fatigue and/or function.[68,74,87,92] Avoiding overexercising and underexercising (i.e., staying within one's energy envelope) was also beneficial. This represents an insufficient body of evidence, as the results have not been duplicated and the applicability of these results to other patients is not known.

Conclusions

Eight case definitions for ME/CFS exist, and several diagnostic methods have been studied. Case definitions with criteria for ME and ME/CFS that require symptoms of postexertional malaise, neurological impairment, and autonomic dysfunction identify patients with more impairment, lower functioning, and more severe symptoms than case definitions with criteria for CFS alone. However, none of the case definitions or other diagnostic methods have been adequately tested to determine how well they differentiate patients with ME/CFS from patients with other conditions. No studies evaluated how diagnostic tests vary by patient subgroups or how to rule out related conditions before making an ME/CFS diagnosis. Studies indicated that an ME/CFS diagnosis is associated with perceived stigma, financial instability, difficulty in social interactions and relationships, and a greater chance of receiving a psychiatric diagnosis. One study identified feelings of legitimacy upon receiving the diagnosis of ME/CFS.

Thirty-five trials of treatments included medication, complementary and alternative medicine approaches, counseling or behavioral therapy, and exercise therapy. Two trials of rintatolimod showed improvement in some measures of performance, while one trial showed improvement in fatigue, activities of daily living, and reduced use of other medications for relief of ME/CFS symptoms. Single trials enrolling only 30 participants reported improved measures of fatigue with valganciclovir and improved physical health and function scores with rituximab. The benefits of pollen extract, homeopathy, and L-carnitine preparations remain uncertain, because improvement was found in some but not other measures of the same outcome. When all counseling and behavioral therapy trials were combined, measures of fatigue and global improvement were significantly improved, although results were not consistent across all trials. GET improved measures of function, global improvement, and to a lesser degree, fatigue. Although harms were not well reported across trials, GET was associated with a higher number of reported harms and withdrawals in some trials. For all other treatments, effects are uncertain because important outcomes were not measured, the study methods were inadequate, or too few participants were enrolled to provide useful estimates. Most treatments were evaluated in only a single trial and were conducted in referral settings. Participants' baseline function and severity of symptoms were not usually reported, and it is not clear how well the results of the trials apply to clinical practice.

Limitations

The main limitation of this review is the lack of studies to address important questions, particularly regarding methods of diagnosis. Available studies generally enrolled small numbers of participants, and many treatment trials were too small to detect significant differences between groups. Most treatment trials did not describe their methods in sufficient detail to assess their quality. Studies used a variety of methods to measure outcomes, limiting comparisons across studies. While this review focused on outcomes that patients can experience, such as fatigue, a review of other types of outcomes such as postexertional malaise would provide additional evidence.

Future Research

- Consensus about which case definition is appropriate to use as the gold standard will further advance the study of diagnostic methods for ME/CFS. In the absence of consensus, future studies aimed at clarifying the diagnosis of ME/CFS should consider reporting how well a diagnostic test compares with more than one of the case definitions. A national longitudinal registry of patients with a diagnosis of ME/CFS would allow for comparison of diagnostic criteria between patients and clarification of diagnoses over time. This strategy could also identify a well-characterized population for use in both diagnostic and treatment trials.
- Future studies evaluating the capability of diagnostic methods for ME/CFS should include a broad range of patients with conditions that require clinical distinction from ME/CFS, such as fibromyalgia and depression. Additionally, studies should report how well a particular method distinguishes ME/CFS from other conditions using standard performance measures, such as concordance, sensitivity, and specificity.

Treatment trials should use consistent case definitions and outcome measures to improve comparisons across trials, and should refrain from using the Oxford (Sharpe, 1991) case definition because it is less specific for ME/CFS than the other definitions are. Definitive treatment trials require larger numbers of participants based on appropriate power calculations for primary outcomes to determine efficacy, and more rigorous adherence to methodological standards such as blinding of outcome assessors, intention-to-treat analysis, and strategies to minimize patients lost to followup. Future trials should enroll more men, more racial and ethnic minorities, and broader age ranges. Given the fluctuating nature of ME/CFS, followup periods greater than 1 year would help determine effectiveness and harms over time. The development of a set of core outcome measures, including patient-centered outcomes, such as quality of life, employment, and time spent in activity, would help guide research and facilitate future analyses. Trial registries and collaborations would help consolidate and standardize data. Reporting more information about concomitant treatments and adherence to treatment would improve the applicability of study findings. Similarly, stratification of results by patient characteristics, such as age, sex, race, and intermediate outcomes, would help determine the applicability of different treatments for specific patients and situations.

Studies should report findings according to important features of ME/CFS, such as postexertional malaise, neurocognitive status, and autonomic function, to identify subgroups that may respond differently to specific treatments. Studies also need to report harms more completely to help identify patients negatively affected by certain treatments. Given the devastating impact that this condition has had on patients and families, researchers planning and developing trials should consider involving the patient and/or advocate voice so that future research is relevant and meaningful to those affected by ME/CFS.

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Introduction

Background

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a multi-system debilitating condition that often robs patients of independence and quality of life.[1] It follows a relapsing and remitting course and is characterized by chronic and disabling fatigue. Various additional manifestations include neurological and cognitive changes, motor impairment, pain, sleep disturbance, and altered immune and autonomic responses.[1-4] Experts consider post-exertional malaise/neuroimmune exhaustion (PEM) and memory or concentration problems as key components.[5-7] ME/CFS will be the topic of the National Institute of Health (NIH) 2014 Pathways to Prevention (P2P) Workshop and this systematic review was commissioned by the Office of Disease Prevention (ODP), sponsored by the NIH Office of Research on Women's Health and co-sponsored by the Trans-NIH ME/CFS Research Working Group, to inform the NIH 2014 P2P Workshop, an evidence-based methodology workshop, on the current evidence for diagnosing and treating the syndrome. The intent is to inform the panel of the gaps and limitations of current evidence in order to direct future research. This systematic review is not intended to form the basis for treatment guidance.

Although reports of similar symptom clusters date back to the 1930s, the term myalgic encephalomyelitis (ME) was first used to describe the condition in the 1950s and was recognized by the World Health Organization in the 1960s.[8] The term chronic fatigue syndrome (CFS) was coined in the 1980s after research failed to identify a clear viral association with what was previously labeled chronic Epstein-Barr virus syndrome.[9-12] Other terms such as post viral fatigue syndrome and chronic fatigue immune dysfunction syndrome have been used in an attempt to associate the syndrome with possible underlying etiologies.[2,4,9,10] The most recent international consensus report advocates moving away from the term CFS in favor of the term ME to better reflect an underlying disease process involving widespread inflammation and neuropathology.[3,7] Some feel that the lack of specificity surrounding the name, CFS, may delegitimize and negatively characterize the condition, and stigmatize patients.[13,14] For this review, we used the combined term ME/CFS, except when referring to criteria specific to one term or the other, and we included the populations studied under either ME or CFS.

Uncertainty persists regarding the etiology of ME/CFS, whether it is a pathologically discrete syndrome, [3,7] whether ME should be considered a subset of CFS or its own distinct disease,[5] or whether the symptom set is nonspecific and shared by other disease entities. Some suggest that an inciting event triggers an immune response and promotes immune and/or neuroendocrine dysregulation that perpetuates the body's response and symptom experience that becomes ME/CFS.[15,16] Viral etiologies have been predominantly studied based on the observation that the majority of patients report a sudden onset of symptoms associated with a preceding febrile illness and enlarged lymph nodes. However, no specific virus or other infectious agent has been identified, and not all patients experience a preceding febrile illness.[15] Numerous studies have attempted to identify risk factors for developing ME/CFS. A systematic review in 2008 of 11 studies assessing predictive models of multiple risk factors found no evidence of any definitive factors.[17] For example, although some models found association with older age, women, and febrile viral illness, others did not.[17] It is known that ME/CFS is more common among women with the average age of diagnosis between 30 and 40 years.[18] This review is not intended to address the question of etiology nor underlying factors that lead to the onset or perpetuation of ME/CFS but rather to focus on the diagnosis and treatment of this syndrome.

Diagnosing a patient with ME/CFS relies on the use of a set of clinical criteria (case definitions) to distinguish ME/CFS from other conditions that may also present with fatigue. There are eight published case definitions that have evolved since the first one was published by the Centers for Disease Control and Prevention (CDC) in 1988[10] (Table 1). All but one of the definitions include persistent fatigue not attributable to a known underlying medical condition, as well as additional clinical signs and symptoms that do not all need to be present to establish the diagnosis.[5] The case definitions overlap but vary greatly in their symptom set, leading to concern that they do not all represent the same disease or identify the same cohort of patients.[7] The international ME consensus panel of experts recommends that patients meeting the International Consensus Criteria (ICC) be given the name ME, and that those meeting the criteria for CFS but not the ICC for ME be given the name CFS.[7] For this report we have considered all case definitions, recognizing that no case definition has been accepted as a reliable reference standard ("gold standard") and that unresolved issues persist.

Table 1. Case definitions

Symptoms	London ME	Canadian ME/CFS	Revised Canadian ME/CFS	Inter-national ME	CDC – CFS Holmes	Oxford CFS	CDC – CFS Fukuda	CDC – CFS Reeves
General physical	X	X	X		X	X	X	X
Neurological; neurocognitive	X	X	X	X	X	X	X	X
Post exertional malaise	X	X	X	X	X		X	X
Neuroendocrine; immune		X	X	X	X		X	X
Other system involvement				X				

Abbreviations: CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis.

As with other medical syndromes that involve a multitude of symptoms and lack a definitive diagnostic test, differentiating one disease state from another similar or overlapping condition becomes a challenge. Some clinicians are reluctant to diagnose ME/CFS, believing that the diagnosis will harm the patient or that the patient will be inappropriately labeled.[19] This makes the prevalence of ME/CFS difficult to assess.[18,20] The CDC reported a U.S prevalence rate of 0.3 percent corresponding to over 1,000,000 adults in 1997.[21] By using different case definitions, the rate may be as high as 2.5 percent.[9,22] A recent systematic review found that when using the same case definition (CDC Fukuda, 1994), the prevalence was higher when determined by self report (3.28%; 95% confidence interval [CI], 2.24 to 4.33) compared with clinical assessment (0.76%; 95% CI, 0.23 to 1.29).[23] The prevalence and symptom patterning of childhood ME/CFS is similar but is more likely to develop after an acute flu-like or mononucleosis-like illness, and the prognosis appears to be better.[24-26] The natural history of ME/CFS in adults is not well studied, but symptoms and disability in adults tend to persist over time.[27] Although 40 percent (8 to 63%) of adult patients improve, only 5 percent (0 to 31%) fully recover,[21] in contrast to childhood studies that suggest that over 50 percent of patients will recover within 6 months.[25] However, a recent review highlighted the variability in which studies defined recovery in adults, limiting the utility of this term as a meaningful outcome until a universal definition for recovery

is accepted.[28] The review authors recommended using a more global assessment that captured fatigue, function, and perception of health.[28] Regardless, economic impact is considerable with most adult patients never returning to work.[15,29]

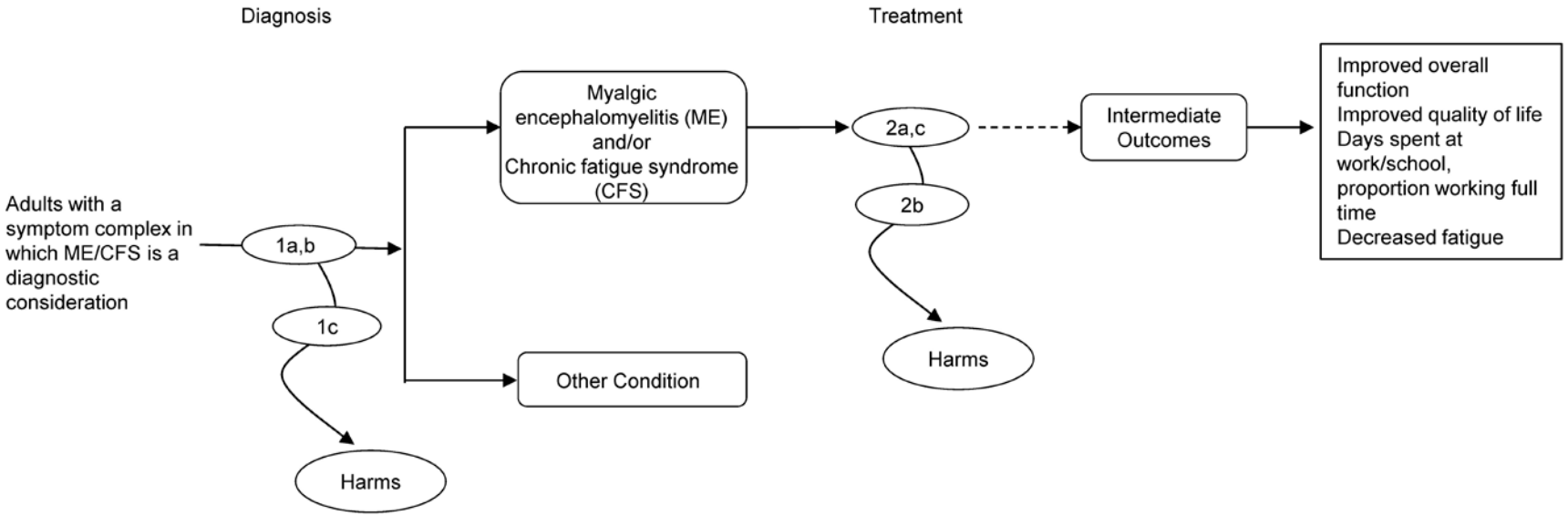
Currently there are no medications for the treatment of ME/CFS approved by the U.S Food and Drug Administration (FDA), but many have been used without review and approval ("off-label"), and some have been obtained from other countries and are not currently approved for any indication in the United States (i.e., isoprinosine, rintatolimod). In an FDA survey, patients identified treatments that fell into two broad categories: those intended to treat the underlying cause of the disease and those targeting specific symptoms or perpetuating factors.[30] Medications to treat underlying causes include immune modulators, antivirals, and antibiotics. Interventions targeting symptoms include medications to treat specific symptoms such as pain, fatigue, autonomic dysfunction, and sleep dysfunction, and nondrug therapies such as yoga, exercise techniques, counseling, pacing strategies, and mental exercises.[30] In practice, there are wide variations in the clinical management of patients, and many patients receive a multifaceted approach to treatment.

The variable symptomatology of ME/CFS, lack of a clearly identifiable etiology and/or disease process, and lack of an agreed upon reference standard for diagnostic testing have challenged researchers and clinicians in their attempts to better understand the condition and treat patients. This review summarizes the research on diagnosis and treatment of the syndrome, including the methods and criteria used to diagnose ME/CFS, their utility in differentiating patients with similar but distinct symptoms, the harms associated with carrying a diagnosis of ME/CFS, and the evidence on treatment effectiveness and associated harms. Although they are recognized as important components in advancing the research and understanding of ME/CFS, this review does not address theories surrounding etiology/pathophysiology nor intermediate outcomes of treatment, such as changes in biomarker values, as these topics will be addressed by other presenters at the workshop. This review identifies limitations and gaps in the current state of the literature and how the existing research applies to patients in order to assist the P2P panel in their recommendations regarding future research.

Scope of Review and Key Questions

The research questions were developed by the P2P Working Group, that included experts and a patient advocate, and they focus on diagnosis and treatment of the syndrome ME/CFS. The scope of the review is intended to inform the P2P panel on how multiple case definitions of ME/CFS have contributed to the state of the current scientific literature on diagnosis, treatment, and recovery; the utility of current measurement tools in identifying meaningful change and identifying subsets of patients; and how effective therapies might lead to a better understanding of the underlying pathology, which might in turn lead to the development of effective and safe treatments. The analytic framework (Figure 1) and Key Questions used to guide this review are shown below. The analytic framework shows the target populations, interventions, and health outcomes examined, with numbers corresponding to the Key Questions.

Figure 1. Analytic framework



The report focuses on the following Key Questions:

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

Key Question 1a. What are the accuracy and concordance of methods used to diagnose ME/CFS?

Key Question 1b. How does the use of these methods vary by patient subgroups?

Key Question 1c. What harms are associated with diagnosing ME/CFS?

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS. and how do they vary by patient subgroups?

Key Question 2c. What are the characteristics of responders and nonresponders to interventions?

Methods

This systematic review follows the methods of the Agency for Healthcare Research and Quality (AHRQ) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews."[31]

Topic Development and Refinement

The initial Key Questions were provided by the Trans-National Institutes of Health (NIH) myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) Research Working Group and further developed and refined in conjunction with the NIH Pathways to Prevention (P2P) Working Group. AHRQ with input from a Technical Expert Panel (TEP) convened for this report, further developed the approach to the review. The TEP consisted of experts in ME/CFS spanning six disciplines and two patients, who all disclosed no conflicts of interest that precluded participation. The investigators with the Pacific Northwest Evidence-based Practice Center strove to inform themselves of the disease ME/CFS by reviewing Web sites, publications by advocacy groups, and viewing videos of patient experiences. A local infectious disease physician who has treated ME/CFS patients for almost 30 years also participated as a consultant throughout the topic refinement and systematic review process. Two attendees to the International Association for ME/CFS Biennial Conference in San Francisco (March 2014) further informed the team of investigators as to the current state of knowledge about the disease and assisted in identifying important outcomes of interest to patients and researchers.

With input from the TEP, the NIH, and AHRQ, the final protocol was developed and posted on the AHRQ Web site on May 1, 2014 at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=1906&pageaction=displayproduct. The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.[32]

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE (1988 to September 2014), PsycINFO (1988 to September 2014), the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through September 2014), and the Database of Abstracts of Reviews of Effects and the National Health Sciences Economic Evaluation Database (through the third quarter 2014). See Appendix A for the search strategies. Searches were supplemented with hand searches of reference lists of relevant studies. In addition, scientific information packets were requested from drug and device manufacturers that potentially had data on the use of medications or devices for myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS); they had the opportunity to submit data using the portal for submitting scientific information packets on the Effective Health Care Program Web site. Seventeen submissions were received.

Process for Study Selection

Criteria for inclusion and exclusion of studies were developed based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies, and setting (PICOTS) approach (Appendix B). Papers were selected for review if they were about diagnosis or treatment of ME or CFS in adult populations, were relevant to a Key Question, and met the

prespecified inclusion criteria. Studies of nonhuman subjects and studies with no original data were excluded. Abstracts were reviewed by two investigators for inclusion for each Key Question. Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion. Inclusion was restricted to English-language articles. A list of the included studies appears in Appendix C; a list of excluded studies and primary reasons for exclusion can be found in Appendix D. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

Population and Conditions of Interest

For Key Question 1, studies of adults 18 years or older with a multifaceted fatiguing syndrome in which ME/CFS was a diagnostic consideration were included. For Key Question 2, we included studies of adults 18 years or older, diagnosed with ME, CFS, or both by fulfilling criteria from at least one of the case definitions and without another underlying diagnosis. Studies varied in how they described which case definition they used; for consistency in this report we have used the names identified in Table 1 throughout the report. To minimize heterogeneity in patient populations, we did not include studies in which patients who may have met criteria for ME/CFS were included as part of a broader grouping of an overlapping condition (i.e., depression, fibromyalgia).

Interventions, Comparisons, and Study Designs

For Key Question 1, any diagnostic test or case definition (set of clinical criteria) for diagnosing ME/CFS was included. Because there is no single accepted definition for ME/CFS and therefore no "gold standard," any of the eight case definitions published since 1988 was accepted as a reference standard and compared for similarities and differences. Measures of diagnostic accuracy and concordance were considered. Diagnostic accuracy is a measure of how well the test can separate those who do and do not have the disease of interest and is measured by the model's concordance statistic or c-stat. The c-stat is determined by the area under the receiver operator curve (AUROC) which is a measure of discrimination, the ability of a test to distinguish people with a condition from people without the condition, and is based on the sensitivity and specificity of the test.[33,34] An AUROC of 1.0 indicates perfect discrimination, and an AUROC of 0.5 indicates complete lack of discrimination and would result from chance alone. Interpretation of AUROC values between 0.5 and 1.0 is somewhat arbitrary, but a value of 0.90 to 1.0 has been classified as excellent, 0.80 to less than 0.90 as good, 0.70 to less than 0.80 as fair, and less than 0.70 as poor.[35] Concordance refers to how well two tests agree. We excluded studies designed to inform etiology and studies that reported on diagnosing a specific symptom of ME/CFS (e.g., post-exertional malaise[36]) without reporting on diagnosis of ME/CFS by comparing with a case definition as a reference standard. In the absence of studies reporting accuracy/concordance measures, descriptive studies comparing diagnostic clinical criteria were included. For harms of diagnosis, studies that evaluated harms by surveys, qualitative interviews, or trials designed to identify perceptions of diagnosis or treatment for ME/CFS were included.

For Key Question 2, we included randomized trials comparing medication management (immune modulators, beta blockers, antidepressants, anxiolytics, stimulants, other), complementary and alternative medicine (CAM) approaches (acupuncture, relaxation, massage, other), counseling and behavior therapy, and exercise therapies with placebo, no

treatment, usual care, or other active interventions, including combination therapies and head-to-head trials. For harms, cohort studies with control groups were also included.

Outcomes

For Key Question 1, outcomes of diagnostic accuracy or concordance were considered, including sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, C-statistic, receiver operator curve (ROC) and area under curve (AUC), net reclassification index, concordance, and any potential benefit or harm from diagnosis (i.e., psychological harms, labeling, risk from diagnostic test, misdiagnosis).

For Key Question 2, outcomes were included if they were patient-centered and included patient reported measures considered clinically relevant, such as function (e.g., 36-item Short Form Survey [SF-36]), quality of life, days spent at work or school, proportion working full- or part-time, and fatigue (Multidimensional Fatigue Inventory 20-item [MFI-20] or similar). Fatigue was included as it was the only symptom that was universal to all case definitions. Other individual symptom-based outcomes (e.g., pain, sleep, memory, PEM) and intermediate outcomes (e.g., biomarker values) were excluded. Harms included, but were not limited to withdrawals, withdrawals due to harms, and rates of harms due to interventions.

Timing

There was no duration or timing restriction on studies included for Key Question 1. For Key Question 2, only studies with a minimum duration of 12 weeks of treatment were included, given the fluctuating nature of the condition characterized by an intermittent pattern of relapse and remission.[37]

Setting

Studies for all Key Questions had to be conducted in a clinical setting or a setting that was generalizable to clinical practice settings. Studies conducted with inpatients or institutionalized individuals were excluded.

Data Extraction and Data Management

The following information was extracted from included studies into evidence tables: study design, setting, inclusion and exclusion criteria, population characteristics (including sex, age, race, and co-morbidities), sample size, duration of followup, attrition, intervention characteristics, case definition used for diagnosis, duration of illness, and results. Data extraction for each study was performed by two investigators: the first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

For studies of diagnostic accuracy and concordance, when reported we extracted relative measures of risk (relative risk [RR], odds ratio [OR], hazards ratio [HR]), sensitivity, specificity, ROC, and AUC).

Individual Study Quality Assessment

The quality (risk of bias) of each study was assessed based on predefined criteria adapted from methods proposed by the U.S. Preventive Services Task Force. The criteria used are consistent with the approach recommended by AHRQ in the AHRQ Methods Guide.[31] The term "quality" was used rather than the alternate term "risk of bias;" both refer to internal validity. Two investigators independently assessed the quality of each study. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

To determine the quality of each study evaluating diagnostic tests, we used questions from the AHRQ "Methods Guide for Medical Test Reviews"[38] and adapted them to improve their clinical relevance to ME/CFS. Quality was based on whether the study evaluated a representative spectrum of patients, including patients with overlapping conditions and those with diagnostic uncertainty; whether it enrolled a random or consecutive sample of patients meeting prespecified criteria; whether it used a credible reference standard; whether the same reference standard was applied to all patients; whether the reference standard was interpreted independently from the test under evaluation; and whether thresholds were prespecified.[31,39,40] Given the lack of a universally accepted reference standard for ME/CFS, use of more broadly accepted research and clinical criteria were accepted as a comparator (CDC, Canadian, and International definitions). Descriptive papers that compared diagnostic criteria and reported harms were not quality rated.

The quality of intervention trials was based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.[31,40]

Following assessment of individual quality criteria, individual studies were rated as "good," "fair," or "poor" quality, as defined below.[31,38]

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results.

Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are probably *in*valid.

Poor-quality studies have significant flaws that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. Poor-quality studies were not excluded a priori, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present. For detailed quality assessment criteria see Appendix E.

Assessing Research Applicability

Applicability is defined as the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention is applied to the population of interest under "real-world" conditions.[31] It is an indicator of the extent to which research included in a review might be useful for informing clinical decisions in specific situations. Applicability depends on the particular question and the needs of the user of the review. There is no generally accepted universal rating system for applicability. In addition, applicability depends in part on context. Therefore, a rating of applicability (such as "high" or "low") was not assigned because applicability may differ based on the user of this review. Rather, factors important for understanding the applicability of studies were recorded, such as how similar patients were to the population of interest, how large the sample size was, and the characteristics of the clinical setting.[41] The funding source for treatment trials was also recorded.

Data Synthesis

Results of diagnostic accuracy studies (such as creating summary AUROCs) were not quantitatively pooled due to differences in methods, case definitions, and heterogeneity in the outcomes. Instead, descriptive statistics were used, such as the median sensitivity and specificity at specific cutoffs and reported AUROCs, along with associated ranges, and calculated positive and negative likelihood ratios based on the median sensitivities and specificities. For the results of intervention trials, the appropriateness of meta-analysis was determined by considering the internal validity of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Appropriate measures were chosen based on the type of data for meta-analysis, according to the guidance for the Evidence-based Practice Center Program.[42] Random-effects models were used to estimate pooled effects.[43] When only two studies were available we chose not to pool the results.[43] We calculated pooled RR where the data were reported as proportions of dichotomous outcomes (e.g., proportion with improvement in intervention and control groups). For continuous outcomes, we calculated pooled weighted mean differences using the means and standard deviations (SDs) (e.g., mean change in function based on a scale). The Q statistic and the I-squared statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[44,45] When statistical heterogeneity was found, we explored the reasons by using subgroup analysis. In meta-analysis, we combined RRs and ORs for such outcomes.

Grading the Body of Evidence for Each Key Question

The overall strength of evidence was assessed for each Key Question and outcome in accordance with the AHRQ Methods Guide.[31,38] Strength of evidence was based on the overall quality of each body of evidence, the study limitations (graded low, moderate, or high); the consistency of results between studies (graded consistent, inconsistent, or consistency unknown when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); the precision of the estimate of effect, based on the number and size of studies and confidence intervals (CI) for the estimates (graded precise or imprecise); and whether reporting bias was suspected (graded suspected or undetected). There was no way to formally assess for publication bias due to the small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. For a more detailed description of the categories used see Appendix F. Studies

included to answer Key Question 1 were not formally evaluated for strength of evidence, but key concepts of strength of evidence are discussed.

The strength of evidence was rated for Key Question 2 using the four categories recommended in the AHRQ Methods Guide:[31,38] A "high" grade indicates high confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies and the findings are stable (i.e., another study would not change the conclusions). A "moderate" grade indicates moderate confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies and findings are likely to be stable, but some doubt remains. A "low" grade indicates low confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both) and additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. An "insufficient" grade indicates inability to estimate an effect or no confidence in the estimate of effect for this outcome, no evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Peer Review and Public Commentary

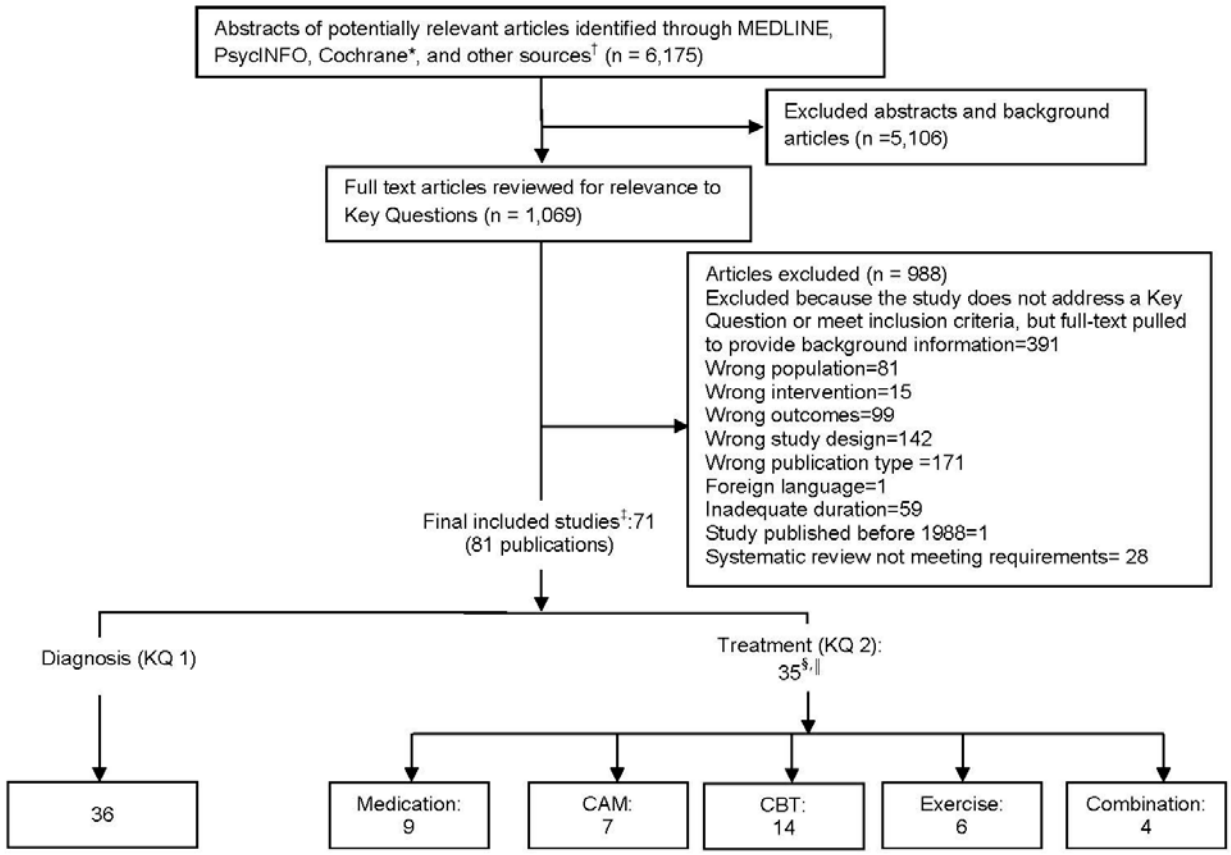
Experts in ME/CFS, individuals representing important stakeholder groups, and TEP members were invited to provide external peer review of this systematic review. The AHRQ Task Order Officer and a designated Evidence-based Practice Center Associate Editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks in September and October 2014. The draft report was further edited in response to these reviews and comments, and the specific responses were outlined in a table that will be made available after AHRQ posts the final systematic review on the public Web site.

Results

Results of Literature Searches

Results of the literature search and selection process are summarized in the literature flow diagram (Figure 2). Database searches resulted in 6,175 potentially relevant citations. After dual review of abstracts and titles, 1,069 articles were selected for full-text review. After dual review of full text articles, 71 studies (in 81 publications) were included. Data extraction and quality assessment tables for included studies by Key Question are available in Appendixes G and H.

Figure 2. Literature flow diagram



Abbreviations: CAM = complementary alternative medicine; CBT = cognitive behavioral therapy; KQ = Key Question.
*Cochrane databases include the Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment, National Health Sciences Economic Evaluation Database, and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, hand searching, suggested by experts, etc.
‡Studies that provided data and contributed to the body of evidence were considered "included."
§ Studies may have more than one published article, this number indicates the number of unique studies included; there were a total of 45 publications included.
‖Studies may have provided data for more than one treatment area

Description of Included Studies

Of the 71 studies included in this review, 36 observational studies addressed Key Question 1, pertaining to aspects of diagnosis. Most were of fair-quality, enrolled predominantly female

patients, had small sample sizes, and were conducted in the United States and Western Europe. Thirty-five randomized trials were included for Key Question 2, addressing the benefits and harms of interventions to treat myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (9 for medications; 7 for complementary and alternative medicine [CAM]; 14 for counseling and behavioral therapies; and 6 for exercise, including 4 comparing interventions). Most were of fair- or poor-quality, enrolled predominantly female patients from ME/CFS specialty clinics based on the CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) case definition, had small sample sizes, and were conducted in the United States and Western Europe.

Key Question 1. What methods are available to clinicians to diagnose ME/CFS, and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?

Key Points

- Eight different case definitions have been used to identify patients with ME/CFS; all include a set of clinical criteria and are applied by clinicians.
- The Oxford (Sharpe, 1991) case definition has the least overlap with other definitions.
- Most ME/CFS case definitions require that other conditions be excluded prior to assigning a diagnosis of ME/CFS; however, no studies compared strategies for ruling out alternative diagnoses.

Detailed Synthesis

Case definitions have evolved since the first set of clinical criteria were published by the Centers for Disease Control and Prevention (CDC) in 1988 (Table 2 below and Appendix I).[10] Despite being developed as consensus guidelines and with endorsement of national groups, none of these published case definitions is agreed upon as the single preferred method for distinguishing ME/CFS from other conditions that may also present with fatigue. The Oxford (Sharpe, 1991) case definition requires the presence of the smallest symptom set (new onset of fatigue with impairment of physical and mental function), suggesting less specificity for ME/CFS.[46] Four definitions are labeled as myalgic encephalomyelitis (ME) or ME/CFS and all of these require the presence of post-exertional malaise (PEM). All case definitions address the diagnostic workup that is required prior to diagnosing chronic fatigue syndrome (CFS).[2,3,47,48] In general, prior to diagnosing ME/CFS, other explanations for fatigue must to be ruled out. Recommendations for workup are included with the published case definitions, but no studies specifically evaluated diagnostic workup strategies or compared strategies for ruling out alternative diagnoses prior to assigning a diagnosis of ME/CFS.

Table 2. Case definitions and criteria

		ME ± CFS				CFS			
	Criteria	**London ME Dowsett, 1994[47]**	**Canadian ME/CFS Carruthers, 2003[2]**	**Revised Canadian ME/CFS Jason, 2010[48]**	**International ME Carruthers, 2011[3]**	**CDC Holmes, 1988[10]**	**Oxford Sharpe, 1991[46]**	**CDC Fukuda, 1994[4]**	**CDC Reeves, 2005*[49]**
General Physical	**Fatigue**	X	≥ 6 months	≥ 6 months		≥6 months	≥ 6 months or >50% of time	≥6months	≥ 6 months
	Sudden or New Onset		X[†]			X[‡]	X		X[§]
	Impairment of Daily Function					≥ 50%	X		
Neurological/ Neurocognitive	**Muscle Weakness**			X		X[‡]			
	Muscle Pain		X		X[‖]	X[‡]		X[§]	X[§]
	PEM	X	X	X	X	X[‡]		X[§]	X[§]
	New Headaches		X			X[‡]		X[§]	X[§]
	Arthralgias (migratory)		X	X	X[‖]	X[‡]		X[§]	X[§]
	Sleep Disturbances	X[¶]	X	X	X[‖]	X[‡]		X[§]	X[§]
	Neurological or Neuropsychiatric complaints	X[¶]	X**		X[‖]	X[‡]			
	Memory or Cognitive Impairment	X[¶]	X**	X[††]	X[‖]		X	X[§]	
	Dysequilibrium	X							
	Temperature Dysregulation				X[‡‡]				
Neuroendocrine/ Immune	**Autonomic Dysfunction**		X[§§]	X[§§]					
	Fever or Chills					X[‡]			
	Sore Throat					X[‡]		X[§]	X[§]
	Lymph Node Pain					X[‡]		X[§]	X[§]
	Neuroendocrine Dysfunction		X[§§]	X[§§]	X[‖‖]				
	Immune Manifestations		X[§§]	X[§§]					
Other System Involvement	**Cardiovascular Impairment**				X[‡‡]				
	Pulmonary Impairment				X[‡‡]				
	Gastrointestinal Impairment				X[‖‖]				
	Genitourinary Impairment				X[‖‖]				

Abbreviations: CDC=Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; ME= myalgic encephalomyelitis; PEM=post-exertional malaise.
* Defined functional impairment by 36-item Short Form Survey scores, fatigue by Multidimensional Fatigue Inventory, and symptoms by Symptom Inventory Case Definition subscale; [†]Onset may be gradual; [‡]8 of 11 minor symptoms; [§] ≥ 4 symptoms present concurrently for ≥6 months; [‖] ≥1 from 3 of the 4 symptom categories (neurocognitive, pain, sleep, neurosensory/motor); [¶]≥1 of 3 symptoms; **≥2 neurological/cognitive manifestations; [††]≥2 cognitive manifestations; [‡‡]≥1 energy production/transportation impairment (cardiovascular, pulmonary, thermostatic, temperature); [§§]≥1 symptoms from 2 of the categories of autonomic, neuroendocrine and immune manifestations; [‖‖]≥1 symptoms for ≥3 categories of immune, gastrointestinal and genitourinary impairments

Key Question 1a. What are the accuracy and concordance of methods used to diagnose ME/CFS?

Key Points

- Diagnostic studies of ME/CFS are limited by the lack of an accepted reference standard (case definition) or an agreed upon set of clinical criteria.
- Concordance was assessed in seven studies reporting variations in symptom prevalence in populations that are defined by different case definitions. Three studies evaluated case definitions by comparing ME/CFS patients with other populations.
- Patients identified by clinical criteria labeled as ME or ME/CFS had more severe symptoms or more functional impairment than those identified by clinical criteria labeled as CFS. Patients with ME or ME/CFS had more severe symptoms than healthy control patients and some groups of patients with other chronic diseases.
- Accuracy, sensitivity, and specificity of clinical criteria for the diagnosis of ME/CFS were assessed in 11 studies; none provided evidence that a single set of clinical criteria is better than other criteria at differentiating ME/CFS from other conditions that may also present with fatigue however the Oxford (Sharpe, 1991) case definition has not been formally compared with other case definitions nor evaluated for diagnostic accuracy or concordance.
- Three studies, one good- and two fair-quality, found that computerized modeling can have good sensitivity and specificity for identification of patients who meet one of the ME/CFS case definitions when compared with healthy controls. These have not been tested in a clinical setting or in patients with diagnostic uncertainty.

Detailed Synthesis

Evaluation of accuracy of a diagnostic test generally requires an accepted diagnostic reference standard ("gold standard"). Diagnostic studies of ME/CFS are limited by the lack of a single accepted reference standard. The use of clinical criteria is the accepted approach to diagnosis, however as noted above in Table 1 there are multiple case definitions in use. This is an ongoing challenge in terms of evaluating diagnostic tests because studies have used various case definitions as the reference standard against which they measure the utility of a diagnostic test. We evaluated whether these case definitions identify similar or different groups of people; our findings are discussed below.

Studies Comparing Case Definitions for ME/CFS

Eight studies evaluated the concordance of different diagnostic criteria (Table G1 of Appendix G).[5,9,50-55] One study considered the comparison based on age variance and will be discussed under Key Question 1b.[53] These studies examined patients who met the clinical criteria for various case definitions and reported on differences in symptom prevalence between patient populations. These were primarily observational cohort studies and descriptive studies, therefore not amenable to quality rating. Differences reported here are those that were statistically significant between groups (see Table G1 for a complete report).

Studies consistently demonstrate that symptom reporting varies between populations defined by different clinical criteria. In general, populations defined by ME or ME/CFS criteria were more symptomatic and impaired than those defined by CFS criteria.[5,9,50-56]

Sore throat and lymph node pain were more common in 14 subjects who met the Holmes, 1988 CDC criteria compared with those meeting the Fukuda, 1994 CDC criteria (n=18) and with fatigued patients due to psychiatric illness (n=33).[50] This study also compared the 36-item Short Form Survey (SF-36) measurements among these groups and found no consistent differences in terms of bodily pain, general health, physical health composite score, mental health composite score, and self-reported degree of impairment (see Table G1 for details). A similar study compared symptom prevalence for CFS identified by CDC (Fukuda, 1994) criteria with ME/CFS identified by Canadian (Carruthers, 2003) criteria using data from three populations and comparing scores on the DePaul Symptom Questionnaire and the SF-36.[5] The SF-36 scores indicated significantly less impairment for the CFS group compared with the ME/CFS group in all three populations on the subscales of physical functioning and bodily pain. Symptom reporting indicated less impairment in the CFS group compared with the ME/CFS group in the majority of PEM, pain, autonomic, and immune symptom subcategories. Responses to other symptom subcategories were less consistent across the populations: 4 of 13 neurocognitive symptoms were significantly lower in the CFS group compared with the ME/CFS group for all three populations, and the other seven neurocognitive symptoms were significantly lower in the CFS group compared with the ME/CFS group in just two of the populations (DePaul sample and BioBank). Likewise, only one of six sleep symptoms was lower for CFS compared with ME/CFS in all three populations, whereas three of six sleep symptoms were lower in two of the populations. This may reflect differences in the populations—the DePaul and BioBank demonstrated more consistent differences in symptoms for CFS compared with ME/CFS, whereas the Newcastle sample (those referred by primary care for suspected CFS) did not demonstrate as many differences between those who were identified as having CFS by the CDC (Fukuda, 1994) criteria and those identified as having ME/CFS by the Canadian (Carruthers, 2003) criteria.[5]

SF-36 and symptom scales were compared among 74 patients who had been labeled as CFS defined by CDC (Fukuda, 1994) criteria with 39 patients labeled as ME defined by the international consensus criteria (Carruthers, 2011).[51] In this study, SF-36 subscale scores indicated less impairment among the CFS group versus the ME group on the physical functioning, bodily pain, vitality, and social functioning subscales. Symptom ratings also indicated less impairment among the CFS group compared with the ME group for PEM, neurological, and pain symptoms.

Using a similar population, another study compared the Canadian (Carruthers, 2003) criteria with the CDC (Fukuda, 1994) criteria and an ME definition created from multiple sources, based on the cardinal features of ME (acute onset plus PEM, neurological manifestations, and autonomic manifestations).[9] Of the 114 people who met the CDC (Fukuda, 1994) criteria, 56 were also classified as ME/CFS and 27 as ME. There were significant differences among these groups in multiple symptoms; symptom reporting was lower for the group who met CDC (Fukuda, 1994) criteria (but not ME) versus those who met the ME/CFS Canadian (Carruthers, 2011) criteria, and lower for those who met the CDC (Fukuda, 1994) criteria (but not the ME/CFS criteria) versus those who met the ME criteria (defined in this study and based on prior definitions and cardinal features). The ME/CFS group had higher psychiatric comorbidity rates compared with the CFS group. Objective measures of heart rate, cognitive function (trail making tests), and the Kroenke 13 symptom inventory were also compared across groups, demonstrating that ME and ME/CFS groups had higher heart rates lying down and 2 and 10 minutes after standing compared with the CFS-only group, longer times on the trail making tests, and higher

scores on the Kroenke symptom and psychiatry comorbidity scale. These findings were consistent with those of two other studies.[54,55]

Another study compared 41 patients meeting CDC (Fukuda, 1994) criteria with 26 patients meeting London ME (Dowsett, 1994) criteria using the SF-36, Multidimensional Fatigue Inventory 20-item (MFI-20), Karnofsky Performance Scale (KPS), and exercise testing. CFS patients had lower functioning than ME patients on the role-emotional and mental health subscales of the SF-36 (other subscales of the SF-36 were not significantly different between the two groups). The general fatigue score of the MFI-20 was significantly higher for CFS versus ME but the other four components of the MFI-20 were not different. There were no meaningful differences in treadmill exercise test variables for ME subjects versus CFS (5 of the 7 variables were not significant); age predicted hazard ratio (HR) and oxygen consumption (VO_2) were both higher for the ME group compared with the CFS group (p=0.049).[52]

In summary, most studies that compared patients meeting case definitions of ME or ME/CFS with patients meeting case definitions of CFS showed that patients diagnosed using an ME or ME/CFS case definition reported worse symptoms and had more impairment in physical and cognitive domains than patients being diagnosed using the CFS case definition. One study comparing patients diagnosed with the London ME (Dowsett, 1994) criteria with the CDC (Fukuda, 1994) criteria found few differences between the two groups; but where there were differences, the CFS patients had worse symptoms than ME patients. Both studies comparing ME with CFS or ME/CFS are small. In the larger studies that compare ME/CFS with CFS there seems to be a consistent finding of more significant differences, favoring the theory that ME/CFS and CFS identify different populations. It may be that the CFS criteria capture a broader population (such that ME and ME/CFS are subsets of CFS), or that ME and ME/CFS identify separate groups entirely.

Studies Comparing Symptoms Among ME/CFS and Non-ME/CFS Populations

Three studies compared symptoms of CFS patients diagnosed with the CDC (Fukuda, 1994) criteria with other groups of patients: controls that were healthy and nonfatigued, controls that were fatigued but did not meet CFS criteria, and controls with fatigue and another chronic illness (Table G1).[57-59] Although not technically measuring concordance between case definitions, these studies identified scales that distinguished patients meeting criteria for one of the case definitions versus those who did not meet criteria for that case definition. These studies demonstrated significant differences in reported symptoms between patient groups. Differences were measured by the Fatigue Impact Scale (FIS), Chalder Fatigue Scale, Hospital Anxiety and Depression Scale depression subscale (HADS-D), and certain SF-36 subscales or combinations of SF-36 variables with the Zung Self-Rating Depression Scale. These scales may help to identify CFS patients, but they will need to be evaluated in a broad spectrum of patients with diagnostic uncertainty to determine their ability to differentiate between conditions and/or identify clinical subgroups of patients[57-59] (see Appendix J for more details).

Variables from the SF-36 and Zung Self-Rating Depression Scale were used to distinguish between 51 women with CFS, 55 with idiopathic chronic fatigue (defined as chronic fatigue not meeting criteria for CFS), and 53 nonfatigued controls matched to the CFS subjects.[57] In this study, computer modeling using latent class analysis was able to empirically derive a solution that was comparable with the established case definition. Thus, the computer modeling validated

the ability of the CDC (Fukuda, 1994) criteria to differentiate a group of CFS patients from a group of non-CFS patients.

Differences were found in symptom reporting in a study comparing 19 consecutive patients presenting to an academic medical center's chronic fatigue clinic who met CDC (Fukuda, 1994) criteria with 31 subjects with rheumatoid arthritis (RA).[58] General Health Questionnaire scores were highest for the CFS group and lowest for the RA group; the SF-36 role function scores indicated lowest impairment in the RA group and highest in the CFS group; SF-36 mental function was best in the RA group and lowest in the CFS group; SF-36 health perception was highest in the RA group and lowest in the CFS group; no differences in the other SF-36 subscales or in the Modified Symptoms Perception Questionnaire or the Pennebaker Inventory of Limbic Languidness.[58]

Functional status and well-being were evaluated in 223 patients who met criteria for CFS using the CDC (Holmes, 1988) criteria with both a population-based control sample and a group with various chronic diseases using the SF-36.[59] CFS patients had lower functioning than the general population on all SF-36 subscales, and lower functioning than almost all disease groups on most subscales: the exceptions were that the CFS group did not differ from the group of 25 multiple sclerosis patients in terms of physical functioning, vitality, and role-emotional, nor did the CFS group differ from the congestive heart failure group on the role-emotional subscale.

Based on these three studies, symptom reporting varies between CFS patients and other populations but the utility of these symptom-based scales in differentiating patients with diagnostic uncertainty remains inconclusive.

Accuracy of Measures Used To Diagnose ME/CFS as Defined by Any of the CFS Case Definitions

Eleven cross-sectional and longitudinal studies with comparison groups evaluated methods currently used to diagnose ME/CFS. Two studies evaluated how well symptom scales could predict a subset of patients who fail to recover from cardiopulmonary exercise testing (CPET) and will be discussed under Key Question 1b.[60,61] All of these studies provided data on discriminative value (receiver operating curve [ROC], area under the curve [AUC]), sensitivity/specificity, or concordance of diagnoses (Table G2).[56,60-69] One study was good-quality,[63] seven fair-quality,[56,60,61,64-69] and one poor-quality[62] (Table H1 of Appendix H). The studies were conducted in the United States[56,60,61,65] and western Europe,[62-64,66-68] were generally small (range: 25 to 798 participants, with only two studies enrolling >200 participants) and predominately enrolled women (43 to 100% female when reported). Several studies used the same or very similar study populations to report on different outcomes, recruiting from CFS self-help groups,[66-68] or a community sample outside Chicago.[56,65]

Overall the identified studies lacked robustness needed for rigorous evaluation of diagnostic tests for ME/CFS. Major limitations of these studies include: enrolling fewer than 50 total subjects,[60-62,66-68] recruitment from specialty clinics,[60,61,63] lack of clear blinding to the reference standard result,[56,60-68] and comparing cases with either healthy or nonfatigued controls. The use of healthy controls and the case-control design are problematic for diagnostic test studies; ideally, a diagnostic test is able to differentiate patients with the disease from those without in a population of patients with diagnostic uncertainty. Thus, a robust evaluation of a diagnostic test requires a broad spectrum of patients and includes patients who would be reasonable candidates for the test—in this case, patients presenting with fatigue and other symptoms that suggest a

diagnosis of ME/CFS. Only one study used a population with overlapping symptoms and tested a strategy for diagnosis in both a derivation and a validation cohort.[63]

Biomarkers as Diagnostic Tests

Four studies evaluated the ability of serum parameters to identify CFS (using the CDC [Fukuda, 1994] and Oxford [Sharpe, 1991] criteria) versus healthy controls, and reported on the AUC for the ROC curve for these measures. The tests included hypothalamic-pituitary axis testing (cortisol response to dexamethasone suppression test),[67] insulin tolerance testing and adrenocorticotropic hormone (ACTH), plasma and salivary cortisol responses to insulin injection,[66] pro-inflammatory cytokine response to standardized psychological stress,[68] and RNase L-isoforms.[62] All of the biomarker studies were small (sample size range: 25 to 42). [62,66-68] Three were fair-quality and utilized the same CFS self-help group population in Germany, and one was poor-quality.

Three of the biomarker studies from the same group of investigators[66-68] found that biochemical responses to stimuli were abnormal in the ME/CFS group compared with healthy controls. The morning plasma and salivary cortisol responses to low-dose overnight dexamethasone suppression testing were significantly lower in the ME/CFS group versus controls ($F=12.16$, $p=0.003$ for morning cortisol and $F=11.51$, $p=0.001$ for salivary free cortisol); this finding was consistent when comparing the logAUC (total) between groups.[67] The AUC of ACTH response to insulin tolerance testing was significantly associated with reported duration of symptoms ($F=4.92$, $p=0.03$), but there were no differences between ME/CFS patients and controls for plasma total and salivary free cortisol ($F=0.73$, $p=0.4$; $F=2.12$, $p=0.15$).[66] Response to stress was tested using the Trier Social Stress Test (TSST), a standardized psychological stress test, and found an inverted pro-inflammatory cytokine response for ME/CFS subjects compared with controls; ME/CFS subjects' levels of IL-6 and TNF-α decreased at 10 minutes and returned to normal by 60 minutes, whereas the IL-6 and TNF-α levels for controls increased at 10 minutes and returned to normal at 60 minutes (IL-6 $F=3.93$, $p=0.03$; TNF-α $F=4.64$, $p=0.02$).[68] ACTH response also varied between the groups, but cortisol did not (AUC for ACTH response curve $F=6.34$, $p=0.02$; AUC for plasma cortisol $F=0.1$, $p=0.91$; AUC for salivary cortisol $F=1.03$, $p=0.32$).[68] These three studies recruited from a CFS self-help group population in Germany and utilized essentially the same patients for all three studies. Although the CFS diagnosis was confirmed subsequently by physician examination or interview, the recruitment process of these studies has potential to provide a limited spectrum of patients with CFS. In addition, because they utilize the same population, these three studies are not independent of each other.[66-68]

The fourth of these biochemical studies evaluated the sensitivity and specificity of RNase L levels in peripheral blood mononuclear cells for discrimination of ME/CFS subjects from controls. The ratio of RNase L isoforms at a cutoff of 0.4 had a sensitivity of 0.91 and specificity of 0.71; other thresholds resulted in lower sensitivity and specificity.[62] Although these tests were able to distinguish between healthy controls, their usefulness remains uncertain without testing in a broader spectrum of patients including those with overlapping features.

Self-Reported Symptom Scales as Diagnostic Tests

Three studies created new assessment tools.[63,64,69] One good-quality study evaluated an appropriately broad spectrum of subjects, including 41 with systemic lupus erythematosis, 58 with fibromyalgia, and 99 with CFS as defined by Oxford (Sharpe, 1991) criteria; subjects were randomly assigned to either a derivation or validation cohort.[63] A new tool was developed by administering prospectively defined criteria via questionnaire; each symptom was assessed for

sensitivity and specificity and the symptoms with the best sensitivity and specificity were elected to contribute to the new criteria. Four methods for classification of ME/CFS were tested using the derivation cohort, and for each algorithm sensitivity, specificity, and accuracy were determined using the validation cohort. One of the four strategies that included 24 symptoms, the artificial neural network, had the best results (sensitivity 0.95; specificity 0.85 and accuracy 0.90).[63] One other large (n=368 CFS patients diagnosed by a combination of methods including physician interview about the confidence of their diagnosis and 430 controls) fair-quality study tested the Schedule of Fatigue and Anergia for CFS scale in ME/CFS patients and healthy controls using latent class analysis; this study demonstrated good sensitivity (0.81) and specificity (0.98).[64] A third fair-quality large (n=691) study used K-means clustering to identify the most predictive symptoms from the DePaul Symptom Questionnaire (DSQ), define thresholds for symptoms, and then calculate sensitivity, specificity, and accuracy for each symptom comparing three definitions of CFS: CDC-CFS (Fukuda, 1991), Canadian, ME/CFS (Carruthers, 2003), and International-ME (Carruthers, 2011). The study authors concluded that the DSQ can provide an accurate basis for diagnosing CFS as compared with these three case definitions and that some high yield symptoms may enhance the predictive capacity of CFS, specifically symptoms that reflect fatigue, general pain, PEM, sleep dysfunction, and neurocognitive issues.[69] These findings have not been replicated in other populations.

Three small, fair-quality studies that reported on cortisol testing also reported the AUC values for the MFI-20, Hospital Anxiety and Depression Scale (HADS), the Symptom Checklist 90, Revised (SCL-90-R), and the Sickness Impact Profile 8-item (SIP-8), using essentially the same patient population; these studies found that all measures were significantly different between CFS cases (CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)) and healthy controls (no medications, no current/lifetime psychiatric symptoms or disorders).[66-68] While AUCs were different, these studies do not further the diagnostic strategy for ME/CFS because of their methodological limitations: small sample size, case-control design, unclear recruitment methods, and unclear reporting of attrition and blinding (Table H1). These results show that patients with ME/CFS have more depression, anxiety, and decreased functionality in several other domains; but because the comparison population consisted of healthy controls there is no evidence that these tests could adequately distinguish a ME/CFS population from another population of depressed, anxious, or medically ill patients. Overall, it is unclear whether these measures could diagnose ME/CFS if used by themselves (in the absence of the clinical criteria), because alone these measures do not satisfy the multiple symptom domains that currently comprise the syndrome of ME/CFS.

Two studies evaluated the ability of existing symptom scales to identify ME/CFS patients or to correlate with specific aspects of the diagnostic criteria such as disability or fatigue, in hopes of providing a more standard assessment tool for use in diagnosing ME/CFS. A fair-quality small study (24 ME/CFS patients and 84 healthy controls) evaluated the SF-36, the CDC Symptom Inventory, and the MFI-20 for identifying ME/CFS subjects who met the disability criterion for the CDC (Reeves, 2005) criteria.[49] The MFI-20 had reasonable sensitivity (0.95) for the criteria but poor specificity (0.27); none of the AUCs for the MFI-20 were above 0.90.[56] In this study, the CDC Symptoms Inventory had poor sensitivity and specificity, as did the SF-36 subscales of physical functioning, role physical, social functioning, and role-emotional (none with AUC, sensitivity, or specificity above 0.90).[56]

In a subsequent paper, also fair-quality, the SF-36 was further evaluated using two different ME/CFS populations: 32 CFS patients recruited from the community and 114 CFS patients

recruited from tertiary care defined by CDC (Fukuda, 1994) criteria, as well as 47 nonfatigued controls. Similar to the previous findings, none of the AUCs for the community-based CFS patients were above 0.90, whereas three AUCs for subscales of the SF-36 in the tertiary care CFS population were close to or above 0.90 (vitality, role-physical, and general health all had AUC of 0.91; social functioning had AUC of 0.87). Additional analysis focused on vitality, role-physical, and social functioning to determine cutoffs and assess whether the use of combinations of scales could identify ME/CFS subjects in both the community and the tertiary care samples as distinguished from healthy controls. The study authors determined that meeting the cutoffs for two or more of these three subscales could be used to designate substantial reductions in function and to potentially distinguish those with ME/CFS from those without ME/CFS. For the community-based ME/CFS sample, sensitivity was 0.93 and specificity was 0.75; for the tertiary care sample, sensitivity was 0.96 and specificity was 0.75.[65] These researchers also used the MFI-20, the CDC Symptom Inventory, and the SF-36 to assess the sensitivity and specificity of the CDC-CFS (Reeves, 2005) criteria for identifying CFS in the community population compared with healthy controls; the AUC for Reeves criteria was 0.70 (sensitivity 0.65; specificity 0.76).[65] These studies do not appear to contribute to operationalizing the ME/CFS criteria given the inconsistencies in the results. The subscales of the SF-36 show promising results in a tertiary care, recruited population (the SF-36 scores for vitality, role-physical, and general health were above 0.90);[56] however, this was not true for the community-recruited ME/CFS patients.

Key Question 1b. How does the use of these methods vary by patient subgroups?

Key Points

- One study reported that older patients were more impaired, but it did not consider how symptom evaluation might vary with age.
- Two studies found that CPETs were different between ME/CFS patients and healthy controls, and that certain subscales of the SF-36 were associated with slow recovery after exercise. No studies evaluated differences in the performance of case definitions among patients with specific symptom sets (autonomic/neuroendocrine, neurological/neurocognitive, or presumed infectious etiologies).

Detailed Synthesis

Three studies evaluated potential diagnostic tests in subgroups of ME/CFS patients.[53,60,61] Using a unique approach, one study evaluated whether symptoms vary for younger versus older CFS patients. They studied 50 CFS patients, diagnosed using the CDC (Fukuda, 1994) criteria, matching 25 older subjects (>50 years) by sex and duration of CFS diagnosis with 25 subjects aged 16 to 29 years.[53] Older CFS patients were more impaired, having higher FIS scores, higher Chalder Fatigue scores, higher HADS-D scores, lower functioning by SF-36, and lower self-efficacy. The two groups did not differ on the Cognitive Failures Questionnaire, HADS total, HADS anxiety subscale (HADS-A), pain rating, Epworth Sleepiness Scale, and Orthostatic Grading Scale. Several autonomic and hemodynamic measures differed between older and younger CFS patients: older patients had lower resting heart rates, higher left ventricular ejection time, lower baroreflex sensitivity (ability to maintain blood pressure) than younger patients, but

there were no differences in systolic, diastolic, or mean blood pressure, total heart rate variability during a supine 10 minute rest, baroreflex effective index, and systolic blood pressure with active stand.

Diagnostic tests to predict recovery from exercise testing were evaluated in two fair-quality studies of the same population.[60,61] The first of these studies demonstrated that CPET capacity was significantly different between CFS patients defined by CDC (Fukuda, 1994) criteria and nondisabled sedentary controls. SF-36 and MFI-20 were then tested to determine whether these two scales could distinguish those who would fail to recover from testing within 1 day. The AUC analysis demonstrated that SF-36 subscales of physical function, role-physical, bodily pain, general health, vitality, and social functioning were significant for failure to recover at 1 day; and the subscales role-emotional, vitality, and bodily pain were significant for failure to recover at 1 week.[60] A separate study evaluated whether individual symptoms could identify CFS patients defined by CDC (Fukuda, 1994) criteria versus controls and found that the symptoms of fatigue, neuroendocrine dysfunction, immune dysfunction, pain, and sleep disturbance all had significant AUC, whereas muscle stiffness, autonomic, and "other" symptoms were not significant.[61] These studies are limited by small size and case-control design and preclude any valid conclusion about the utility of SF-36 or MFI-20 for prediction of failure to recover at 1 day or 1 week.

Key Question 1c. What harms are associated with diagnosing ME/CFS?

Key Points

- Fourteen studies evaluated consequences of the diagnostic process or diagnosis of ME/CFS.
- Five studies found that patients with ME/CFS feel stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their character, social isolation, and interactions with the health care system.
- Prejudice and stereotypes within the medical profession were identified in two studies; medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and what treatment is being given.
- One study described patients' fear, anxiety, confusion, self-doubt, and bitterness when they lacked a diagnosis for their problems, as well as their feelings of both social and medical legitimacy upon obtaining a diagnosis.
- Six studies describe a substantial burden of misdiagnosis among the CFS population.

Detailed Synthesis

Consequences of the diagnostic process or the diagnosis of ME/CFS were evaluated in 14 studies that used primarily descriptive methods not amenable to quality rating (Table G3).[14,21,70-81] Studies used a variety of methods to assess patients' experiences and understanding of their disease including qualitative interviews, surveys, and an internet discussion group. Verification of registry referral criteria, review of specialty clinic referral rejections by chart review, and interviews of providers were used to assess misdiagnosis and provider perceptions of diagnosis. One study performed thorough psychiatric evaluation to identify the frequency of missed psychiatric disease in CFS.[73] Two studies randomized participants to various disease names but

with identical case descriptions in order to test the effect of the disease name on perceptions by medical trainees and undergraduate students.[14,70]

The five studies that used either survey or interview methods to assess harms found that ME/CFS patients experience social stigma as a result of their disease. These include decrease in financial stability (lower standard of living in 92 of 207 patients, new job that required fewer skills or pay cut in 30 to 35 of 207 patients), decrease in social life (174 of 207 patients) and loss of friends, (79 of 207 patients) feeling estranged (42 of 45 patients), decrease in recreational activities (186 of 207 patients), feeling like they needed to conceal their symptoms (17 of 44 patients), delegitimization (10 of 14 patients) and difficult interactions with the medical profession (stereotypes perpetuated and doctors having decided before meeting them that they had a psychological diagnosis), and feeling like their moral character was questioned.[71,72,74-76] A separate study described patients' fear, anxiety, confusion, self-doubt, and bitterness when they lacked a diagnosis for their problems, as well as their feelings of both social and medical legitimacy upon obtaining a diagnosis.[81] In this study, 45 of 50 people interviewed reported that diagnosis was the single most helpful event in the course of their illness.

Two publications describe a study of undergraduate students (n=105) and medical trainees (n=141) who were randomized to being told that the diagnosis for a patient case presentation (identical among all groups) was either CFS, ME, or Florence Nightingale Disease.[14,70] Medical trainees' perceptions of diagnostic accuracy, physiological etiology, and prognosis varied between groups; CFS label was considered most accurate, while the ME label carried worse prognosis. Mental health practitioners were randomized to being told that an identical CFS patient was getting one of three treatments. The assigned treatment appeared to influence subsequent attributions of the patient's disease. Specifically, practitioners who were told that the patient was getting an intravenous immune modulator as the treatment were more likely to think that the patient was correctly diagnosed as having CFS and was more disabled ($p<0.05$ for both).[70]

Attempting to understand the possible benefits conferred by a diagnosis, one group surveyed 20 general practitioners and 50 patients with CFS. Providers reported feeling reluctant to diagnosis CFS because of uncertainty about the impact of a diagnosis on the patient, complexity of offering care, and concern that the diagnosis might become a self-fulfilling prophecy. Meanwhile, patients described fear, anxiety, confusion, self-doubt, and bitterness when they lacked a diagnosis for their problems, followed by a feeling of both social and medical legitimacy upon obtaining a diagnosis. While it did not diminish the severity of symptoms, getting a diagnosis seemed to positively influence the way the patients managed their symptoms.[81]

Missed diagnoses, whether exclusionary or concomitant (such as psychiatric), are common among patients being evaluated for ME/CFS. A prospective evaluation of the frequency of misdiagnosis in patients with CFS studied 68 patients who met the Oxford (Sharpe, 1991) criteria. Patients participated in a standardized structured interviews with a consultant psychiatrist, and a full medical, psychiatric, family, and personal history was obtained. Of 68 patients evaluated, 31 (46%) reported having been given a psychiatric diagnosis (2 out of 3 of them had been incorrectly diagnosed).[73] Specifically, 21 patients had been given a psychiatric diagnosis when one did not exist, and 13 patients who had never been given a psychiatric diagnosis actually had a treatable psychiatric condition in addition to CFS.[73]

Likewise, a case series of 135 patients who were enrolled in the PACE trial using the Oxford (Sharpe, 1991) criteria, reported that 76 patients (56%) had psychiatric co-morbidity.[79] Indeed,

the prevalence of alternate diagnoses in people for whom a diagnosis of CFS is being considered has been well-described. Among those with a preliminary diagnosis of CFS, over half had at least one exclusionary diagnosis.[21,77] Among patients referred to the Newcastle CFS Clinical Service and meeting CDC (Fukuda, 1994) criteria, three clinical phenotypes emerged: 3 percent had positional orthostatic tachycardia syndrome (POTS), 3 percent had a CFS/fibromyalgia overlap phenotype, and 20 percent had symptoms precipitated by a viral/bacterial infection. In this study, those who were referred but did not meet the CDC (Fukuda, 1994) criteria had the following alternative diagnoses: chronic disease (47%), sleep disorders (20%), psychological disorders (15%), idiopathic disorders (13%), cardiovascular disorders (4%), and other disorders (1%).[80] Of 418 referrals to a specialty CFS clinic in London, 52 (26%) had a likely alternative psychiatric diagnosis and 67 (35%) had a likely alternative medical diagnosis.[78]

Key Question 2. What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

Key Points

- Thirty-five trials provided evidence of benefits and harms of treatment; all were small, most had methods rated as poor- or fair-quality, and comparisons across trials were limited by dissimilar outcome measures.

Medications

- Nine trials met inclusion criteria for medical treatment of ME/CFS, although none of the medications have been approved by the U.S. Food and Drug Administration (FDA) for this indication.
- Two fair-quality trials of rintatolimod, an immune modulator not currently approved for use in the United States, enrolled severely debilitated participants and found improvement in measures of exercise performance (low strength evidence). Improvement in other measures of function and reduction of use in other medications for relief of CFS symptoms was also found in one of the studies, but evidence was insufficient to draw conclusions.
- A small fair-quality trial of valganciclovir enrolled patients with suspected viral onset of ME/CFS and elevated antibody titers and reported improved fatigue compared with placebo based on one scale, no differences for other outcome measures, this study will need to be replicated to provide adequate proof of efficacy.
- Small single trials of isoprinosine, hydrocortisone, immunoglobulin G, and fluoxetine did not show significant improvement compared with placebo. Differences were also not found in a larger dose-ranging trial of galantamine. These studies provided insufficient evidence of treatment effects.
- Additional trials with durations less than 12 weeks indicated no differences with placebo for acyclovir, and improved scores for physical health and function with rituximab, although both studies enrolled 30 or fewer participants and the clinical implications of these results are not clear.
- Harms of medications included suppression of adrenal glucocorticoid responsiveness, increased appetite, weight gain, and difficulty sleeping with hydrocortisone; flu-like

syndrome, chills, vasodilatation, dyspnea, and dry skin with rintatolimod; headaches with immunoglobulin G; and nephrotoxicity with acyclovir. Withdrawals due to harms were greater with fluoxetine than placebo.

Complementary and Alternative Medicine

- Seven trials compared one CAM approach with usual care, placebo, or alternative CAM intervention. Interventions included dietary supplements (insulin-like growth factor, antioxidant, acetyl-carnitine), distant healing, homeopathy, melatonin, and phototherapy.
- All outcomes studied have insufficient evidence due to small single studies with methodological limitations.
- Three small fair-quality trials of CAM interventions (one with homeopathy, one with pollen extracts, and one with L-carnitine preparations) found improvement in some measure of fatigue and/or function or well-being but not others.
- One good-quality study found that being aware that one is not receiving distant healing resulted in smaller improvements in function.
- All other trials of CAM interventions found no significant improvements compared with placebo, usual care, or an alternative CAM approach.
- Adherence was low in one trial of a low sugar/low yeast diet but otherwise adherence and harms were not well reported.

Counseling and Behavior Therapies

- Fourteen trials (23 publications) comparing one counseling or behavioral therapy with usual care, wait list control, no treatment, relaxation techniques only, adaptive pacing, anaerobic therapy, graded exercise treatment (GET), or an alternate form of counseling or behavioral therapy were included.
- When considering all studies comparing any type of counseling with no treatment, support, relaxation, or adaptive pacing there is low strength of evidence that counseling decreases fatigue (7 of 11 trials showed positive effect), low strength of evidence for improvement in measures of functioning (4 of 11 trials showed positive effect; 2 of 11 showed mixed results on different measures), low strength of evidence for improvement in quality of life (2 of 4 trials showed positive effect), and moderate strength of evidence for global improvement (2 of 2 trials showed positive effect).
- Low strength of evidence suggests that at followup, patients receiving counseling had better SF-36 physical functioning subscale scores than control patients, based on a pooled analysis of eight trials; weighted mean difference score of 7.73 (95% confidence interval [CI], 3.58 to 11.87). However, when results were limited to the four studies that used CBT specific techniques the results were similar but no longer statistically significant.
- There is low strength of evidence from a small fair-quality trial that face-to-face counseling is similar to telephone counseling in improving function, employment measures, and global change.
- Harms of counseling and behavioral therapies were poorly reported but there is low strength of evidence that counseling is not associated with harms, based on one moderate-sized and one large-sized trial.

Exercise Therapy

- Six trials (7 publications) provided evidence on the effectiveness and harms of exercise therapies.
- GET improved measures of fatigue (low strength of evidence), function (moderate strength of evidence), and clinical global impression of change (moderate strength of evidence); treatment effectiveness may not be generalizable to all patients and may overestimate the benefit as no study used a case definition selecting for more disabled patients.
- Although single small studies found qigong exercise provided improvement in measures of fatigue and that home orthostatic training was similar to usual care or sham orthostatic training, this evidence was insufficient due to small sample sizes and methodological limitations of the studies.
- Harms were not well reported. Although total withdrawal rates were similar to controls in three of four trials, due to the high rate (20%) of patients refusing repeat exercise testing in one study, lack of subgroup analysis throughout, and no studies selecting for a more disabled population (ME case definition), evidence remains insufficient to determine harms of exercise therapies and whether subsets of patients may experience more or fewer harms.

Combination Therapy and Head-to-Head Comparisons

- Four trials (8 publications) were included that compared either head-to-head interventions or combinations of two interventions.
- GET and cognitive behavioral therapy (CBT) had similar improvement on measures of function (low strength of evidence). Fatigue measures are also likely similar; however, results are mixed (insufficient evidence).
- Evidence on the comparison of GET and fluoxetine is insufficient because there was only one small study with methodological flaws. This study found GET improved measures of fatigue and function, whereas fluoxetine did not.
- CBT appears to be associated with fewer harms than GET.

Detailed Synthesis

Thirty-five trials of interventions for patients with ME/CFS in 45 publications met inclusion criteria; 9 trials of medications, 7 of CAM interventions, 14 of counseling and behavior therapies, 6 of exercise therapies, and 4 of either head-to-head comparisons or combinations of these interventions (Table G4). Seven were rated good-quality, while 23 were rated fair- and 5 poor-quality (Table H2).

Trials enrolled from 16 to 641 patients with ME/CFS and most (25 of 35, 71%) used the CDC (Fukuda, 1994) criteria. Outcome measures included the SF-36 physical functioning subscale, Medical Outcome Study Short Form (MOS-SF), Checklist of Individual Strength (CIS), Profile of Mood States (POMS) fatigue subscale, KPS, and SIP-8 scale to measure overall function; MFI-20, Chalder Fatigue Scale, Krupp Fatigue Severity Scale (FSS), FIS, and Visual Analogue Scale (VAS) to measure fatigue; Quality of Life Inventory (QOLI), Quality of Life Index (QLI), Quality of Life Scale (QLS), EuroQol Scale, Global Wellness Scale, Short Form 12-item Health Survey (SF-12), and Fibromyalgia Impact Questionnaire (FIQ) to measure quality of life; Clinical Global Impression Change (CGI) scales to measure improvement over

time; and the Work and Social Adjustment Scale to measure impairment in work. These are described in Appendix J.

Medications

- Nine randomized trials provided evidence for the medical treatment of ME/CFS, including placebo-controlled trials of galantamine,[82] hydrocortisone,[83] hydrocortisone plus fludrocortisone,[84] immunoglobulin G,[85] valganciclovir,[86] rintatolimod,[87,88] isoprinosine,[89] and fluoxetine[90] (Table 3 below; Table G4). None of these medications have been approved by the FDA for this indication. Two medications are still investigational and not currently FDA approved for any indication, intravenous rintatolimod[87,88] and oral isoprinosine.[89] Additional trials not meeting inclusion criteria because they had durations less than 12 weeks indicated no differences with placebo for acyclovir,[91] and improved SF-36 scores for physical health and function with rituximab.[92] Both studies enrolled 30 or fewer participants and the clinical implications of these results are not clear.

Eight trials met criteria for fair-quality,[82-88,90] and one for poor (Table H2).[89] Major limitations of studies include enrolling fewer than 20 subjects in an arm,[85,86,89] high loss to followup,[82,90] lack of intention-to-treat analysis of outcomes,[84,87] lack of reporting between-group comparisons for key outcomes,[88] unclear randomization process,[89] and lack of blinding.[89] Most trials were either funded by pharmaceutical companies (fully or in part)[82,85-88] or the funding source was not reported.[83,84]

Most trials were designed to treat the potential underlying pathology of ME/CFS. All but two trials[89,90] enrolled participants in the United States. Only three enrolled more than 100 participants,[82,88,90] and three were multi-center.[82,87,88] Participants were predominantly women, and their mean ages ranged from 32 to 50 years. Although most participants were white, many trials did not report race or ethnicity. Most trials used the CDC (Fukuda, 1994) criteria in their inclusion criteria except for one study predating it that used the CDC (Holmes, 1988) criteria,[85] and one trial that used the Oxford (Sharpe, 1991) criteria.[90] The duration of illness varied widely with some trials enrolling participants with durations under 3 years[83,84,89,90] while others were 10 years or more.[86,88]

Outcome measures of fatigue differed between trials, precluding direct comparisons. These included the CGI scale, Chalder Fatigue Scale, POMS (fatigue and vigor subscales only), VAS (degree of fatigue; abbreviated fatigue questionnaire), FSS, fatigue scale specific to the trial, hours of rest per day, Symptom Severity Scale (fatigue, prolonged post-exertion fatigue), CPET tolerance, exercise duration and work, MFI-20, and CDC CFS Symptom Inventory. Additional measures of function and quality of life were also used as outcomes.

Strength of evidence ratings indicated low strength of evidence for intravenous rintatolimod in improving exercise performance in patients with ME/CFS, because results were based on two trials with differing outcome measures. All other trials found no differences or inconsistent results compared with placebo and were limited by small sizes and methodological limitations, leading to insufficient evidence ratings.

Three trials compared immune modulating drugs with placebo, including trials of intravenous rintatolimod[87,88] and oral isoprinosine, both not currently FDA approved for any indication in the United States.[89] In an early trial of rintatolimod, 92 severely debilitated patients (KPS scores of 20 to 60) were randomized to rintatolimod 200 mg twice weekly for 4 weeks, then 400 mg twice

weekly for a total of 24 weeks, or placebo.[87] The median percentage changes from baseline to week 24 were significantly different between groups for exercise duration (10.3 for rintatolimod vs. 2.1 for placebo; p=0.007), exercise work (11.8 for rintatolimod vs. 5.8 for placebo; p=0.011), activities of daily living (23.1 for rintatolimod vs. 14.1 for placebo; p=0.034), and KPS (20 for rintatolimod vs. 0 for placebo; p=0.023). Attrition was 9 percent and adherence 91 percent, and harms did not differ between groups. This trial was limited by lack of intention-to-treat analysis.

A second trial randomized 240 participants (KPS scores of 40 to 60) to rintatolimod 400 mg twice weekly for 40 weeks or placebo.[88] The mean percentage change in CPET tolerance from baseline to week 40, the primary outcome, was greater for the treatment versus placebo group (37% vs. 15%; p=0.047). Although other performance scores were measured, they were not compared between groups (KPS, activities of daily living, SF-36 vitality and general health perception subscales). More participants in the treatment group reported decreased use of medications for relief of CFS symptoms (68% vs. 55%; p=0.048). Attrition was 19 percent and adherence 83 percent. Flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in the treatment group (p<0.05).

A single-blinded trial of isoprinosine randomized 10 patients to treatment and 6 to placebo.[89] The treatment group received 3 g/day of isoprinosine in divided doses for 12 weeks that varied over time. Mean changes in KPS scores from baseline did not differ between groups (p=0.93).

A randomized double-blind placebo controlled trial of valganciclovir, an antiviral agent, enrolled 30 participants with suspected viral onset of ME/CFS and elevated antibody titers.[86] The treatment group received oral valganciclovir 900 mg twice daily for 21 days, then 900 mg once daily for a total of 6 months. Participants were followed for another 6 months, and outcomes were measured at 9 months. Differences were statistically significant from placebo for scores on the FSS (-0.06 for valganciclovir vs. 0.02 for placebo; p=0.006), but not the MFI-20, CDC CFS Symptom Inventory, or self-reported physical function. Attrition was 9 percent and adherence 91 percent. No harms were reported for either group.

To evaluate the efficacy of galantamine, an acetyl-cholinesterase inhibitor, participants from 35 clinical centers in the United Kingdom, western Europe, and the United States were randomized to oral galantamine at various doses (7.5, 15, 22.5, or 30 mg/day) or placebo for 16 weeks (8 weeks at full dose).[82] Outcome measures indicated no statistically significant differences or dose effect between groups for the primary outcome of global improvement (CGI scale), or secondary outcomes of fatigue (Chalder Fatigue Scale) and quality of life (FIQ). The overall withdrawal rate was 23 percent and attrition rate 30 percent, but rates were highest among groups given galantamine doses of 15 mg or more per day. Overall, 90 percent reported harms, with depression, nausea, and headache most common in both groups. Two percent of the galantamine participants experienced serious events, but none was attributed to the study drug.

Two trials evaluated corticosteroids versus placebo, including a trial randomizing 70 participants to oral hydrocortisone (20 to 30 mg every am and 5 mg every pm) or placebo for 12 weeks,[83] and a crossover trial of 100 participants using hydrocortisone (5 mg/day) plus 9-alpha fludrocortisone (50 µg/day) for 12 weeks.[84] Neither study reported statistically significant differences in outcomes between treatment and placebo groups for fatigue (POMS; VAS), quality of life (Global Wellness scale; VAS), or function (activity scale; SF-36). Attrition rates were 10 percent[83] and 20 percent.[84] Harms that significantly differed between treatment and placebo groups included suppression of adrenal glucocorticoid responsiveness (12 vs. 0; p<0.001); increased appetite (17 vs. 8; p=0.02); weight gain (19 vs. 8; p=0.006); and difficulty sleeping (17 vs. 8; p=0.02).[83]

Intravenous immunoglobulin G (1 gm/kg) versus placebo (1% albumen solution) given once every 30 days for 6 months was evaluated in a trial of 30 participants.[85] While measures of fatigue, prolonged post-exertion fatigue (Symptom Severity Scale), and physical function (MOS-SF) were not statistically significantly different between groups, social function (MOS-SF) improved for the placebo group ($p<0.05$). Overall, attrition was 7 percent, and 20 percent experienced harms including 93 percent of treatment and 60 percent of placebo participants reporting headaches ($p=0.03$).

Fluoxetine was compared with placebo in a 6-month, 4-arm fair-quality trial that also included a GET group which will be described separately below.[90] Differences between fluoxetine and placebo were not statistically or clinically significant for fatigue (Chalder Fatigue Scale), functional capacity measured as the amount of oxygen consumed in the final minute of exercise per kg of body weight, or rates of nonfatigue (Chalder Fatigue score of <4) Attrition was higher with fluoxetine than placebo (32% vs. 17%) and adherence was not reported. Withdrawals due to medication side effects were greater with fluoxetine (9 of 68, 13%) than placebo (2 of 68, 3%) although there were no differences in total withdrawals.

In summary, there is low strength evidence that rintatolimod improves measures of exercise performance (improved CPET tolerance 36.5% vs. 15.2%, $p=0.047$; exercise duration 10.3% vs. 2.1%, $p=0.007$; exercise work 11.8% vs. 5.8%, $p=0.01$); and insufficient evidence for other medications because few differences were found between treatment and placebo groups and each was evaluated by only one small trial with important methodological limitations (Appendix K).

Table 3. Trials of medications for ME/CFS

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect: Treatment Compared With Placebo
Blacker, et al., 2004[82] N=423 Fair	CDC (Fukuda, 1994) criteria	4 months (16 weeks, 8 weeks at full dose)	A. Galantamine 2.5 mg TID B. Galantamine 5 mg TID C. Galantamine 7.5 mg TID D. Galantamine 10 mg TID E Placebo	**Fatigue:** Chalder Fatigue Scale (mean change from baseline) Physical scores: NS Mental scores: NS **Quality of life:** FIQ (mean change from baseline): NS Global Well Being (composite): NS **Other:** % Improvement on modified CGI: NS
Blockmans, et al., 2003[84] N=80 Fair	CDC (Fukuda, 1994) criteria	3 month treatment; 3 month placebo crossover	A. Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day B. Placebo	**Fatigue**: VAS degree of fatigue: NS SFQ score: NS **Quality of life:** VAS degree of well-being: NS **Function:** SF-36: NS
Diaz-Mitoma, et al., 2003[89] N=15 Poor	CDC (Holmes, 1988 and Fukuda, 1994) criteria	3 months (12 weeks) of treatment	A. Oral Isoprinosine 1 g TID in weeks 1, 3, 5, 7, 9, and 11 only on Monday-Friday; and 1 g/day in weeks 2, 4, 6, 8, 10, and 12 only on Monday-Friday. B. Placebo	**Fatigue:** KPS (% change from baseline): NS **Other:** Activities of daily living scale; no differences but data not provided
McKenzie, et al., 1998 [83] N=60-70 varied by outcome Fair	CDC (Holmes, 1988) and Fukuda, 1994) criteria	3 months (12 weeks)	A. Oral hydrocortisone 20-30 mg every morning and 5 mg every evening B. Placebo	**Fatigue:** POMS fatigue subscale: NS POMS vigor subscale: NS **Quality of life:** Global Wellness scale: NS **Function:** Activity Scale: NS
Montoya, et al., 2013[86] N=30 Fair	CDC (Fukuda, 1994) criteria	6 months treatment, 6 months followup	A. Oral valganciclovir 900 mg BID for 21 days, then 900 mg/day for total of 6 months B. Placebo	**Fatigue:** FSS (change in score, negative indicates better health): -0.06 vs. 0.02; p=0.006 MFI-20: NS **Function:** Self-reported physical function: NS **Other:** CDC Symptom Inventory: NS

Table 3. Trials of medications for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect: Treatment Compared With Placebo
Peterson, et al., 1990[85] N=28 Fair	CDC (Holmes, 1988) criteria	6 months	A. IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) B. Placebo	**Function:** MOS-SF score for social function higher in placebo group: 5.2 (5.5) vs. 9.4 (7.9); p<0.05 MOS-SF physical: NS
Strayer, et al., 1994[87] N=76-84 varies by outcome Fair	CDC (Holmes,1988) and Fukuda, 1994) criteria	6 months	A. IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks B. Placebo	**Function:** Exercise duration (% change from baseline): 10.3 vs. 2.1; p=0.007 Exercise work (% change from baseline): 11.8 vs. 5.8; p=0.011 ADL score (% change from baseline): 23.1 vs. 14.1; p=0.034 KPS score (% change from baseline): +20 vs. 0; p=0.023 **Other:** Decreased used of medications for relief of CFS symptoms declined for rintatolimod but not placebo
Strayer, et al., 2012[88] N=240 Fair to good	CDC (Holmes,1988) and Fukuda, 1994) criteria	10 months (40 weeks)	A. IV rintatolimod 400 mg twice weekly for 40 weeks B. Placebo	**Function:** Cardiopulmonary exercise tolerance (% change from baseline: 36.5% vs. 15.2%; p=0.047 KPS score, ADLs, Vitality Score (SF-36), and General Health Perception (SF-36) measured pre and post, but not compared between rintatolimod and placebo groups **Other:** Decreased use of medications for relief of CFS symptoms: 68% vs. 55%; p=0.048
Wearden, et.al 1998[90] N=68 Fair Same study as on Table 6 and 7	Oxford (Sharpe, 1991) criteria	6.5 months	A. Fluoxetine 20 mg/day B. Placebo	**Fatigue:** Chalder Fatigue Scale (mean change from baseline): NS Chalder Fatigue Scale (non-cases of fatigue with score <4): NS **Function:** Functional work capacity (mean change): NS

Abbreviations: ADL= Activities of Daily Living; BID=twice a day; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical Global Impression change score; FIQ= Fibromyalgia Impact Questionnaire; FSS= Fatigue Severity Scale; g= gram; IgG= immunoglobulin G; IV= intravenous; kg= kilogram; KPS= Karnofsky Performance Scale; MFI-20= Multidimensional Fatigue Inventory; mg= milligram; MOS-SF= Medical Outcome Study Short Form; N= sample size; NS= not significant; POMS= Profile of Mood States; SF-36= 36-item Short Form Survey; SFQ= abbreviated fatigue questionnaire; TID= three times a day; µg= microgram; VAS=visual analogue scale; vs.= versus

Complementary and Alternative Medicine Therapies

Seven trials comparing one CAM approach with usual care, placebo, or alternative CAM intervention were included (Table 4 below; Table G4).[93-99] Three trials aimed at treating a potential underlying pathology (insulin-like growth factor, antioxidant, acetyl-carnitine deficiency)[94-96] whereas the others targeted perpetuating factors. Two trials were of good-quality,[95,97] four fair-quality,[93,96,98,99] and one poor-quality[94] (Table H2). Trials evaluated different dietary approaches or supplements, distant healing, homeopathy, melatonin, and phototherapy. Most were conducted in Europe and all but one[97] of the trials were of small sample size (n<100). Five of the trials enrolled patients based on the CDC (Fukuda, 1994) criteria and two of the trials used the Oxford (Sharpe, 1991) criteria. Major limitations of studies include inadequate or unclear randomization,[94,99] enrolling fewer than 20 subjects in an arm,[93,94] high loss to followup,[93] lack of intention-to-treat analysis of outcomes,[93,98,99] unclear or inadequate blinding,[93,96,99] and groups not similar at baseline.[95] Trials were either funded by foundations or trusts,[97-99] pharmaceutical companies (fully or in part),[95,96] or the funding source was not reported.[93,94]

The evidence on CAM interventions was insufficient to draw conclusions as interventions included only single trials, were of small sample size, and most had significant methodological limitations. Two fair-quality trials, one with homeopathy and one with L-carnitine preparations, found improvement in some measure of fatigue and/or function, with no differences found in other measures. All other trials of CAM interventions found no significant improvements compared with placebo, usual care, or an alternative CAM approach. Adherence was low in one trial of a low sugar/low yeast diet but otherwise adherence and harms were not well reported.

One good-quality trial (n=57) compared Acclydine©, a combination of amino acids and a food supplement derived from the plant *Solanum dulcamara* proposed to increase biologically active insulin-like growth factor (IGF-1), with an identical placebo.[95] Patients were identified based on the CDC (Fukuda, 1994) criteria and followed over 14 weeks for measures of fatigue and function. Although adherence was not reported, they found no differences in fatigue severity based on the CIS fatigue severity subscale questionnaire (1.1; 95% CI, -4.4 to 6.5) or self assessed daily fatigue level (-0.2; 95% CI, -1.2 to 0.9). They also found no difference in function based on the SIP-8 (59.1; 95% CI, -201.7 to 319.8), and physical activity measured with an actometer motion-sensing device (4.1; 95% CI, -5.9 to 14.0).[95] Of note, they also found no difference in IGF-1 blood levels between groups. Attrition was low and no harms were reported.

One fair-quality study (n=89) compared acetyl-L-carnitine (2 g/day) with propionyl-L-carnitine (2 g/day) and with a combination of both.[96] Patients were eligible based on CDC (Fukuda, 1994) criteria and outcomes included CGI and MFI-20 comparing scores 8 weeks prior to intervention and after 24 weeks of treatment. They had 20 percent attrition (18 of 90 enrolled) and did not report adherence but found improvement in CGI for acetyl-l-carnitine (59%) and propionyl-L-carnitine (63%) and not for the combination therapy (37%). For the secondary outcomes of fatigue, propionyl-L-carnitine and the combination therapy showed a reduction on the 20-point general fatigue axis (from 18.4 SD 1.8 to 16.5 SD 3.1, and from 19.1 SD 1.4 to 17.3 SD 3.3, respectively), whereas acetyl-L-carnitine showed a reduction on the 20-point mental fatigue axis (from 16.3 SD 2.5 to 13.9 SD 3.5). No differences were found on the physical fatigue axis. Patients reported sleeplessness and feeling overstimulated although withdrawal due to harms were similar between groups. Although statistical improvement was found on several measures, the evidence leaves no clear indication as to whether one formulation was truly

superior to another or whether the differences were by chance alone, and the clinical meaningfulness remains uncertain given the small incremental change that occurred.

A poor-quality crossover trial randomized patients to an extract of pollen (antioxidant) or placebo for 3 months followed by a 2-week washout and then to the pollen extract or placebo for an additional 3 months resulting in five people in placebo/pollen extract arm, five people in pollen extract/placebo arm, six people in placebo/placebo arm, and six people in pollen extract/pollen extract arm. They measured total well-being, fatigue, and fatigability on a 10-point Likert scale (0 =no problem and 10=serious symptoms).[94] They found no difference in any of their measures but did note that in the pollen extract group, 62 percent (13 of 21) reported general improvement compared with 23 percent (5 of 22) in the placebo group. Adherence was not reported and no serious harms were noted.

A small fair-quality trial (n=86), randomized patients diagnosed with CFS based on the Oxford (Sharpe, 1991) criteria to homeopathy or placebo.[98] Homeopathic prescriptions included different single or multiple remedies prescribed at each consultation over a 6-month period and found improvement on the general fatigue subscale of the MFI-20 (mean change 2.70, SD 3.93 vs. 1.35, SD 2.66, p=0.04) but no difference on other dimensions or on the Fatigue Impact Scale and in the proportion of patients clinically improving (a change from baseline of 15% on MFI-20 subscales). They did report improvement on the physical dimension subscale of the Functional Limitations Profile (FLP) with a mean change of 5.11 (SD 8.82) compared with 2.72 (SD 8.40) in the placebo arm. Attrition was similar between groups (overall 11 of 103, 11%) and neither adherence nor harms were reported. Although some improvement was noted in some measures of fatigue, the lack of specificity in the treatment received, the inconsistencies in results measuring the same outcome, and methodological issues, leave uncertainty regarding any potential benefit.

One small (n=39) fair-quality trial compared a low sugar/low yeast diet with healthy eating in a group of primarily female patients (88%) diagnosed with ME/CFS using the CDC (Fukuda, 1994) criteria.[93] The low sugar/low yeast diet involved omission of all sugar containing foods, refined carbohydrates, yeast containing foods, alcohol, and caffeine with a limited consumption of fruit and milk except a daily yogurt. Those randomized to the healthy eating approach were advised to consume a high fiber diet with five servings of fruit and vegetables per day, two servings of fish per week, and reduced fat and refined carbohydrate. Patients were followed for 24 weeks for outcomes of fatigue and quality of life. They found no difference in either outcome based on the Chalder Fatigue Scale and the SF-36 but did note high loss to followup (25%, which were not included in analysis) and low adherence (24% in the low sugar/low yeast group vs. 67% in the healthy eating group).

A large good-quality trial (n=409) randomized patients to distant healing versus usual care (waiting) and used the CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) criteria for inclusion.[97] The median duration of illness ranged from 9.6 to 11.9 years. This study measured adherence of the healers who were from 21 European countries with a mean healing experience of 9.7 years (SD 7.9 years) and replaced those not complying with the study design (34 of 462, 7%). In addition to other outcomes not included in this report, this study considered the Physical Health Component Summary score of the SF-36 and found no differences (1.11; 95% CI, -0.255 to 2.473). Although there was no interaction effect for treatment and blinding (p=0.32), patients who knew they were not being treated had much lower scores at followup (mean difference between groups: -1.544; 95% CI, -2.913 to -0.176).[97]

A final fair-quality crossover study compared melatonin with phototherapy.[99] Thirty patients identified using the Oxford (Sharpe, 1991) criteria were given placebo initially for 12 weeks followed by melatonin (5 mg every evening) or phototherapy (2500 Lux for 1 hour in the morning). This was followed by a 12-week washout (phototherapy group) or placebo (melatonin group) and then a crossover to the reverse schedule.[99] They reported no differences on a 10-point VAS of fatigue, the Mental Fatigue Inventory, or the SF-36 physical functioning dimension.

In summary, there is insufficient evidence to determine the effectiveness or harms of CAM interventions due to finding only small single studies with methodological limitations.

Table 4. Trials of complementary and alternative medicine therapies for ME/CFS

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Hobday, et al., 2008[93] N=39 Fair	CDC (Fukuda, 1994) criteria	6 months (24 weeks)	A. Low sugar/low yeast B. Healthy eating	**Fatigue outcomes:** Chalder Fatigue Scale scores: NS SF-36 vitality subscale scores: NS **Function outcomes:** SF-36 physical functioning subscale scores: NS
Ockerman, 2000[94] N=22 Poor	CDC (Fukuda, 1994) criteria	3 months	A. Pollen: Antioxidant extract of pollen (Polbax) B. Placebo	**Fatigue outcomes:** Fatigue scores improved in the pollen group on the Likert at 3 months: -0.43 vs. -0.18; p<0.05 **Quality of life outcomes:** Total well-being scores lower in the placebo group at 3 months: 7.14 vs. 6.66; p=NR Change from baseline in the pollen group vs. placebo: -1.66 vs. -0.21; p<0.01 Change in total well-being after treatment: p=NR Worse: 9.5% (2/21) vs. 18% (4/22) No change: 29% (6/21) vs. 59% (13/22) Better: 62% (13/21) vs. 23% (5/22)
The, et al., 2007[95] N=57 Good	CDC (Fukuda, 1994) criteria	3.5 months (14 weeks)	A. Acclydine B. Placebo	**Fatigue outcomes:** CIS fatigue severity scores: NS **Function outcomes:** SIP-8 scores: NS **Other outcomes:** Physical activity level over a 12-day period: NS
Vermeulen and Scholte, 2004[96] N=89 Fair	CDC (Fukuda, 1994) criteria	6 months (24 weeks)	A. Acetyl-L-carnitine (ALC) B. Propionyl-L-carnitine (PLC) C. Combination, Acetyl-L-carnitine 2 g/day + propionyl-L-carnitine 2 g/day (combo)	**Fatigue outcomes:** General fatigue scores better in ALC group based on MFI-20 scores at 24 weeks, mean (SD): 15.9 (4.2) vs. 16.5 (3.1) vs. 17.3 (3.3) However, both other interventions improved more from baseline: p=0.004 for PLC change from baseline; p=0.000 for combo change from baseline Mental fatigue at 24 weeks: 15.1 (3.6) vs. 13.9 (3.5) vs. 14.6 (4.0); p=0.015 for ALC change from baseline **Other outcomes:** % Improved from baseline was higher in the PLC group on CGI at 24 weeks: 59% (17/29) vs. 63% (16/unclear) vs. 37% (11/30)

Table 4. Trials of complementary and alternative medicine therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Walach, et al., 2008[97] N=409 Good	CDC (Fukuda, 1994) criteria	6 months treatment Followup to 18 months	A. Distant healing B. Usual care	**Function outcomes:** SF-36 physical functioning: NS SF-36 physical functioning subscale: NS Covariance analysis effect for blinded vs. unblinded treatment, 95% CI : -1.54 (SE 0.70) -2.91 to -0.18
Weatherly-Jones, et al., 2004[98] N=86 Fair	Oxford (Sharpe, 1991) criteria	6 months	A. Homeopathy B. Placebo	**Fatigue outcomes:** General fatigue scores better in placebo group on MFI-20 scores at 6 months, mean (SD): 2.70 (3.93) vs. 1.35 (2.66), p=0.04 Physical fatigue: NS Mental fatigue: NS FIS Cognitive dimension: NS FIS Physical dimension: NS FIS Social dimension: NS **Function outcomes:** Functional Limitations Profile scores: NS
Williams, et al., 2002[99]N=30 Fair	Oxford (Sharpe, 1991) criteria	12 months (12 weeks treatment, 12 week washout, then 12 week crossover and 12 week washout)	A. Melatonin B. Phototherapy	**Fatigue outcomes:** (IQR) VAS score: NS Mental Fatigue Inventory scores: NS (IQR) SF-36 vitality subscale scores: NS **Function outcomes:** (IQR) SF-36 physical functioning subscale scores: NS

Abbreviations: ACL = Acetyl-L-carnitine; CDC= Centers for Disease Control and Prevention; CGI= Clinical Global Impression change score; CI= confidence interval; CIS= Checklist of Individual Strength; FIS= Fatigue Impact Scale; g= gram; IQR= interquartile range; MFI-20= Multidimensional Fatigue Inventory 20-Item; N= sample size; NR= not reported; NS= not significant; PCL= Propionyl-L-carnitine; SD= standard deviation; SE= standard error; SF-36= 36-item Short Form Survey; SIP-8= Sickness Impact Profile 8-Item; VAS= visual analog scale; vs.= versus.

Counseling and Behavior Therapies

Fourteen trials (23 publications) comparing one counseling or behavioral therapy with usual care, wait list control, no treatment, relaxation techniques only, adaptive pacing, anaerobic therapy, GET, or an alternate form of counseling or behavioral therapy met inclusion criteria.[100-121] Eleven trials (16 publications) included only counseling and behavior therapies as the active intervention compared with a control group[100,102-104,107,109,110,112-120] and two trials (6 publications) included an exercise group as a comparison group, in addition to a control group.[105,106,108,121-123] The results that pertain to the comparisons between the counseling or behavior therapy and "control" groups (defined as wait list, no treatment, usual care, support, relaxation, and adaptive pacing) on outcomes will be discussed in this section (Table 5 below; Table G4); results based on comparisons with exercise programs or GET will be discussed in the Exercise Program section below. One trial compared face-to-face cognitive behavioral therapy (CBT) with telephone CBT and did not include a control group.[101] All trials were designed to target symptoms of ME/CFS, not treat the underlying cause. Five trials were rated good-quality,[113,114,116,118,121] six fair-quality,[100-102,108,109,112] and three poor-quality[104,107,110] (Table H2). Most of the trials (64%) were of small sample size (n<100), predominately enrolled females (54 to 100%), with mean ages ranging from 31 to 58 years, and the duration of illness ranged from 6 months to 52 years. Half of the trials used the CDC (Fukuda, 1994) criteria to identify people with ME/CFS, while others used the Oxford (Sharpe, 1991) criteria, one developed by Schluederberg in 1992, and one study instead used a combination of a CFS questionnaire, psychiatric assessment, and medical assessment to rule out other conditions and diagnose ME/CFS.[108]

Five used cognitive and CFS specific techniques,[100,108,112,113,121] one used CBT techniques focused on activity,[102] one used traditional CBT techniques aimed at a CFS population delivered either over the phone or face-to-face,[101] and one used relaxation, didactic discussion, and cognitive techniques for CFS.[110] Three of the interventions were conducted in group formats[100,110,112] instead of individual. Three good-quality,[114,116,118] one fair-quality,[109] and two poor-quality[104,107] trials evaluated other counseling techniques, which included guided self-instruction programs, group illness management instruction, pragmatic rehabilitation, peer-to-peer counseling, and symptom consultation.

The largest trial was the PACE trial, a 12 month good-quality 4-arm trial that included a comparison of CBT (n=155) with adaptive pacing (n=159), and usual care (n=157). This trial measured outcomes of fatigue (Chalder Fatigue Scale), function (SF-36 physical function subscale), clinical global impression of change, and work impairment (work and social adjustment scale).[121] The GET arm is discussed in the Exercise Therapies and Head-to-Head/Comparison Trials Sections. Patients were selected from multiple specialty care centers in the United Kingdom and were eligible based on the Oxford (Sharpe, 1991) criteria for CFS as well as a Chalder fatigue score of 6 or greater (of possible 11) and SF-36 score of 60 or less (of possible 100), which was subsequently changed to 65 or less to increase enrollment. CBT was based on the fear avoidance theory of ME/CFS that regards symptoms as being "reversible and that cognitive responses (fear of engaging in activity) and behavioral responses (avoidance of activity) are linked and interact with physiological processes to perpetuate fatigue."[121] CBT consisted of up to 14 individual sessions over 23 weeks, with a booster session at 36 weeks. The aim was to "change the behavioral and cognitive factors assumed to be responsible for perpetuation of the participant's symptoms and disability."[121] Strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity, by testing them in

behavioral experiments consisting of gradual increases in both physical and mental activity. Adaptive pacing consisted of a maximum of 15 sessions of therapy aimed at achieving optimum adaptation to the illness through activity pacing and advice to avoid activities that demand more than 70 percent of participant's perceived energy; therapy was delivered by occupational therapists. Usual care was provided by physicians specializing in ME/CFS. In other studies, CBT and adaptive pacing had similar aims and strategies. Pragmatic rehabilitation was also based on a physiological dysregulation theory of ME/CFS with patients and therapists collaboratively setting goals for activity, sleep, and cognitive function.[118] Counseling and supportive listening were empathic and nondirective in nature.

Adherence was not reported in eight of the trials,[100,102,104,107,109,110,116,121] one trial only reported that the adherence was "good,"[114] while another trial stated that all completed CBT.[113] One trial reported that 28 percent of participants did not receive their intended treatment.[101] One trial reported that the participants completed an average of 10 out of 13 counseling sessions, but no other information,[108] and two trials reported contamination, not specifically adherence (6% in the CBT group received support, while 8% in the support group received CBT[112] and 3% in the counseling group received support, while 1% in the support group received pragmatic rehabilitation and 10% in the support group did not receive any treatment).[118] Attrition was reported in most trials and was generally low (<20%) and similar between groups. Three trials reported high or differential attrition; two trials were in group settings, but reported opposite information, with higher attrition in group CBT compared with control (14% vs. 20%)[110] in one trial and higher attrition in the usual care group compared with group CBT (14% vs. 25%) in the other trial.[112] The third trial reported higher attrition in the telephone CBT group compared with the face-to-face CBT group, but both were high (56% vs. 34%).[101] One trial conducted a stepped care approach, providing participants with a self-instruction program to follow for 16 weeks or delayed care followed by CBT; this study found that after 16 weeks, 57 percent of those in the self-instruction group and 22 percent in the delayed group did not want to continue on to CBT, and therefore dropped out of the study.[115] Major limitations of these trials included enrolling fewer than 20 subjects in an arm,[107] high loss to followup,[101] unclear if use of intention-to-treat analysis,[104,107,108,110] unclear randomization or allocation process,[100,104,107,108,110,114] more men allocated to the intervention group,[112] and lack of or unclear information about blinding of the outcome assessor.[100,101,104,108,109,113,114,116] Due to the nature of the interventions, most trials could not blind patients or care providers. Trials were either funded by government or organizational grants (fully or in part)[100,104,107,108,110,112-114,116,118,121] or the funding source was not reported.[101,109]

There is low strength evidence, based on 14 trials, that CBT, either group or individual; self-instruction booklets; pragmatic rehabilitation; peer-to-peer counseling; and symptom consultation provide improvement in fatigue, function, quality of life, and employment in adult patients with ME/CFS. When comparing any type of counseling or behavioral therapy to no treatment, support, relaxation, or adaptive pacing there is low strength of evidence that counseling decreases fatigue (7 of 11 trials showed positive effect) and improves functioning measures (4 of 11 trials showed positive effect; 2 of 11 showed mixed results on measures), quality of life (2 of 4 trials showed positive effect), and global improvement (2 of 2 trials showed positive effect). Harms of counseling and behavioral therapies were poorly reported, but there is low strength of evidence that CBT is not associated with harms based on one moderate-sized trial.

Function Outcomes

Eleven trials (n=1,720) of counseling techniques compared with no treatment, support, relaxation, or adaptive pacing, reported overall functioning measured by the SF-36 physical functioning subscale, KPS, SIP-8, and the functional impairment scale.[100,102,104,107-109,112,113,115,118,121] Results were mainly positive, but mixed. In four trials[102,108,113,121] counseling improved overall functioning compared with controls on various measures, while two trials reported mixed results using different measures in the same study,[109,112] one trial reported improvement in the control group compared with counseling,[100] and the other four trials reported no differences between groups.[104,107,115,118]

Eight trials used the SF-36 physical functioning subscale to measure overall functioning[102,107-109,112,115,118,121] and results were mixed. Four trials[102,108,109,121] reported significantly more improvement in the CBT group compared with controls (71% vs. 49% improved by ≥8 points from baseline at 1 year, p=0.0068[121] and 63% vs. 17% with a score >83 at 6 months followup, p<0.001[102]) or better scores (mean scores of 58.64 vs. 39.72 at 1 year, p<0.01[108] and mean scores of 65.9 vs. 60.2 at about 6-12 months, p=0.011[109]). However, by 5 years in one trial the results were no longer significantly different,[103] and in another trial on the SIP-8 the outcome was reversed with worse functioning reported in the self-instruction group compared with the wait list control (mean scores of 1,515 vs. 1,319, p<0.001).[109] The other four trials reported no differences between the counseling group and controls.[107,112,115,118] However, one trial also measured functioning using a walking speed test and found improved walking speed in the CBT group compared with controls (difference from baseline to 12 months for CBT vs. support: 1.77; 95% CI, 0.025 to 3.51; p=0.0055 and difference from baseline to 12 months for CBT vs. no intervention: 2.83; 95% CI, 1.12 to 5.53; p=0.0055).[112] Another trial conducted a post hoc analysis on those with baseline functional disability (defined as SF-36 physical functioning baseline score ≤70) and reported a significant improvement in the self-instruction group compared with the wait list control (mean change from baseline CBT vs. control: 9.05; 95% CI, 0.2 to 17.9; p<0.05).[115] When trials using the SF-36 physical functioning subscale were pooled there was a significant effect for the intervention group to have better scores compared with controls at followup; weighted mean difference of 7.73 (95% CI, 3.58 to 11.87, Figure 3). Even when one outlier that showed a more significant difference than the other trials[102,103] was removed the difference was still significant with a weighted mean difference of 7.18 (95% CI, 4.53 to 9.83). However, when the analysis was limited to the four trials that used formal CFS specific CBT techniques, though the result was similar, the difference was no longer significant owing to the wide CI (weighted mean difference of 9.12, 95% CI, -3.10 to 21.35, p=0.14, I^2=69%).[102,108,112,121]

One trial used the KPS to measure overall functioning[113] and reported significantly more improvement in the CBT group compared with controls (73% vs. 23% improved by ≥10 point at 12 months; difference of 50% CBT vs. no intervention; 95% CI, 28 to 72%).

One trial only used the SIP-8 to measure overall functioning[100] and reported worse functional impairment in the CBT group compared with the wait list control (mean change from baseline at 6 months: 29 vs. -293; p=0.004). Along with the other outcomes reported above, the SIP-8 showed mixed results. One trial only used the functional impairment scale to measure overall functioning and found no differences between counseling and the wait list control at 6 months followup.[104]

The PACE trial performed a sensitivity analysis for those patients who fulfilled the CDC (Reeves, 2003) criteria for CFS (n=321) and for those patients who fulfilled the London

(Dowsett, 1994) criteria for ME (n=245) at baseline and found similar results for the outcomes of function; however, primary data were not provided.[121-123]

Fatigue Outcomes

Eleven trials (n=1,691) of counseling compared with no treatment, support, relaxation, or adaptive pacing, reported decreased fatigue measured by the Chalder Fatigue Scale, FSS, CIS, POMS-fatigue, Profile of fatigue-related symptoms scale, and the SF-36 vitality subscale.[100,102,104,107-110,112,115,118,121] Results were primarily positive, but mixed. In seven trials counseling significantly decreased fatigue compared with controls on various measures,[102,104,107,109,112,115,116,121] while the other four trials showed no differences between groups.[100,108,110,118]

Four trials used the Chalder Fatigue Scale to measure fatigue[102,112,118,121] and results were primarily positive. Three trials reported significantly more decreases in fatigue in the counseling group compared with the controls (63% vs. 15% were non-cases of fatigue with a score <4 at 6 months; p=0.001[102]) or better scores (difference in scores from baseline at 1 year for CBT vs. support: -3.16; 95% CI, -5.59 to -0.74; p=0.011 and CBT vs. no intervention: -2.61; 95% CI, -4.92 to -0.30; p=0.027[112] and at 52 weeks for CBT vs. no intervention: -3.4; 95% CI, -5.0 to -1.8; p=0.0001[121]). However, by 5 years in one trial the results were no longer significantly different.[103] The other trial that used the Chalder Fatigue Scale reported statistically significantly better fatigues scores in the pragmatic rehabilitation group than the usual care group (treatment effect estimate of -1.18; 95% CI, -2.18 to -0.18; p=0.021), but by 70 weeks there were no differences.[118] Due to the variability in how the Chalder Fatigue Scale was used across studies, these results could not be pooled.

Three trials used the CIS to measure fatigue[100,109,115] and results were primarily positive. Two trials reported significantly less fatigue in the counseling groups compared with the controls (27% vs. 7% improved at about 6 to 12 months; OR 4.9; 95% CI, 1.9 to 12.9; p<0.001,[109] and 33% vs. 9% at 6 months; OR 5.0; 95% CI, 1.69 to 14.57;[116] both used a reliable change score of >1.64 and final score of ≤36 to indicated improved). Only one non randomized trial found no differences between groups at 6 months.[100]

Two trials used the FSS to measure fatigue[107,108] and both found significantly lower fatigue scores in the counseling groups compared with the controls (mean scores of 52.9 vs. 59.4 at 4 months; p=0.04[107] and mean scores of 5.37 vs. 5.62 at 1 year, but p value not reported[108]). One trial conducted post hoc analyses and compared fatigue and functioning outcomes based on homework compliance.[105] Homework included assignments such as of readings, sleep diaries, and activity diaries, and at home practices such as activity goals, relaxation exercises, and use of coping skills. They identified three groups based on the amount of homework completed; minimum compliance completed 0 to 25 percent, moderate compliance completed 25.1 to 75 percent, and maximum compliance completed 75.1 to 100 percent of their assigned homework. When they assigned individuals to groups they noted that the highest percentage in the maximum group (56%) were in the cognitive therapy group, the highest percentage in the moderate group (34%) were in the CBT group, and the highest percentage in the minimum group (38%) were in the anaerobic and relaxation groups. At 12 months, though there was a trend toward decreased fatigue and better improvement in functioning scores for the maximum compliance group compared with the other groups, this trend did not reach significance.

One trial used only the Profile of fatigue-related symptoms scale to measure fatigue[104] and reported better scores in the counseling group compared with the wait list control (mean scores

of 2.68 vs. 3.84 at 6 months; p=00.04), while one trial reported no differences in fatigue scores using the POMS.[110]

The PACE trial performed a sensitivity analysis for those patients who fulfilled the CDC (Reeves, 2003) criteria for CFS (n=321) and for those patients who fulfilled the London (Dowsett, 1994) criteria for ME (n=245) at baseline and found similar results for the outcome of decreased fatigue, but primary data were not provided.[121-123]

Quality of Life Outcomes

Four trials (n=372) of counseling compared with no treatment, support, or relaxation, reported quality of life measured by the QOLI, QLI, QLS, EuroQol, and the health utilities index.[108,110,112,114] Results were mixed, but primarily positive. Two trials reported better scores in the counseling group compared with controls (mean QOLI scores at 12 weeks: 2.81 vs. 3.26; p=0.02[110] and mean change in QLI scores from baseline at 12 months: 2.6 vs. 0.6; p<0.05[114]), one trial[108] reported slightly better scores on the QLI in the cognitive group compared with CBT and controls at 1 year, but the p value was not reported (69.10 for CBT vs. 72.52 for cognitive vs. 63.00 for anaerobic activity vs. 72.00 for relaxation), and the fourth study reported no differences between groups.[112]

Employment Outcomes

Four trials (n=869) of counseling compared with no treatment, support, relaxation, or adaptive pacing reported employment outcomes including proportion working full- or part-time, hours worked per week, and level of work impairment measured by the Work and Social Adjustment Scale.[100,102,103,108,121] Results were primarily positive. Both trials measuring work impairment with the Work and Social Adjustment Scale reported significantly better scores for the CBT group compared with controls (mean scores of 3.3 vs. 5.4 at 6 months; p<0.001 on scale scored with range 0 to 8;[102] mean scores of 21.0 vs. 24.5 at 1 year; p=0.0001 on scale scored with range 0 to 45[121]). Two trials reported the number of hours per week individuals were working. One trial reported significantly more hours worked per week, of those working, for the CBT group compared with relaxation (mean hours of 35.57 vs. 24.00 at 5 years; p<0.04)[103] and the other trial reported no differences between groups.[100] Two trials reported no differences in the proportion of individuals working full- or part-time at 1 year[108] or 5 years.[103]

Global Impression of Improvement Outcomes

Two trials (n=690) of counseling compared with no treatment, relaxation, or adaptive pacing reported global improvement using the CGI, spontaneous reporting of fully recovered or feeling much better, relapses, full recovery, and no longer meeting ME/CFS criteria.[102,103,121] Significantly more individuals in the CBT group reported improvement compared with controls in both trials (70% vs. 31%; p<0.01[102] and 41% vs. 31%; p=0.013[121]). One trial[103] also followed up 5 years after counseling and continued to report more improvement in the CBT group compared with relaxation (68% vs. 43% with symptoms “steadily improved” not “consistently absent’ or “mild”; p=0.05; 24% vs. 4% with complete recovery; p=0.04; 36% vs. 7% with no relapses; p=0.02; and mean number of relapses of 2.58 vs. 4.08; p<0.01); however, there was no difference in the number of individuals currently meeting the Oxford (Sharpe, 1991) criteria for ME/CFS (52% vs. 39%; p=0.42).

Recovery Outcomes

The PACE trial considered the outcome of recovery (trial recovery was defined as: within the normal range in fatigue [Chalder Fatigue Scale score <18] and physical function scales [SF-36 physical function subscale score ≥60], no longer meeting Oxford [Sharpe, 1991] criteria, and reporting much or very much improvement on the CGI scale; clinical recovery was defined as: meeting all criteria for trial recovery plus no longer meeting the London [Sharpe, 1991] or the CDC [Reeves, 2003] criteria).[121] Although trial recovery remained low for all treatment arms (<25%), they found CBT to be superior to adaptive pacing therapy (OR 3.36; 95% CI, 1.64 to 6.88) and usual care (OR 3.69; 95% CI, 1.77 to 7.69), with similar results for clinical recovery. Although the PACE trial has performed measures to minimize risk of bias and is one of the best available in the ME/CFS literature given its size and methodology, there are limitations. Although blinding patients and providers to the intervention was not feasible, and statisticians were blinded, the study may be open to risk of observer bias by not blinding researchers assessing outcomes. They did, however use self-reported outcome measures to reduce the risk of observer bias, which are valid tools for measuring the outcomes of interest. The study may also be at risk of attention bias given the total number of visits by participants were greater in the CBT (17) and adaptive pacing (16) groups compared with the usual care group (5). The nature of the approach to CBT, using providers and training manuals that teach patients that the treatment is effective, can cause an expectation bias in the direction of improvement. Additionally, there are reservations about the interpretation of the recovery results. Given that a score of 65 or less on the SF-36 physical functioning scale was defined as disability for entry into the trial, using a score of 60 or greater on the same scale to define recovery is contradictory. The authors reportedly derived their threshold for recovery based on the mean score for a normal adult minus two SDs (84 to 16). Furthermore, they defined deterioration as greater than a 20 point reduction in the SF-36, yet they defined improvement as an increase of 8 point or more. These threshold values likely favor results in the direction of improvement. For fatigue outcomes they considered recovery as a Chalder Fatigue Scale score less than 18 yet other studies have considered a score of less than 4 to indicate a return to normal.[118] Finally, although statistically significant changes were noted, the meaningfulness of these change remains uncertain. For instance, the mean score of the SF-36 physical function score remained at or above 60 (used in the definition of trial recovery) for all groups, while the 6-minute walk test was much less than for normal older adults (379 meters vs. 631 meters).[124]

Face-to-Face Versus Telephone CBT

One fair-quality trial (n=80) compared face-to-face CBT with telephone CBT, without using a control group,[101] followed them for 12 months, and measured fatigue using the Chalder Fatigue Scale, functioning using the SF-36 physical functioning subscale, work impairment using the Work and Social Adjustment scale, and overall improvement using a self-rated global improvement Likert style scale, similar to the CGI scale (ranging from very much worse to very much better). There were no significant differences between groups on any of the outcomes at any time point. Both groups showed significant improvement at 12 months after the end of treatment from baseline on the SF-36 physical functioning subscale and the Work and Social Adjustment scale, and the majority of participants rated themselves as much better or very much better on the self-rated global improvement scale (56%).

Harms Outcomes

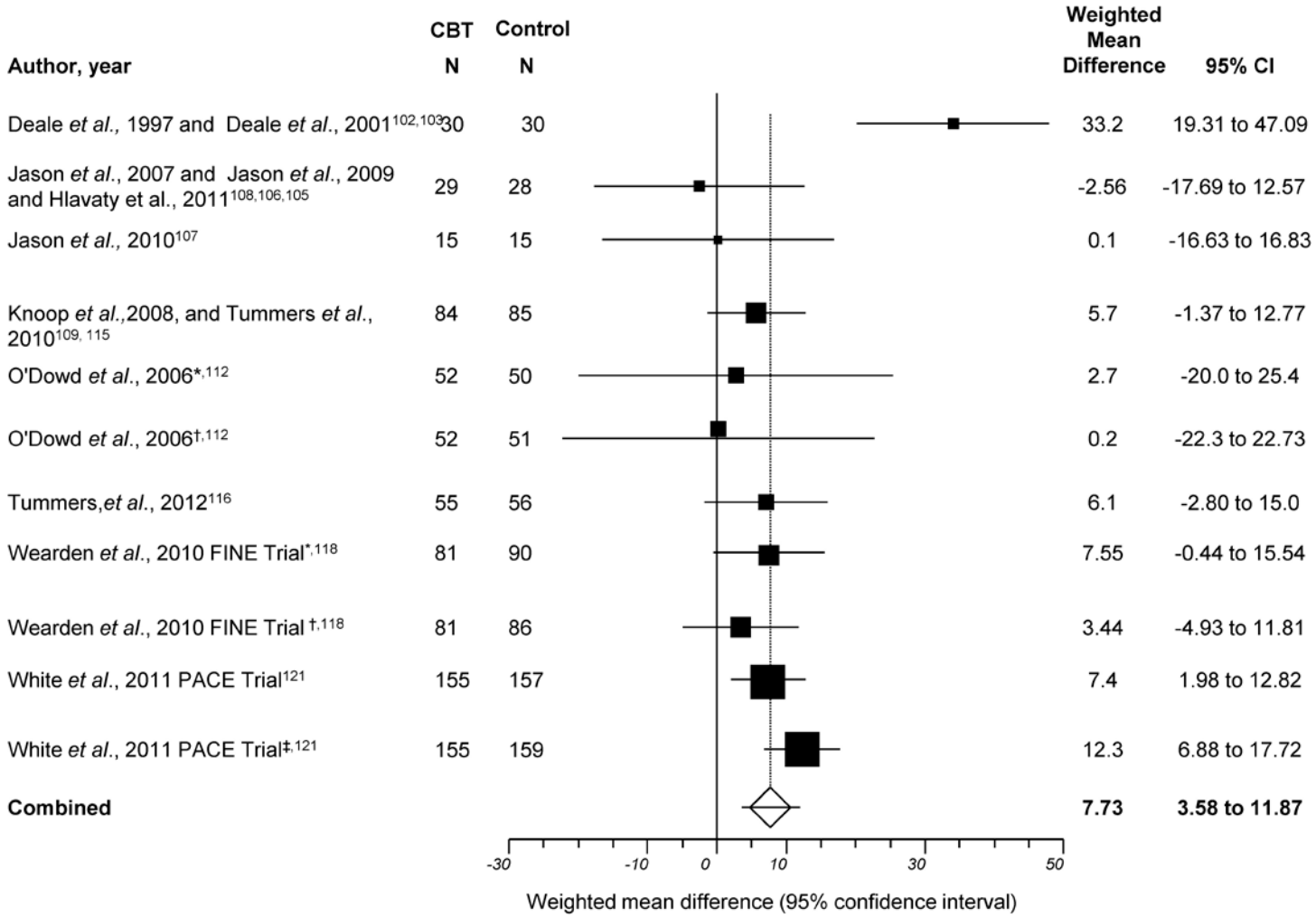
Only three good-quality trials reported anything about harms after counseling or behavior therapies. The PACE trial specifically defined adverse events as "any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatment" and serious adverse events as "an event that resulted in one of the following outcomes: a) death, b) threat to life (i.e., an immediate, not hypothetical, risk of death at the time of the event), c) required hospitalization except for elective treatment of a pre-existing condition, d) increased severity and persistent disability, defined as: (i) severe, i.e. significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound); and (ii) symptom and disability persistent, i.e. of at least 4 weeks continuous duration, e) any other important medical condition which, though not included in the above, might require medical or surgical intervention to prevent one of the outcomes listed, and f) any episode of deliberate self-harm." [122] All serious adverse events were further analyzed after breaking blinding to determine whether the event was related to the intervention, which were deemed serious adverse reactions. Nonserious adverse events were reported often, however the CBT group reported significantly less (848) than both the adaptive pacing group (949, p=0.0081) and usual care group (977, p=0.0016).[121] Although serious adverse events were uncommon, there were more reported in the adaptive pacing group (16) than the CBT group (8) or the usual care group (7), and there were more serious adverse reactions in the CBT group (4) compared with the adaptive pacing (2) or the usual care group (2). No one withdrew from CBT due to worsening. There was a significant difference in deterioration of physical function across treatment arms (adaptive pacing 25% vs. usual care 18% vs. CBT 9%, p<0.001), but no differences in serious deterioration defined by a composite score of reduced function, worsening clinical global impression, withdrawal rates, and serious adverse reactions.[121,122]

One small trial (n=47) reported none withdrew due to harms[114] and a moderate-sized trial (n=257) reported no differences between groups for reported harms or withdrawals due to harms,[118] but no other information was provide about harms.

Summary of Counseling and Behavior Therapy Trials

In summary, there is moderate strength of evidence that counseling techniques was associated with global improvement (41 to 70% vs. 25 to 31%), and low strength of evidence that counseling techniques improved overall functioning (SF-36 physical function weighted mean difference 7.73; 95% CI, 3.58 to 11.87), fatigue (27 to 76% vs. 7 to 65%), and employment outcomes in ME/CFS patients. The effects may not be generalizable to a more disabled population as no study used a case definition for ME and only one study analyzed patients fulfilling the London ME (Dowsett, 1994) case definition and may have been underpowered to detect a difference.[121] Whether these effects can be sustained is uncertain as benefit was no longer seen in one trial that evaluated patients 5 years later. In addition, trials used various measures to detect change making it difficult to compare results and few trials reported the clinical significance, if available, of the improvement in scores. Recovery has rarely been tested and measurements used to determine effectiveness may be overestimating the effect and not reflective of true recovery. Harms were rarely reported Only one large trial (n=630), the PACE trial, reported significantly less harms in the CBT group.

Figure 3. Meta-analysis of mean changes in SF-36 physical function subscale scores for CBT compared with controls



*Using support as the comparison
†Using usual care as the comparison
‡ Using adaptive pacing as the comparison
Abbreviations: CBT= cognitive behavioral therapy CI= confidence interval; N= sample size; SF-36= Short Form 36-item survey.

Table 5. Trials of counseling and behavioral therapies for ME/CFS

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Bazelmans, et al., 2005[100] Nonrandomized trial N=65 Fair	CDC (Fukuda, 1994)	6 months	A. Group CBT B. Wait list control	**Function:** Functional impairment improved in control group on SIP-8 at 6 months, mean change in scores from baseline: 29 vs. -293; p=0.004 **Fatigue:** CIS: NS **Employment:** Hours worked/week: NS **Harms:** Not reported
Burgess, et al., 2012[101] N=43 Fair	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria	12 months	A. Face-to-face B. Telephone	**Function:** SF-36 physical functioning subscale: NS for between groups; p=0.043 for change from baseline for both groups **Fatigue:** Chalder Fatigue Scale scores: NS **Employment:** Work and social adjustment scale scores: NS for between groups; p=0.013 for change from baseline for both groups **Other:** Global improvement score of “much better or very much better” at 6 and 12 months were higher in the face-to-face group: 60% (15/25) vs. 40% (8/20), 12 months: 57% (13/23) vs. 55% (11/20)’ p=NR **Harms:** Not reported

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Deale, et al., 1997[102] N=60 Deale, et al., 2001[103] N=53 Fair	Oxford (Sharpe, 1991) and United States (Schluederberg, 1992) criteria	Deale, 1997: 6 months Deale, 2001: 5 years	A. CBT B. Relaxation	**Function:** % With good outcome on SF-36 physical functioning subscale better in CBT group at 6 months: 63% (19/30) vs. 17% (5/30); difference of 46% (95% CI, 24 to 68), p<0.001 5 year followup: NS Functioning rating by assessor at 3 months as "better or much better" higher in CBT group: 80% (20/25) vs. 26% (6/23); p<0.001 **Fatigue:** Fatigue rating by assessor at 3 months as "better or much better" higher in the CBT group: 72% (18/25) vs. 17% (4/23); p<0.001 Non-cases of fatigue (score <4 on Chalder Fatigue Scale) at 6 months higher in the CBT group: 63% (17/27) vs. 15% (4/26); p=0.001 5 year followup: NS **Employment:** Work and social adjustment scale subscale scores better in CBT at 6 months, mean (SD): 3.3 (2.2) vs. 5.4 (1.8) p<0.001, between group differences over time Hours worked per week at 5 years was higher in CBT group, mean (SD): 35.57 (8.11) vs. 24.00 (4.97); p<0.04 % With full- or part-time employment at 5 year followup: NS **Other:** Global improvement rating "better or much better" higher in the CBT group at 6 months: 70% (19/27) vs. 31% (8/26); p<0.01 Global improvement rating "better or much better" higher in the CBT group at 5 years: 68% (17/25) vs. 36% (10/28); p=0.05 **Outcomes at 5 year followup:** Symptoms "steadily improved" not "consistently absent' or "mild" higher in the CBT group: 68% (17/25) vs. 43% (12/28); p=0.05 Complete recovery higher in the CBT group: 24% (6/25) vs. 4% (1/28); p=0.04 No relapses higher in the CBT group: 36% (9/25) vs. 7% (2/28); p=0.02 Fewer number of relapses in CBT group, mean (SD): 2.58 (2.21) vs. 4.08 (1.55); p<0.01 No longer meeting U.K criteria for CFS: 52% (13/25) vs. 39% (11/28); p=NS **Harms:** Not reported
Goudsmit, et al., 2009[104] N=44 Poor	Oxford (Sharpe, 1991) criteria	6 months	A. Counseling B. Wait list	**Function:** Functional impairment scale scores: NS **Fatigue:** Profile of fatigue-related symptoms scale scores better in counseling group at 6 months, mean (SD): 2.68 (1.41) vs. 3.84 (1.40); p=0.04 **Harms:** Not reported

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Jason, et al., 2007[108] Jason, et al., 2009[106] Hlavaty, et al., 2011[105] N=114 Fair Same study as on Table 7	CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment	12 months	A. CBT B. COG C. ACT D. Relaxation	**Function:** Functional scores better in CBT, COG, and relaxation group than ACT on SF-36 physical functioning subscale scores at 12 months, mean (SD): 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70) p<0.01, for CBT and COG over time vs. ACT over time Comparison by energy envelope for those who stayed within envelope vs. outside envelope at 12 months: 65 vs. 43, change at 12 months from baseline: 17 vs. 0; p=0.03 Comparison by homework compliance level, change in score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR % Achieving clinically significant improvement: NS **Fatigue:** Fatigue scores better in CBT group for FSS scores at 12 months, mean (SD): 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR Comparison by energy envelope for those who stayed within envelope vs. outside envelope at 12 months was 5.3 vs. 6.3 Change at 12 months from baseline: -0.9 vs. 0.1; p<0.01 The comparison by homework compliance level, change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR **Quality of life:** Quality of life slightly better in COG group based on QLS scores at 12 months mean (SD): 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR **Employment:** % Employed at 12 month followup: NS **Harms:** Not reported
Jason, et al., 2010[107] N=30 Poor	CDC (Fukuda, 1994) criteria	4 months	A. Buddy counseling B. Control, no treatment for 4 months	**Function:** SF-36 physical functioning subscale: NS **Fatigue:** FSS scores better in buddy counseling group at 4 months, mean (SD): 52.9 (10.5) vs. 59.4 (3.7); p=0.04 SF-36 vitality subscale scores better in buddy counseling group at 4 months, mean (SD): 29.3 (13.9) vs. 24.7 (9.7); p<0.05 **Harms:** Not reported

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Knoop, et al., 2008[109] Tummers, et al., 2010[115] N=169 Fair	CDC (Fukuda, 1994) criteria	6-12 months depending on length of treatment	A. Self-instruction B. Wait list control Tummers, 2010 A. Stepped care B. Usual care	**Function (Knoop):** SF-36 physical functioning subscale better in self-instruction group at second assessment, mean (SD): 65.9 (23.2) vs. 60.2 (23.7); p=0.011 Functional impairment SIP-8 scores worse in self-instruction group at second assessment, mean (SD): 1,515 (545) vs. 1,319 (619); p<0.001 *Tummers, 2010 additional stepped care vs. usual care analysis* **Fatigue (Knoop):** CIS fatigue severity scores better in self-instruction group at second assessment, mean (SD): 38.9 (12.1) vs. 46.4 (8.7); p<0.001 % With reduction in CIS fatigue severity scores higher in self-instruction group: 27% (23/84; 95% CI 18 to 37) vs. 7% (6/85; 95% CI 2 to 13); OR 4.9 (95% CI, 1.9 to 12.9); p<0.001 **Function:** SF-36 physical functioning subscale: NS **Fatigue:** CIS fatigue severity scores: NR % With reduction in CIS fatigue severity scores: NR **Other:** Number of CBT sessions for stepped care vs. usual: 10.9 (4.4) vs. 14.5 (5.3); p<0.01 Median minutes in sessions (range): 420 (120-1,440) vs. 720 (120-2,040); p=0.01 **Harms:** Not reported
Lopez, et al., 2011[110] N=58 Poor	CDC (Fukuda, 1994) criteria	3 months (12 weeks)	A. Group CBT B. Control, 1 session of psychoeducation summarizing strategies	**Fatigue:** POMS-Fatigue subscale: NS **Quality of life:** Category scores with lower scores indicating better health after treatment better in group CBT, mean (SD): 2.81 (1.15) vs. 3.26 (0.87); p=0.02 Raw score after treatment: 1.17 (1.83) vs. 0.82 (1.37); p=0.05 T score after treatment: 39.28 (14.17) vs. 36.42 (10.56); p=0.05 **Harms:** Not reported

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
O'Dowd, et al., 2006[112] N=153 Fair	CDC (Fukuda, 1994) criteria	12 months	A. Group CBT B. Group support C. Usual care	**Function:** Normal walking speed higher in CBT group on mean incremental shuttle walking test; at 6 and/or 12 months: 11.58 (0.71) vs. 9.82 (0.53) vs. 8.76 (0.47); p=0.006 Difference between groups from baseline to 12 months for CBT vs. support: 1.77 (95% CI, 0.025 to 3.51); p=0.0055 Difference between groups from baseline to 12 months for CBT vs. usual care: 2.83 (95% CI, 1.12 to 5.53); p=0.0055 SF-36 physical functioning subscale: NS **Fatigue:** Fatigue difference between groups from baseline for CBT vs. support at 12 months: -3.16 (95% CI, -5.59 to -0.74); p=0.011 Fatigue difference between groups from baseline for CBT vs. usual care at 12 months: -2.61 (95% CI, -4.92 to -0.30); p=0.027 **Quality of life:** Health related quality of life utility scores: NS **Harms:** Not reported
Sharpe, et al., 1996[113] N= 60 Good	Oxford (Sharpe 1991) criteria	12 months	A. CBT B. Usual care	**Function:** Functional scores of ≥80 on KPS better in CBT group at 12 months: 73% (22/30) vs. 27% (8/30); difference of 47% (95% CI, 24 to 69) Improvement of ≥10 points on KPS better in CBT group at 12 months: 73% (22/30) vs. 23% (7/30); difference of 50% (95% CI 28 to 72%) **Harms:** Not reported
Taylor, 2004[114] N=47 Good	CDC (Fukuda, 1994) criteria	12 months	A. Counseling B. Wait list	**Quality of life**: QLI scores better in counseling group at 12 months, mean (SD): 15.7 (3.7) vs. 14.6 (4.1); mean change from baseline: 2.6 vs. 0.6; p<0.05 Health and function subscale at 12 months: 14.1 (1.7) vs. 13.6 (1.8) Social and economic subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Psychological and spiritual subscale at 12 months: 15.5 (1.1) vs. 15.1 (1.2) Family subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9); mean change from baseline: 0.2 vs. -0.2; p<0.05 **Harms:** None withdrew due to harms, otherwise NR

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Tummers, et al., 2012[116] N=111 Good	CDC (Fukuda, 1994) criteria	6 months	A. Self-instruction B. Wait list	**Function:** SF-36 physical functioning subscale (main analysis): NS Of those within the disabled range at baseline (SF-36 physical functioning subscale score ≤70, n=99), those in the self-instruction group improved more at the second assessment, mean change from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05 **Fatigue:** Fatigue severity scores better in self-instruction group on CIS fatigue scale at second assessment, mean (SD): 39.6 (14.1) vs. 48.3 (8.1); p<0.01 % With reduction in CIS fatigue severity scores: 33% (18/55) vs. 9% (5/56); OR 5.0 (95% CI, 1.69 to 14.57) Of those within the disabled range at baseline (SF-36 physical functioning subscale score ≤70, n=99), those in the self-instruction group improved more at the second assessment, mean change from baseline: -12.4 vs. -2.4; difference: -9.9 (95% CI, -5.4 to -14.3); p<0.01 **Harms:** Not reported
Tummers, et al., 2013[117] "See Knoop, 2008 and Tummers, 2012" (Fair) Secondary analysis of Knoop, et al., 2008 & Tummers, et al., 2012 combined	CDC (Fukuda, 1994) criteria	6-12 months (based on the RCTs)	A. Self-instruction B. Wait list	**Fatigue:** *Interaction tests for potential moderators from linear regression models (95% CI):* Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 Avoidance of activity: 0.17 (0.03 to 1.78); p=0.04 Perpetuating factors: self-efficacy: NS, somatic attribution: NS, focus on bodily symptoms: NS *Interaction tests for potential moderators from logistic regression models (95% CI):* Avoidance of activity: 1.34 (1.03 to 1.74); p=0.03 Depression: 1.40 (1.08 to 1.82); p=0.01 Age (years): NS Perpetuating factors: self-efficacy: NS, somatic attribution: NS, focus on bodily symptoms: NS **Harms:** Not reported

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Wearden, et al., 2010[118] **FINE Trial** Wearden, et al., 2012[119] Wearden, et al., 2013[120] N=257 Good	Oxford (Sharpe,1991) criteria	4.5 months (18 weeks) treatment; 17.5 months (70 weeks) total followup	A. Pragmatic rehab B. Supportive listening C Usual care	**Function:** Functional scores better in usual group on SF-36 physical functioning subscale at 20 weeks, mean (SD): 39.94 (25.21) vs. 33.28 (22.94) vs. 40.27 (26.45); treatment effect estimate -7.54; 95% CI, -2.96 to -0.11; p=0.035 for supportive listening vs. usual care At 70 weeks: NS **Fatigue:** Chalder Fatigue Scale scores at 70 weeks: NS *Significant regression coefficients for interaction between putative moderators and treatment:* HADS baseline depression score: -0.67 (95%, CI -1.25 to -0.10); p=0.022 HADS baseline total score: -0.30 (95% CI, -0.58 to -0.02); p=0.039 EQ-5D self-care scale, those with severe problems: -28.72 (95% CI, -32.14 to -25.31); p<0.001 *Significant regression coefficients to predict change in Chalder Fatigue Scale scores:* Age: -0.10 (95% CI, -0.19 to -0.003); p=0.044 Duration of illness: -0.01 (95% CI, -0.02 to -0.003); p=0.008 EQ-5D mobility scale; those with severe problems: -2.95 (95% CI, -5.51 to -0.40); p=0.024 **Harms:** Overall: 4 (herpes simplex infection, attempted suicide, bleeding peptic ulcer, and recurrence of cancer; all deemed unrelated to interventions)

Table 5. Trials of counseling and behavioral therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
White, et al., 2011[121] **PACE Trial** N=480 Good Same study as on Table 6 and 7	Oxford (Sharpe, 1991) criteria	13 months (52 weeks)	A. CBT B. APT D Usual care	**Function:** Functional scores better in CBT group on SF-36 physical functioning subscale at 52 weeks, mean (SD): 58.2 (24.1) vs. 45.9 (24.9) vs. 50.8 (24.7) Mean difference CBT vs. APT at 52 weeks (95% CI): 10.5 (5.4 to 15.6) p=0.0002 Mean difference CBT vs. usual care at 52 weeks (95% CI) : 7.1 (2.0 to 12.1) p=0.0068 % Improved from baseline (by ≥8 points) was higher in CBT group: 71% (105/148) vs. 49% (75/153) vs. 58% (88/152) 6MWT: NS **Fatigue:** Fatigue scores better in CBT group on Chalder Fatigue Scale at 52 weeks, mean (SD): 20.3 (8.0) vs. 23.1 (7.3) vs. 23.8 (6.6) Mean difference CBT vs. APT at 52 weeks (95% CI): -2.7 (-4.4 to -1.1) p=0.0027 Mean difference CBT vs. usual care at 52 weeks (95% CI): -3.4 (-5.0 to -1.8) p=0.0001 % Improved from baseline (by ≥2 points) was higher in the CBT group: 76% (113/148) vs. 65% (99/153) vs. 65% (98/152) **Employment:** Work and social adjustment scale scores better in CBT group at 52 weeks, mean (SD): 21.0 (9.6) vs. 24.5 (8.8) vs. 23.9 (9.2); p=0.0001 for CBT vs. control and CBT vs. APT **Other:** More with positive change in CBT group on self-rated CGI at 52 weeks: 41% (61/147) vs. 31% (47/153) vs.25% (38/152) Minimum change: 52% (77/147) vs63% (96/153) vs.66% (100/152) Negative change: 6% (9/147) vs. 7% (10/153) vs. 9% (14/152) *The positive change vs. negative change, OR (95% CI)* CBT vs. APT: 1.7 (1.0 to 2.7) p=0.034 CBT vs. usual care: 2.2 (1.2 to 3.9) p=0.011 **Harms:** Number of nonserious adverse events: 848 vs. 949 vs. 977, p=0.0081 for CBT vs. APT and p=0.0016 for CBT vs. control % with physical function worse: 9 (15/161) vs. 25 (39/159) vs. 18 (28/160); p=0.0007 % With ≥1 nonserious adverse event: NS % With serious adverse events: NS % With serious adverse reactions: NS

Abbreviations: 6MWT=6 minute walk test; ACT= anaerobic activity therapy; APT= adaptive pacing therapy; CBT= cognitive behavioral therapy; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CI= confidence interval; CIS= Checklist of Individual Strength; COG= cognitive therapy; DSM-IV= Diagnostic and

Statistical Manual fourth edition; FSS= fatigue severity scale; HADS= Hospital Anxiety and Depression Scale; KPS= Karnofsky Performance Scale; N= sample size; NR= not reported; NS= not significant; OR= odds ratio; POMS= Profile of Mood States; QLI= Quality of Life Index; QLS= Quality of life scale; RCT= randomized controlled trial; SD= standard deviation; SF-36= 36-item Short Form Survey; SIP-8= Sickness Impact Profile 8-Items; U.K.= United Kingdom; vs. = versus.

Exercise Therapies

One good-quality[121] and five fair-quality randomized trials compared one form of exercise with another form of exercise, standard medical care, adaptive pacing, or placebo (Table 6 below; Tables G4 and H2).[90,125-128] Studies were conducted in the United Kingdom,[90,121,125,128] United States,[108] New Zealand,[127] and China[126] and enrolled patients based on the CDC (Fukuda, 1994) criteria[108,126-128] or the Oxford (Sharpe, 1991) criteria.[90,121,125] The majority of patients were female (range 68 to 82%), mean ages of 37 to 48 years, with mean duration of illness ranging from 28 to 36 months when reported.[90,121,125,127] All were intended to target symptoms of ME/CFS. Major limitations of studies include dissimilarity of groups,[125,127] high loss to followup,[128] lack of intention-to-treat analysis of outcomes,[128] and unclear or inadequate blinding.[90,121,125-127] One trial was funded by a ME/CFS network and all other trials were funded by research agencies or trusts. GET was superior to control groups in measures of fatigue, clinical impression of change, and function. These findings however cannot be generalized to all patients with ME/CFS as no study enrolled patients whereby PEM was a diagnostic requirement (ME case definitions) and only one study performed a subgroup analysis to determine if similar results were found in patients meeting the diagnosis of ME. Recovery was only evaluated in one study and the clinical significance/meaningfulness of the results is questionable as several of the thresholds used to gauge recovery were lower than a normal population. The harms of exercise may be underestimated as it has been inadequately evaluated and reported particularly in patients with specific symptom subsets (i.e., PEM, autonomic dysfunction). Qigong exercise may be beneficial based on one small trial and home orthostatic training was ineffective based on one small trial but the evidence is insufficient without replication.

Graded Exercise Therapy

The effectiveness of GET compared with control groups (usual care, placebo, placebo exercise, adaptive pacing) was studied in four trials.[90,121,125,127] The largest of these was the PACE trial, a 12 month good-quality 4-arm trial that included a comparison of GET (n=159) with adaptive pacing (n=159) and usual care (n=157), and measured outcomes of fatigue (Chalder Fatigue Scale), function (SF-36 physical function subscale), clinical global impression of change, and work impairment (Work and Social Adjustment Scale).[121] The CBT arm is discussed in the Cognitive and Behavioral Therapies and Head-to-Head/Combination Therapies Sections. Patients were selected from multiple specialty care centers in the United Kingdom and were eligible based on meeting the Oxford (Sharpe, 1991) criteria as well as having a Chalder Fatigue Scale score of 6 or greater (of possible 11) and SF-36 score of 60 or less (of possible 100) which was subsequently changed to 65 or less to increase enrollment. GET consisted of a maximum of 15 sessions including education and a negotiated exercise plan with incremental activity increases aimed at 30 minutes of light exercise 5 times a week, delivered by physical therapists or exercise physiologists. Adaptive pacing consisted of a maximum of 15 sessions of therapy aimed at achieving optimum adaptation to the illness through activity pacing and advice to avoid activities that demand more than 70 percent of patient's perceived energy, and was delivered by occupational therapists. Usual care was provided by physicians specializing in ME/CFS. Compared with the usual care group and the adaptive pacing therapy group, at 1 year the GET groups reported statistically significantly better fatigue scores (mean difference GET vs. usual care: -3.2; 95% CI, -4.8 to -1.7; p=0.0003; GET vs. adaptive pacing therapy: -2.5; 95% CI, -4.2 to -0.9; p=0.0059), functioning scores (mean difference GET vs. usual care: 9.4; 95% CI,

4.4 to 14.4; p=0.0005; GET vs. adaptive 12.8; 95% CI, 7.7 to 17.9; p<0.0001), and work impairment scores (mean score: 20.5 GET vs. 23.9 usual care, p<0.001; GET vs. 24.5 adaptive pacing therapy, p<0.001). GET groups reported greater improvement on the self-rated CGI at 1 year compared with both the usual care and adaptive pacing therapy groups (OR of positive change vs. negative change for GET vs. usual care: 2.0; 95% CI, 1.2 to 3.5; p=0.013; GET vs. adaptive pacing therapy: 1.5; 95% CI, 1.0 to 2.3; p=0.028). They also found improvement in the 6-minute walk test distance across all groups at 52 weeks but a significantly greater improvement in the GET group (+ 35.3 m, p<0.001 vs. usual care; +41.0 m, p<0.001 vs. adaptive pacing). Symptoms of PEM were lower in the exercise group compared with both usual care (OR 0.5, p=0.003) and adaptive pacing (OR 0.5, p=0.004). The authors performed a sensitivity analysis for those patients who fulfilled the CDC (Reeves, 2003) criteria (n=321) and for those patients who fulfilled the London ME (Dowsett, 1994) criteria (n=245) and found similar results for the outcomes of fatigue and function. The investigators also considered the outcome of recovery, described above in the Counseling and Behavioral Therapies Section.[123] Although trial recovery remained low for all treatment arms (<25%), they found GET to be superior to adaptive pacing (OR 3.38; 95% CI, 1.65 to 6.93) and usual care (OR 3.71; 95% CI, 1.78 to 7.74), with similar results for clinical recovery.[123] Nonserious adverse events (whether or not related to treatment) were reported often and were similar between groups (usual care: 977; adaptive pacing therapy: 949; GET: 992). Although serious adverse events were uncommon, there were more reported in the GET group (17) than the usual care group (7), p=0.04. Although there was a significant difference in deterioration of physical function across treatment arms (adaptive pacing 25% vs. usual care 18% vs. GET 11%, p<0.001), there were no differences in serious deterioration defined by a composite score of reduced function, worsening clinical global impression, withdrawal rates, and serious adverse reactions due to the treatment.[121,122] There were no differences in harms attributable to the treatment received.

As discussed above, the PACE trial may be exposed to risk of observer bias by not blinding the research assessors, and attention bias given the total number of visits by participants were greater in the GET (16) and adaptive pacing (16) groups compared to the usual care group (5). Additionally, patients are educated that they will improve with GET which can add an expectation bias in the direction of improvement.

A smaller fair-quality trial conducted in New Zealand and of shorter duration found similar results on outcomes of fatigue and CGI, but did not find improvement in the physical function subscale of the SF-36. This was a 12-week trial with 6-month followup comparing GET with standard medical care (n=49) and enrolled patients meeting the CDC (Fukuda, 1994) criteria.[127] Exercise consisted of treadmill walking starting at 10 to 15 minutes, 4 to 5 times per week at a heart rate of 40 percent of VO_2 max (50% maximal heart rate) and increased by 3 to 5 minutes per week for the first 6 weeks and then by an increase in heart rate by 5 beats per minute per week with a goal of achieving 30 minutes of exercise at 70 percent VO_2 maximum (80% maximal heart rate) at 12 weeks.[127] The primary outcome was the CGI, which was significantly improved in the GET group compared with the standard medical care group at 12 weeks (55% rated as much or very much better compared with 24% of the control, p=0.04). Sixty-eight percent of patients rated their exercise therapy as ‘effective’ or ‘highly effective.’ Compared with standard therapy, GET showed improvement in all of the secondary fatigue outcomes at 12 weeks (Chalder Fatigue Scale scores; total score: -10.54 vs. -0.94, p=0.02; physical fatigue subscale: -6.64 vs. -0.34, p=0.02; mental fatigue subscale: -3.90 vs. 0.60, p=0.03), but showed no difference in the SF-36 physical functioning subscale (15.95 vs. 9.35, p=0.49). In their intention-

to-treat analysis with a 12 percent dropout rate (3 per group), neither the Chalder Fatigue Scale mental fatigue subscale nor SF-36 physical functioning subscale were significant.[127] Notably, the GET group was younger (mean age 37 vs. 45 years) and had a shorter duration of illness (2.7 vs. 5.0 years). They received 77 percent of the questionnaires at the 6 month followup and found sustained improvement on the CGI and the Chalder Fatigue Scale physical fatigue whereas the Chalder Fatigue Scale mental fatigue subscale scores showed no difference between groups at 6 months.[127] They also considered physiological assessment of fitness with incremental testing on a treadmill to determine maximum aerobic capacity (VO_2 peak) and found no difference between groups, however, complete data were only available for just over half (65%) the sample as many patients refused to have a second test due to perceived harm from the initial testing (10 of 49, 20%), or stopped prior to maximal effort (5 of 49, 10%), while the equipment failed on two patients.

An earlier fair-quality 12-week trial conducted in the United Kingdom found similar results for CGI, measures of fatigue, and function measured by the SF-36 when comparing GET with flexibility exercises.[125] Sixty-six patients fulfilling the Oxford (Sharpe, 1991) criteria and without concurrent psychiatric or insomnia disorders attended weekly sessions in which they were prescribed a home program consisting of either exercise (primarily walking) or stretching and relaxation to be performed 5 days per week. The initial exercise prescription consisted of 5 to 15 minutes of aerobic exercise at an intensity of 40 percent of peak oxygen consumption (50% maximum heart rate) to be increased by 1 or 2 minutes to a maximum of 30 minutes. Once achieved, the intensity was then increased to a maximum of 60 percent of peak oxygen consumption, as monitored by heart rate. If fatigue increased, patients were advised to maintain the same level of exercise until fatigue lessened. The flexibility and relaxation group started at 10 minutes of stretching/relaxation and were advised to increase to a maximum of 30 minutes while avoiding any extra physical activities. A greater number of patients in the GET group reported “much” or “very much” improvement on the CGI (16 of 29, 55% vs. 8 of 30, 27%; p=0.05).[125] Intention-to-treat analysis including seven patients who dropped out (4 exercise, 3 flexibility/relaxation) found similar results (17 of 33 vs. 9 of 33, p=0.04). They also evaluated changes in fatigue using various measures and found significant improvement on all measures with the exception of the mental fatigue subscale of the Chalder Fatigue Scale based on differences in means (Chalder Fatigue Scale total score: -8.40 vs. -3,10, p<0.01; VAS total fatigue score [normal=200]: -59 vs. -39, p=0.04; VAS physical fatigue score [normal=100]: -31 vs. -23, p<0.01; VAS mental fatigue score [normal=100]: not significant). Improvement was also noted in function based on SF-36 total scores (137 vs. 84, p=0.05) and physical function score (47.5 vs. 8.0, p=0.01). Although they reported a significant difference in the SF-36 general health score between groups at 12 weeks, there was a difference between the groups at baseline with the change being similar (4.0 vs. 4.0). Differences were also noted in peak oxygen consumption, mean heart rate during submaximal treadmill testing, and mean submaximal perceived exertion score favoring the exercise group (13% vs. 6%; 143 beats per minute, SD 13 vs. 150 beats per minute, SD 13; 14.5, SD 3.4 vs. 16.2, SD 2.8, respectively). Twenty-three of thirty patients in the flexibility/relaxation group were allowed to crossover to the exercise intervention at 12 weeks. One dropped out due to an unrelated condition and of the 22 who completed the program, 54 percent (12 of 22) rated themselves as better. At 1 year they found persistent improvement in measures of function with 66 percent (31 of 47) of those working or studying at least part time compared with only 39 percent (26 of 66) at baseline (95% CI, 9% to 44%).

A final fair-quality 4-arm study (n=136) enrolled 136 patients fulfilling the Oxford (Sharpe, 1991) criteria and compared fluoxetine with GET, placebo, or a combination of GET and fluoxetine, followed them for 6 months, and measured fatigue using the Chalder Fatigue Scale (14-item) and functional capacity measuring the amount of oxygen consumed in the final minute of exercise per kg of body weight.[90] Attrition was highest in the combination group (42%), but was also high in the individual intervention groups (32% in fluoxetine group and 29% in GET group), while the control group had lower attrition (17%). Adherence was not reported in considering only the results of the GET (n=34) versus placebo (n=34) arms, after 6 months of treatment there was greater improvement in fatigue (-5.7 vs. -2.7) and more non-cases of fatigue (Chalder score <4) in the exercise interventions (18% vs. 6%). The exercise interventions showed an improvement in functional capacity, with a mean change from baseline at 6 months of 2.8 ml O_2/kg per minute (95% CI, 0.8 to 4.8). The exercise arm had a greater number of withdrawals compared with placebo (11 of 34, 32% vs. 5 of 34, 15%).

Pooling of three of these studies found a significant improvement in CGI (RR 1.58; 95% CI, 1.25 to 1.98, Figure 4), and SF-36 physical function subscale (weighted mean difference 10.29; 95% CI, 6.71 to 13.88, Figure 5).[121,125,127] Due to the variability in how the Chalder Fatigue Scale was used across studies, these results could not be pooled.

Qigong Exercise

Qigong exercise was compared with no qigong exercise in a 4-month randomized trial in China. Patients 18 to 55 years and meeting the Oxford (Sharpe, 1991) criteria were recruited through online or newspaper advertising in Hong Kong (n=137).[129] Those randomized to the exercise group received group qigong twice weekly for 5 weeks (2 hours of education, relaxation, stretching, and 1 hour of qigong training per session) followed by 12 weeks of home based qigong (30 minutes per day). The control group was asked to refrain from qigong exercise. Attrition was 19 percent and similar between groups. Improvement was reported in the Chalder Fatigue Scale total score (mean change: -13.1 vs. -6.6, p<0.001), physical fatigue subscale score (mean change: -8.8 vs. -3.8, p<0.001), and mental fatigue subscale score (mean change: -4.4 vs. -2.8, p=0.01) in both groups with a significantly greater improvement in the qigong exercise group.[129] No change was noted in the SF-36 physical function subscale score (3.2 vs. 2.1, p=0.48) in a smaller subgroup that were also being tested for telomerase activity (n=64).[126]

Home Orthostatic Training

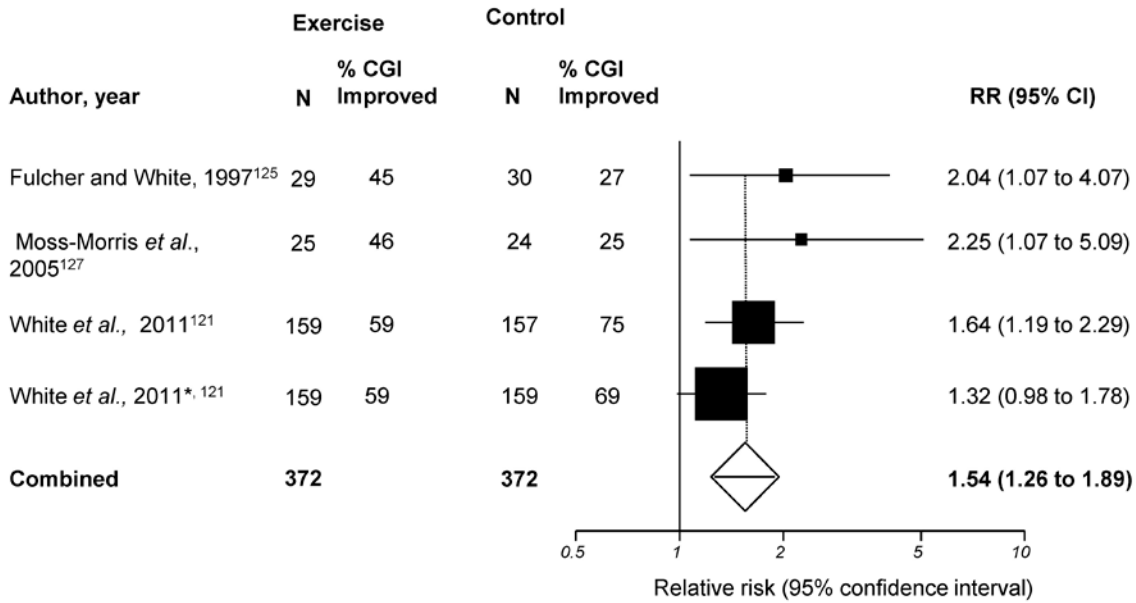
Home orthostatic training (40 minutes of standing against a wall with their heels 15 cm from the wall) was compared with a sham home exercise program (10 minutes of wall standing while performing intermittent calf contractions) in a fair-quality 6-month trial of 38 patients fulfilling the CDC (Fukuda, 1994) criteria.[128] No differences in fatigue as measured by the fatigue impact score in those who completed the trial and submitted a final questionnaire (n=25). At 6 months, the sham group had a significantly greater drop in blood pressure when standing compared with the intervention group (-6 mmHg; 95% CI, 0.0 to 12.6, p=0.05), but the clinical significance of this was not reported. Of note, they did not perform any subgroup analysis to determine if differences existed in those with subjective autonomic symptoms at baseline.

Summary of Exercise Therapies

In summary, compared with control groups, there is moderate strength of evidence that GET improved function (weighted mean difference on SF-36 physical function (10.29; 95% CI, 6.71

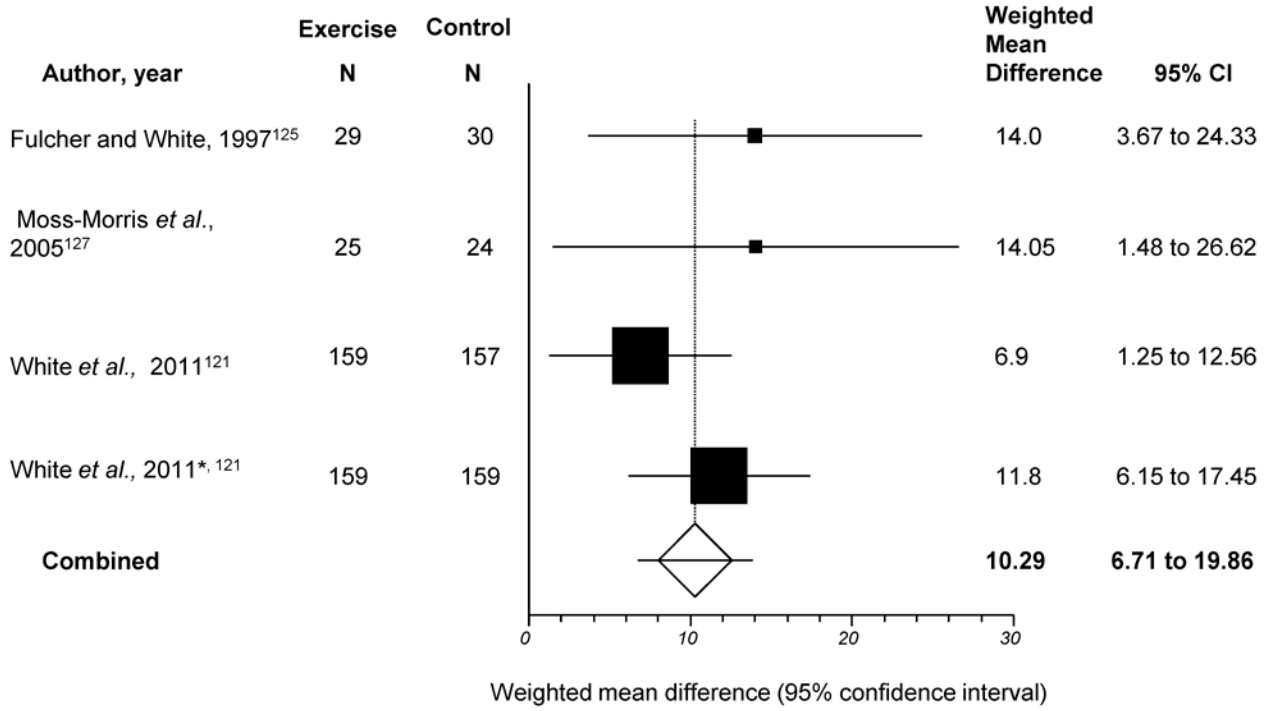
to 13.86), and global change scores (RR 1.54; 95% CI, 1.26 to 1.89), and low strength of evidence that GET improved fatigue in ME/CFS patients fulfilling the Oxford (Sharpe, 1991) and/or CDC (Fukuda, 1994) criteria. However, subgroup analysis was inadequate to determine whether these benefits extend to patients with more disability meeting the criteria for ME. Although qigong exercise was found to improve some measures of fatigue, and orthostatic training did not change measures of fatigue, the studies were small and with methodological limitations which leaves uncertainty in the results. Harms were not well reported and although total withdrawal rates were similar in three of four trials, the high rate (20%) of patients refusing repeat exercise testing in one study, limitations in subgroup analysis throughout, and lack of studies using a more disabled population suggest that this outcome has not been adequately studied.

Figure 4. Meta-analysis of improvement on CGI scale for exercise compared with controls



*Using adaptive pacing as the comparison
Abbreviations: CGI = Clinical Global Impression of Change Score; CI= confidence interval; N= sample size; RR= relative risk.

Figure 5. Meta-analysis of mean changes in SF-36 physical function subscale scores for exercise compared with controls



*Using adaptive pacing as the comparison
Abbreviations: CI= confidence interval; N= sample size; RR= relative risk; SF-36= Short Form 36-item survey.

Table 6. Trials of exercise therapies for ME/CFS

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Chan, et al., 2013[126] Ho, et al., 2012[126] RCT N= 52 Fair	CDC (Fukuda, 1994) criteria	4 months	A. Qigong exercise B. Control group	**Function:** SF-12 mental functioning subscale mean (SD): 42.7 (7.2) vs. 35.7 (9.5); p=0.001 SF-12 physical functioning subscale: NS **Fatigue:** Chalder Fatigue Scale mean (SD): 26.6 (13.6) vs. 33.2 (6.3); p<0.001 Physical fatigue scores, Chalder Fatigue Scale mean (SD): 15.9 (8.0) vs. 20.8 (5.7); p<0.001 Mental fatigue scores on Chalder Fatigue Scale mean (SD): 10.6 (6.1) vs. 12.4 (4.9); p=0.05 **Other:** Telomerase activity at 4 months (arbitrary unit): 0.178 (0.201) vs. 0.104 (0.059); p=0.029 **Harms:** Not reported
Fulcher and White, 1997[125] RCT N=59 Fair	Oxford (Sharpe, 1991) criteria	3 months (12 weeks), 1 year followup	A. Exercise group B. Control group	**Function:** SF-36 physical functioning subscale mean (SD): 69 (18.5) vs. 55 (21.8); p=0.01 **Fatigue:** Chalder Fatigue Scale mean (SD): 20.5 (8.9) vs. 27.4 (7.4); p=0.004 Physical fatigue scores better mean (SD): 130 (28) vs. 154 (34); p=0.006 Other VAS fatigue scores: NS **Employment:** working full- or part-time at 1 year followup: 66% (31/47) vs. 39% (26/66); 95% CI, 9% to 44% **Other:** Self-rated CGI scores of “very much better” :: 31% (9/29) vs.7% (2/30), p=0.05 Median (IQR) peak O_2 consumption: NS Median increase in peak O_2 consumption: NS Median increase in isometric strength: NS **Harms:** Total withdrawals: NS

Table 6. Trials of exercise therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Moss-Morris, et al., 2005[127] RCT N= 49 Fair	CDC (Fukuda, 1994) criteria	3 months (12 weeks), 6 month followup	A. Exercise group B. Control group	**Function:** SF-36 physical functioning: NS **Fatigue:** Chalder Fatigue Scale mean (SD): 13.91 (10.88) vs. 24.41 (9.69); p=0.02 Physical fatigue scores on Chalder Fatigue Scale mean (SD): 7.91 (7.06) vs. 14.27 (5.75); p=0.02 Mental fatigue scores on Chalder Fatigue Scale mean (SD): 6.00 (4.06) vs. 10.14 (4.27); p=0.03 **Other:** Self-rated CGI scores of % “much or very much improved” at 6 months: 54 (12/22) vs. 23.8 (5/21); p=0.04 **Harms:** Total withdrawals: NS
Sutcliffe, et al., 2010[128] RCT N= 36 Fair	CDC (Fukuda, 1994) criteria	6 months	A. Orthostatic training B. Control group	**Function:** Mean systolic blood pressure: NS Mean heart rate (beats per minute): NS **Fatigue:** Mean FIS scores: NS **Harms:** Not reported
Wearden, et al., 1998[90] N=68 Fair Same study as on Table 3 and 7	Oxford (Sharpe, 1991) criteria	6.5 months (26 weeks)	A. GET B. Placebo control*	**Function:** Functional work capacity based on amount of O_2 consumed in the final minute of exercise per kg of body weight improved in GET group at 26 weeks, mean change (95% CI) : 2.8 (0.8 to 4.8) vs. -0.1 (-1.7 to 1.6) Effect of exercise on functional work capacity, mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03 **Fatigue:** Fatigue scores significantly improved in GET group on Chalder Fatigue Scale at 26 weeks, mean change from baseline (95% CI): -5.7 (-9.5 to -1.9) vs. -2.7 (-5.4 to 0.01) Non-cases of fatigue on Chalder Fatigue Scale (score <4) at 26 weeks: 18% (6/33) vs. 6% (2/34), p=0.025 for exercise interventions combined vs. control **Harms:** Total withdrawals: GET > UC (11/34, 32% vs. 5/34, 15%)

Table 6. Trials of exercise therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
White, et al., 2011[121] **PACE Trial** N=479 Good Same study as on Table 5 and 7	Oxford (Sharpe, 1991) criteria	13 months (52 weeks)	A. GET B. APT C. Usual care†	**Function:** SF-36 physical function subscale mean (SD): 57.7 (26.5) vs. 45.9 (24.9) vs. 50.8 (24.7) Mean difference vs. APT (95% CI): 12.8 (7.7 to 17.9) p<0.001 Mean difference vs. usual care (95% CI) : 9.4 (4.4 to 14.4) p<0.001 % Improved from baseline (by ≥8 points): 70% (108/154) vs. 49% (75/153) vs. 58% (88/152) **Fatigue:** CFS, mean (SD): 20.6 (7.5) vs. 23.1 (7.3) vs. 23.8 (6.6) Mean difference vs. APT (95% CI): -2.5 (-4.2 to -0.9) p<0.01 Mean difference vs. usual care (95% CI): -3.2 (-4.8 to -1.7) p<0.001 % Improved from baseline (by ≥2 points): 80% (123/154) vs. 65% (99/153) vs. 65% (98/152) **Employment:** Work and social adjustment scale, mean (SD): 20.5 (9.4) vs. 24.5 (8.8) vs. 23.9 (9.2); p<0.001 for GET **Other:** CGI positive change: 41% (62/152) vs. 31% (47/153) vs. 25% (38/152) CGI negative change: 7% (10/152) vs. 7% (10/153) vs. 9% (14/152) Positive change vs. Negative change, OR (95% CI) GET vs. APT: 1.5 (1.0 to 2.3) p=0.028 GET vs. usual care: 2.0 (1.2 to 3.5) p=0.013 **Trial Recovery**: GET vs. APT (OR 3.38, 95% CI, 1.65 to 6.93) GET vs. usual care (OR 3.71, 95% CI, 1.78 to 7.74 **Harms:** Serious adverse events: GET greater than usual care: 11 % (17/160) vs.4% (7/160),p=0.04 No difference: nonserious adverse events (992 vs. 949 vs. 977), serious adverse reactions (1%), serious deterioration (10/160, 6% vs. 13/159, 8% vs. 15/160, 9%); and total withdrawals (10/160, 6% vs. 11/159, 7% vs.14/160, 9%)

*Comparisons between Fluoxetine and placebo are presented in Table 2 and comparisons with GET + fluoxetine are presented in Table 6.
†Comparisons for CBT with APT and usual care are presented in Table 3 and comparisons for CBT with GET are presented in Table 6.
Abbreviations: APT= adaptive pacing therapy; CDC= Centers for Disease control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical Global Impression Change Score; CI= confidence interval; FIS= Fatigue Impact Scale; GET= graded exercise therapy; IQR= interquartile range; kg= kilogram; N= sample size; NR= not reported; NS= not significant; O_2= oxygen; OR= odds ratio; RCT= randomized controlled trial; SD= standard deviation; SF-36= 36-item Short Form Survey; SF-12= Short Form 12-item Survey; UC=usual care; VAS= visual analog scale; vs.= versus.

Head-to-Head Comparisons and Combination Therapies

Four included trials (8 publications) compared either head-to-head interventions or combinations of two interventions (Table 7 below; Table G4).[90,101,105,106,108,111,121] Three trials (in 7 publications) compared head-to-head interventions, one comparing CBT with GET and adaptive pacing and a usual care group,[121] one comparing CBT with cognitive therapy and anaerobic activity therapy and relaxation,[105,106,108] and one of fluoxetine compared with GET,[90] which also had a group of the combination of fluoxetine plus GET for comparison. The fourth trial compared a combination treatment of CBT plus GET with usual care.[111] The results for the head-to-head- trials that pertain to the comparison of one intervention to another, not a control group, on outcomes will be discussed in this section; results based on comparisons with control groups, such as GET or CBT were discussed in those previous sections. All trials were designed to target symptoms of ME/CFS, not treat the underlying cause. One trial was good-quality[121], while the other three were rated fair-quality[90,101,108,111] (Table H2). Three of the trials were of larger size (n>100) and illness duration, when reported, was at least greater than 6 months. Two trials used the Oxford (Sharpe, 1991) criteria to identify patients with CFS,[90,121] one used the CDC (Fukuda, 1994) criteria,[111] while the other used a combination of a CFS symptom questionnaire, psychiatric assessment, and medical assessment.[108]

Adherence was reported in only one trial, which found that participants completed an average of 10 out of 13 sessions.[108] Attrition was reported in three trials and was relatively high (>20%) in one.[108] The trial of fluoxetine and GET reported the highest attrition in the combination group (42%), followed by the fluoxetine only group (32%), and the GET only group (29%) in comparison with the lowest in the placebo group (17%).[90] The other two trials reported low attrition rates (0.6 to 5%).[111,121]

There is low strength of evidence that GET and CBT or cognitive therapy had similar results on measures of fatigue and function in one good-quality and two fair-quality head-to-head trials. GET was superior to fluoxetine on measures of fatigue and function in one fair-quality trial but represents an insufficient strength of evidence given that it was a single study of small sample size. Harms were not well reported leaving insufficient evidence, however patients receiving GET reported more adverse events compared with CBT, adaptive pacing, or usual care in one good-quality trial, and fewer patients in the CBT group reported having serious adverse events versus all others combined (6% vs. 11%, p=.03). [121]

The PACE trial described previously was a large 12-month good-quality trial (n=641) comparing four interventions: CBT, GET, an adaptive pacing therapy, and a usual care control group.[121] Attrition was low with only 1.7 percent withdrawing overall and adherence was not reported. Compared with the control and adaptive pacing groups, at 1 year the CBT and GET groups reported similar improvement in fatigue scores, functioning scores, and work impairment scores. Both CBT and GET groups reported greater improvement on the self-rated CGI at 1 year compared with both the control and adaptive pacing therapy groups (OR of positive change vs. negative change for CBT vs. control: 2.2; 95% CI, 1.2 to 3.9; p=0.011; CBT vs. adaptive pacing therapy: 1.7; 95% CI, 1.0 to 2.7; p=0.034; GET vs. control: 2.0; 95% CI, 1.2 to 3.5; p-0.013; GET vs. adaptive pacing therapy: 1.5; 95% CI, 1.0 to 2.3; p-0.028). Similar results for fatigue and function were found when the data were reanalyzed for those patients fulfilling the CDC (Reeves, 2003) criteria (n=427), and London (Dowsett, 1994) criteria (n=329). The investigators also considered the outcome of recovery (trial and clinical recovery described earlier).[123] They found no difference between CBT (32 of 143, 22%) and GET (32 of 143, 22%), both of which

were better than adaptive pacing (12 of 149, 8%) and usual care (11 of 150, 7%).[123] Harms were reported as nonserious and serious adverse events, serious adverse reactions attributed to the treatment, and serious deterioration. Nonserious adverse events were reported often; however, the CBT group reported fewer events (848) compared with all groups (usual care: 977; adaptive pacing therapy: 949; GET: 992), and fewer patients in the CBT group reported having serious adverse events versus all others combined (6% vs. 11%, p=.03).[122] A post-hoc analysis revealed that frequency of nonserious adverse event reporting was associated with the center at which the patient was seen. When adjusted for center, factors affecting the reporting of a nonserious adverse event included baseline CFS symptom count (OR 1.12; 95% CI, 1.01 to 1.24, p=0.03), baseline current depressive disorder (OR 1.47; 95% CI, 1.04 to 2.07), and log body mass index (OR 2.55; 95% CI, 1.09 to 5.96, p=0.03).[122] Serious adverse reactions attributed to the treatment were rare, and although more were reported by the GET group (17) compared with all groups (control: 7; adaptive pacing therapy: 16; CBT: 8), this was not statistically significant. The limitations of this study have already been extensively reviewed in the section on Counseling and Behavioral Therapies.

One fair-quality trial (n=114) compared CBT with cognitive therapy, with an anaerobic activity therapy, and with a relaxation techniques control group; this study followed participants for 12 months and measured fatigue using the FSS, quality of life using the QLS, functioning using the SF-36 physical functioning subscale, and employment status.[108] Overall 25 percent of individuals dropped out (not reported per group) and individuals attended an average of 10 out of 13 sessions. At 12 months the CBT group and the cognitive therapy group had statistically significantly better functioning scores compared with the anaerobic activity therapy group (mean scores: 58.64 vs. 61.09 vs. 39.72; p<0.01). There were no differences in employment status, fatigue scores, 6-minute walk test, or quality of life scores, and harms were not reported. Most continued to meet the criteria for CFS at completion and there were no significant differences between groups.

Fluoxetine and/or GET were compared in a previously described trial with 6-month measurements of fatigue (Chalder Fatigue Scale) and functional capacity measuring the amount of oxygen consumed in the final minute of exercise per kg of body weight.[90] GET was superior to fluoxetine and/or placebo on all measures. Total withdrawal was greatest in the GET group compared with the nonexercise groups (37% vs. 22%). The other combination trial was a fair-quality trial (n=120) that compared group CBT and group GET with a usual care control group; this study followed participants for 12 months and measured fatigue using the FIS and function using the SF-36 physical functioning subscale.[111] Adherence was not reported, but attrition was low overall (4.2%). Neither fatigue nor functioning scores were significantly different at 12 months followup and harms were not reported.

In summary, head-to-head trials had mixed results. Functional improvement with CBT and GET, as well as CBT and cognitive therapy appear similar and better than control groups.[108,121] Fatigue may be similar between CBT and GET, and better than control groups as noted in one large trial[121] but one trial of CBT plus GET found no difference compared with the control.[111] In considering non-head-to-head trial data, CBT and GET provided similar improvement in measures of function and possibly fatigue, while the evidence was insufficient for other outcomes and comparisons. No study used a case definition selecting for more disabled patients and subgroup analysis of patients with PEM or cognitive impairment was lacking; these factors limit interpretation of the overall results. GET was superior to fluoxetine but the strength of evidence is insufficient, given that this comparison was only studied in one small fair-quality

trial. Harms were again poorly reported and have not been adequately studied in subgroups with PEM or more severely disabled patients. When reported, harms of CBT appear to be less than with GET.

Table 7. Trials of combination therapies for ME/CFS

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105] N=114 Fair *Same study as on Table 5*	CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment	12 months	A. CBT B. COG C. ACT D. Relaxation	**Function:** SF-36 physical functioning subscale scores mean (SD): 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70) p<0.01, for CBT and COG over time vs. ACT over time Comparison by energy envelope for those who stayed within envelope vs. outside envelope at 12 months: 65 vs. 43, change at 12 months from baseline: 17 vs. 0; p=0.03 Comparison by homework compliance level, change in score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR % Achieving clinically significant improvement: NS 6 MWT: NS **Fatigue:** FSS scores mean (SD): 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR Comparison by energy envelope for those who stayed within envelope vs. outside envelope at 12 months was 5.3 vs. 6.3 Change at 12 months from baseline: -0.9 vs. 0.1; p<0.01 The comparison by homework compliance level, change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR **Quality of life:** QLS scores mean (SD): 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR **Employment:** % Employed at 12 month followup: NS **Harms:** Total withdrawals: 25% but not reported per group
Núñez, *et al.,* 2011[111] N=115 Fair	CDC (Fukuda, 1994) criteria	2.5-3 months of treatment, 12 months followup after treatment	A. CBT + GET B. Usual care	**Function:** SF-36 physical function subscale for CBT + GET vs. usual care: NS **Fatigue:** FIS score for CBT + GET vs. usual care: NS **Harms:** Not reported

Table 7. Trials of combination therapies for ME/CFS (continued)

Author, Year Study Type N Quality	Case Definition	Duration/ Followup	Interventions	Overall Effect Intervention A vs. Intervention B vs. Intervention C, etc.
Wearden, *et al.,* 1998[90] N=136 Fair *Same study as on Table 3 and 6*	Oxford (Sharpe, 1991) criteria	6.5 months (26 weeks)	A. GET + fluoxetine B. GET + drug placebo C. Fluoxetine + exercise placebo D. Placebo control	**Function:** Functional work capacity based on amount of O_2 consumed in the final minute of exercise per kg of body weight higher in GET group at 26 weeks, mean change (95% CI) : 2.0 (0.4 to 3.5) vs. 2.8 (0.8 to 4.8) vs. 1.0 (-0.9 to 3.0) vs. -0.1 (-1.7 to 1.6) Effect of exercise on functional work capacity, mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03 **Fatigue:** Chalder Fatigue Scale a, mean change from baseline (95% CI): -6.0 (-9.7 to -2.3) vs. -5.7 (-9.5 to -1.9) vs. -3 (-5.9 to -0.2) vs. -2.7 (-5.4 to 0.01) Non-cases of fatigue on Chalder Fatigue Scale (score <4) at 26 weeks: 18% (6/33) vs. 18% (6/34) vs. 6% (2/ 35) vs. 6% (2/34), p=0.025 for exercise interventions combined vs. others Exercise improved fatigue scale scores: NS **Harms:** Total withdrawals: greatest in the GET-Fluoxetine arm (42%) vs. Exercise-Drug placebo (32%) vs. Exercise placebo-Fluoxetine (28%) vs. Exercise placebo-Drug placebo (15%)
White, *et al.,* 2011[121] ***PACE Trial*** N=630 Good *Same study as on Table 5 and 6*	Oxford (Sharpe, 1991) criteria	13 months (52 weeks)	A. APT B. CBT C. GET D. Usual care	**Function:** SF-36 Physical Functions subscale (0-100): CBT vs. GET, p=NS % Improved from baseline (by ≥8 points) was similar in the CBT and GET groups: 49% (75/153) vs. 71% (105/148) vs. 70% (108/154) vs. 58% (88/152) **Fatigue:** Chalder fatigue scale (0-33) CBT vs. GET, p=NS % Improved from baseline (by ≥2 points) was similar in CBT and GET groups: 65% (99/153) vs. 76% (113/148) vs. 80% (123/154) vs. 65% (98/152) **Employment:** Work and social adjustment scale scores: CBT vs. GET, p=NS **Other:** More with positive change in CBT and GET groups on self-rated CGI at 52 weeks: 31% (47/153) vs. 41% (61/147) vs. 41% (62/152) vs. 25% (38/152) **Harms:** Nonserious adverse events: fewer in CBT group (848) compared with all others (usual care: 977; adaptive pacing therapy: 949; GET: 992), CBT with no serious adverse events versus all others combined (6% vs. 11%, p=.03).

Abbreviations: 6MWT= 6 minute walk test; ACT=anaerobic activity therapy; APT= adaptive pacing therapy; CBT= cognitive behavioral therapy; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical Global Impression of Change; CI= confidence interval; COG= cognitive therapy DSM-IV= Diagnostic and Statistical Manual, fourth edition; FIS= Fatigue Impact Scale; FSS= Fatigue Severity Scale; GET= graded exercise therapy; kg= kilogram; N= sample size; NR= not reported; NS= not significant; O_2= oxygen; QLS= Quality of Life Scale; RR= relative risk SF-36= 36-item Short Form Survey; SD= standard deviation; vs.=versus

Key Question 2c. What are the characteristics of responders and nonresponders to interventions?

Key Points

- Evidence on patient characteristics associated with response/nonresponse to treatment was insufficient—evidence was limited to four small fair-quality trials that considered different characteristics.
- One trial found that those who had lower functional impairment, less fatigue, and less pain at baseline were more likely to improve after group CBT.
- One trial found that younger patients with shorter illness durations and less severe mobility problems at baseline responded better.
- One trial found that a reduction in symptom focusing was associated with improvement in self-reported measures of function, fatigue, and global improvement.
- One trial found that patients who avoided over or under exertion (stayed within their energy envelope) and had 75 percent or better compliance with their home program had improvement in fatigue and function measures.

Detailed Synthesis

Four trials contribute to the understanding of characteristics of patients more likely to respond to therapies for ME/CFS. Results of these studies suggest that younger patients with less impairment, have less symptom focusing, and are compliant with homework are more likely to improve in some measures of fatigue and/or function.[100,105,106,119,127] Staying within one's energy envelope also appeared beneficial; however, evidence for these factors is insufficient to determine its applicability to all patients with ME/CFS.

One fair-quality trial described above[100] compared group CBT with a wait list control and conducted a separate analysis to compare the baseline measures of those who improved with group CBT (n=10) and those who did not improve (n=17) at 6 months (Table G4). Those who improved were more likely to have less functional impairment on the SIP-8 (1,330 vs. 1,985; p=0.031), less daily self-rated observed fatigue on the Chalder Fatigue Scale (7.4 vs. 9.7 on a scale of 0 to 11; p=0.023), and less daily self-rated observed pain (4.5 vs. 7.8; p=0.026) compared with those who did not improve with group CBT. Though the difference did not reach statistical significance, those who improved were more likely to be working more hours per week compared with those who did not improve (10.9 vs. 2.6; p=0.062). There were no differences between those who improved on group CBT and those who did not on baseline measures of age, education, duration of illness, CIS fatigue score, psychological distress, depression, physical attributes, self-efficacy, avoidance of activity, and focusing on bodily symptoms.

One trial comparing GET with usual care[127] performed multiple regression analysis to determine possible cognitive or physiological mediators affecting response to GET. This study found that self-reported improvement in mental and physical fatigue, global change, and physical functioning in the exercise group were all associated with a reduction in symptom focusing.[127] Critical to this analysis, however, is that patients in the exercise group were also instructed in ways to reduce symptom focusing and to attend to the heart rate monitor for feedback as to whether their activity level was safe or not. This places an expectation bias into the results.

One trial conducted post hoc analyses to determine which factors may predict change on the Chalder Fatigue Scale in patients who received pragmatic rehabilitation. This study found significant effect for age (-0.10; 95% CI, -0.19 to -0.003; p=0.044), duration of illness (-0.01; 95% CI, -0.02 to -0.003; p=0.008), and severity as measured by the EQ-5D mobility scale (-2.95; 95% CI, -5.51 to -0.40; p=0.024). Those who were younger, had shorter illness durations, and less severe mobility problems at baseline showed greater improvements in fatigue at 70 weeks.[119]

One trial conducted post hoc analyses based on whether or not individuals stayed within their energy envelope, meaning they avoided overexertion and under exertion by exerting a comfortable range of energy, or strayed outside their energy envelope.[106] Individuals rated their perceived energy and expended energy and this was used to determine which individuals stayed within their energy envelope (n=49) and which were outside their energy envelope (n=32). At 12 months there was a statistically significant improvement in mean fatigue and functioning scores from baseline for those who stayed within their energy envelope compared with those who were outside their energy envelope (fatigue scores: -0.9 vs. 0.1; p<0.01 and functioning scores: 17 vs. 0; p=0.03). The second additional analysis compared fatigue and functioning outcomes based on homework compliance.[105] The researchers identified three groups based on the amount of homework completed; minimum compliance completed 0 to 25 percent, moderate compliance completed 25.1 to 75 percent, and maximum compliance completed 75.1 to 100 percent of their assigned homework. When they assigned individuals to groups they noted that the highest percentage in the maximum group (56%) were in the cognitive therapy group, the highest percentage in the moderate group (34%) were in the CBT group, and the highest percentage in the minimum group (38%) were in the anaerobic and relaxation groups. At 12 months, though there was a trend toward better improvement in fatigue and functioning scores for the maximum compliance group compared with the other groups, this did not reach significance.

No other studies evaluated characteristics of responders and nonresponders to interventions.

Discussion

Key Findings

Thirty-six studies contributed to our understanding of diagnostic methods, diagnostic accuracy or concordance, and benefits or harms associated with a diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Multiple case definitions have been used to define ME/CFS, and those that are labeled as myalgic encephalomyelitis (ME) and require the presence of post-exertional malaise (PEM) and other neurological and autonomic manifestations appear to represent a smaller but more impaired population. Validating new diagnostic tests is challenged by the lack of a 'gold standard' or universally accepted case definition. A self-reported symptom scale, the artificial neural network test, was found to have good sensitivity (95%), specificity (85%), and accuracy (90%) for identifying patients with ME/CFS compared with healthy controls. Another, the Schedule of Fatigue and Anergia for Chronic Fatigue Syndrome (CFS) scale, and certain 36-item Short Form Survey (SF-36) subscales or combination of subscales show moderate ability to discriminate between patients with ME/CFS compared with those without the condition. However, none have been adequately tested in a large population to determine validity and generalizability. Other tests, including serum parameters and cardiopulmonary function and recovery, have been insufficiently tested in broad populations to determine utility. We found little evidence on how diagnostic tests for ME/CFS vary by subgroups of the population and few studies that evaluated strategies on approaching the diagnostic workup to rule out other conditions prior to making a ME/CFS diagnosis. Evidence suggests that having an ME/CFS diagnosis is associated with perceived stigma, financial instability, difficulty in social interactions and relationships, and a greater risk of receiving a psychiatric diagnosis

Thirty-five trials contributed to our understanding of the efficacy of interventions to treat ME/CFS. Although most of the medication trials targeted an underlying pathophysiological dysfunction, most of the other treatments targeted associated symptoms of the disease. Trials of the immune modulator, rintatolimod, found improvement in exercise performance and suggested potential improvement in symptoms, including activities of daily living, and reduced use of other medications for relief of ME/CFS symptoms. A trial of the antiviral, valganciclovir, suggested improvement in fatigue, but further studies are required to determine if this is replicable. Different complementary and alternative (CAM) therapies have been studied only in small pilot trials with methodological limitations, and although homeopathy, pollen extracts, and carnitine preparations showed some benefit, the results have been inconsistent across different measurement tools precluding any determination of potential effectiveness. Harms of CAM therapies have been poorly reported. Counseling, behavioral therapies, and graded exercise therapy (GET) were found to be beneficial compared with control groups for outcomes of fatigue, function, and clinical global impression of change. Counseling techniques were also beneficial for outcomes of quality of life and employment. The magnitude of benefit is likely similar between cognitive behavioral therapy (CBT) and GET; however, the studies selected for less disabled patients as they did not use a case definition of ME. Only one study of CBT and GET performed a subgroup analysis on patients meeting the London (Dowsett, 1994) criteria and may have been underpowered to detect a difference. Furthermore, benefit was lost in a sub-analysis that only considered studies using formal CBT approaches. The ultimate goal is recovery and the lack of consistent and meaningful outcome thresholds for measuring recovery limit any interpretation of the results from the few trials that considered this outcome. Results of

four small trials suggest that younger, less disabled patients who focus less on their symptoms and avoid over or under exertion seem to do better. No differences were found for all other interventions and outcomes, as outcomes were either not reported, the study quality was poor, and/or the sample size was inadequate to provide a useful estimate. Although harms were not well reported across trials, GET was associated with a higher number of reported harms in several trials, higher withdrawal rates in one trial, and refusal for repeat exercise testing in another.

The key findings for this review are summarized in the summary of evidence table (Table 8, below) and the factors used to determine the overall strength of evidence grades are summarized in Appendix K.

Strength of Evidence

Our assessment of the strength of the evidence for major clinical outcomes is summarized in the strength of evidence table (Appendix K). We did not summarize the strength of evidence on diagnostic methods (Key Question 1) because the methods for doing so are not yet sufficiently developed to account for the variety of study designs, the uncertainty around determination of precision for estimates of test performance, the lack of consensus about the case definition for identifying a consistent study population, and the absence of a reference standard ("gold standard").[38] For intervention trials, major clinical outcomes are those explicitly stated in Key Question 2. The National Institutes of Health (NIH) Working Group and Technical Expert Panel members identified these as important outcomes because they are most relevant to patients, clinicians, and policymakers. Outcomes of benefit included in the strength of evidence table are overall function, fatigue, quality of life, days spent at work/school, proportion working full- or part-time, and clinical global impression of change. Harms outcomes included in the strength of evidence table are withdrawals due to harms, rates of harms, total withdrawals, serious harms, and total harms.

The strength of evidence table includes the four required domains: study limitations, directness, consistency, precision, and reporting bias (these terms are defined in Appendix F).[31] The table summarizes the strength of evidence. Whenever possible, a quantitative estimation of the effect size was provided. When a quantitative estimate was not possible due to the heterogeneity in measuring outcomes and the small number of studies per intervention, a symbolic representation of effect was included, with + representing benefit, <> representing no difference, and – representing a negative effect.

We qualitatively rated the overall strength of evidence as high, moderate, low, or insufficient for each outcome. Strength of evidence is high for outcomes with a low level study limitations, consistency in results, and adequate precision (certainty surrounding the result). The strength of evidence was downgraded to moderate for outcomes with a medium level of study limitations, imprecise estimates, and inconsistency between trials. Strength of evidence was ranked low if multiple deficiencies existed. Strength of evidence was moderate for GET compared with usual care, support, relaxation or adaptive pacing for outcomes of function, and global improvement, and for CBT for global improvement. Strength of evidence was low for CBT on measures of fatigue, function, quality of life, and employment; for GET on measures of fatigue and work impairment; and for rintatolimod on measures of function. There is low strength of evidence that CBT is not associated with an increase in harms. For all other interventions and outcomes, strength of evidence was insufficient because these outcomes either were not reported, the study quality was poor, and/or the sample size was inadequate to provide a useful estimate.

Table 8. Summary of evidence

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
KQ1 What methods are available to clinicians to diagnose ME/CFS and what conditions are required to be ruled out or excluded before assigning a diagnosis of ME/CFS?			
Available methods	Not applicable	Eight case definitions that include clinical criteria have been developed to identify patients with ME/CFS and are used by clinicians to distinguish ME/CFS from other conditions that also present with fatigue.	Not applicable
KQ1a What is the accuracy and concordance of methods used to diagnose ME/CFS?	11 observational descriptive studies (n=1,738)	8 studies evaluated concordance found that the symptoms reported by different case definitions varied. In general, populations defined by ME or ME/CFS criteria had more severe symptoms or more functional impairment than those defined by CFS criteria alone. 3 studies found that symptoms reported by various case definitions distinguished patients with ME/CFS from other populations.	Not applicable
	11 observational descriptive studies (n=2,067)	11 studies evaluated accuracy of various scales/tools compared to one of the case definitions. Artificial neural networks, the Schedule of Fatigue and Anergia for CFS scale, and subscales of the SF-36 were able to differentiate ME/CFS patients from healthy controls, however no studies evaluated these methods using an adequate sample size and spectrum of patients.	
KQ1b How does the use of these methods vary by patient subgroups?	3 observational/ descriptive studies (n=80, 2 studies used the same population of 30)	Older patients with CFS have more impairment than younger patients. Subscales of the SF-36 can distinguish the subset of CFS patients who fail to recover from cardiopulmonary exercise testing (CPET) 1 day and 1 week.	Not applicable
KQ1c What harms are associated with diagnosing ME/CFS?			
Psychological harm, including stigma from label	5 observational studies (n=329)	5 studies found that patients with CFS feel stigmatized by their diagnosis in terms of financial stability (1 study), work opportunities (1 study), perceived judgments on their character (1 study), social isolation (2 studies), or interactions with the health care system (3 studies).	Not applicable
Benefit of diagnosis	1 observational study (n=50)	1 study described benefit in having a name for their suffering, and the medical and social legitimacy conferred by having a diagnosis.	Not applicable

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Misdiagnosis	6 observational study (n=1,678)	6 studies identified a substantial burden of misdiagnosis in the CFS population.	Not applicable
Risk from diagnostic test	No studies	No studies identified that reported objective risks directly related to the process of conducting a diagnostic test for CFS.	Not applicable
Prejudice and stereotyping	2 observational studies (both used same population of n=146)	2 studies identified prejudice and stereotypes within the medical profession; medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and what treatment is being given.	Not applicable
KQ2a What are the benefits of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?			
Galantamine vs. placebo			
Decreased fatigue and improved quality of life	1 RCT (n=423)	No significant differences between 4 intervention groups and placebo.	Insufficient
Global improvement	1 RCT (n=423)	No significant differences between 4 intervention groups and placebo.	Insufficient
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies	No studies.	Insufficient
Hydrocortisone vs. placebo			
Improved overall function, decreased fatigue, and improved quality of life	1 RCT (n=68)	No significant differences between intervention and placebo.	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies	No studies.	Insufficient
Hydrocortisone + fludrocortisone vs. placebo			
Improved overall function, decreased fatigue, and improved quality of life	1 RCT (n=80)	No significant differences between intervention and placebo.	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies	No studies.	Insufficient
Immunoglobulin G vs. placebo			
Improved overall function	1 RCT (n=28)	Significantly better scores on SF-36 social functioning scale after intervention compared with placebo ($p<0.05$), but no difference on physical functioning scale.	Insufficient
Improved fatigue and quality of life, increased days spent at work/school and proportion working full- or part-time	No studies	No studies.	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Rintatolimod vs. placebo			
Improved overall function	1 RCT (n=84)	Significant increase in activities of daily living after intervention compared with placebo (23% vs. 14%, p=0.034), but no difference in change in KPS scores from baseline.	Insufficient
Increased exercise work capacity	2 RCT (n=316)	The intervention group compared with placebo had significant increases in exercise duration (10% vs. 2%, p=0.007), exercise work (12% vs. 6%, p=0.011), and cardiopulmonary exercise tolerance (37% vs. 15%, p=0.047).	Low
Improved quality of life, increased days spent at work/school and proportion working full-or part-time	No studies	No studies.	Insufficient
Valganciclovir vs. placebo			
Decreased fatigue	1 RCT (n=30)	Significant decrease in fatigue based on FSS scores decreasing in intervention group compared with placebo (mean change from baseline: -0.06 vs. 0.02, p=0.006).	Insufficient
Improved overall function	1 RCT (n=30)	No significant differences between intervention and placebo.	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full-or part-time	No studies	No studies.	Insufficient
Isoprinosine vs. placebo			
Improved overall function and decreased fatigue	1 RCT (n=15)	No significant differences between intervention and placebo.	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full-or part-time	No studies	No studies.	Insufficient
Fluoxetine vs. placebo			
Improved overall function	1 RCT (n=68)	No significant differences between intervention and placebo.	Insufficient
Decreased fatigue	1 RCT (n=68)	No significant differences between intervention and placebo.	Insufficient
Acclydine vs. placebo			
Improved overall function, decreased fatigue, and increased physical activity (actometer)	1 RCT (n=57)	No significant differences between intervention and placebo.	Insufficient
Improved quality of life, increased days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination			
Decreased fatigue	1 RCT (n=89)	Acetyl-L-carnitine had lower fatigue scores at 24 weeks, but propionyl-L-carnitine and the combination group improved more from baseline (p=0.004 and p<0.001, respectively).	Insufficient
Global improvement	1 RCT (n=89)	Significant improvement in propionyl-L-carnitine (63%, p<0.001) and acetyl-L-carnitine (59%, p<0.001) compared with the combination group (37%, p=0.084).	Insufficient
Improved overall function, quality of life, increased days spent at work/school, proportion working full- or part-time	No studies	No studies.	Insufficient
Pollen extract vs. placebo			
Decreased fatigue	1 RCT (n=22)	Significant improvement on fatigue scores in the pollen group compared with placebo at 3 months (-0.43 vs. -0.18, p<0.05).	Insufficient
Improved quality of life	1 RCT (n=22)	Significant improvement in quality of life scores in the pollen group compared with placebo at 3 months (-1.66 vs. -0.21; p<0.01).	Insufficient
Improved overall function, increased days spent at work/school, proportion working full- or part-time	No studies	No studies.	Insufficient
Low sugar/low yeast diet vs. healthy eating			
Decreased fatigue, improved quality of life	1 RCT (n=39)	No significant differences between interventions.	Insufficient
Improved overall function, increased days spent at work/school, proportion working full- or part-time	No studies	No studies.	Insufficient
Distant healing vs. no treatment			
Improved overall function	1 RCT (n=409)	Significant improvement on functioning scores for those who were blinded to the treatment compared with those who were not blinded to the treatment (covariance analysis effect for blinded vs. unblinded treatment: -1.54 [SE 0.70] 95% CI -2.91 to -0.18) No other significant differences between intervention and no treatment.	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school, proportion working full- or part-time	No studies	No studies.	Insufficient
Homeopathy vs. placebo			
Decreased fatigue	1 RCT (n=89)	Significantly better scores on MFI-20 for placebo group compared with intervention at 6 months (mean: 2.70 vs. 1.35, p=0.04).	Insufficient
Improved overall function	1 RCT (n=89)	No significant differences between intervention and placebo.	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Improved quality of life, increased days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient
Melatonin vs. phototherapy			
Improved overall function and decreased fatigue	1 RCT crossover design (n=30)	No significant differences between interventions.	Insufficient
Improved quality of life, increased days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing			
Improved overall function	11 RCT (n=1,441)	Results were mainly positive, but mixed. When 8 trials using the SF-36 physical functioning subscale were pooled there was a significant effect for the intervention group to have better scores vs. control at followup: weighted mean difference of 7.73 (95% CI 3.58 to 11.87). In 4 trials counseling improved overall functioning vs. controls on various measures (49 to 80% improved in counseling groups vs. 17 to 58% in controls), while 2 trials reported mixed results with different measures in the same study, 1 trial reported improvement in the control group compared with counseling, and the other 4 trials reported no differences between groups.	Low
Decreased fatigue	11 RCT (n=1,439)	Results were primarily positive, but mixed In 7 trials counseling significantly decreased fatigue vs. controls on various measures (27 to 76% improved in counseling groups vs. 7 to 65% in controls), while the other 4 trials reported no differences between groups.	Low
Improved quality of life	4 RCT (n=343)	Results were mixed In 2 trials counseling showed an improvement in quality of life vs. controls on various measures (mean QOLS at 12 weeks: 2.81 vs. 3.26; p=0.02 and mean change in QLI scores from baseline at 12 months: 2.6 vs. 0.6; p<0.05) and the other 2 trials reported no differences between groups.	Low
Increased proportion working full- or part-time	2 RCT (n=145)	No significant differences between intervention and control.	Low
Increased hours worked	2 RCT (n=125)	Significantly more hours worked per week for CBT group vs. control (mean 35.57 vs. 24.00; p<0.04) for 1 trial. The other trial reported no significant differences between intervention and no intervention.	Low

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Decreased work impairment	2 RCT (n=531)	Significant improvement reported in both studies for CBT group on work and social adjustment scale compared with controls (mean at 6 months: 3.3 vs. 5.4; p<0.001 on scale scored with range 0-8; mean at 1 year: 21.0 vs. 24.5; p=0.0001 on scale scored with range 0-45).	Low
Global improvement	2 RCT (n=531)	Both trials report better global improvement for CBT vs. control (41% and 70% improved in CBT vs. 25% and 31% in controls).	Moderate
Face-to-face CBT vs. telephone CBT			
Clinical global improvement	1 RCT (n=65)	More individuals rated as much better or very much better in face-to-face group compared with telephone group (6 months: 60% vs. 40%; p=NR and 12 months: 57% vs. 55%; p=NR).	Insufficient
Improved overall function, decreased fatigue and work impairment	1 RCT (n=65)	No significant differences between interventions.	Insufficient
Quality of life, days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing			
Improved overall function	4 RCT (n=619)	Results from 3 studies that used the SF-36 physical functioning subscale were pooled, there was a significant effect for the intervention group to have better scores vs. control at followup: weighted mean difference 10.29 (95% CI 6.71 to 13.86). Increase in the 6MWT in 1 trial (+35.3 m vs. usual care, +41 m vs. adaptive pacing, p<0.001	Moderate
Decreased fatigue	4 RCT(n=619)	Significantly better Chalder Fatigue Scale scores reported for exercise groups compared with controls in 3 of the studies:Mean total: 13.91 vs. 24.41; p=0.02, physical fatigue scores: 7.91 vs. 14.27; p=0.02; and mental fatigue scores: 6.00 vs. 10.14; p=0.03 at 12 weeks; mean total: 20.5 vs. 27.4; p=0.004 at 12 weeks; and mean difference in change from baseline from adaptive pacing: -2.5; 95% CI -4.2 to -0.9; p=0.0059 and no treatment: -3.4; 95% CI -5.0 to -1.8; p=0.0001.1 study reported no differences between groups.	Low
Increased proportion working full- or part-time	1 RCT (n=59)	More in the exercise group were working at 1 year compared with control (66% vs. 39%; 95% CI 9% to 44%)	Insufficient
Decreased work impairment	1 RCT (n=475)	Significant improvement reported for exercise group on work and social adjustment scale compared with adaptive pacing and no treatment at 1 year (20.5 vs. 24.5 vs. 23.9; p=0.0004 and p<0.001, respectively)	Low

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Global improvement	3 RCT (n=583)	Significantly more improvement reported in exercise groups (31% and 54%) compared with controls (7%, p=0.05 and 24%, p=0.04) RR 1.54 (95% CI 1.26 to 1.89)	Moderate
Recovery (Chalder fatigue score <18, SF-36 physical function score >60, no longer meeting Oxford case definition criteria, and reporting much or very much improvement on CGI)	1 RCT (n=475)	Significant improvement in recovery in the exercise group compared with adaptive pacing (OR 3.38, 95% CI, 1.65 to 6.93) and usual care (OR 3.71, 95% CI, 1.78 to 7.74)	Insufficient
Improved quality of life, increased days spent at work/school	No studies	No studies.	Insufficient
Home orthostatic training vs. sham home orthostatic training			
Improved overall function	1 RCT (n=36)	No significant differences between interventions.	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school, proportion working full- or part-time	No studies	No studies.	Insufficient
Qigong exercise vs. no qigong exercise			
Improved overall function	1 RCT (n=52)	Significantly better SF-12 physical functioning scores for qigong exercise compared with no exercise at 4 months (mean: 42.7 vs. 35.7, p=0.001).	Insufficient
Decreased fatigue	1 RCT (n=52)	Significantly better Chalder Fatigue Scale scores in exercise group compared with no exercise group at 4 months (mean total: 21.6 vs. 32.1, p<0.001; mean physical fatigue subscale: 12.9 vs. 20.3, p<0.001; mean mental fatigue subscale: 8.8 vs. 11.9, p=0.012).	Insufficient
Improved quality of life, increased days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient
GET ± fluoxetine vs. fluoxetine ± placebo			
Improved overall function	1 RCT (n=136)	Significant improvement for exercise groups (either alone or combination) on functional work capacity at 26 weeks (mean change from baseline: 1.9; 95% CI 0.15 to 3.69; p=0.03) compared with other groups.	Insufficient
Decreased fatigue	1 RCT (n=136)	Significantly more individuals in exercise groups (either alone or combination) did not meet the threshold of “caseness” for fatigue on Chalder Fatigue Scale (18% for both exercise groups and 6% for both other groups; p=0.025).	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Increased days spent at work/school and proportion working full- or part-time	No studies	No studies.	Insufficient
CBT + GET vs. usual care			
Improved overall function, and decreased fatigue	1 RCT (n=115)	No significant differences between intervention and control.	Insufficient
Improved quality of life, decreased work impairment, increased days spent at work/school, proportion working full-or part-time	No studies	No studies.	Insufficient
KQ2b What are the harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?			
Galantamine vs. placebo	1 RCT (n=434)	90% (389/434) reported harms; 23% (88/389) withdrew due to harms; 2% (8/389) in galantamine reported serious harms but none attributed to the study drug; no significant differences reported between groups.	Insufficient
Hydrocortisone vs. placebo	1 RCT (n=70)	More harms reported with hydrocortisone vs. placebo (suppression of adrenal glucocorticoid responsiveness: 12 vs. 0; p<0.001; increased appetite: 17 vs. 8; p=0.02; weight gain: 19 vs. 8; p=0.006; difficulty sleeping: 17 vs. 8; p=0.02); no other significant differences between groups.	Insufficient
Hydrocortisone + fludrocortisone vs. placebo	1 RCT (n=80)	1.3% (1/80) withdrew due to acne and weight gain, no serious harms reported; no other harms data reported.	Insufficient
Immunoglobulin G vs. placebo	1 RCT (n=28)	Significantly more with headaches in immunoglobulin G group vs. placebo (93% vs. 60%; p=0.03); 20% total harms overall; 1 in each group withdrew due to harms; 2 in immunoglobulin G and 3 in placebo developed serious harms.	Insufficient
Rintatolimod vs. placebo	2 RCT (n=324)	Flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in rintatolimod vs. placebo (p<0.05); no other differences between groups.	Insufficient
Valganciclovir vs. placebo	1 RCT (n=30)	No one withdrew due to harms, 1 in each group developed cancer, deemed unrelated; no other harms data reported.	Insufficient
Isoprinosine vs. placebo	1 RCT (n=15)	No one withdrew due to harms; no other harms data reported.	Insufficient
Fluoxetine vs. placebo	1 RCT (n=68)	More total withdrawals in the fluoxetine group compared with placebo.	Insufficient
Acclydine vs. placebo	No studies	No studies.	Insufficient
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination	1 RCT (n=89)	No differences reported between groups for withdrawals due to harms; no other harms data reported.	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
Pollen extract vs. placebo	No studies	No studies.	Insufficient
Low sugar/low yeast diet vs. healthy eating	No studies	No studies.	Insufficient
Distant healing vs. no treatment	No studies	No studies.	Insufficient
Homeopathy vs. placebo	No studies	No studies.	Insufficient
Melatonin vs. phototherapy	No studies	No studies.	Insufficient
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing			
Withdrawals due to harms	1 RCT (n=47)	1 trial reported none withdrew due to harms.	Insufficient
Rates of harms	1 RCT (n=257)	1 trial reported no differences between groups for reported harms.	Insufficient
Total harms	2 RCT (n=728)	1 large trial reported fewer total harms in the CBT group (848) vs. adaptive pacing (949, p=0.0081) and no treatment (977, p=0.0016) The other study did not report harms by group, but deemed all unrelated to the intervention.	Low
Serious harms	2 RCT (n=728)	1 large trial (n=471) reported fewer serious harms in the CBT group per 100 person-years (5.0; 95% CI 2.2 to 9.8) vs. adaptive pacing (10.1; 95% CI 5.8 to 16.3), but was similar to no treatment (4.4; 95% CI1.8 to 9.0) The other trial reported that no serious harms were reported.	Low
Face-to-face CBT vs. telephone CBT	No studies	No studies.	Insufficient
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing			
Withdrawals due to harms	1 RCT (n=49)	1 trial reported 40% (10/25) of GET group refused to repeat the required fitness test due to feeling initial test was harmful and 1 person withdrew due to a calf injury.	Insufficient
Total harms	2 RCT (n=524)	1 trial reported similar harms in the GET group (992) vs. adaptive pacing (949) and no treatment (977), but p=NR The other trial reported 2% (1/49) experienced a harm.	Insufficient
Serious harms	1 RCT (n=475)	1 large trial reported similar serious harms in GET group per 100 person-years (10.6; 95% CI 6.2 to 17.0) vs. adaptive pacing (10.1; 95% CI 5.8 to 16.3) but fewer in no treatment (4.4; 95% CI 1.8 to 9.0).	Insufficient
Home orthostatic training vs. sham home orthostatic training	No studies	No studies.	Insufficient
Qigong exercise vs. no qigong exercise	1 RCT (n=52)	No harms were reported by either group, no other harms data provided.	Insufficient

Table 8. Summary of evidence (continued)

Key Question Outcome	Study Design Number of Studies (n)*	Findings and Direction of Effect	Strength of Evidence Grade
GET vs. fluoxetine vs. combination or placebo	1 RCT (n=136)	11 withdrawals due to medication side effects 13% in fluoxetine group vs. 3% in placebo group; no other harms data reported in study.	Insufficient
CBT + GET vs. usual care	No studies	No studies.	Insufficient
KQ2c What are the characteristics of responders and nonresponders to interventions?			
CBT vs. no treatment			
Baseline differences	1 RCT (n=27)	Significant differences between those who responded to CBT and those who did not on baseline measures of functional impairment on SIP-8 (mean: 1,330 vs. 1,985; p=0.031), daily observed fatigue (mean on scale 0-16: 7.4 vs. 9.7; p=0.023), and daily observed pain (mean on scale 0-16: 4.5 vs. 7.8; p=0.026); but not for hours worked per week (mean: 10.9 vs. 2.6; p=0.062).	Insufficient
GET vs. usual care			
Mediating factors affecting response to GET	1 RCT (n=49)	Reduced symptom focusing was associated with self-reported improvement in mental and physical fatigue, global change, and physical functioning	Insufficient
CBT vs. cognitive therapy, vs. anaerobic therapy vs. relaxation			
Energy envelope comparisons	1 RCT (n=81)	Patients who avoided over or under exertion (stayed within their energy envelope) and had 75% or better compliance with their home program had improvement in fatigue and function measures.	Insufficient
Pragmatic rehabilitations vs. supportive listening			
Baseline differences	1 RCT (n=257)	Those who were younger, had shorter illness durations, and less severe mobility problems at baseline showed greater improvements in fatigue at 70 weeks	Insufficient

* Sample size includes only those analyzed

Abbreviations: 6MWT= 6 minute walk test; CBT= Cognitive Behavioral Therapy; CFS = chronic fatigue syndrome; GCI= clinical global impression change score; CI= Confidence Interval; FSS= Fatigue Severity Scale; GET= graded exercise therapy; KPS = Karnofsky Performance Score; KQ= Key Question; m= meter; ME = Myalgic encephalomyelitis; MFI-20= Multidimensional Fatigue Inventory; n= sample size; NR= not reported; OR= odds ratio; QLI= Quality of Life Index; QOLS= quality of life scale; RCT = randomized controlled trial; SE= standard error; SF-12= Short Form 12-item Health Survey; SF-36= 36-item Short Form Survey; SIP-8 = Sickness Impact Profile 8-items; SOFA-CFS= Schedule of Fatigue and Angina for CFS scale; vs.= versus.

Findings in Relationship to What Is Already Known

The lack of a clear etiology for ME/CFS, the multisystem involvement of the syndrome, and its overlap with other chronic conditions all contribute to the difficulty in diagnosing ME/CFS. Furthermore, there exists the risk of misdiagnosing a patient with an overlapping condition or incorrectly labeling a patient with ME/CFS. ME/CFS is a condition that does not have a universally accepted diagnostic (gold) standard, a set of criteria that defines the condition. The lack of a gold standard poses significant challenges for evaluation of diagnostic tests, and yet this is a situation that arises commonly with conditions that are syndromes. A syndrome is a "combination of symptoms and signs which have been observed to occur together so frequently and to be so distinctive that they constitute a recognizable clinical picture."[130] That is, the combination of findings is so unusual as to be thought not a coincidence. In such situations, the traditional evaluation of a diagnostic test is more challenging The ME/CFS literature is beginning to test diagnostic strategies but as yet has not presented data that would sufficiently differentiate the diagnosis of ME/CFS from other similar conditions in a population of patients with substantial diagnostic uncertainty.

One of the primary limitations in the literature about diagnostic tests for ME/CFS was that very few studies included a validation cohort. Instead, these studies primarily evaluated a diagnostic test in a single initial population (a derivation cohort). Derivation studies are a necessary first step when attempting to achieve a valid diagnostic test, but they also have inherent methodological problems. They often involve the use of cases and controls, two very distinct populations, in order to determine whether the test can distinguish between those two groups. If the test is capable of distinguishing between two distinct groups, then further testing should use populations that are more closely related (i.e., they have overlap in terms of symptoms), in order to more rigorously test the diagnostic capability of a particular test. The more rigorous diagnostic testing studies will include a population for whom the clinician is likely to face diagnostic uncertainty, and then test how well the test performs in classifying that population accurately. The studies identified for evaluation of diagnostic tests for ME/CFS fell into three main categories. The first are those that evaluated how those case definitions compare with each other, and whether they identify the same or different populations. While this was not a distinct Key Question, it was felt to shed light on the evolving definition of ME/CFS and the difficulty with identifying a universally acceptable reference standard. A second group of studies evaluated a diagnostic test or a scale against a chosen reference standard. In this case, the reference standard was typically one or more of several case definitions that have been published (CDC Holmes, 1988 or Fukuda, 1994, Canadian ME/CFS definition, International Consensus Criteria for ME, etc.). The third group of studies identified are those that address harms of diagnosis.

There were no studies that quantitatively compared the diagnostic concordance of two case definitions. Several studies attempted to demonstrate that ME, ME/CFS, and CFS case definitions identify clinically different groups of people. Studies did this by identifying people who met one criteria set but not the other.[5,9,50-52] Using this approach, it appears that the ME and ME/CFS case definitions select a population with more impairment, lower functioning, and higher symptom reporting compared with CFS alone. Other studies compared subjects who met a definition of CFS with subjects who had other disease states and/or those who comprised a healthy control population.[57-59] As expected, these studies demonstrated CFS subjects have lower functioning and higher symptom burdens than people from the general population.

Using a slightly different approach, a prior systematic review compared case definitions for ME/CFS to summarize how the prevalence of ME/CFS in a population and the symptom burden for patients vary when using different case definitions.[131] That study attempted to bring some consistency to case definitions for ME/CFS in the absence of a reference standard. The inclusion criteria were broader than those for this report but similarly found that the validation studies were weak and heterogeneous. This group called for the community of ME/CFS researchers to prioritize research on treatments using existing case definitions, rather than development of additional new case definitions.[131] They felt the CDC (Fukuda, 1994) criteria had the most studies on validation and comparison with other measures and was the most appropriate for clinical practice.

Notably, many of the intervention studies used the Oxford (Sharpe, 1991) case definition for inclusion, yet it has been criticized as being so nonspecific that it is unable to differentiate a patient with ME/CFS from a patient with an overlapping condition. The Oxford (Sharpe, 1991) criteria has been shown to include more patients than either the CDC (Fukuda, 1994) or the London ME (Dowsett, 1994) criteria. In the PACE trial, only 30 percent of patients enrolled using the Oxford (Sharpe, 1991) case definition also met the London (Dowsett, 1994) case definition for ME.[121] Indeed, when comparing criteria across different case definitions, the symptom set of the Oxford (Sharpe, 1991) case definition is more generalized and as such is at greater risk of including patients with other overlapping conditions. Based on feedback from public comments to the draft of this review, patients and advocacy groups prefer the Canadian or International case definitions and have argued strongly against using a case definition that does not require the presence of PEM. (An Open Letter was received during the public comment period for this review from 53 advocates and experts).

Much research in this field focuses on discovering etiologies rather than testing diagnostic strategies in patients. Studies that attempted to define an etiology on the basis of a biochemical marker or a particular physiologic test were not included in this review; the intent of these studies was to identify an etiology rather than understand how the specific test could distinguish patients that would respond to treatment. In addition to biomarker studies (cell function, immunologic, virologic/bacteriologic, hormonal, etc.), studies identified subgroups on the basis of exercise testing,[132,133] cerebral blood flow as measured by arterial spin labeling,[134] gait kinetics,[135] impaired blood pressure variability/hemodynamic instability,[136,137] bioenergetics (capacity to recover from acidosis),[138] and many others. These studies did not report diagnostic testing outcomes, such as receiver operating curve (ROC)/area under the curve (AUC), sensitivity, specificity, or concordance, and were therefore not useful in evaluating diagnostic testing for this report. The studies on serum biomarkers and cardiopulmonary function/recovery that did meet the inclusion criteria were not adequately tested in a broad spectrum of patients to determine utility for distinguishing patients with ME/CFS compared with other patients with chronic and disabling conditions.

In research studies, patients with ME/CFS reported feeling stigmatized by their diagnosis in terms of financial stability, work opportunities, perceived judgments on their character, social isolation, and interactions with health care providers. Compounding these difficulties is the substantial burden of misdiagnosis among this patient population. Two studies objectively identified prejudice and stereotypes towards patients with ME/CFS from members of the medical community; medical trainees and mental health practitioners make judgments about a patient's condition based on the name it carries (ME, CFS, or other) and which treatment is being given. While these studies were descriptive and based on survey data, the results suggest valid concerns

about the harm of labeling patients with a diagnosis of ME/CFS. These harms may reflect the chronic and disabling nature of this disease, combined with a lack of understanding about the diagnosis among the medical community and uncertainty about the etiology of ME/CFS. One commentary suggested that the harm is associated with the implications of a label rather than the label itself, and that it is "acceptable and often beneficial to make diagnoses such as CFS, provided that this is the beginning and not the end, of the therapeutic encounter."[139]

Determining the efficacy of medication and CAM interventions to treat ME/CFS was limited because most were only evaluated in single studies at one center and had significant methodological limitations, including small sample sizes with some enrolling fewer than 20 subjects in one arm. Additionally, outcomes were assessed using different methods and different scales. Some medication trials were primarily intended to measure intermediate outcomes, such as natural killer cell-mediated cytotoxicity,[89] and most were underpowered for the health outcomes relevant to this systematic review. While several fatigue and function outcomes were based on validated scales and measures, others were not, and the clinical significance of changes in scores over time are not clear.

Although placebo-controlled trials of immune modulating and antiviral medications suggested potential improvement in fatigue and functioning, some findings were of borderline statistical significance and other outcomes did not differ between groups. The rationale for treating patients with medications that have antiviral or immunomodulatory properties is based on the association of ME/CFS with viruses and immunological abnormalities that may underlie or promote its pathogenesis.[18,140-142] Although small trials of acyclovir,[91] immunoglobulin G,[85,143] and isoprinosine[89] indicated no statistically significant differences between treatment and placebo groups for measures of fatigue, quality of life, or function, two trials of intravenous rintatolimod[87,88] and a trial of oral valganciclovir[86] suggested improvement. These trials differed from the earlier trials by using newer medications and applying selective inclusion criteria for participants that targeted patient subgroups based on clinical history of a likely viral onset of ME/CFS and high antibody titers[86] or severe disability.[87,88] However, most of these trials were meant as pilot studies to determine potential benefit and as a foundation for larger trials of longer duration. The results were not definitive and were limited by inconsistencies in methods and findings, small sample sizes, methodological shortcomings, and lack of long term followup. Trials of galantamine, hydrocortisone, and immunoglobulin G indicated no significant improvement compared with placebo. Harms related to medications that were statistically significantly higher for the treatment versus placebo groups included suppression of adrenal glucocorticoid responsiveness, increased appetite, weight gain, and difficulty sleeping with hydrocortisone; flu-like syndrome, chills, vasodilatation, dyspnea, and dry skin with rintatolimod; and headaches with immunoglobulin G.

Consistent with other systematic reviews, both CBT and GET were found to improve symptoms, primarily based on fatigue and function outcomes, whereas evidence on other nonpharmacological interventions was inconclusive.[144-147] Results need to be interpreted with caution given that studies often used multiple methods of evaluating outcomes and several had mixed results on the same outcome when comparing different tools. No study included patients based on a case definition for ME and only one included homebound patients. One study performed a subgroup analysis of those meeting the London ME (Dowsett, 1994) case definition but may have been too small to detect a difference even if a difference existed.[121] Recovery as an outcome was reported in few trials and the variability in definition and thresholds leave the results meaningless for comparison. In the PACE trial, the criteria for inclusion was a SF-36

physical functioning score of 65 or less (revised protocol), yet the threshold for recovery was a score of 60 or more, and the Chalder fatigue score was less than 18, while normal is considered less than 4. An ideal definition of recovery would really mean a return to baseline function, which would be unique to each individual. Since this would be a difficult measure for research purposes, refining an acceptable definition with meaningful values is needed. Another critique of this literature is that some investigators teach patients that the disease is psychologically-based and caused by misperceptions and volitional deconditioning. By then educating and training patients that they can overcome their disease by changing attitudes, patients would expect to do better and consequently they report improvement on self-reported surveys.

When considering responders compared with nonresponders to treatments, one study comparing GET with usual care found that a reduction in symptom focusing was associated with improvement in self-reported measures of function, fatigue, and global change.[127] In a different fair-quality study using a cluster analysis to identify coping strategies for ME/CFS patients, the investigators determined standardized discriminant function and structure coefficients for three clusters.[148] One function separated the clusters and was significant ($F=3.31$, $p=0.01$) and accounted for 10 percent of the variance between groups ($R_c=0.32$). Adaptive coping accounted for 56 percent of the variance explained by the function ($R_s=0.75$) and less adaptive coping accounted for 25 percent ($R_s=0.50$). These strategies have obvious merit in general but also raise the question of whether reported improvements translate into meaningful change (i.e., returning to work, maintaining a household, meeting the demands of parenting). This question remains unanswered in the current literature. Additionally, although some of the studies attempted to measure adherence, inherent inaccuracies exist with self-reporting, particularly when it applies to home exercise programs. The one trial that considered homework compliance found that degree of improvement paralleled degree of homework compliance; however, only the cognitive therapy group had 75 percent or greater compliance and GET was not evaluated. It remains uncertain whether improved adherence, particularly with GET, is associated with greater benefit and meaningful change or greater harm.

Harms were not well reported throughout all of the nonpharmacological and CAM interventions. When reported, the harms associated with exercise included total, serious adverse events, nonserious adverse events, harms attributable to treatment, or withdrawal due to harms, but the specific harms were not delineated.[90,108,121,127] In the combination trials, the greatest number of adverse events reported were in the GET arm of one trial,[121] lowest adherence was in the exercise arm in another trial,[108] and one trial had greatest withdrawal in the exercise arm.[90,125,127] Significant number of patients refusing to repeat physiological testing implies significant harm in at least some of the patients.[127] Although not scientific, a survey sponsored by the ME Association found that patients believed that GET made more people worse compared with other treatments.[149,150] One study comparing CBT with cognitive therapy, anaerobic exercise, or relaxation found that those patients who remained within their energy envelope (avoided overexertion and under exertion by exerting a comfortable range of energy) had a significant improvement in mean fatigue and functioning scores regardless of treatment arm.[106] This line of therapy needs to be further studied in varied settings to determine its utility over time and whether these interventions can widen one's energy envelope and reduce harm.

A serious gap in the body of the evidence is the lack of subgroup analysis based on factors or symptom sets such as clinical features at baseline (extent of PEM, autonomic dysfunction, neurocognitive impairment, etc.), severity of disease, duration of disease, and patient demographics. In the current literature, ME definitions were not used for inclusion into any

treatment trials and subgroup analysis was rarely performed. Effectiveness and/or harms may differ between patient subgroups, and given the small sample size of most of the trials, combining all patients may have lessened the effect size. A recent systematic review that compared different case definitions agreed that patients should be classified according to their severity and symptom patterns in order to optimally guide therapy and predict prognosis.[131]

Applicability

The applicability of our findings to real-world clinical settings is supported by several features of the body of literature we reviewed. First, we included all recognized case definitions of ME/CFS in order to allow a broad representation of patients. Studies were conducted primarily in the United States or Western Europe and the patient population was predominantly female, which is consistent with clinical practice. Duration of symptoms, while not consistently reported, was broadly represented across studies. The interventions and comparators represented most of the therapeutic modalities commonly used in clinical practice.

However, there are several features of this body of evidence that limit its generalizability to the broader population of patients with ME/CFS, including factors surrounding the diagnosis itself. Given that the condition is a syndrome with a constellation of symptoms and lacking a gold standard for diagnostic comparison, diagnosis is at inherent risk of bias by the opinion of experts. Additionally, numerous comments on the draft report of this review emphasized that PEM is the critical feature of ME/CFS, yet most diagnostic studies used CDC CFS case definitions as reference standards (Holmes, 1988, Fukuda, 1994, or Reeves, 2005), which do not require the presence of PEM; no intervention trial used an ME case definition. Many of the diagnostic studies were conducted in a referral based environment and lacked a broad-based spectrum of patients, some with and some without the disease. Patients from specialty clinics may also represent more severe forms of the condition. Additionally, patients from rural centers or who lack insurance or financial resources may not have access to specialty clinics or clinical trials. Patients in research studies tended to be white middle-aged women, and it is unknown if the results in this population are generalizable to other demographic populations. The largest trial, PACE, excluded patients who could not read or speak English and only 7 percent of the study participants were from ethnic minority populations.[121] Few trials enrolled homebound patients, with most trials requiring patients to be well enough to attend multiple sessions of treatment.

We elected to include trials using any predefined case definition but recognize that some of the earlier criteria, in particular the Oxford (Sharpe, 1991) criteria, could include patients with 6 months of unexplained fatigue with physical and mental impairment but no other specific features of ME/CFS. Applying this has the potential of inappropriately including patients that would not otherwise be diagnosed with ME/CFS and may provide misleading results. Most of the intervention trials used the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions for inclusion and the results may not be applicable to patients meeting case definitions for ME.

In clinical practice, treatment of ME/CFS often involves multiple concurrent therapies but we found few trials that compared one intervention with another or that compared a combination of concurrent therapies with another. We also found few trials that selected patients based on symptom patterning. The trial on valganciclovir, an antiviral medication, preselected patients with an inciting febrile event with lymphadenopathy and found improvement in fatigue in this population of ME/CFS, while the trials on immune modulators, which included patients who were severely disabled, found some improvement in exercise capacity. Both counseling

techniques and GET showed improvement in most outcomes but studies to date have focused on efficacy rather than effectiveness. The combination of CBT and GET has not been adequately studied (one trial) to determine if this is more effective than a single intervention or if some patients may do better with this combination. It remains uncertain whether these results apply to all patients with ME/CFS or if there are patient subgroups that might receive greater benefit or experience greater harm, particularly in the GET trials, due to the lack of subgroup analysis.

Limitations of the Evidence Base

The main limitation of the evidence base in our review was poor study quality. Most trials did not specify randomization method, did not conceal allocation, and did not mask outcomes assessment. Most studies were small and many were underpowered to detect significant differences. Studies were also highly variable in terms of methods used to measure outcomes limiting our ability to combine or compare results across studies.

A potential limitation of our review is that important studies whose findings might influence clinical and policy decisionmaking may not have been identified. We conducted a comprehensive, broadly inclusive search that produced 6,175 study titles and abstracts. Although we excluded non-English language studies and studies published before 1988, we do not believe that important studies of therapies used in current practice were missed; the general consistency of our findings with other systematic reviews provides some assurance that our review was not biased by our selection criteria. Our review focused on diagnostic methods that provided data on a test's utility in identifying patients with ME/CFS (receiver operator curve [ROC]/area under the curve [AUC], sensitivity, specificity, concordance). Other testing strategies were not reviewed and may provide further insight methods of identifying patients with ME/CFS.

To evaluate the benefits and harms of treatments, we included studies with durations of 12 weeks or longer because of the fluctuating nature of ME/CFS. This approach may have excluded studies of antiviral or other types of medications that are traditionally prescribed for shorter durations. To account for this, we searched the excluded studies for medication trials that were appropriately given for a shorter duration, and identified two trials.[91,92] A crossover trial of intravenous acyclovir enrolled 27 adults with CFS who met serologic criteria for Epstein-Barr virus.[91] All patients were treated with acyclovir or placebo for 37 days, then they crossed over to the alternate treatment. Fatigue, vigor, and wellness scores, as well as other outcomes, did not differ between groups, although three patients developed acyclovir-induced nephrotoxicity. The second trial randomized 30 patients with CFS to intravenous rituximab, a monoclonal antibody, or placebo given as an infusion at two different times spaced 2 weeks apart.[92] More participants in the rituximab compared with placebo group had improved SF-36 physical health and function scores and unadjusted fatigue scores , although adjusted differences were not statistically significant. Neither study change the overall conclusions of this report.

We included outcomes of overall improvement, fatigue, function, quality of life, and employment, which represents patient-centered functional health outcomes. Some interventions may have provided benefit for other symptoms of ME/CFS, and this review would not have identified these outcomes.

There may have been biased reporting of results in the literature such that only selected studies were published and retrievable and that published studies may have been affected by conflicts of interest, outcome reporting bias, or analysis reporting bias. Reporting bias and conflicts of interest are concerns with any systematic review. We were not able to conduct quantitative analyses to evaluate the possibility of publication bias for our findings because of

the heterogeneity across studies in our review, and in many cases the lack of key information needed to perform quantitative syntheses generally precluded meaningful comparison of effect sizes. Weighing against the likelihood of publication bias in our review, however, is the fact that the majority of studies in our review were small (most <100 patients, many <50) and most reported no significant effect of the intervention. Publication bias typically results in selective publication of larger studies and/or those with positive findings, and studies biased by conflicts of interest would also be more likely to report positive findings. We also conducted gray literature searches to look for unpublished data and did not find evidence of unreported studies. The limited and vague reporting of harms in many studies may suggest outcome reporting bias for these outcomes.

Future Research and Implications for the Pathways to Prevention Workshop

What Are the Future Research Needs for Definition, Diagnosis, and Treatment of ME/CFS?

Given the prevalence and health impacts of ME/CFS, future research is necessary in several areas:

- Case Definitions: Consensus about which case definition is appropriate to use as the gold standard will further advance the study of diagnostic methods for ME/CFS. In the absence of consensus, future studies aimed at clarifying the diagnosis of ME/CFS should consider reporting how well a particular diagnostic test compares with more than one of the published case definitions. The lack of a definitive diagnostic test should not discourage the support of intervention and treatment studies. Ideally future intervention studies would consistently use an agreed upon single case definition to reduce variability in the patient samples and facilitate comparison of therapeutic benefit across studies. If a single definition cannot be agreed upon, future research should retire the use of the Oxford (Sharpe, 1991) case definition, given that it is at high risk of including patients who may have an alternate fatiguing illness, or whose illness resolves spontaneously with time.
- Diagnostic Instruments: Future studies evaluating the diagnostic capability of instruments for the identification of ME/CFS should include populations that include a broad range of people with relevant conditions that require clinical distinction from ME/CFS, such as fibromyalgia. Thus, the ideal diagnostic test for ME/CFS would adequately distinguish between ME/CFS and these conditions. Additionally, studies should report statistics on how well a particular measure distinguishes a group with ME/CFS from a group that does not meet these criteria—using concordance and the net reclassification index. For physiological and metabolic testing, selection of a broader spectrum of patients as a comparative group rather than healthy controls is needed.
- ME/CFS registry: A national longitudinal registry of patients with a diagnosis of ME/CFS would allow for comparison of diagnostic criteria between patients and clarification of diagnoses over time. This strategy could also identify a well-characterized population for use in both diagnostic and treatment trials.
- Treatment Inclusion Criteria: Use of selective inclusion criteria as was performed in some of the antiviral and rintatolimod trials may help to identify those with greater

immunological versus neurological symptom sets, which may aid in furthering the understanding of etiology and diagnosis, as well as targeting treatment approaches. Consideration of the biomarker studies may aid in identifying these subsets of patients.

- Treatment Interventions: Reflective of the current clinical environment in which patients receive more than one treatment, interventions should be in multiple sites, use multicomponent treatments, larger sample sizes based on power calculations for key outcomes, and more rigorous adherence to methodological standards for clinical research. Given the fluctuating nature of the condition, followup periods greater than 1 year would be optimal to determine effectiveness over time.
- Treatment Analyses: Reporting of information about co-interventions, the timing of studied interventions in relation to other interventions, and adherence to interventions would improve the applicability of study findings. Similarly, stratification of findings by patient characteristics (e.g., baseline severity, comorbidities, demographics, symptom sets) would help determine the applicability of different interventions for specific patients and situations. It is particularly important for future studies to report findings according to the cardinal features of ME/CFS such as PEM, neurocognitive status, and autonomic function, as treatment choices may differ for subsets of the population.
- Outcome Evaluation: Given the plethora of outcome measures, the development of a set of core outcomes including patient-centered outcomes such as quality of life, employment, and time spent supine versus active, would help guide research and facilitate future data syntheses. In 2003 Reeves and colleagues recommended using an activity recorder to quantify activity, yet no study included in our review reported on this outcome. With today's readily available personal activity trackers that can record activity as well as physiological responses, these outcomes should be easily obtained. Recovery needs to be better defined and should include functionally meaningful outcomes. Clearly reporting harms, particularly surrounding exercise therapy and testing and treatment for specific subgroups, may help identify patients more negatively affected by these interventions. Personal activity trackers could also be used to identify harms that result in reduced activity.
- Other: Research is ongoing in diagnosing and treating specific symptoms such as PEM or orthostasis, and synthesizing this literature and evaluating its utility in diagnosing the syndrome of ME/CFS or subsets of the population is needed.[6,151-157] Further studies are needed to determine the utility of 2-day cardiopulmonary exercise testing to identify or monitor symptoms of post-exertional malaise.

The stories that were shared by patients and advocates in response to the draft report of this review iterated the devastating impact that this condition has had on patients and their loved ones. Although this review has focused on scientific literature, these messages have been heard and appreciated. It is recommended that future studies include the patient and/or advocate voice in the planning and development phases so that future research is relevant and meaningful to those affected by ME/CFS.

Conclusions

Multiple case definitions for ME/CFS exist. Those that require symptoms of PEM, neurological impairment, and autonomic dysfunction representing a more severe form of the condition. No current diagnostic tool or method has been adequately tested to identify patients

when diagnostic uncertainty exists. Reports suggest stigmatization as a potential harm of receiving a diagnosis of ME/CFS; however, no studies specifically evaluated the potential positive aspects of getting a diagnosis such as relief at having an explanation for the symptoms. Although counseling approaches and GET have shown benefit in some measures of fatigue, function, and global improvement, they have not been well studied in subgroups of the population. Most other interventions have insufficient evidence to direct clinical practice. Harms reporting has been poor, and although GET appears to be associated with worsening symptoms in some patients, the cause remains uncertain. Acceptance of a single case definition and development of a core outcomes set would aid future research efforts to study effectiveness of interventions. Use of selective inclusion criteria such as symptom subsets (e.g., neuroendocrine/immune, neurological/neurocognitive, etc.) is needed to better inform diagnosis and treatment of ME/CFS. In general, future research focused on correcting limitations of current evidence is important to move the science forward.

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Abbreviations and Acronyms

ACTH	adrenocorticotropic hormone
AHRQ	Agency for Healthcare Research and Quality
AUC	area under the curve
AUROC	area under the receiver operating characteristic
CAM	complementary and alternative medicine
CBT	cognitive behavioral therapies
CDC	Centers for Disease Control and Prevention
CFS	chronic fatigue syndrome
CGI	Clinical Global Impression Change
CI	confidence interval
CIS	Checklist of Individual Strength
CPET	Cardiopulmonary exercise test
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FIS	Fatigue Impact Scale
FLP	Functional Limitations Profile
FSS	Fatigue Severity Scale
GET	graded exercise treatment
HADS	Hospital Anxiety and Depression Scale
HADS-A	anxiety subscale of HADS
HADS-D	depression subscale of HADS
HR	hazard ratio
IGF-1	insulin-like growth factor one
KPS	Karnofsky Performance Scale
ME	myalgic encephalomyelitis
MFI-20	Multidimensional Fatigue Inventory, 20-item
MOS-SF	Medical Outcome Study Short Form
NIH	National Institutes of Health
ODP	Office of Disease Prevention
OR	odds ratio
PEM	post exertional malaise
PICOTS	populations, interventions, comparators, outcomes, timing, setting
POMS	Profile of Mood States
QLI	Quality of Life Index
QLS	Quality of Life Scale
QOLI	Quality of Life Inventory
RA	rheumatoid arthritis
ROC	receiver operating curve
RR	relative risk
SCL-90-R	Symptom Checklist-90-revised
SD	standard deviation
SF-12	Short Form 12-item Health Survey
SF-36	36-item Short Form Survey
SIP-8	Sickness Impact Profile 8-item

TEP	technical expert panel
TSST	Trier Social Stress Test
VAS	visual analog scale

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1988 to September Week 3 2014>

Search Strategy:
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1 exp Fatigue Syndrome, Chronic/
2 exp Encephalomyelitis/
3 exp Fatigue/
4 2 and 3
5 1 or 4
6 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7 (myalg$ adj3 encephal$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8 6 or 7
9 5 or 8
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <September 2014>

Search Strategy:
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1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (myalg$ adj3 encephal$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 or 2

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2014>

Search Strategy:
---
1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, full text, keywords, caption text]
2 (myalg$ adj3 encephal$).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 or 2

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2014>

Search Strategy:

---

1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, full text, keywords]
2 (myalg$ adj3 encephal$).mp. [mp=title, full text, keywords]
3 1 or 2

Database: EBM Reviews - Health Technology Assessment <3rd Quarter 2014>

Search Strategy:

---

1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, text, subject heading word]
2 (myalg$ adj3 encephal$).mp. [mp=title, text, subject heading word]
3 1 or 2

Database: EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2014>

Search Strategy:

---

1 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, text, subject heading word]
2 (myalg$ adj3 encephal$).mp. [mp=title, text, subject heading word]
3 1 or 2

Database: PsycINFO <1988 to September Week 3 2014>

Search Strategy:

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1 exp Chronic Fatigue Syndrome/
2 exp Encephalomyelitis/
3 exp Fatigue/
4 2 and 3
5 1 or 4
6 (chronic$ adj3 fatig$ adj3 syndrom$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7 (myalg$ adj3 encephal$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
8 6 or 7
9 5 or 8
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11

Appendix B. Inclusion and Exclusion Criteria

Table B1. Inclusion and exclusion criteria

	Include	Exclude
Population	KQ 1: Symptomatic adults ≥18 years old with fatigue KQ 2: Symptomatic adults ≥18 years, diagnosed with ME, CFS, or both and without another underlying diagnosis	All KQs: Populations containing children or adolescents. Patients with another underlying diagnosis.
Interventions	KQ 1: Case definitions (e.g., Fukuda/CDC, Canadian, International, and others) KQ 2: Forms of counseling and behavior therapy, graded exercise programs, complementary and alternative medicine (acupuncture, relaxation, massage, other), and symptom-based medication management (immune modulators, beta blockers, antidepressants, anxiolytics, stimulants, other)	KQ 2: Medications not available in the U.S.
Comparators	KQ 1: Diagnostic accuracy studies and diagnostic concordance studies KQ 2: Placebo, no treatment, usual care, other active interventions (including combination therapies and head-to-head trials)	KQ 1: No comparator KQ 2: No comparator
Outcomes	KQ 1: Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, C statistic (AUROC), net reclassification index; concordance, any potential harm from diagnosis (such as psychological harms, labeling, risk from diagnostic test, misdiagnosis, other) KQ 2: Overall function (i.e. 36-item Short Form Survey), quality of life, days spent at work/school, proportion working full- or part-time, fatigue (Multidimensional Fatigue Inventory or similar), adverse effects of interventions, withdrawals and withdrawals due to adverse events, rates of adverse events due to interventions	KQ 1: Not listed as an included outcome KQ 2: Not listed as an included outcome
Settings	All KQs: Clinical settings and those generalizable to a U.S. primary care setting	All KQs: Studies performed in countries with populations not similar to the U.S.; studies conducted in schools or work-sites, unless primary-care feasible
Timing	KQ 1: Any duration KQ 2: ≥12 weeks of treatment	KQ 1: None KQ 2: <12 weeks of treatment
Study types and designs	All KQ: Studies published in 1988 or after KQ 2: Systematic reviews or meta-analyses of randomized or controlled clinical trials, primary reports of randomized or controlled clinical trials, and large cohort studies	All KQ: Non-systematic reviews, letters to the editor, before and after studies, case-control studies, non-comparative studies; reviews not in English; and studies published before 1988

Abbreviations: AUROC = area under the receiver operating characteristics curve; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; KQ = key question; ME = myalgic encephalomyelitis; U.S. = United States

Appendix C. List of Included Studies

Asbring P, Narvanen A-L. Women's experiences of stigma in relation to chronic fatigue syndrome and fibromyalgia. Qual Health Res. 2002;12(2):148-60. PMID: 11837367.

Aslakson E, Vollmer-Conna U, White PD. The validity of an empirical delineation of heterogeneity in chronic unexplained fatigue. Pharmacogenomics. 2006;7(3):365-73. PMID: 16610947.

Assefi NP, Coy TV, Uslan D, et al. Financial, occupational, and personal consequences of disability in patients with chronic fatigue syndrome and fibromyalgia compared to other fatiguing conditions. J Rheumatol. 2003;30(4):804-8. PMID: 12672203.

Bazelmans E, Prins JB, Lulofs R, et al. Cognitive behaviour group therapy for chronic fatigue syndrome: a non-randomised waiting list controlled study. Psychother Psychosom. 2005;74(4):218-24. PMID: 15947511.

Blacker CVR, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. JAMA. 2004;292(10):1195-204. PMID: 15353532.

Blockmans D, Persoons P, Van Houdenhove B, et al. Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. Am J Med. 2003;114(9):736-41. PMID: 12829200.

Brimmer DJ, Maloney E, Devlin R, et al. A pilot registry of unexplained fatiguing illnesses and chronic fatigue syndrome. BMC Res Notes. 2013;6:309. PMID: 23915640.

Brown AA, Jason LA, Evans MA, et al. Contrasting case definitions: The ME International Consensus Criteria vs. the Fukuda et al. CFS criteria. N Am J Psychol. 2013;15(1):103-20. PMID: 25364305.

Burgess M, Andiappan M, Chalder T. Cognitive behaviour therapy for chronic fatigue syndrome in adults: face to face versus telephone treatment: a randomized controlled trial. Behav Cogn Psychother. 2012;40(2):175-91. PMID: 21929831.

Chan JSM, Ho RTH, Wang CW, et al. Effects of qigong exercise on fatigue, anxiety, and depressive symptoms of patients with chronic fatigue syndrome-like illness: A randomized controlled trial. Evidence based Complementary and Alternative Medicine. 2013

Davenport TE, Stevens SR, Baroni K, et al. Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. Disabil Rehabil. 2011;33(25-26):2596-604. PMID: 21682669.

Davenport TE, Stevens SR, Baroni K, et al. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. Disabil Rehabil. 2011;33(19-20):1768-75. PMID: 21208154.

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Diaz-Mitoma F, Turgonyi E, Kumar A, et al. Clinical improvement in chronic fatigue syndrome is associated with enhanced natural killer cell-mediated cytotoxicity: The results of a pilot study with Isoprinosine. J Chronic Fatigue Syndr. 2003;11(2):71-93.

Dickson A, Knussen C, Flowers P. Stigma and the delegitimation experience: An interpretative phenomenological analysis of people living with chronic fatigue syndrome. Psychol Health. 2007;22(7):851-67.

Dougall D, Johnson A, Goldsmith K, et al. Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res. 2014;77(1):20-6.

Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ. 1997;314(7095):1647-52. PMID: 9180065.

Gaab J, Engert V, Heitz V, et al. Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome. J Psychosom Res. 2004;56(4):419-24. PMID: 15094026.

Gaab J, Huster D, Peisen R, et al. Low-dose dexamethasone suppression test in chronic fatigue syndrome and health. Psychosom Med. 2002;64(2):311-8. PMID: 11914448.

Gaab J, Rohleder N, Heitz V, et al. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. Psychoneuroendocrinology. 2005;30(2):188-98. PMID: 15471616.

Goudsmit EM, Ho-Yen DO, Dancey CP. Learning to cope with chronic illness. Efficacy of a multi-component treatment for people with chronic fatigue syndrome. Patient Educ Couns. 2009;77(2):231-6. PMID: 19576714.

Green J, Romei J, Natelson BH. Stigma and chronic fatigue syndrome. J Chronic Fatigue Syndr. 1999;5(2):63-95.

Guise J, McVittie C, McKinlay A. A discourse analytic study of ME/CFS (Chronic Fatigue Syndrome) sufferers' experiences of interactions with doctors. J Health Psychol. 2010;15(3):426-35. PMID: 20348363.

Hadzi-Pavlovic D, Hickie IB, Wilson AJ, et al. Screening for prolonged fatigue syndromes: validation of the SOFA scale. Soc Psychiatry Psychiatr Epidemiol. 2000;35(10):471-9. PMID: 11127722.

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Ho RTH, Chan JSM, Wang C-W, et al. A randomized controlled trial of qigong exercise on fatigue symptoms, functioning, and telomerase activity in persons with chronic fatigue or chronic fatigue syndrome. Ann Behav Med. 2012;44(2):160-70. PMID: 22736201.

Hobday RA, Thomas S, O'Donovan A, et al. Dietary intervention in chronic fatigue syndrome. J Hum Nutr Diet. 2008;21(2):141-9. PMID: 18339054.

Jason L, Benton M, Torres-Harding S, et al. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Educ Couns. 2009;77(2):237-41. PMID: 19356884.

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Jason LA, Brown A, Clyne E, et al. Contrasting case definitions for chronic fatigue syndrome, Myalgic Encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. Eval Health Prof. 2012;35(3):280-304. PMID: 22158691.

Jason LA, Brown A, Evans M, et al. Contrasting chronic Fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013;1(3). PMID: 23914329.

Jason LA, Evans M, Brown A, et al. Sensitivity and specificity of the CDC empirical chronic fatigue syndrome case definition. Psychology. 2010;1(1):9-16. PMID: 23685416.

Jason LA, Roesner N, Porter N, et al. Provision of social support to individuals with chronic fatigue syndrome. J Clin Psychol. 2010;66(3):249-58. PMID: 19902489.

Jason LA, Sunnquist M, Brown A, et al. Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis. J Health Psychol. 2014PMID: 24510231.

Jason LA, Taylor RR. Measuring attributions about chronic fatigue syndrome. J Chronic Fatigue Syndr. 2001;8(3-4):31-40.

Jason LA, Taylor RR, Stepanek Z, et al. Attitudes regarding chronic fatigue syndrome: The importance of a name. J Health Psychol. 2001;6(1):61-71. PMID: 22049238.

Jason LA, Torres-Harding S, Friedberg F, et al. Non-pharmacologic interventions for CFS: a randomized trial. J Clin Psychol Med Settings. 2007;14(4):275-96.

Jason LA, Torres-Harding SR, Jurgens A, et al. Comparing the Fukuda et al. criteria and the Canadian case definition for chronic fatigue syndrome. J Chronic Fatigue Syndr. 2004;12(1):37-52.

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Katon WJ, Buchwald DS, Simon GE, et al. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med. 1991;6(4):277-85. PMID: 1890495.

Knoop H, van der Meer JWM, Bleijenberg G. Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry. 2008;193(4):340-1. PMID: 18827302.

Komaroff AL, Fagioli LR, Doolittle TH, et al. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am J Med. 1996;101(3):281-90. PMID: 8873490.

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McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA. 1998;280(12):1061-6. PMID: 9757853.

Montoya JG, Kogelnik AM, Bhangoo M, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol. 2013;85(12):2101-9. PMID: 23959519.

Moss-Morris R, Sharon C, Tobin R, et al. A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol. 2005;10(2):245-59. PMID: 15723894.

Newton JL, Mabillard H, Scott A, et al. The Newcastle NHS Chronic Fatigue Syndrome Service: not all fatigue is the same. J R Coll Physicians Edinb. 2010;40(4):304-7. PMID: 21132135.

Núñez M, Fernandez-Sola J, Núñez E, et al. Health-related quality of life in patients with chronic fatigue syndrome: group cognitive behavioural therapy and graded exercise versus usual treatment. A randomised controlled trial with 1year of follow-up. Clin Rheumatol. 2011;30(3):381-9. PMID: 21234629.

Öckerman PA. Antioxidant treatment of chronic fatigue syndrome. Clin Pract Alternat Med. 2000;1(2):88-91.

O'Dowd H, Gladwell P, Rogers CA, et al. Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006;10(37):iii-iv, ix-x, 1-121. PMID: 17014748.

Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. Am J Med. 1990;89(5):554-60. PMID: 2239975.

Reyes M, Nisenbaum R, Hoaglin DC, et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003;163(13):1530-6. PMID: 12860574.

Sharpe M, Hawton K, Simkin S, et al. Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. BMJ. 1996;312(7022):22-6. PMID: 8555852.

Strayer DR, Carter WA, Brodsky I, et al. A controlled clinical trial with a specifically configured RNA drug, poly(I) midline dot poly(C12U), in chronic fatigue syndrome. Clin Infect Dis. 1994;18(SUPPL. 1):S88-S95. PMID: 8148460.

Strayer DR, Carter WA, Stouch BC, et al. A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. PLoS ONE. 2012;7(3):e31334. PMID: 22431963.

Sutcliffe K, Gray J, Tan MP, et al. Home orthostatic training in chronic fatigue syndrome--a randomized, placebo-controlled feasibility study. Eur J Clin Invest. 2010;40(1):18-24. PMID: 19912315.

Taylor RR. Quality of life and symptom severity for individuals with chronic fatigue syndrome: findings from a randomized clinical trial. Am J Occup Ther. 2004;58(1):35-43. PMID: 14763634.

The GKH, Bleijenberg G, van der Meer JWM. The effect of acclydine in chronic fatigue syndrome: A randomized controlled trial. PLoS Clinical Trials. 2007;2(5)PMID: 17525791.

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Tummers M, Knoop H, Bleijenberg G. Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol. 2010;78(5):724-31. PMID: 20873907.

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Van Hoof E, De Meirleir K. Chronic Fatigue Syndrome and Myalgic Encephalomyletis: Are Both Conditions on the Same Continuum? N Am J Psychol. 2005;7(2):189-204.

Vermeulen RCW, Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med. 2004;66(2):276-82. PMID: 15039515.

Walach H, Bosch H, Lewith G, et al. Effectiveness of distant healing for patients with chronic fatigue syndrome: a randomised controlled partially blinded trial (EUHEALS). Psychother Psychosom. 2008;77(3):158-66. PMID: 18277062.

Watson SP, Ruskin AS, Simonis V, et al. Identifying Defining Aspects of Chronic Fatigue Syndrome via Unsupervised Machine Learning and Feature Selection. International Journal of Machine Learning & Computing. 2014;4(2):133-8.

Wearden AJ, Dowrick C, Chew-Graham C, et al. Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. BMJ. 2010;340:c1777. PMID: 20418251.

Wearden AJ, Dunn G, Dowrick C, et al. Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome. Br J Psychiatry. 2012;201(3):227-32. PMID: 22844025.

Wearden AJ, Emsley R. Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. J Consult Clin Psychol. 2013;81(5):831-8. PMID: 23796316.

Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome.[Erratum appears in Br J Psychiatry 1998 Jul;173:89]. Br J Psychiatry. 1998;172:485-90. PMID: 9828987.

Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. J Psychosom Res. 2004;56(2):189-97. PMID: 15016577.

White PD, Goldsmith K, Johnson AL, et al. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychol Med. 2013;43(10):2227-35. PMID: 23363640.

White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823-36. PMID: 21334061.

Williams G, Waterhouse J, Mugarza J, et al. Therapy of circadian rhythm disorders in chronic fatigue syndrome: no symptomatic improvement with melatonin or phototherapy. Eur J Clin Invest. 2002;32(11):831-7. PMID: 12423324.

Woodward RV, Broom DH, Legge DG. Diagnosis in chronic illness: disabling or enabling--the case of chronic fatigue syndrome. J R Soc Med. 1995;88(6):325-9. PMID: 7629762.

Appendix D. List of Excluded Studies

Key to exclusion codes

Code	Reason for exclusion
2,3,4	Excluded because the study does not address a Key Question or meet inclusion criteria, but full text pulled to provide background information
5	Wrong population
6	Wrong intervention
7	Wrong outcomes
8	Wrong study design for Key Question
9	Wrong publication type
10	Foreign language
11	Not a human population
12	Inadequate duration
13	Study published before 1988
14	Review not meeting our requirements

Alleged link between hepatitis B vaccine and chronic fatigue syndrome. CMAJ. 1992;146(1):37-8. PMID: 1530818.
Exclusion code: 2

Campaign for an Irish ME Clinic. Available at: http://www.me-ireland.com/. Accessed October 9, 2014.
Exclusion code: 2

Cognitive behavioral therapy and exercise for chronic fatigue syndrome. J Pain Pall Care Pharmacother. 2002;16(3):110-1. PMID: 14640363.
Exclusion code: 9

From the Centers for Disease Control and Prevention. Inability of retroviral tests to identify persons with chronic fatigue syndrome, 1992. JAMA. 1993;269(14):1779. PMID: 8459495.
Exclusion code: 5

Government Response to the CFS/ME Independent Working Group's Report. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4059507.pdf. Accessed July 3, 2014.
Exclusion code: 9

Managing my M.E. What people with ME/CFS and their carers want from the UK's health and social Services. The ME Association. Gawcott, England. Available at: http://www.meassociation.org.uk/wp-content/uploads/MEA-Management-Survey-2010.pdf. Accessed June 23, 2014.
Exclusion code: 9

Mendelian genetic predisposition to weakly virulent mycobacterial infections in human. Human Genetics of Infectious Diseases.
Exclusion code: 6

Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(13)-EHC063-EF. Rockville (MD) :Agency for Healthcare Research and Quality. January 2014. Available at: www.effectivehealthcare.ahrq.gov.
Exclusion code: 2

MORE CFIDS/ME MARKERS AND IONIZING RADIATION. The National Forum. 2013
Exclusion code: 9

A Report of the CFS/ME Working Group. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4064945.pdf. Accessed July 3, 2014.
Exclusion code: 9

Report of the working group on the possible relationship between hepatitis B vaccination and the chronic fatigue syndrome. CMAJ. 1993;149(3):314-9. PMID: 8339178.
Exclusion code: 2

Voices from the Shadows. Film. Available at: https://vimeo.com/ondemand/22513/108797012. Accessed November 3, 2014.
Exclusion code: 9

Aaron LA, Arguelles LM, Ashton S, et al. Health and functional status of twins with chronic regional and widespread pain.[Erratum appears in J Rheumatol. 2002 Dec;29(12):2667 Note: Buchwald, Dedra [corrected to Buchwald, Debra]]. J Rheumatol. 2002;29(11):2426-34. PMID: 12415604.
Exclusion code: 8

Aaron LA, Buchwald D. Fibromyalgia and other unexplained clinical conditions. Curr Rheumatol Rep. 2001;3(2):116-22. PMID: 11286667.
Exclusion code: 2

Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med. 2001;134(9 Pt 2):868-81. PMID: 11346323.
Exclusion code: 3

Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med. 2000;160(2):221-7. PMID: 10647761.
Exclusion code: 3

Aaron LA, Herrell R, Ashton S, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001;16(1):24-31. PMID: 11251747.
Exclusion code: 3

Abbey SE. Psychotherapeutic perspectives on chronic fatigue syndrome. Chronic fatigue syndrome: An integrative approach to evaluation and treatment. New York, NY: Guilford Press; 1996:185-211.
Abbey SE, Garfinkel PE. Chronic fatigue syndrome and depression: cause, effect, or covariate. Rev Infect Dis. 1991;13 Suppl 1:S73-83. PMID: 2020805.
Exclusion code: 2

Abbey SE, Toner BB, Garfinkel PE, et al. Self-report symptoms that predict major depression in patients with prominent physical symptoms. Int J Psychiatry Med. 1990;20(3):247-58. PMID: 2265887.
Exclusion code: 5

Abdel-Khalek AM. Chronic fatigue syndrome and its association with obsession compulsion among a non-clinical sample using questionnaires. J Chronic Fatigue Syndr. 2008;14(3):89-100.
Exclusion code: 2

Adamowicz JL, Caikauskaite I, Friedberg F. Defining recovery in chronic fatigue syndrome: a critical review. Qual Life Res. 2014PMID: 24791749.
Exclusion code: 4

Adams D, Wu T, Yang X, et al. Traditional Chinese medicinal herbs for the treatment of idiopathic chronic fatigue and chronic fatigue syndrome. Cochrane Database Syst Rev. 2009(4):CD006348. PMID: 19821361.
Exclusion code: 14

Adolphe AB. Chronic fatigue syndrome: possible effective treatment with nifedipine. Am J Med. 1988;85(6):892. PMID: 2848418.
Exclusion code: 8

Afari N, Buchwald D. Chronic fatigue syndrome: a review. Am J Psychiatry. 2003;160(2):221-36. PMID: 12562565.
Exclusion code: 14

Agardy S. 'Recovery' in PACE, the 6 Minute Walking Test and Other Issues: How Well Can 'Recovered' Patients Walk? Available at: https://listserv.nodak.edu/cgi-bin/wa.exe?A2=ind1308b&L=co-cure&F=&S=&P=9449. Accessed November 13,2014.
Exclusion code: 3

Akagi H, Klimes I, Bass C. Cognitive behavioral therapy for chronic fatigue syndrome in a general hospital - Feasible and effective. Gen Hosp Psychiatry. 2001;23(5):254-60.
Exclusion code: 8

Akarsu S, Tekin L, Ay H, et al. The efficacy of hyperbaric oxygen therapy in the management of chronic fatigue syndrome. Undersea Hyperb Med. 2013;40(2):197-200. PMID: 23682549.
Exclusion code: 12

Alberts M, Smets EM, Vercoulen JH, et al. ['Abbreviated fatigue questionnaire': a practical tool in the classification of fatigue]. Ned Tijdschr Geneeskd. 1997;141(31):1526-30. PMID: 9543741.
Exclusion code: 2

Alraek T, Lee MS, Choi T-Y, et al. Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Altern Med. 2011;11:87. PMID: 21982120.
Exclusion code: 14

Amel Kashipaz MR, Swinden D, Todd I, et al. Normal production of inflammatory cytokines in chronic fatigue and fibromyalgia syndromes determined by intracellular cytokine staining in short-term cultured blood mononuclear cells. Clin Exp Immunol. 2003;132(2):360-5. PMID: 12699429.
Exclusion code: 5

Amsterdam JD, Shults J, Rutherford N. Open-label study of s-citalopram therapy of chronic fatigue syndrome and co-morbid major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(1):100-6. PMID: 17804135.
Exclusion code: 8

Andersen MM, Permin H, Albrecht F. Illness and disability in Danish Chronic Fatigue Syndrome patients at diagnosis and 5-year follow-up. J Psychosom Res. 2004;56(2):217-29. PMID: 15016582.
Exclusion code: 2

Anderson JS, Ferrans CE. The quality of life of persons with chronic fatigue syndrome. J Nerv Ment Dis. 1997;185(6):359-67. PMID: 9205421.
Exclusion code: 2

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Exclusion code: 5

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Exclusion code: 3

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Exclusion code: 2

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Exclusion code: 5

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Exclusion code: 2

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Exclusion code: 2

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Exclusion code: 9

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Exclusion code: 7

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Exclusion code: 2

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Exclusion code: 2

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Exclusion code: 7

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Exclusion code: 2

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Exclusion code: 5

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Exclusion code: 3

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Exclusion code: 14

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Exclusion code: 3

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Exclusion code: 2

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Exclusion code: 12

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Exclusion code: 9

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Exclusion code: 12

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Exclusion code: 8

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Exclusion code: 2

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Exclusion code: 2

Appendix E. Quality Rating Criteria

Randomized Controlled Trials

Criteria:

- Initial assembly of comparable groups**:**
    - adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: intention-to-treat analysis.

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and intention-to-treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and intention-to-treat analysis is done for randmised, controlled trials.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and intention-to-treat is lacking.

Diagnostic/Concordance Studies

Criteria:

- Test applied to an appropriate spectrum of patients (with and without disease/condition), avoiding case-control design
- Population tested was consecutive or random
- Clear eligibility criteria described and rigorous assessment of disease/condition
- Attrition reported and minimal loss to followup
- Test is adequately described and reproducible
- Test was validated in a second population group
- Test is an available standard case definition

- Diagnostic test is applied to all patients
- Blinding of outcome assessors to the reference standard

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 500) broad-spectrum patients with and without disease; study attempts to enroll a random or consecutive sample of patients who meet inclusion criteria screening cutoffs pre-stated.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (100 to 500 subjects) and a "medium" spectrum of patients (i.e. applicable to many settings where the diagnostic test would be applied).

Poor: Has important limitation such as: uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; small sample size (<100) of very narrow selected spectrum of patients (components of study not well described).

Sources: USPSTF Procedure Manual[1], AHRQ Methods Guide,[2] and AHRQ Methods Guide for Medical Test Reviews[3]

References

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2. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(13)-EHC063-EF. Rockville (MD):Agency for Healthcare Research and Quality. January 2014. Available at: www.effectivehealthcare.ahrq.gov.
3. Methods Guide for Medical Test Reviews. AHRQ Publication No. 12-EC017. Rockville, MD: Agency for Healthcare Research and Quality; June 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm. Also published as a special supplement to the Journal of General Internal Medicine, July 2012. PMID: 22834019.

Appendix F. Strength of Evidence Criteria[1]

Table F1. Required domains and their definitions

Domain	Definition and Elements	Score and Application
Study Limitations	Study limitations is the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design: Whether RCTs or other designs such as nonexperimental or observational studies. • Study conduct. Aggregation of ratings of risk of bias of the individual studies under consideration.	Score as one of three levels, separately by type of study design: • Low level of study limitations • Medium level of study limitations • High level of study limitations
Directness	Directness relates to (a) whether evidence links interventions directly to a health outcome of specific importance for the review, and (b) for comparative studies, whether the comparisons are based on head-to-head studies. The EPC should specify the comparison and outcome for which the SOE grade applies. Evidence may be indirect in several situations such as: • The outcome being graded is considered intermediate (such as laboratory tests) in a review that is focused on clinical health outcomes (such as morbidity, mortality). • Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare interventions A and B—e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not direct comparisons of A vs. B. • Data are available only for proxy respondents (e.g., obtained from family members or nurses) instead of directly from patients for situations in which patients are capable of self-reporting and self-report is more reliable. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.	Score as one of two levels: • Direct • Indirect If the domain score is indirect, EPCs should specify what type of indirectness accounts for the rating.
Consistency	Consistency is the degree to which included studies find either the same direction or similar magnitude of effect. EPCs can assess this through two main elements: • Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference [MID]) • Magnitude of effect: The range of effect sizes is similar. EPCs may consider the overlap of CIs when making this evaluation. The importance of direction vs. magnitude of effect will depend on the key question and EPC judgments.	Score as one of three levels: • Consistent • Inconsistent • Unknown (e.g., single study) Single-study evidence bases (including mega-trials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”

[1]The set of five required domains comprises the main constructs that Evidence-based Practice Centers (EPCs) should use for all major outcomes and comparisons of interest. As briefly defined below in Table F1, these domains represent related but separate concepts, and each is scored independently. The concepts are explained in more detail below.

Domain	Definition and Elements	Score and Application
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events. • A body of evidence will generally be imprecise if the optimal information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered. • If EPCs performed a meta-analysis, then EPCs may also consider whether the CI crossed a threshold for an MID. • If a meta-analysis is infeasible or inappropriate, EPCs may consider the narrowness of the range of CIs or the significance level of p-values in the individual studies in the evidence base.	Score as one of two levels: • Precise • Imprecise A precise estimate is one that would allow users to reach a clinically useful conclusion (e.g., treatment A is more effective than treatment B).
Reporting Bias	Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes: • Study publication bias, i.e., nonreporting of the full study. • Selective outcome reporting bias, i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes. • Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. Assessment of reporting bias for individual studies depends on many factors–e.g. availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rarely available. Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.	Score as one of two levels: • Suspected • Undetected Reporting bias is suspected when: • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, And/or • A qualitative assessment suggests the likelihood of missing studies, analyses, or outcomes data that may alter the conclusions from the reported evidence. Undetected reporting bias includes all alternative scenarios.

CI = confidence internal; EPC = Evidence-based Practice Center; MID = minimally important difference; OIS = optimal information size; RCT = randomized, controlled trial; SOE = strength of evidence

Study Limitations Domain Definition

Scoring the study limitations domain is the essential starting place for grading strength of the body of evidence. It refers to the judgment that the findings from included studies of a treatment (or treatment comparison) for a given outcome are adequately protected against bias (i.e., have good internal validity), based on the design and conduct of those studies. That is, EPCs assess the ability of the evidence to yield an accurate estimate of the true effect without bias (nonrandom error).

Directness Domain Definition

Directness of evidence expresses how closely available evidence measures an outcome of interest. Assessing directness has two parts: directness of outcomes and directness of comparisons. Applicability of evidence (external validity) is considered explicitly but separately from strength of evidence.

Consistency Domain Definition

Consistency refers to the degree of similarity in the direction of effects or the degree of similarity in the effect sizes (magnitudes of effect) across individual studies within an evidence base. EPCs may choose which of these two notions of consistency (direction or magnitude) they are scoring; they should be explicit about this choice.

Precision Domain Definition

Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. It is based on the potential for random error evaluated through the sufficiency of sample size and, in the case of dichotomous outcomes, the number of events. A precise body of evidence should enable decisionmakers to draw conclusions about whether one treatment is inferior, equivalent, or superior to another.

Reporting Bias Definition

Reporting bias occurs when authors, journals, or both decide to publish or report research findings based on their direction or magnitude of effect. Table 2 defines the three main types of reporting bias that either authors or journals can introduce: publication bias and outcome and analysis reporting bias.

Four Strength of Evidence Levels

The four levels of grades are intended to communicate to decisionmakers EPCs' confidence in a body of evidence for a single outcome of a single treatment comparison. Although assigning a grade requires judgment, having a common understanding of the interpretation will be useful for helping EPCs as they conduct their own global assessment and for improving consistency across reviewers and EPCs.

Table F2 summarizes the four levels of grades that EPCs use for the overall assessment of the body of evidence. Grades are denoted high, moderate, low, and insufficient. They are not designated by Roman numerals or other symbols. EPCs should apply discrete grades and should not use designations such as "low to moderate" strength of evidence.

Table F2. Strength of evidence grades and definitions

Grade	Definition
High	**We are very confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	**We are moderately confident that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	**We have limited confidence that the estimate of effect lies close to the true effect for this outcome.** The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	**We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome**. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Each level has two components. The first, principal definition concerns the level of confidence that EPCs place in the estimate of effect (direction or magnitude of effect) for the

benefit or harm; this equates to their judgment as to how much the evidence reflects a true effect. The second, subsidiary definition involves an assessment of the level of deficiencies in the body of evidence and belief in the stability of the findings, based on domain scores and a more holistic, summary appreciation of the possibly complex interaction among the individual domains.

Assigning a grade of high, moderate, or low implies that an evidence base is available from which to estimate an effect for either the benefit or the harm. The designations of high, moderate, and low should convey how confident EPCs would be about decisions based on evidence of differing grades, which can be based on either quantitative or qualitative assessment.

For comparative effectiveness questions, the comparison is typically a choice of either direction (A>B, A=B, A<B) or magnitude (difference between A and B). In some instances assigning different grades regarding the direction and the magnitude of an effect may be appropriate. An example of this situation is when studies consistently find that an intervention improves an outcome (e.g., apnea-hypopnea index is reduced by a statistically significant amount or beyond a minimally important difference), but the degree of heterogeneity about the estimate is high (e.g., range -10 to -46 events/minute; I^2=86%).

The importance of the distinctions among high, moderate, and low levels (and the distinction with insufficient strength of evidence) can vary by the type of outcome, comparison, and decisionmaker. EPCs understand that some stakeholders may want to take action only when evidence is of high or moderate strength, whereas others may want to understand clearly the implications of low versus insufficient evidence. Even when strength of evidence is low or insufficient, consumers, clinicians, and policymakers may find themselves in the position of having to make choices and decisions, and they may consider factors other than the evidence from a specific systematic review, such as patient values and preferences, costs, or resources.

Reference

1. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(13)-EHC063-EF. Rockville (MD):Agency for Healthcare Research and Quality. January 2014. Available at: www.effectivehealthcare.ahrq.gov.

Appendix G. Data Abstraction Tables

Table G1. Evidence table of included studies evaluating the accuracy and/or concordance of different diagnostic criteria

Author, year	Objectives	Case definition	Methods/measures
Aslakson, et al., 2006[57]	To Compared 38 variables in a series of latent class analyses to the Reeves 1994 case definition of ICF/CFS and CDC criteria.	Reeves, 1994 case definition of ICF/CFS and CDC (Fukuda, 1994) criteria	SF-36 Zung depression scale Used latent class analysis to compare empiric classification to the CDC (Fukuda, 1994) categories (CFS, idiopatich chronic fatigue, and nonfatigued)
Brown, et al., 2013[51]	To compare the ME International Consensus (Carruthers, 2011) criteria with the CDC (Fukuda, 1994) criteria.	CDC (Fukuda, 1994) ME International Consensus (Carruthers, 2011)	International Consensus Fukuda CFS questionnaire DSM-IV SCID interview and medical appointment to rule out other reason for symptoms SF-36 Cognitive test: Trailmaking Tests A and B from Halstead-Reitan Battery
Jason, et al., 2001[50]	To compare symptom frequency and MOS-SF outcomes between patients who meet CDC (Holmes, 1988) criteria, CDC (Fukuda, 1994) criteria and those with fatigue explained by psychiatric illness.	CDC (Fukuda, 1994) CDC (Holmes, 1988)	Comparison of symptom frequency; and SF-36

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Aslakson, et al., 2006[57]	159 women; 51 with CFS, 55 with chronic fatigue of insufficient symptom/severity for CFS diagnosis and 53 nonfatigued controls matched by age, sex ethnicity and BMI to those with CFS	**Inclusion:** Residents of Wichita, ages 18-69 years. Women with CFS meeting the CDC (Fukuda, 1994) criteria, chronic fatigue of insufficent symptoms/severity for CFS diagnosis, nonfatigued controls matched by age, sex, ethnicity and BMI against those with CFS. Some CFS patients had comorbid depressive disorder; some met criteria for melancholia. **Exclusion:** NR Medical and psychiatric conditions considered exclusionary by CDC (Fukuda, 1994) criteria except melancholic depression. **Recruitment:** Subset of a sample recruited for the Wichita, Kansas clinical study.
Brown, et al., 2013[51]	Enrolled: 114 Analyzed: 113 (1 patient excluded for missing data) Patients met CDC (Fukuda, 1994): 74 Patients met ME International Consensus (Carruthers, 2011): 39	**Inclusion:** Patients >18 years, not pregnant, able to read and speak english, capable of attending the sessions, individuals diagnosed with CFS according to the CDC (Fukuda, 1994) criteria. **Exclusion:** Persons who used wheelchairs, those who were bedridden or housebound. **Recruitment:** Participants recruited from various sources in the Chicago metropolitan area including physician referrals.
Jason, et al., 2001[50]	Overall: 55 CDC (Holmes, 1988): 14 CDC (Fukdua, 1994): 18 Chronicaly fatigued psychiatric group: 33	**Inclusion:** Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report (Therefore termed, “CFS-like”; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient’s file.) **Exclusion:** exclusionary medical or psychiatric conditions detected in evaluation **Recruitment**: Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults > age 18 from several neighborhoods in Chicago). The control group was randomly selected from those who screened negative.

Author, year	Findings
Aslakson, et al., 2006[57]	Empirically derived latent class solution compares favorably against established research criteria for CFS and idiopathic chronic fatigue.
Brown, et al., 2013[51]	**CDC (Fukuda, 1994) vs. International ME (Carruthers, 2011)** *Demographics differences* Concurrent psychiatric diagnosis: 27% (20/74) vs. 62% (24/39); p<0.001 Sudden onset of illness (<1 month): 26% (19/74) vs. 44% (16/39); p=0.05 *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* Physical functioning: 51.0 (22.63) vs. 36.64 (23.32); p=0.001 Bodily pain: 46.65 (21.42) vs. 27.28 (19.45); p<0.001 Vitality: 19.86 (15.26) vs. 13.85 (13.15); p=0.04 Social functioning: 45.25 (24.22) vs. 30.45 (21.99); p=0.002 *Symptom complaints more common in International ME vs. CDC* PEM: p=0.004 Neurological: memory/concentration (p=0.01), slowness of thought (p=0.001), absent mindedness (p=0.02), confusion/disorientation (p=0001), difficulty reasoning (p=0.01), forgetting what you're trying to say (p=0.001), difficulty finding the right word (p=0.002), need to focus on one thing at a time (p<0.001), frequently lose train of thought (p=0.001), trouble expressing thoughts (p>0.001), difficulty retaining information (p<0.001), difficulty recalling information (p<0.001), put words/numbers in wrong order (p=0.04), slow to react (p<0.001), attention deficit (p=0.05), poor hand-eye coordination (p=0.02). Pain: muscle pain (p<0.001), pain in multiple joints (p<0.001), headaches (p=0.02)
Jason, et al., 2001[50]	**CDC (Holmes, 1988) criteria vs. CDC (Fukuda, 1994) criteria vs. chronically fatigued psychiatric group** *% symptom frequency* Sore throat: 85.7 vs. 44.4 vs. 51.5; p<0.05 Lymph node pain 85.7 vs. 27.8 vs. 27.3; p<0.01 for Fukuda vs. psychiatric group All others symptoms p=NS *Mean SF-36 sub-scales scores (0-100 scale, higher scores indicate better health)* Bodily pain: 33.3 vs. 44.5 vs. 53.7; p<0.05 General health: 34.9 vs. 55.5 vs. 49.9; p<0.05 Physical health composite: 30.9 vs. 37.0 vs. 39.9; p<0.05 for Fukuda vs. psychiatric group All other subscales and composite scales p=NS *Mean degree of impairment (0-100 scale, lower scores indicate better health)* 64.1 vs. 46.5 vs. 65.6; p<0.05 for Fukuda vs. psychiatric group

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.,* 2013[5]	To compare patients who met Canadian (Carruthers, 2003) criteria with CDC (Fukuda, 1994) criteria.	CDC (Fukuda, 1994) Canadian (Carruthers, 2003)	DePaul Symptom Questionnaire SF-36

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.,* 2013[5]	Overall: 189 DePaul Sample: 217 recruited, 189 included BioBank sample: 242 individuals in database, included: NR Newcastle sample: 100 recruited, 96 included	*DePaul sample* **Inclusion:** Patiens ages 18-65 years, capable of reading and writing English, self-reported current diagnosis of CFS, ME/CFS or ME. **Exclusion:** Endorsing lifelong fatigue, exclusionary medical of psychological conditions based on CDC (Fukuda, 1994) criteria. **Recruitment:** Patients recruited from a variety of sources including internet forums, suport groups, re-contacting prior study participants, contacting individuals who had previously indicated interest in study participation. Participants completed surveys. *BioBank sample* **Inclusion:** Patiens >18 years, diagnosed by a licensed physician specialzing in CFS, ME/CFS and ME. **Exclusion:** NR **Recruitment:** Participants were recruited by the CFIDS Association of America through their website, social networking, internet forums and physician referal. *Newcastle sample* **Inclusion:** Patiens ages 18-65 years, capable of reading and writing English, referred by physician for suspected diagnosis of CFS, ME/CFS or ME. **Exclusion:** Morbid obesity, endorsing lifelong fatigue **Recruitment:** participants were identified by primary care physicians who refered patients with a suspected diagnosis of CFS for a complete medical assessment at the Newcastle-upon-Tyne Royal Victoria Infirmary clinic.

Author, year	Findings
Jason, *et al.*, 2013[5]	**CDC (Fukuda, 1994) vs. Canadian (Carruthers, 2003)** *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* <u>DePaul sample</u> Physical functioning: 35.6 (19.6) vs. 28.1 (17.9); p<0.05 Bodily pain: 59.3 (24.3) vs. 36.6 (19.7); p<0.001 <u>BioBank sample</u> Physical functioning: 46.8 (22.9) vs. 33.2 (21.6); p<0.001 Bodily pain: 60.0 (24.8) vs. 41.1 (21.0); p<0.001 General health: 29.8 (17.8) vs. 22.8 (14.2); p<0.01 Social functioning: 42.7 (28.8) vs. 24.0 (21.6); p<0.001 Mental health: 72.2 (13.7) vs. 66.0 (19.6); p<0.05 Vitality: 20.6 (13.7) vs. 12.0 (12.3); p<0.001 <u>Newcastle sample</u> Physical functioning: 49.1 (25.8) vs. 29.6 (25.4); p<0.05 Bodily pain: 45.2 (25.0) vs. 29.5 (21.3); p<0.05 General health: 35.3 (18.9) vs. 20.7 (12.5); p<0.01 Social functioning: 39.4 (20.9) vs. 25.0 (20.5); p<0.05 *Symptom complaints more common in Canadian (Carruthers, 2003) vs. CDC (Fukuda, 1994); p<0.05 for those noted below.* PEM: 3/5 subcategories in all 3 samples; 4/5 in DePaul and Solve samples Sleep parameters (unrefreshing sleep): 1/6 in all 3 samples; 3/6 other sleep parameters in DePaul and Solve samples only Pain: 5/7 subcategories in all 3 samples, 7/7 in DePaul and Solve samples Neurocognitive: 4/13 in all 3 samples; 15/15 in DePaul and Solve samples Autonomic: 4/7 in all 3 samples, 7/7 in DePaul and Solve samples Neuroendocrine: 5 /10 in all 3 samples; 10/10 in DePaul and Solve samples Immune: 4/5 in all 3 samples; 5/5 in DePaul and Solve samples

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.,* 2012[56]	To compare the Canadian (Carruthers, 2003) criteria to the CDC (Fukuda, 1994) criteria, and other ME case definitions.	CDC (Fukuda, 1994) Canadian (Carruthers, 2003) Revised Ramsay, 1988	CFS questionnaire (validated by Jason 1997) to assess symptoms, with modified scoring system ranging from 0-100 with higher scores indicating more impairment DSM-IV SCID interview, medical, and neurological history and exam, other explanation for CFS-like symptoms CFS Questionnaire (Komaroff 1996) to rule out other disorders MOS-SF Cognitive test: Trailmaking Test Parts A and B Heart rate lying down, 2 minutes after standing, and 10 minutes after standing Used symptom counts, chi-square and MANOVA to assess differences between group

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.,* 2012[56]	114 meeting Fukuda criteria for CFS (24 individuals were screened and then excluded for alternative diagnosis or not meeting criteria (<4 Fukada symptoms)	**Inclusion:** Patients >18 years, not pregnant, able to read and speak english, capable of attending the sessions, individuals diagnosed with CFS according to the CDC (Fukuda, 1994) criteria. **Exclusion:** Persons who used wheelchairs, those who were bedridden or housebound. **Recruitment:** Participants recruited from various sources in the Chicago metropolitan area including physician referrals.

Author, year	Findings
Jason, *et al.,* 2012[56]	Of 114 people meeting Fukuda CFS criteria, 56 did not meet the ME/CFS criteria and 97 did not meet the ME criteria (56 were classified as ME/CFS and 27 as ME). 1 person was unable to be categorized. **ME/CFS vs. CFS not ME/CFS** *Demographics differences* Disability: 32% (18/57) vs. 16% (9/56); p=0.06 Current psychiatric diagnoses: 58% (33/57) vs. 20% (11/56); p=0.05 Sudden illness onset (<1 month): 41% (22/57) vs. 24% (13/56); p=0.0 Physical cause of fatigue: 64% (36/57) vs. 65% (35/56); p=0.04 *Mean (SD) SF-36 subscales (0-100 scale, higher scores indicate better health); only significant outcomes are reported here* Physical functioning: 38.0 (21.9) vs. 53.8 (23.4); p=0.00 Bodily pain: 32.2 (20.0) vs. 48.0 (22.1); p=0.00 General health: 28.5 (16.0) vs. 36.5 (18.3); p=0.02 Vitality: 14.8 (12.0) vs. 20.9 (16.6); p=0.02 Social functioning: 34.0 (22.7) vs. 46.6 (24.2); p=0.01 *Symptom complaints more common among ME/CFS vs. CFS not ME/CFS* Fatigue: p=0.00; PEM: p=0.00; unrefreshing sleep: p=0.00; need to nap each day: p=0.05; difficulty falling asleep: p=0.01; all pain parameters (muscle pain, pain in multiple joints, headaches, chest pain, abdomen pain, eye pain): all p<0.02; all neurological parameters (impaired memory and concentration, abnormal sensitivity to light, slowness of thought, confusion/disorientation, difficulty finding the right work, difficulty comprehending information, need to have focus on one thing at a time): p=0.00; all autonomic parameters (racing heart, shortness of breast, dizziness, feel unsteady on feet): p<0.01; and tender/sore lymph nodes: all p=0.00 *Symptom complaints more common among ME vs. CFS not ME/CFS* Headaches: p=0.05; chest pain: p=0.04; abdomen pain: p=0.00; eye pain: p=0.00; difficulty finding the right word: p=0.05; need to have focus on one thing at a time: p=0.02; all autonomic parameters (racing heart, shortness of breast, dizziness, feel unsteady on feet): all p<0.02; tender/sore lymph nodes: p=0.02; and hot/cold spells: p=0.05 **ME/CFS vs. CFS not ME/CFS; ME vs. CFS not ME** Mean (SD) heart rate (bpm) Lying down: 80.7 (14.8) vs. 74.5 (11.1); p=0.02; 84.4 (16.4) vs. 75.4 (11.4); p=0.00 Standing 2 minutes: 94.2 (17.1) vs. 85.7 (14.6); p=0.00; 96.9 (18.9) vs. 87.7 (14.9); p=0.00 Standing 10 minutes: 94.6 (14.5) vs. 86.2 (13.6); p=0.00; 97.8 (14.4) vs. 88.1 (13.9); p=0.00 Mean (SD) Trailmaking test scores A-time: 32.9 (13.6) vs. 26.8 (9.9); p=0.02; 35.3 (15.8) vs. 28.2 (10.3); p=0.02 B-time: 56.1 (25.1) vs. 46.8 (14.9); p=0.03; 61.2 (28.3) vs. 48.5 (17.3); p=0.00 Symptoms and Psychiatric Comorbidity: ME/CFS group had 7.3 of the 13 Kroenke (2003) symptoms vs 5.1 for Fukuda CFS (p<0.05); ME group had 8.1 of the 13 Kroenke (2003) symptoms vs 5.6 for Fukuda CFS (p<0.01).

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.*, 2004[55]	To compare the CDC (Fukuda, 1994) and the Canadian case definitions	CDC (Fukuda, 1994) Canadian (Carruthers, 2003) Revised Ramsay, 1988	Work status Psychiatric comorbidity Symptoms Functional impairment as measured by medical outcomes study (SF-36)

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.* , 2004[55]	Telephone survey, random population sample of 28,673 households, 780 of whom reported fatigue; who underwent structured psychiatric interview and then a medical examination.	**Inclusion:** 32 individuals met CDC (Fukuda, 1994) criteria; 45 had idopathic chronic fatigue; 33 had chronic fatigue explained by psychiatric reasons. 23 met Canadian (Carruthers, 2003) criteria.

Author, year	Findings
Jason, *et al.* , 2004[55]	**Canadian vs. CFS Fukuda vs. CFS-Psych** No differences between groups on the Fatigue Scale or the Mental composite score of the SF-36. Physical composite score: 32.5 vs. 37.8 vs. 39.9 No different in psychiatric status Rates of current psychiatric diagnoses: 47.8% vs. 75.0% vs. 87.9% (p<0.01) Rates of lifetimes psychiatric diagnoses: 78.3% vs. 83.3% vs.100% (p<0.050. Symptoms (all significant at p<0.05): *Fatigue* General muscle weakness: 82.6% vs. 66.7% vs. 54.5% Neck weak: 52.2% vs. 25.0% vs. 24.2% Shoulders weak: 52.2% vs. 25.0% vs.24.2% Back weak: 47.8% vs. 33.3% vs. 18.2% *Disturbed Sleep* Trouble staying asleep: 30.4% vs. 66.7% vsd. 39.4% *Neuropsychiatric* Confusion or Disorientation: 39.1% vs. 8.3% vs. 12.1% Difficulty retaining information: 56.5% vs. 41.7 % vs. 27.3% Need to focus on one thing at a time: 65.2% vs. 25.0% vs. 24.2% Slow to process visual and auditory information: 30.4% vs. 8.3% vs. 6.1% Disturbances in eyesight: 43.5% vs. 33.3% vs. 18.2% *Infectious* Lymph node pain: 34.8% vs. 25.0% vs.12.1% *Rheumatolgocial* Neck muscles ache: 65.2%vs. 75.0% vs. 36.4% Back muscles ache: 65.2% vs. 66.7% vs. 36.4% Stiff after sitting: 39.1% vs. 58.3% vs. 21.2% Sinus infection: 4.3% vs. 41.7% vs. 12.1% Sinus congestion: 26.1% vs. 50.0% vs. 15.2% *Cardiopulmonary* Chest pains: 34.8% vs. 33.3% vs. 9.1% *Gastrointestinal* Bloating: 26.1% vs. 50.0% vs.15.2% Lower abdominal pain: 26.1% vs. 41.7% vs. 9.1% *Neurological* Feel weak or dizzy after standing: 43.5% vs. 41.7% vs. 18.2% Dizziness when move head suddenly: 47.8% vs. 16.7% vs. 18.2% Alcohol intolerance: 47.8% vs. 33.3% vs. 15.2% *Reproductive* Decreased sexual interest/function: 30.4% vs. 58.3% vs. 18.2%

Author, year	Objectives	Case definition	Methods/measures
Jason, *et al.,* 2014[54]	To compare the CDC (Fukuda, 1994) and the ME-ICC(Carruthers, 2011) case definitions in two samples	CDC (Fukuda, 1994) ME-ICC (Carruthers, 2011)	DePaul Symptom Questionnaire SF-36
Katon, *et al.,* 1991[58]	To identify psychiatric differences between patients with chronic fatigue and those with rheumatoid arthritis, and to investigate whether patients meeting the CDC (Holmes, 1988) criteria can be differentiated from patients with chronic fatigue on measures of disability and psychosocial distress.	CDC (Holmes, 1988)	General Health Questionnaire total score MOS-SF Modified Somatic Perception Questionnaire Pennebaker inventory of Limbic Languidness
Komaroff, *et al.,* 1996[59]	To measure functional status and well-being of patients with CFS vs. general population and 6 disease comparison groups.	CDC (Fukuda, 1994)	SF-36

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Jason, *et al.,* 2014[54]	DePaul sample: 73 had CFS, 112 had ME; Newcastle sample: 27 had CFS, 58 had ME.	**Inclusion**: Self-identified or suspected CFS **Exclusion**: NR **Recruitment**: DePaul sample was a convenience sample from adults self-identifying as ME/CFS; The Newcastle sample was recruited from patients referred to CFS clinic and who fulfilled Fukuda CFS criteria.
Katon, *et al.,* 1991[58]	79 with chronic fatigue; 19 with CFS; 31 with rheumatoid arthritis	**Inclusion:** Physician or self referred for CFS. Controls were RA patients. **Exclusion:** NR **Recruitment**: Subjects referred by community PCP or self-referred. 31 consecutive RA patients recruited from rheumatology clinic (all meeting ACR criteria).
Komaroff, *et al.,* 1996[59]	223 with CFS recruited from CFS clinic; 2,474 population-based control sample; and chronic disease comparison group (2,089 with HTN, 216 with CHF, 163 with DM, 107 with acute MI, 107 with MS, and 502 with depression)	**Inclusion:** Patients who fully met the CDC (Holmes, 1988) criteria and seen since 1990. **Exclusion:** NR **Recruitment:** CFS patients drawn from an NIH-supported CFS Cooperative Research Center at Brigham and Women's Hospital and Harvard Medical School. General population comparison came from SF-36 administered as part of National Survey of Functional Health Status. Disease comparison groups came from a group who had SF-36 administered as part of the Medical Outcomes Study and others seen at the Brigham & Women's Hospital ambulatory practices.

Author, year	Findings
Jason, *et al.,* 2014[54]	**CFS vs. ME** General health: 28.6 vs. 22.6 for the DePaul sample; 32.3 vs.19.1 for the Newcastle sample (p=0.01) Bodily pain 50.0 vs. 25.6 for the DePaul sample (p<0.001); no difference for the Newcastle sample Physical functioning 34.1 vs. 26.9 for the DePaul sample (p<0.01); no difference for the Newcastle sample Role physical 7.9 vs. 2.5 (p<0.05) for the DePaul sample; no difference for the Newcastle sample Vitality 15.4 vs. 11.2 (p<0.05); no difference for the Newcastle sample
Katon, *et al.,* 1991[58]	**CFS vs. RA** *GHQ scores* Mean (SD) total score: 12.5 (8.0) vs. 5.1 (4.6); p<0.001 Score of ≥11: 53% (47/98) vs. 13% (3/31); p<0.001 *Mean (SD) MOS-SF (1-100 scale, higher score indicates better health); significant results only reported here* Mental health: 17.7 (5.5) vs. 23.0 (5.4); p<0.01 Health perception: 3.4 (1.4) vs. 5.3 (2.1); p<0.001 No significant difference for SF-36 physical function and role functional, Modified Symptoms Perception Questionnaire, or the Pennebaker Inventory of Limbic Languidness.
Komaroff, *et al.,* 1996[59]	**Significant p values for means on SF-36 subscales: comparisons vs. CFS** Physical functioning: p<0.00001 general population, HTN, DM, AMI, and depression; p=0.00004 CHF Role physical: p<0.00001 all Bodily pain: p<0.00001 all General health: p<0.00001 all Vitality: p<0.00001 all but MS which was NS (p=0.1369) Social functioning: p<0.00001 Role emotional: p<0.00001 general population, HTN, DM, and depression; p=0.3918 CHF; p=0.1077 MS Mental health: p<0.00001 all but MS which p=0.0005

Author, year	Objectives	Case definition	Methods/measures
Lewis, *et al.,* 2013[53]	To compare clinical and autonomic features of CFS in patients >50 years to those age 16-20 years.	CDC (Fukuda, 1994)	Heart rate variability Baroreceptor sensitivity FIS CFQ HADS, HADS-A and HADS-D SF-36 Chalder fatigue scale ESS OGS - 5 items, each graded 0-4 t-tests statistics
Van Hoof and De Meirleir, 2005[52]	To compare ME and CFS regarding cognitive problems and functionality using standardized objective test batteries.	CDC (Fukuda, 1994) London criteria for ME (National Task Force, 1994)	SF-36 MFI-20 KPS Exercise

Author, year	Total N/populations	Eligibility criteria/recruitment methods
Lewis, *et al.,* 2013[53]	179 subjects recruited; study sample includes 25 subjects >50 years matched by sex and length of history for 25 CFS subjects ages 16-29 years	**Inclusion:** Attending the clinic between November 2008 and June 2011 and diagnosed with CFS using CDC (Fukuda, 1994) criteria. **Exclusion:** Secondary causes for fatigue (such as hypothyroidism, diabetes), fulfilled CDC (Fukuda, 1994) exclusionary criteria. **Recruitment:** Consecutive patients attending the Northern Regional Department of Health Funded CFS Clinical Service (Newcastle upon Tyne, UK) with a diagnosis of CFS using Fukuda criteria.
Van Hoof and De Meirleir, 2005[52]	67; 41 with CFS and 26 with ME	**Inclusion:** Patients visiting the outpatient Chronic Fatigue clinic to be screened for CFS or ME and fulfilled either the CDC (Fukuda, 1994) criteria for CFS or the London criteria for ME. **Exclusion:** NR **Recruitment:** Recruited from Chronic Fatigue Clinic of the Vrije Universiteit Brussel. Recruited consecutive patients, and every second patient was enrolled.

Author, year	Findings
Lewis, et al., 2013[53]	**Age 16-29 years vs. ≥50 years; only significant results reported here** Mean (SD) BMI (kg/m^2): 22 (3) vs. 26 (3); p=0.002 Mean (SD) FIS: 85 (33) vs. 107 (27); p=0.02 Mean (SD) Chalder Fatigue severity scale (0-56 scale, lower score indicates better health): 9 (3) vs. 11 (1); p=0.002 Mean (SD) HADS-D: 7 (3) vs. 10 (4); p=0.005 Mean (SD) total SF-36 score (0-100, higher scores indicate better health): 20 (5) vs. 16 (5); p=0.03 Mean (SD) self-efficacy scores: 31 (12) vs. 22 (14); p=0.02 Mean (SD) heart rate (bpm): 80 (15) vs. 71 (8); p=0.007 Mean (SD) LVET (ms): 274.6 (16) vs. 285.8 (9); p=0.004 Mean (SD) LFnu: 51.5 (17) vs. 63.8 (18); p=0.01 Mean (SD) HFnu: 49.1 (18) vs. 36.2 (18); p=0.01 Mean (SD) LF/HF: 1.5 (0.9) vs. 2.2 (1.4); p=0.04 Mean (SD) BRS: 19.7 (12) vs. 9.9 (5); p=0.0004 Autonomic and hemodynamic differences: higher LVET (p=0.004), heigh LFnu (p=0.01), higher HFnu (p=0.01), higher LF/HF (p=0.04), lower BRS (p=0.0004) for the subjects >50 vs. those age 16-26. No difference in HR, systolic BP, diastolic BP, mean BP, total HRV, BEI, or systolic BP with active stand.
Van Hoof and De Meirleir, 2005[52]	**CFS vs. ME** *Demographic differences; only significant differences reported here* Mean age (SD): 43 (10) vs. 34 (7) years; p=0.001 *Mean (SD) SF-36 subscale scores (0-100 scale, higher scores indicate better health)* Role emotional: 62 (44.05) vs. 83 (31.05); p=0.024 Mental health: 60 (17.90) vs. 69 (13.41); p=0.049 *Mean (SD) MFI-20 (4-20 scale, lower score indicates better health)* General fatigue: 18 (2.73) vs. 17 (2.88); p=0.029 *Physical parameters; only significant differences reported here* Mean (SD) age predicted heart rate (bpm): 178.04 (10.67) vs. 185.57 (6.64); p=0.049 Mean (SD) VO_2 predicted: 26.81 (3.66) vs. 29.39 (2.28); p=0.049 *Note:* Only the Role Emotional SF-36 subscale seemed able to discriminate ME patients from CFS patients. The analysis correctly classified 59.7% of the cases. 73% of the ME cases, and 51% of the CFS patients were correctly classified.

Abbreviations: ACR= American College of Rheumatology; AMI= acute myocardial infarction; BEI= baroreflex effective index; BMI= body mass index; BP= blood pressure; bpm= beats per minute; BRS= baroreflex sensitivity; CDC= Centers for Disease Control and Prevention; CFIDS= chronic fatigue and immune dysfunction syndrome; CFQ= cognitive failures questionnaire; CFS= chronic fatigue syndrome; CHF= congestive heart failure; DM= depressed mood; DSM-IV= Diagnostic and Statistical Manual fourth edition; ESS= Epworth sleepiness scale; FIS= fatigue impact scale; GHQ= general health questionnaire; HADS= Hospital Anxiety and Depression Scale; HADS-A= anxiety subscale of HADS; HADS-D= depression subscale of HADS; HF= high frequency; HFnu= high frequency normalized units; HR= heart rate; HRV = heart rate variability; HTN= hypertension; ICF= idiopathic chronic fatigue; kg= kilogram; KPS= Karnofsy Performance Scale; LF= low frequency; LFnu= low frequency normalized units; LVET= left ventricular ejection time; m= meter; MANOVA= multivariate analysis of variance; ME= myalgic encephalomyelitis; MFI-20= Multidimensional fatigue inventory; MI = myocardial infarction; MOS-SF= medical outcomes study short form; ms = milliseconds; MS= multiple sclerosis; NIH = National Institutes of Health; NR= not relevant; NS= not significant; OGS= orthostatic grading scale; PCP = primary care physician; PEM= post exertional malaise; RA= rheumatoid arthritis; SCID= structured clinical interview for DSM-IV; SD= standard deviation; SF-36= 36-item Sort Form Survey; UK= United Kingdom; VO_2= volume oxygen; vs.= versus

Table G2. Evidence table of included studies of methods used to diagnose ME/CFS

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Davenport, *et al.,* 2011[60]	To determine the validity and reliability of the SF-36 in sub-groups of individuals with fatigue.	CDC (Fukuda, 1994)	Each subject completed the SF-36 and MFI-20 prior to and 1 week after completing 2 maximal cardiopulmonary exercise tests approximately 24 hours apart. **Procedures:** pedaling for <1 minute, then workload was increased 15 watts/minute until voluntary exhaustion. **Outcomes:** Each subject completed a questionnaire with open-ended questions about recovery (operationally defined as full return to pre-test symptoms and activity levels).	30;16 with CFS and disabled sedentary United States; 100%

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Davenport, *et al.,* 2011[60]	**Inclusion:** Patients meeting CDC (Fukuda, 1994) criteria for CFS, as confirmed by a recruiting physician. **Exclusion:** Other fatiguing health conditions. **Recruitment:** 2 physicians who specialized in the clinical management of CFS referred subjects with CFS into the study. Another sample of otherwise non-disabled sedentary individuals (exercising to the point of perspiration 1 time per week or less) were recruited to participate as control subjects. Effort made to match CFS and control subjects on sex, age and BMI.	Pairwise comparison between groups, intraclass correlation coefficients for the SF-36 scores using formula 2.1. Strength of reproducibility among the variables based on Munro's criteria (very low=0.15-0.24, low=0.25-0.49, moderate=0.50-0.69, high=0.79-0.89, and very high=0.90-1.00). Content and concurrent validity assessed using Mann-Whitney U test for significance between means, and Spearman's rho for bivariate correlations. Predictive validity using ROC curve analysis to estimate the value of the SF-36 score needed to predict failure to achieve self-reported recovery following cardiopulmonary exercise tests at 1 day and 1 week. Sensitivity to change of SF-36 sub-scale scores determined by calculating minimal detectable change outside a 95% CI for each sub-scale.

Author, year	Findings	Conclusions
Davenport, *et al.,* 2011[60]	The diagnostic accuracy of SF-36 v2 subscales to predict recovery within 1 week: ROC AUC analysis was significant for the role emotional (AUC: 0.875; 95% CI, 0.699 to 1.00, p<0.01), vitality (AUC: -0.792; 95% CI, 0.630 to 0.953, p<0.05) and bodily pain (AUC: 0.829; 95% CI, 0.681 to 0.977, p<0.01). Their cut scores were identified as 71%, 22%, and 39% respectively. **AUC (95% CI), sensitivity, specificity, positive likelihood ratio, negative likelihood ratio** *Subscales of SF-36 for failure to recover at 1 day* Physical function: 0.880 (0.697 to 1.00, p=0.001), 0.82, 0.82, 4.5, 0.21 Role physical : 0.865 (0.706 to 1.00, p=0.001), 0.79, 0.88, 6.9, 0.23 Bodily pain: 0.911 (0.764 to 1.00, p<0.001), 0.85, 0.81,4.4, 0.18 General health: 0.898 (0.000 to 1.00, p<0.001), 0.85, 0.81, 4.4, 0.18 Role emotional 0.659 (0.449 to 0.869, p=0.157) Vitality: 0.836 (0.672 to 1.00, p=0.003), 0.85, 0.81, 4.4, 0.18 Social function: 0.854 (0.695 to 1.00, p=0.002), 0.79, 0.90, 0.79, 0.23 Mental health: 0.672 (0.467 to 0.876, p=0227) Health transition: 0.424 (0.180 to 0.669, p=0.551) *Subscales of SF-36 v2 for failure to recover at 1 week* Physical function: 0.771 (0.594 to 0.947, p=0.061) Role physical: 0.717 (0.531 to 0.903, p=0.133) Bodily pain: 0.829 (0.681 to 0.977, p=0.009), 0.90, 0.58, 2.2, 0.17 Role emotional: 0.875 (0.699 to 1.00, p=0.009), 0.90, 0.58, 2.2, 0.17 Vitality: 0.792 (0.630 to 0.953, p=0.043), 0.88, 0.58, 2.1, 0.20 Social function: 0.683 (0.438 to 1.00, p=0.204) Mental health: 0.742 (0.483 to 1.00, p=0.094) General health: 0.758 (0.550 to 0.967, p=0.073) Health transition: 0.242 (0.00 to 1.00, p=0.073)	Differential importance of SF-36 subscales for varying levels of dis severity (different set of subscales found to predict failure to recover day vs. 1 week). Role emotional subscale was found to be significa and robustly predictive of recover week, in addition to vitality and bo pain.

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Davenport, *et al.,* 2011[61]	To determine the diagnostic accuracy for single symptoms and clusters of symptoms to distinguish between individuals with and without CFS; specifically to look at recovery duration after standardized exercise challenge, single PEM symptoms and clusters of PEM symptoms to predict presence of CFS.	CDC (Fukuda, 1994)	Each subject completed 2 maximal cardiopulmonary exercise tests approximately 24 hours apart. **Procedures:** pedaling for <1 min, then workload was increased 14 watts/min until voluntary exhaustion. **Outcomes:** 7 days after the cardiopulmonary exercise test, each subject completed a questionnaire with open-ended questions: how they felt immediately after the exercise test, how they felt the next day and how long it took them to recover from the test; also asked to describe symptoms they may have experienced as a result of the test.	30; 16 with CFS and disabled sedentary United States; 100%
Gaab, *et al.,* 2004[66]	To assess the associations between psychological morbidity, symptoms severity , CFS duration and the extent of neuroendocrine dysregulations in CFS patients using a centrally acting stress paradigm.	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)	Insulin tolerance test performed at 9am after overnight fast: measures of glucose , ACTH, plasma total cortisol and salivary free cortisol collected at 20, 30, 45, 60, 90, and 120 minutes after injection of insulin (0.15U/kg H-insulin). German translation of the Fatigue Scale (Chalder, 1993).	42; 21 patients with 21 healthy controls. Germany; 43% fema

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Davenport, *et al.,* 2011[61]	**Inclusion:** Subjects meeting CDC (Fukuda, 1994) criteria, history of fatigue lasting >6 months, unexplained by another physical, or psychological health condition. **Exclusion:** NR **Recruitment:** Convenience sample. Controls were non-disabled sedentary individuals (exercising to the point of perspiration one time per week or less). Effort made to match CFS and control subjects on sex, age and BMI.	Descriptive statistics, paired t-tests, chi-square, sens/spec, ROC curve analysis for AUC.
Gaab, *et al.,* 2004[66]	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe,1991) requirements. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire.	chi-square, ANOVA/ANCOVA, Pearson correlations, AUC.

Author, year	Findings	Conclusions
Davenport, *et al.,* 2011[61]	No difference between groups in terms of cardiopulmonary exercise test duration. At 1-week followup, 93% of controls reported full recovery within 24 hours vs. 25% of the CFS subjects. ROC AUC for failure to recover within 1 day: 0.864, p=0.001 ROC AUC for failure to recover within 7 days: 0.598, p=0.371 ≥3 symptoms: AUC 0.871 (p=0.001; 95% CI 0.717 to 1.00), sensitivity: 0.93, specificity: 0.81, +LR 4.5; -LR 0.09 a final model including prioritized variables (according to logistic regression) included immune dysfunction, sleep disturbance, and pain: this model predicts 88% of CFS subjects and 92% of control subjects accurately **AUC (95% CI), sensitivity, specificity, positive likelihood ratio, negative likelihood ratio** *Diagnostic accuracy of individual symptoms* Fatigue: 0.750 (0.564 to 0.936, p<0.05), 0.70, 1.0, --, 0.30 Muscle stiffness: 0.603, (0.397 to 0.808, p=NR), 0.64, 0.56, 1.5, 0.64 Autonomic dysfunction: 0.643, (0.442 to 0.843, p=NR), 0.27, 0.58, 0.64, 1.3 Neuroendocrine dysfunction: 0.808, (0.645 to 0.971, p<0.01), 0.92, 0.72, 3.3, 0 Immune dysfunction: 0.719, (0.533 to 0.904, p<0.05), 1.0, 0.61, 2.6, 0 Pain: 0.772, (0.597 to 0.947, p<0.01), 0.85, 0.71, 2.9, 0.21 Sleep disturbance: 0.839, (0.687 to 0.992, p<0.01), 0.92, 0.76, 3.8, 0.11 Other: 0.487, (0.276 to 0.697, p=NR) , 0.50, 0.41, 0.85, 1.2	The optimal number of PEM symp ≥3 to distinguish between CFS an control subjects.
Gaab, *et al.,* 2004[66]	AUC of the ACTH response vs.duration of CFS: -0.69, p=0.005 AUC of the ACTH response vs.Chalder fatigue scale total score: -0.41, p=0.045 AUC of the ACTH response vs.HADS depression scale: -0.53, p=0.014 AUC of the ACTH response vs.HADS anxiety scale: -0.63, p=0.003 AUC of the ACTH response vs.SIP-8 total score: 0-0.29, p=0.12 AUC of the plasma cortisol response vs.duration of CFS: 0.10, p=0.34 AUC of the plasma cortisol response vs.Chalder fatigue scale total score: 0.11, p=0.34 AUC of the plasma cortisol response vs.HADS depression scale: 0.09, p=0.36 AUC of the plasma cortisol response vs.HADS anxiety scale: -0.12, p=0.32 AUC of the plasma cortisol response vs.SIP-8 total score: -0.38, p=0.32 AUC of the salivary free cortisol response vs.duration of CFS: -0.06, p=0.41 AUC of the salivary free cortisol response vs.Chalder fatigue scale total score: 0.12, p=0.32 AUC of the salivary free cortisol response vs.HADS depression scale: 0.31, p=0.11 AUC of the salivary free cortisol response vs.HADS anxiety scale: 0.15, p=0.27 AUC of the salivary free cortisol response vs.SIP-8 total score: 0.32, p=0.09	CFS patients had reduced integra ACTH response to insulin challen Cortisol responses were normal i patients. Concurs with theory of d corticotrophin releasing hormone secretion and compensatory up- regulation of adrenal sensitivity a CFS patients.

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Gaab, *et al.,* 2002[67]	To explore alterations in negative feedback control of the HPA axis in patients with CFS.	CDC (Fukuda, 1994)	Salivary cortisol measured on 3 consecutive days: waking, and 15, 30, 45, and 60 minutes thereafter; also 8am, 11am, 3pm, and 8pm. All subjects completed visual analog scale for pain and fatigue, MFI-20, SIP-8, HADS, BDS and SCL-90R before during and after the sampling dates.	35; 18 CFS patients controls. Germany; female.
Gaab, *et al.,* 2005[68]	To assess the LPS-induced production of pro-inflammatory cytokines before and after a standardized psychological stress test in CFS patients and healthy controls and relate these finding to HPA responses and general fatigue syndromes.	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)	ACTH, plasma cortisol, salivary cortisol, differential blood count, IL-6 and TNF-alpha (baseline, and 10, 60 minutes after the TSST) German translation of the Fatigue Scale (Chalder 1993), SIP-8, SCL-90R, HADS All subjects underwent the TSST: after basal blood and saliva samples were taken they were told to prepare for a fake job interview, then given a mental arithmetic task in front of an audience and told they would be videotaped for further analysis of their behavior.	41; 21 CFS patients controls. Germany; female.

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Gaab, *et al.,* 2002[67]	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe 1991) requirements, acute onset of CFS, ages 30-50 years, no current use of antidepressant, anziolytic, antibiotic, antihypertensive, or steroid. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria, cause for chronic fatigue on routine laboratory testing, thyroid hormone levels indicative of hypofunction and primary adrenal insufficiency. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire. Patients were matched for age and sex with 21 healthy volunteer control subjects, randomly recruited by telephone.	Repeated measures ANOVA. Used log-transformed cortisol values because they were not normally distributed. AUC (total) calculated using trapezoidal method relative to baseline.
Gaab, *et al.,* 2005[68]	**Inclusion:** Fulfillment of symptom requirements listed in postal questionnaire containing CDC (Fukuda, 1994) and Oxford (Sharpe,1991) requirements, acute onset of CFS, ages 30-50 years, no current use of antidepressant, anziolytic, antibiotic, antihypertensive, or steroid. All patients medically examined by the same physician, and interviewed by a trained psychologist. **Exclusion:** Medical or psychiatric diagnosis defined as exclusion criterion by CDC (Fukuda, 1994) criteria, cause for chronic fatigue on routine laboratory testing. **Recruitment:** Patients contacted through German self-help organization and screened for inclusion via postal questionnaire. Patients were matched for age and sex with 21 healthy volunteer control subjects, free of medication, randomly recruited by telephone.	AUC calculated using trapezoidal method

Author, year	Findings	Conclusions
Gaab, *et al.,* 2002[67]	There was no difference in the AUC for awakening salivary cortisol on days 1 and 2 for CFS group vs. control. The decrease in salivary cortisol was lower for all subjects after administration of dexamethasone; with a stronger decrease in patients with CFS:12.16, p=0.003 AUC for awakening cortisol on day 3 for CFS subjects vs.controls: 6.6 (0.9) vs.23.4 (5.2), F=22.43, p<0.000. AUC for circadian cortisol profile on day 3 for CFS subjects vs.controls: 5.67 (0.9) vs.11.67 (1.5), F=10.60, p=0.002. All subscales of the MFI-20, HADS, SCL-90R and SIP-8 were significantly different for CFS subjects vs.controls. See table in paper for subscales; totals reported here: MFI-20 F=67.5, P<0.000 HADS: F=24.6, p<0.000 SCL-90R: F=27.5, p<0.000 SIP-8 F=12.81, p<0.000	CFS subjects show normal increa salivary free cortisol after awaken exhibit an almost similar circadiar salivary cortisol profile. After administration of 0.5 mg of dexamethasone at 11pm, both sa free cortisol profiles were suppres both groups; but in CFS group the remained suppressed for the enti
Gaab, *et al.,* 2005[68]	The HADS, SCL-90R and SIP-8 scores were all significantly higher in the CFS group AUC for IL-6 vs. Chalder fatigue scale total score: CFS 0.46, p=0.02; control 0.18, p=0.22 AUC for IL-6 vs.Chalder fatigue scale mental fatigue: CFS 0.26, p=0.13 vs.control 0.16, p=0.25 AUC for IL-6 vs.Chalder fatigue scale physical fatigue: CFS 0.51, p=0.01 vs.control 0.19, p=0.21 AUC for TNF-alpha vs.Chalder fatigue scale total score: CFS 0.60, p=0.002 vs.control 0.16, p=0.25 AUC for TNF-alpha vs.Chalder fatigue scale mental fatigue: CFS 0.40, p=0.04 vs.control 0.16, p=0.25 AUC for TNF-alpha vs.Chalder fatigue scale physical fatigue: CFS 0.58, p=0.003 vs.control 0.16, p=0.25	CFS patients had significantly red ACTH response in the psychosoc stress test, not followed by a simil different in cortisol parameters. C patients had an inverted pro-inflammatory cytokine response t compared to controls. This confir reports - decreased NF-kB activity response to stress could be a pos intracellular mechanism to mediat assumed increase glucocorticoid sensitivity.

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Jason, *et al.,* 2011[65]	To identify the most appropriate SF-36 subscales for differentiating CFS patients.	CDC (Fukuda, 1994) SF-36	ROC curve analysis including AUC.	193; 2 populations: recruited from tertiar and 2) 32 communit sample with 47 in a fatigued control grou United States; 58%

Jason, *et al.,* 2010[56]	To evaluate the CDC Empiric CFS definition (Reeves et al., BMC Medicine 2005) which assesses 3 areas: disability SF-36), fatigue (MFI-20) and symptoms (CDC symptom inventory). Aim to determine specific instruments and cutoffs to facilitate a more reliable approach to assessment of CFS.	Diagnosis of CFS made by dual rating by physicians, with review by 3rd if any disagreement. Based on medical history and physical examination (including 18 point fibromyalgia evaluation), SCID, and laboratory evaluation. Used refinement of Fukuda, 1994 as recommended by International Research group and the CDC (Reeves, Lloyd et al BMC health services research vol 3, 2003).	Compares MFI-20 vs. SF-36 vs. CDC symptoms Inventory	213 adults from com based sample from neighborhoods in Cl (see above). Final s n= 10824 who had C 84 who did not. Unit States; female NR.

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Jason, *et al.,* 2011[65]	*Tertiary care sample* **Inclusion:** Participants ages ≥18 years, not pregnant, able to read and speak English, and physically capable of attending the sessions. CFS diagnosis according to CDC (Fukuda, 1994) criteria. **Exclusion:** Exclusionary psychiatric diagnoses according to CDC (Fukuda, 1994) criteria. **Recruitment:** 114 patients recruited from physician referrals, newspaper advertisements, and CFS support groups; they were administered a structured clinical interview and medical/laboratory evaluation. *Community sample* **Inclusion:** Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report. (Therefore termed, “CFS-like”; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient’s file.) **Exclusion:** Exclusionary medical or psychiatric conditions detected in evaluation. **Recruitment:** Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults ages >18 years from several neighborhoods in Chicago). The control group was randomly selected from those who screened negative.	ROC curve analysis with AUC

Jason, *et al.,* 2010[56]	**Inclusion**: Self report of chronic fatigue and the concurrent occurrence of ≥4 core symptoms listed in CDC (Fukuda, 1994) case definition. 408 with chronic fatigue and symptoms that met the Fukuda CFS case definition by self-report (Therefore termed, “CFS-like”; Of these 166 completed a structured psychiatric interview; 2 independent rates from a team of 4 physicians and a psychiatrist used Fukuda criteria to rate each patient’s file.) **Exclusion:** Exclusionary medical or psychiatric conditions detected in evaluation. **Recruitment:** Of 18,675 interviewees in a community-based prevalence survey (stratified random sample of adults ages >18 years from several neighborhoods in Chicago).	ROC analysis with AUC.

Author, year	Findings	Conclusions
Jason, *et al.*, 2011[65]	Community-based sample (cases vs. controls) AUC (SE) by subscale of SF-36 Vitality: 0.88 (0.04) Social functioning: 0.87 (0.04) Role-physical: 0.86 (0.04) Bodily pain: 0.85 (0.04) Physical Functioning: 0.84 (0.05) General Health: 0.80 (0.05) Mental Health: 0.75 (0.06) Role-Emotional: 0.67 (0.07) Tertiary care-based sample (cases vs. community controls) AUC (SE) by subscale of SF-36 Vitality: 0.91 (0.03) Social functioning: 0.87 (0.04) Role-physical: 0.91 (0.03) Bodily pain: 0.86 (0.04) Physical Functioning: 0.87 (0.04) General Health: 0.91 (0.35) Mental Health: 0.71 (0.05) Role-Emotional: 0.63 (0.05)	SF-36 subscales of vitality, social functioning, and role-physical hav best sensitivity and specificity and thresholds. Note: this paper also cites discrim by SF-36 subscales based on lite review included in this paper but n focus of the paper (9 studies repo 36 subscales comparing CFS pat and a non-ill control group).

Jason, *et al.,* 2010[56]	**AUC, sensitivity, specificity** *MFI-20 subscale* General fatigue: 0.69, 74%, 39% Reduced activity: 0.64, 74%, 50% Meeting Reeves fatigue criteria: 0.61, 95%, 27% *CDC Symptom Inventory* Meeting Reeves core symptoms criteria (total): 0.69, 59%, 73% *SF-36 subscale* Physical functioning: 0.60, 68%, 51% Role physical: 0.66, 82%, 51% Social functioning: 0.62, 74%, 35% Role emotional: 0.57, 73%, 44% *Meeting Reeves substantial reductions criteria:* 0.56, 96%, 17% *Meeting Reeves CFS criteria:* 0.70, 65%, 76%	CDC empirical CFS definition ide approximately 65% of those with "When diagnostic tests lack reliab and accuracy, the quality of treatr and clinical research can be significantly compromised."

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Hadzi-Pavlovic, *et al.,* 2000[64]	To develop and evaluate the SOFA/CFS instrument for identifying CFS.	Met clinical criteria for CFS, recruited for another study - Lloyd, *et al.*, 1990; also diagnostic confidence rating assigned with consensus between investigator and patient's physician.	General Health Questionnaire 5 items from the Zung depression Scale Chronic Fatigue Symptoms Checklist Somatization Checklist (39 physical symptoms)	Final n=613, plus 43 controls, and 1,593 care attenders. Unit Kingdom; 66%.
Linder, *et al.,* 2002[63]	To investigate different approaches to establish sets of clinical classification criteria to distinguish CFS from systemic lupus erythematosus and fibromyalgia. Used self-learning artificial neural network to general diagnostic criteria sets for CFS, and vs. traditional classification criteria.	Oxford (Sharpe, 1991)	All 198 subjects were randomly assigned to 1 of 2 groups for development and validation (group A n=158 and group B n=40)	198; 99 CFS, 41 sys lupus erythematosu fibromyalgia. Germa female.
Tiev, *et al.,* 2003[62]	To determine if high ratio of Rnase L isoforms identify CFS subjects.	CDC (Fukuda, 1994)	MFI-20 administered to both groups. All had Rnase L isoform ratio measured from PBMC's.	11; 6 women and 5 14 healthy controls. 64% female.

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Hadzi-Pavlovic, *et al.,* 2000[64]	**Inclusion:** Patients with CFS diagnosis. **Exclusion:** Patients who did not have complete data, those who did not report any current fatigue, those for whom a diagnostic confidence rating was unavailable, and those whos diagnostic confidence rating suggested that the original diagnosis of CFS was unreliable. **Recruitment:** 770 subjects with initial clinical diagnoses of CFS were sent followup questionnaire; 624 responded; 613 had usable data. Of those, 368 met final inclusion criteria for CFS. Each CFS subject gave a questionnaire to non-CFS acquaintance (452) and 430 for control. In addition, 1,593 consecutive attenders at primary care completed the self-report scales	Latent class analysis, ROC curves.
Linder, *et al.,* 2002[63]	**Inclusion:** Patients with the leading symptom of severe fatigue >6 month duration, where known medical causes for fatigue had been excluded. **Exclusion:** Known medical causes for fatigue, primary psychiatric disorders. **Recruitment**: Patients were recruited from an outpatient population by the study physicians using a predefined standardized examination procedure. Patients with systemic lupus erythematodes and fibromyalgia who also presented with fatigue were also recruited as a comparison group.	Compared 4 methods to develop criteria sets for the classification of CFS: a) traditional non-weighted use of classification criteria, b) the weighting of criteria with regression coefficients, c) regression tree analysis, and d) an artificial neural network (back procrastination method).
Tiev, *et al.,* 2003[62]	**Inclusion:** Patients fulfilling CDC (Fukuda, 1994) criteria. **Exclusion**: NR **Recruitment:** NR Control group consisted of 14 matched healthy volunteers.	Using 0.4 as the cutoff for Rnase L isoform ratio.

Author, year	Findings	Conclusions
Hadzi-Pavlovic, *et al.,* 2000[64]	Initial phase: clinical sample and their selected controls. 10 items with highest loadings on the first factor - total score of these 10 items. **Sensitivity, specificity** A cut-off score of 1/2 classified 341/368 CFS cases and 409/430 control subjects correctly: 93%, 95% Kraemer's QROC: 87%, 89% Including the 69 CFS subjects who had a diagnosis other than CFS or for whom there was low confidence in the diagnosis as "non-cases" did not change the sensitivity, but reduced the specificity to 83% QROC: 86%, 65% *LCA performed on 368 CFS subjects only* **Sensitivity, specificity** Cut-off of ≥2: 3 class: 100%, 90% 4 class: 97%, 98% Cut-off of ≥3: 3 class: 81%, 100% 4 class: 66%, 100%	Recommend SOFA/GP instructm cutoff score ≥3 to maximize speci Longitudinal LCA analysis indicat symptoms constructs are identafi cross-sectionally by the SOFA/GP that they are stable over time.
Linder, *et al.,* 2002[63]	**Sensitivity, specificity, accuracy** *Applied traditional CDC (Holmes, 1988) definition (group A):* 62.6%, 93.9%, 78.3% *Traditional format classification criteria in validation cohort (group B):* 90.0%, 65.0%, 77.5%. Three symptoms: sudden onset of fatigue, sore throat, and impaired vision have the greatest discriminatory power in differentiating CFS from systemic lupus erythematosus and fibromyalgia. *Weighting of classification criteria with regression coefficients in validation cohort (group B):* 90.0%, 75.0%, 82.5% (optimum accuracy is obtained using sudden onset of fatigue, sore throat, and irritability (positive associations); negative associations with GI disturbances, allergies and dyspnea) *Regression tree analysis in the validation cohort (group B):* 95.0%, 80.0%, 87.5% (at most, 5 symptoms need to be ascertained before a classification can be made) *Artificial neural network in the validation cohort (group B):* 95.0%, 85.0%, 90.0% (uses 24 of the 26 symptoms)	Each method improved upon the methods for distinguishing CFS fr systemic lupus erythematosus an fibromyalgia. The artificial neural network was superior to other me tested. Both regression methods led to good classification of CFS. CFS symptoms with greatest accu were acute onset of fatigue and s throat.
Tiev, *et al.,* 2003[62]	Sensitivity: 91% Specificity: 71%.	In absence of infection or inflamm high RNase L isoform ratio could distinguish CFS subjects from hea controls.

Author, year	Objectives	Case definition	Study design/outcome measures	Total N/population
Watson, *et al.,* 2014[69]	To determine the sensitivity, specificity and accuracy of a symptoms threshold for the DePaul Symptom Questionnaire for identification of ME/CFS as identified by 3 different case definitions: Fukuda 1994, the Canadian ME/CFS 2003 criteria and the 2011 ME-ICC criteria.	CDC (Fukuda, 1994) Canadian (Carruthers, 2003) ME-ICC (Carruthers, 2011)	DePaul Symptom Questionnaire; computerized thresholding usinga k-means clustering approach.	3 cohorts: 283; 187 with CFS a controls 313; 233 with CFS a controls 95 with suspected C

Author, year	Eligibility criteria/recruitment methods	Statistical methods
Watson, *et al.,* 2014[69]	**Inclusion:** suspected CFS with referral or self-reported CFS **Exclusion:** NR **Recruitment**: DePaul sample - 187 patients recruited through internet and 96 controls recruited from undergraduate university population; Biobank sample - 233 patients and 80 controls recruited through internet; Newcastle sample - 95 patients recruited from among referrals to CFS clinic (suspect CFS diagnosis).	Sensitivity, specificity and accuracy of the k-means clustering algorithm set to find two clusters (threshold for symptom present vs symptom not present).

Author, year	Findings	Conclusions
Watson, *et al.,* 2014[69]	**Sensitivity, specificity, accuracy for case deffitionion** *Unsupervised thresholding (UT):* CDC (Fukuda, 1994): 83.1, 85.8, 83.8; Canadian (Carruthers, 2003): 82.9, 87.5, 84.1; ME-ICC (Carruthers, 2011): 74.4, 91.5, 78.7 *Supervised thresholding:* CDC (Fukuda, 1994): 80.8, 86.4, 82.2; Canadian (Carruthers, 2003): 85.8, 87.5, 86.3; ME-ICC (Carruthers, 2011): 89.9, 81.3, 87.7 *Two-two static threshold:* CDC (Fukuda, 1994): 80.8, 85.8, 82.1; Canadian (Carruthers, 2003): 77.9, 89.8, 80.9; ME-ICC (Carruthers, 2011) 67.4, 91.5, 73.5 (sensitivity and accuracy for Fukuda and ME-ICC p=0.01 vs. UT) *One-one static threshold:* CDC (Fukuda, 1994): 98.1, 42.0, 83.8 (p=0.01 vs. UT for sensitivity and specificity); Canadian (Carruthers, 2003): 97.3, 50.0, 85.2 (p=0.01 vs. UT for sensitivity and specificity); ME-ICC (Carruthers, 2011): 93.4, 52.8, 83.1 (p=0.01 vs. UT for sensitivity and specificity)	K-means clustering as a diagnost is at least as good as other diagn methods

* = note this is one item from the questionnaire used for case definition

† = Energy quotient score calculated by dividing the perceived available energy by the amount of expended energy and multiplying by 100; if > 100 then person is outside their energy envelope.

Abbreviations: ACTH= adrenocorticotropic hormone; am= ante meridiem; ANCOVA= analysis of covariance; ANOVA= analysis of variance; AUC= Area under the curve; BDS= Beck depression scale; BMC= BioMed Central; BMI= body mass index; CDC= Centers for Disease Control and Prevention; CFS= Chronic Fatigue Syndrome; CI= Confidence interval; coeff = coefficients; DSM-IV= Diagnostic and statistical manual fourth edition; GP= general practice; HADS= Hospital Anxiety and Depression Scale; HPA= hypothalamus-pituitary- adrenal axis; IL-6= interleukin - 6; kg= kilogram; LCA= latent class analysis; LPS= lipopolysaccharide; LR= likelihood ratio; MFI-20= Multidimensional fatigue inventory; mg= milligram; min = minute; n=sample size; NF-kB= nuclear factor kappa-light-chain-enhancer of activated B cells; NR= not reported; PBMC= peripheral blood derived mononuclear cell; PEM= post exertional malaise; pm= post meridiem; QROC= quality receiver operating characteristic; Rnase L= latent Ribonuclease; ROC= receiver operating characteristic; SCID= structural clinical interview for DSM-IV; SCL-90R= symptom checklist 90-revised; SE= standard error; sens= sensitivity; SF-36= 36-item Sort Form Survey; SF-SIP-8= Sickness Impact Profile 8-item; SOFA= schedule of fatigue and anergia; spec= specificity; TNF= tumor necrosis factor; TSST= Trier social stress test; U= unit; UT=unsupervised threshold; vol = volume; vs.= versus.

Table G3. Evidence table of included studies of harms of diagnosis

Author, year	Objective	N/population	Findings
Åsbring, *et al.,* 2002[71]	To investigate whether patients with CFS and fibromyalgia experience stigma and to examine the strategies they use to avoid enacted stigma.	N=25 women (12 CFS, 13 fibromyalgia) were interviewed to the point of saturation of themes regarding stigma.	**Two main aspects of stigmatization were reported** 1) Women experienced their moral character being called into question. 2) They experienced distress from being psychologized by others, especially doctors (decided in advance that problems were ficticious or psychological; and that this experience was deeply violating).
Assefi, *et al.,* 2003[72]	To examine self-reported disability in patients with CFS and fibromyalgia, subsyndromal fatigue, compared with chronically fatiguing but unrelated medical condition.	N=555 (207 CFS, 76 fibromyalgia, 87 CFS+fibromyalgia, 31 sybsyndromal fatigue, 154 medical conditions) of 630 (88%) patients from a university CFS clinic responded to a survey about financial, occupational, and personal consequences of their illness.	**Disability outcomes reported by >20% of CFS (n=207) group** Lower standard of living: 44% (92/207) Significant decrease in social life: 84% (174/207) Lost friends: 38% (79/207) Significant decrease in recreational activities: 90% (186/207) *Of those CFS patients employed (n=119)* Taking a new job requiring fewer skills: 25% (30/119) Took a substantial pay cut: 30% (35/119)
Brimmer, *et al.*, 2013[77]	To evaluate all patients referred to a CFS registry, to diagnose CFS according to CDC (Fukuda, 1994) criteria	N=93 patients referred to CFS registry over the course of 1 year.	**Review of the CFS registry referrals** 33 patients were classified as having CFS, 13 as insufficient fatigue or symptoms and 47 patients as having an exclusionary condition. 24 (65%) of the provider-referred patients and 13 (35%) of the support group referral patients met criteria for CFS.
Devasahayam, *et al*., 2012[78]	To assess the accuracy of diagnoses made by referrers to a CFS service	N=418 referrals received to CFS service.	**Analysis of referral rejection letters** 52 (36%) of the reasons for rejected referrals were likely alternative pyschiatric diagnosis and 67 (35%) were likely alternative medical diagnosis.
Deale, *et al.,* 2000[73]	To evaluate patient experience with psychiatric diagnoses in CFS patients; evaluate whether psychiatric illness is overdiagnoses in routine clinical practice among CFS patients.	N=68 patients met Oxford criteria (Sharpe, 1991) for CFS completed a questionnaire asking about psychiatric diagnoses or labels given during their illness and then underwent interview to assess for those psychiatric disorders with the DSM III-R.	**Reported psychiatric diagnosis** 46% (31/68) given psychiatric diagnosis (usually depression) 68% (21/31) given depression diagnosis were misdiagnosed 35% (13/37) not given psychiatric diagnosis met DSM III-R criteria for treatable psychiatric disorder, present for ≥6 months

Author, year	Objective	N/population	Findings
Dickson, *et al.,* 2007[74]	To understand participants' prioritizations and understandings of CFS.	N=14 people with with self-reported CFS were interviewed about living with CFS.	**Reported difficulties about living with CFS**71% (10/14) experienced dealy in getting CFS diagnosis57% (8/14) were prescribed antidepressants for depression diagnosis instead of CFS diagnosis**Descriptive results**Participants reported that they perceived many medical practitioners to hold stereotypical views of patients with CFS, namely that disease was either psychological or indicative of an affective disorder. Problems with friends and partners centered on the fact that the patient is not visibly ill, and that the symptoms are inconsistent or variable.
Green, *et al.,* 1999[75]	To evaluate stigma among people with CFS.	N=45 of 67 (67%) initially recruited patients with CFS reported perceptions of stigma.	**Reported perceptions of stigma** 95% reported feeling estranged 70% thought others attribute their symptoms to psychological or personality 40% felt need to be secretive about their symptoms in some circumstances
Guise, *et al.,* 2010[76]	To evaluate ME/CFS sufferers' descriptions of interactions with medical professionals.	N=38 members of an internet-based ME/CFS support group were asked to comment on how they felt about the way medical people treated them.	**Descriptive results** Patients with CFS reported that health professionals lack clinical expertise and empathy; and that they encountered professionals who lacked expectation of treatability, described themselves as fortunate in terms of experiences with medical professionals, and described themselves as able to cope and actively seeking out information and treatment.
Jason and Taylor, 2001[70]	To evaluate perceptions of diagnostic labeling among medical trainees, university undergraduates and practicing mental health practitioners.	N=105 medical trainees (Study 1) N=141 undergraduate psychology students (Study 2) Randomly assigned to being told the case presented to them had CFS, Florence Nightingale Disease, or ME. The case studies were identical.N=93 mental health practitioners (Study 3)Randomly assigned to 1/3 treatments for CFS, and given identical case studies of a woman with prototypic CFS symtpoms, diagnosed by a physician; treatments were 1) Ampligen - IV immmune modulator, 2) CBT with graded activity, or 3) cognitive coping skills therapy.	**Studies 1 and 2: told case was CFS vs. Florence Nightingale Disease vs. ME**Correctly diagnosed: 54% vs. 19% vs. 28%; p<0.01Disease result of as-yet-undiscovered cancer, infection or other illness: 22% vs. 47% vs. 28%; p<0.05Reported patient was likely to improve: 41% vs. 42% vs. 16%; p<0.05**Study 3: Data not shown**Participants assigned to Ampligen were more likely to think that the patient was correctly diagnosed as having CFS (p<0.05) and also thought the patient was signficantly more disabled than did individuals in the CBT with graded activity condition (p<0.05)

Author, year	Objective	N/population	Findings
Jason, et al., 2001[14]	To reproduce a prior study of labeling, in term of whether different names for CFS prompts different attributions regarding cause.	N=105 medical trainees (Study 1) N=141 undergraduate psychology students (Study 2) Randomly assigned to being told the case presented to them had CFS, Florence Nightingale Disease, or ME. The case studies were identical.	**Told case was CFS vs. Florence Nightingale Disease vs. ME** **Mean score of whether correct diagnosis (1-6 scale; 1=not at all and 6=very likely): 4.5 vs. 3.9 vs. 4.0; p<0.01** **Proportion that associated "causal factors" with diagnosis: 28% vs. 31% vs. 49%; p<0.01** **Mean score of whether diagnosis was associated "organ donorship" (1-6 scale; 1=not at all and 6=very likely): 3.7 vs. 3.5 vs. 3.1; p<0.05**
Lawn, et al., 2010[79]	To quantify the number and nature of comorbid psychiatric disorders in patients with CFS.	N=135 patients participating in the PACE trial.	**Psychiatric interview using the Structured Clinical Interview fo DSM-IV Disorders** **102 patients (76%) had a comorbid psychiatric diagnosis; 31% depression, 11% dysthymia, 35% anxiety, 11% social phobia, 15% specific phobia, 6% post-traumatic stress disorder and 2% obsessive compulsive disorder.**

Author, year	Objective	N/population	Findings
Newton, *et al.*, 2010[80]	To examine the proportion of subjects referred to CFS specialist service who fulfill the CDC (Fukuda, 1994) criteria vs. alternative fatigue-associated diagnoses.	N=260 patients referred to CFS specialist service between 2008 and 2009.	**Reviewed medical notes of patients referrend to CFS specialist service** Of those referred, 60% were diagnosed with CFS; 40% had alternative diagnosis including other chronic disease (47%), sleep disorder (20%), psychological (15%), idiopathic fatigue (13%), cardiovascular (4%) and other (1%).
Reyes, *et al.*, 2003[21]	To estimate the prevalence and 1-year incidence of CFS in the population, and to report on exclusionary diagnoses identified by telephone interview.	N=3,528 subjects with fatigue ≥1 month duration (2762 with fatigue ≥6 months). 3 physicians and 2 psychiatrists independently reviewed each subject's clinical and laboratory data and classified the individual according to the CDC (Fukuda, 1994) criteria.	**Descriptive results of exclusionary diagnosis identified in the telephone interview** Among 1,155 subejcts who had fatigue ≥6 months, not relieved by rest with ≥4 of 8 CFS symptoms, 600 had a medical or psychiatric diagnosis. Of 299 subjects without a medical/psychiatric diagnosis who underwent a clinical examination, 43 had CFS, 112 had insufficient symptoms or fatigue, 141 (47.2%) had a medical or psychiatric diagnosis that had not previously been identified and 3 were not classified.
Woodward, *et al.,* 1995[81]	To describe doctors' and patients' perspectives on the risks and benefits of symptomatic diagnosis of chronic fatigue syndrome.	N=20 general practitioners (Study 1) and N=50 patients with diagnosis of CFS (Study 2).	**Descriptive results of interviews** 14/20 physicians reluctant to diagnosis CFS (scientific uncertainties about condition, beliefs about appropriate professional practice and uncertainty about impact of diagnosis on patient's lives). 45/50 patients stated that diagnosis was the single most helpful event over the course of their illness. Described harms from *not* having a diagnosis (fear, anxiety, confusion, self-doubt, bitterness). Subjects in this study did not appear to endorse harm from labeling, but helpful

Abbreviations: CBT= cognitive behavioral therapy; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; DSM-III-R= Diagnostic and Statistical Manual third edition revised; ME= myalgic encephalopathy; n= sample size; vs.= versus

Table G4. Evidence table of included trials of interventions for ME/CFS

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Medications				
Blacker, *et al.,* 2004[82]	RCT of oral galantamine (acetyl-cholinesterase inhibitor) at various doses vs. placebo for underlying cause	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo** Mean ages (years): 39 vs. 39 vs. 39 vs. 37 vs. 38 % Female: 72 (64/89) vs. 71 (61/86) vs. 62 (56/91) vs. 62 (53/86) vs. 62 (51/82) % White: 99 (88/89) vs. 92 (79/86) vs. 98 (89/91) vs. 95 (82/86) vs. 94 (77/82)	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years, modified CDC criteria, illness duration <7 years. **Exclusion:** Concurrent DSM-IV diagnoses: major depressive disorder, psychotic disorders, panic disorder, substance misuse, somatization disorder, anorexia or bulimia nervosa, obesity, and sleep disorders; received inpatient psychiatric care had previously attempted suicide or both; irritable bowel syndrome; peptic ulcer; severe asthma; endocrine or metabolic disease; HIV; know sensitivity to cholinergic agents; possible exposure to organophosphate compounds; diagnosis of Gulf War syndrome; pregnant or lactating; women with irregular menstrual irregularities associated with fatigue.	<7 years
Blockmans, *et al.,* 2003[84]	Crossover RCT of oral hydrocortisone + fludrocortisone (corticosteroid) vs. placebo for underlying cause	Mean age: 38 years % Female: 91 (73/80) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Meet ≥4 CDC minor criteria for CFS. **Exclusion:** History of gastric or duodenal ulcer, arterial hypertension, glaucoma, or diabetes; pregnant; or incomplete screening examination.	Mean (range): 30 (16-60) months
Diaz-Mitoma, *et al.,* 2003[89]	RCT of isoprinosine (antiviral and immunomodulatory drug) vs. placebo for underlying cause	Mean age (SD): 46 (8) years % Female: 81% (13/16) % White: 100	CDC (Holmes, 1988 and Fukuda, 1994) criteria **Inclusion:** Ages 18-60 years with ongoing symptoms for ≥6 months. Females were required to have a negative pregnancy test. **Exclusion:** Malignancy, major organ or system pathology inconsistent with CFS	≥6 months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Medications					
Blacker, *et al.,* 2004[82]	Number approached: NR Number screened: NR Number eligible: 434 Number randomized: 434 Number analyzed: 423	United Kingdom, Western Europe, United States 35 clinic centers	16 weeks (8 weeks at full dose)	**Overall:** 30% (130/434) **Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** 20% (18/89) vs. 36% (31/86) vs. 35% (32/91) vs. 31% (27/86) vs. 27% (22/82)	Non-compliance: 6 (4 interventions vs. 2 placebo)
Blockmans, *et al.,* 2003[84]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 100 Number analyzed: 80	Belgium Single site tertiary care university clinic	3 month treatment; 3 month placebo crossover	20% (20/100)	NR
Diaz-Mitoma, *et al.,* 2003[89]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 16 (10 isoprinosine, 6 placebo) Number analyzed: 15 (10 isoprinosine, 5 placebo)	Canada 1 Research site in Ottawa	12 weeks of treatment	6.3% (1/16, was in placebo group)	NR

Author, year	Interventions	Fatigue outcomes
Medications		
Blacker, *et al.,* 2004[82]	**Galantamine 7.5:** Galantamine 2.5 mg three times per day **Galantamine 15:** Galantamine 5 mg three times per day **Galantamine 22.5:** Galantamine 7.5 mg three times per day **Galantamine 30:** Galantamine 10 mg three times per day **Placebo:** Identical placebo three times per day *Note:* For intervention groups doses were titrated over 3-8 week period, starting at 2.5 mg/day with weekly increments of 2.5-7.5 mg depending on target dose, which was maintained for another 8 weeks	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo** *Chalder Fatigue Rating Scale least square mean change from baseline (positive changes indicate better health)* Physical: 9.25 vs. 8.77 vs. 11.02 vs. 9.99 vs. 9.86 Mental: 6.46 vs. 5.89 vs. 7.74 vs. 6.60 vs. 6.80
Blockmans, *et al.,* 2003[84]	**Hydrocortisone:** Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day **Placebo:** Placebo	**Hydrocortisone vs. placebo** *Visual Analog Scale (0-10)* Degree of fatigue: 6.6 (2.0) vs. 6.7 (2.1); p=0.76 *Mean (SD) SFQ score (4-28, higher scores indicate better health)* : 8 (5) vs. 7 (5); p=0.69
Diaz-Mitoma, *et al.,* 2003[89]	**Isoprinosine:** 2 tablets of oral isoprinosine 500 mg TID (total=3 g/day) in weeks 1, 3, 5, 7, 9, and 11 only on Monday-Friday; and once a day (total=1 g/day) in weeks 2, 4, 6, 8, 10, and 12 only on Monday-Friday. **Placebo:** Identical placebo following the same schedule as the isoprinosine group.	**Isoprinosine vs. placebo** % change on KPS from baseline to 12 weeks: 0.6% (12.1) for 6 treatment group “improved” participants; 0.0% (10.7) for 4 treatment group “not improved” participants; 3.0% (6.9) for 5 placebo participants; p=0.93

Author, year	Quality of life outcomes	Function outcomes
Medications		
Blacker, *et al.,* 2004[82]	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo;** all comparisons are NS between groups *FIQ least square mean change from baseline* Global Well Being (composite): -77.84 vs. -88.65 vs. -29.92 vs. -60.67 vs. -53.89	NR
Blockmans, *et al.,* 2003[84]	**Hydrocortisone vs. placebo** *Visual Analog Scale (0-10)* Degree of well-being: 5.0 (2.4) vs. 4.6 (2.6); p=0.14	**Hydrocortisone vs. placebo** *SF-36 (0-100 scale, higher scores indicate better health)* Physical functioning: 31.7 (18.2) vs. 30.4 (18.1); p=0.34
Diaz-Mitoma, *et al.,* 2003[89]	NR	No difference in activities of daily living scale, data not provided

Author, year	Employment outcomes	Other outcomes
Medications		
Blacker, *et al.,* 2004[82]	NR	**Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo;** all comparisons are NS between groups *% Improved on modified CGI:* 25 (29%) vs. 18 (23%) vs. 19 (22%) vs. 16 (20%) vs. 14 (18%)
Blockmans, *et al.,* 2003[84]	NR	NR
Diaz-Mitoma, *et al.,* 2003[89]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Medications						
Blacker, *et al.,* 2004[82]	**Overall:** 23% (88/389) **Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:** 14% (12/89) vs. 23% (20/86) vs.24% (22/91) vs. 26% (22/86) vs.15% (12/82)	Galantamine: 2% (8/389) none attributed to the study drug	Depression, nausea and headache most common in both groups	90% (389) reported adverse events; 23% (88) withdrew	Shire Pharmaceutical Development Ltd.	Fair
Blockmans, *et al.,* 2003[84]	1 acne and weight gain	None	None	1	NR	Fair
Diaz-Mitoma, *et al.,* 2003[89]	0	NR	NR	NR	Grants from Enterprise Ireland (130590/D)	Poor

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
McKenzie, *et al.,* 1998[83]	RCT of oral hydrocortisone (corticosteroid) vs. placebo for underlying cause	**Hydrocortisone vs. placebo** Mean age: 37 vs. 38 years % Female: 83 (29/35) vs. 77 (27/35) % White: 97 (34/35) vs. 94 (33/35)	CDC (Holmes, 1988) and CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-55 years, illness began over a period 6 weeks or less. **Exclusion:** Contraindication to systemic steroids.	**Hydrocortisone vs. placebo** Mean: 47 vs. 60 months; p=0.07
Montoya, *et al.,* 2013[86]	RCT of oral valganciclovir (antiviral drug) vs. placebo for underlying cause	**Valganciclovir vs. placebo** Mean age: 50 vs. 48 years % Female: 75 (15/20) vs. 50 (5/10) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age18 and older; suspected viral onset of CFS; elevated antibody titer meeting additional criteria. **Exclusion:** Reasons for exclusion include: low antibody titers on repeat testing, exclusionary comorbidities, conflicting medication, declined to participate.	**Valganciclovir vs. placebo** Mean: 12.7 vs. 13.5 years
Peterson, *et al.,* 1990[85]	RCT of IV IgG vs. placebo for underlying cause	Mean age: 41 years % Female: 73 (22/30) Race: NR	CDC (Holmes, 1988) criteria **Inclusion:** Diagnosis of CFS. **Exclusion:** NR	Mean: 3.8 years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
McKenzie, *et al.,* 1998[83]	Number approached: NR Number screened: 638 Number eligible: 179 Number enrolled: 70 Number analyzed: 60-70 varied by outcome	United States Single center at the NIH	12 weeks	10% (7/70)	NR
Montoya, *et al.,* 2013[86]	Number approached: 155 Number screened: 45 Number eligible: 34 Number enrolled: 30 Number analyzed: 30 (20 valganciclovir, 10 placebo)	United States Patients referred to study at Stanford University	6 months treatment and 6 more months followup (unbinding and outcomes measured at 9 months)	1 from each group	100% at 3 weeks; 90% at 12 weeks; 65% at 24 weeks
Peterson, *et al.,* 1990[85]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 30 Number analyzed: 28	United States, Minnesota Single center	6 months	7% (2/30)	NR

Author, year	Interventions	Fatigue outcomes
McKenzie, *et al.,* 1998[83]	**Hydrocortisone:** Oral hydrocortisone 20-30 mg every morning and 5 mg every evening (13 mg/m^2 every morning and 3 mg/m^2 every evening) **Placebo:** Placebo	**Hydrocortisone vs. placebo** *Mean Change in POMS subscales* Fatigue (negative changes indicate better health): -3.6 (5.3) vs. -1.8 (4.5); p=0.21 Vigor (positive changes indicate better health): 1.2 (3.3) vs. 0.7 (3.3); p=0.45
Montoya, *et al.,* 2013[86]	**Valganciclovir:** Oral valganciclovir 900 mg BID for 21 days, then 900 mg once daily for total of 6 months **Placebo:** Placebo	**Valganciclovir vs. placebo** *Change in MFI-20 (negative changes indicate better health)* Baseline to 9 months : -6.15 vs -1.10; p=0.224 *Change in FSS (negative changes indicate better health)* -0.06 vs 0.02; p=0.006
Peterson, *et al.,* 1990[85]	**IgG:** IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) **Placebo:** IV placebo (1% albumen solution) every 30 days for 6 months (6 infusions)	NR

Author, year	Quality of life outcomes	Function outcomes
McKenzie, *et al.,* 1998[83]	**Hydrocortisone vs. placebo** *Global Wellness scale (0-100)* Improvement: 20/30 (67%) vs. 19/35 (54%); p=0.31 Mean change: 6.3 (11.7) vs. 1.7 (8.8); p=0.06	**Hydrocortisone vs. placebo** *Mean change (SD) in Activity Scale (10 point scale)* 0.3 (1.1) vs. 0.7 (1.4); p=0.32
Montoya, *et al.,* 2013[86]	NR	**Valganciclovir vs. placebo** *Change in self-reported physical function (positive change indicates better health)* 1.02 vs 0.46; p=0.217
Peterson, *et al.,* 1990[85]	NR	**IgG vs. placebo** *SF-12 (0-100 scale, higher scores indicate better health)* Physical: 56.0 (23.2) vs. 51.8 (27.2); p=NS Social: 5.2 (5.5) vs. 9.4 (7.9); p<0.05

Author, year	Employment outcomes	Other outcomes
McKenzie, *et al.,* 1998[83]	NR	NR
Montoya, *et al.,* 2013[86]	NR	CDC Symptom inventory: NS
Peterson, *et al.,* 1990[85]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
McKenzie, *et al.,* 1998[83]	1 rash with placebo	None	**Hydrocortisone vs. placebo** Suppression of adrenal glucocorticoid responsiveness: 12 vs. 0; p<0.001	**Hydrocortisone vs. placebo** *Events that differed* Increased appetite: 17 vs. 8; p=0.02 Weight gain: 19 vs. 8; p=0.006 Difficulty sleeping: 17 vs. 8; p=0.02	NR	Fair
Montoya, *et al.,* 2013[86]	0	1 patient with cancer in each group considered not related to intervention	0	0	Hoffman-La Roche; Stanford University	Fair
Peterson, *et al.,* 1990[85]	2 (1 in each group)	2 IgG and 3 placebo	**IgG vs. placebo** Headaches: 93% vs. 60%; p=0.03	20% overall	Baxter Healthcare Corp.	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Strayer, *et al.,* 1994[87]	RCT of IV rintatolimod (Ampligen= antiviral and immunomodulatory drug) vs. placebo for underlying cause	**Rintatolimod vs. placebo** Mean age: 36 vs. 35 years % Female: 64 (no. NR) vs. 85 (no. NR); p=0.003 Race: NR vs.NR	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** CFS diagnosed ≥12 months before study; severe debilitation (KPS 20-60). **Exclusion:** Women who were pregnant or nursing.	**Rintatolimod vs. placebo** Mean: 6.1 vs. 4.4 years
Strayer, *et al.,* 2012[88]	RCT of IV rintatolimod (Ampligen=antiviral and immunomodulatory drug) vs. placebo for underlying cause	**Rintatolimod vs. placebo** Mean age: 43 vs. 44 years % Female: 66 (no. NR) vs. 78 (no. NR) Race: NR	CDC (Holmes,1988) and (Fukuda, 1994) criteria **Inclusion:** Adults ≥18 years with diagnosis of CFS ≥ 12 months resulting in significant debilitation as measured by KPS, with ability to walk on the treadmill. Patients must have baseline laboratory documentation of euthyroid status, negative antinuclear antibody or negative anti-ed DNA, negative rheumatoid factor, and an erythrocyte sedimentation rate. **Exclusion:** Pregnant or lactating females, those who might become pregnant, chronic or intercurrent acute medical disorders, inability to return to investigators site for the study, prior participation in a study of Printatolimond, medical need to continue taking aspirin or NSAIDs, treatment with glucocorticoids, mineralocorticoids, interferons, interleukin-2, systemic antivirals, gamma globulin or investigational drugs within the 8 weeks prior to study baseline.	**Rintatolimod vs. placebo** Mean: 9.6 vs. 9.7 years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Strayer, *et al.*, 1994[87]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 92 Number analyzed: 76-84 varies by outcome	United States 4 clinical sites	24 weeks	9% (8/92) 4 from each group	91% (84/92)
Strayer, *et al.*, 2012[88]	Number approached: NR Number screened: NR Number eligible: 307 Number enrolled: 240 Number analyzed: 240	United States 12 centers	40 weeks	19% (46/240)	83% (194/234)

Author, year	Interventions	Fatigue outcomes
Strayer, *et al.*, 1994[87]	**Rintatolimod:** IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks **Placebo:** Placebo	**Rintatolimod vs. placebo** *Exercise duration* % change from baseline: +10.3 vs. +2.1; p=0.007 *Exercise work* % change from baseline: +11.8 vs. +5.8; p=0.011
Strayer, *et al.*, 2012[88]	**Rintatolimod:** IV rintatolimod 400 mg twice weekly for 40 weeks **Placebo:** Placebo	**Rintatolimod vs. placebo** *Cardiopulmonary exercise tolerance (primary outcome)* Increase from baseline: 36.5% vs. 15.2%; p=0.047

Author, year	Quality of life outcomes	Function outcomes
Strayer, *et al.*, 1994[87]	NR	**Rintatolimod vs. placebo** % change in *KPS score from baseline (0-100 scale, higher scores indicate better health)* +20 vs. 0; p=0.023 % change in *ADL score from baseline (0-100 scale, higher scores indicate better health)* +23.1 vs. 14.1; p=0.034
Strayer, *et al.*, 2012[88]	NR	KPS score, ADLs, Vitality Score (SF-36), and General Health Perception (SF-36) measured pre and post, but not compared between rintatolimod and placebo groups

Author, year	Employment outcomes	Other outcomes
Strayer, *et al.*, 1994[87]	NR	Decreased used of medications for relief of CFS symptoms declined for rintatolimod but not compared with placebo
Strayer, *et al.*, 2012[88]	NR	**Rintatolimod vs. placebo** Decreased used of medications for relief of CFS symptoms: 68% vs. 55%; p=0.048

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Strayer, *et al.*, 1994[87]	None	None	Insomnia more frequent among placebo, dry skin among rintatolimod	**Rintatolimod vs. placebo:** 706 vs. 711 events; p>0.90	Hemispherx Biopharma	Fair
Strayer, *et al.*, 2012[88]	4 (2 in each group)	3 in each group with no differences between rintatolimod and placebo	Flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in rintatolimod vs. placebo (p<0.05)	99% rintatolimod and 97% placebo reported symptoms	Hemispherx Biopharma	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Complementary and alternative medicine				
Hobday, *et al.,* 2008[93]	RCT of low sugar, low yeast vs. healthy eating for symptoms	**Low sugar/low yeast vs. healthy eating** Mean age (SD): 44 (10.2) vs. 42 (11.9) years % Female: 88 (22/25) vs. 78 (21/27) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosis of CFS, no other criteria described. **Exclusion:** Pregnant women; those taking oral contraceptives, hormone therapy, steroids, NSAID, or immunosuppressants; already following significant dietary changes; taking vitamin and mineral supplements above recommended dose; or diagnosed with an eating disorder.	NR
Öckerman, 2000[94]	Crossover RCT of antioxidant of pollen (Polbax) vs. placebo for underlying cause	Mean age: 50 years % Female: 86 (19/22) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-70 years, symptom score ≥49 for 13 symptoms and ≥5 for total well being. **Exclusion:** Active smokers, dental treatment, electrical hypersensitivity, pollen allergy, use of drugs and other medial diseases and/or treatment.	NR
The, *et al.,* 2007[95]	RCT of acclydine (IGF1 stimulant) vs. placebo for underlying cause	**Acclydine vs. placebo** Mean age (SD): 40.9 (9.4) vs. 43.4 (11.2) years % Female: 77 (no. NR) vs. 59 (no. NR) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years, IGFBP3/IGF1 ratio >2.5 **Exclusion:** Psychiatric comorbidities, pregnant or lactating women, lactose intolerance, or taking psychotropic drugs or experimental medications. Note: Healthy controls were included to compare hormone blood levels, outcome NR here	NR

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Complementary and alternative medicine					
Hobday, *et al.,* 2008[93]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 52 Number analyzed: 39	United Kingdom, London CFS clinic	24 weeks	**Overall:** 25% (13/52) **Low sugar/low yeast vs. healthy eating:** 24% (6/25) vs. 26% (7/27)	**Low sugar/low yeast vs. healthy eating:** 24% vs. 67%
Öckerman, 2000[94]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 22 Number analyzed: 22 (5 placebo-pollen, 5 pollen-placebo, 6 placebo-placebo, 6 pollen-pollen)	NR	3 months	**Overall:** 4.5% (1/22)	NR
The, *et al.,* 2007[95]	Number approached: NR Number screened: 112 Number eligible: 88 Number enrolled: 57 Number analyzed: 57	The Netherlands University medical center	14 weeks	**Overall:** 3.5% (2/57) **Acclydine vs. placebo:** 3.3% (1/30) vs. 3.7% (1/27)	NR

Author, year	Interventions	Fatigue outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[93]	**Low sugar/low yeast:** Adapted from Beat Candida Cook Book (White, 1999) - omission of all sugar containing foods, refined carbohydrates, and yeast containing foods, alcohol, caffeine; limited fruit, milk; encouraged to have one live yogurt per day. **Healthy eating:** High fiber, 5 servings of fruit and vegetables per day, reduced fat and refined carbohydrate, fish 2 times a week.	**Low sugar/low yeast vs. healthy eating** *Mean (SD) Chalder Fatigue Scale scores (scores of ≥4 indicate caseness for fatigue, lower score indicates better health)* 24 weeks: 16.0 (8.2) vs. 17.7 (10.0); p=0.6 *Mean (SD) SF-36 vitality subscale scores (0-100 scale, higher score indicates better health)* 24 weeks: 29.8 vs. 36.2; p=0.39
Öckerman, 2000[94]	**Pollen:** Antioxidant extract of pollen (Polbax) **Placebo**: Placebo *Note:* All patients given pollen or placebo for 3 months followed by a 2-week wash-out period with no treatment followed by 3-month of pollen or placebo. Groups equal pollen pollen (given pollen in both 3 month periods), placebo-placebo (given placebo in both 3 month periods), pollen-placebo (given pollen in first 3 month period, then placebo in second 3 month period), and placebo-pollen (given placebo in first 3 month period, then pollen in second 3 month period)	**Pollen vs. placebo** *Mean fatigue score (Likert scale 0=no problem to 10=extremely serious symptom)* 3 months: 7.52 vs. 7.14; p=NR Change from baseline: -0.43 vs. -0.18; p<0.05
The, *et al.,* 2007[95]	**Acclydine:** Acclydine (increases IGF1 levels) with amino acid supplement **Placebo:** Placebo with amino acid supplement	**Acclydine vs. placebo** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* 14 weeks: 42.4 (11.6) vs. 43.0 (12.6); p=0.70

Author, year	Quality of life outcomes	Function outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[93]	NR	**Low sugar/low yeast vs. healthy eating** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)* 24 weeks: 42.3 (29.2) vs. 52.2 (24.1); p=0.25
Öckerman, 2000[94]	**Pollen vs. placebo** *Mean total well-being score (0-10 Likert type scale, lower scores indicate better health; Likert scale 0=no problem to 10=extremely serious symptom)* 3 months: 7.14 vs. 6.66; p=NR Change from baseline: -1.66 vs. -0.21; p<0.01 *Change in total well-being after treatment* ; p value NR Worse: 9.5% (2/21) vs. 18% (4/22) No change: 29% (6/21) vs. 59% (13/22) Better: 62% (13/21) vs. 23% (5/22)	NR
The, *et al.,* 2007[95]	NR	**Acclydine vs. placebo** *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* 14 weeks: 1,228.1 (619.7) vs. 1,120.2 (543.0); p=0.65

Author, year	Employment outcomes	Other outcomes
Complementary and alternative medicine		
Hobday, *et al.,* 2008[93]	NR	NR
Öckerman, 2000[94]	NR	NR
The, *et al.,* 2007[95]	NR	**Acclydine vs. placebo** *Mean (SD) physical activity level over a 12-day period (measured by actometer attached to the ankle)* 14 weeks: 64.9 (23.4) vs. 64.9 (23.5); p=0.42

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Complementary and alternative medicine						
Hobday, *et al.,* 2008[93]	NR	NR	NR	NR	NR	Fair
Öckerman, 2000[94]	NR	None	Gastrointestinal - 1 or 2 patients	NR	NR	Poor
The, *et al.,* 2007[95]	NR	None	NR	NR	Optipharma	Good

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Vermeulen and Scholte, 2004[96]	Open-label RCT of acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination for underlying cause	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Mean age (SD): 37(11) vs. 38 (11) vs. 42 (12) years % Female: 77 (23/30) vs. 77 (23/30) vs. 77 (23/30) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Meet CDC criteria for CFS, no other criteria described. **Exclusion:** Patients with an underlying organic cause, substance misuse, and severe psychiatric disorder.	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** Median (range): 5.5 (1.0-23.0) vs. 3.0 (0.5-25.0) vs. 6.0 (1.0-21.0) years
Walach, *et al.,* 2008[97]	RCT of distant healing vs. usual care (waiting) for symptoms	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Mean age (SD): 47.5 (10.7) vs. 48.1 (10.0) vs. 46.2 (10.9) vs.50.4 (12.8) years % Female: 74.3 vs. 76.5 vs. 76.6 vs. 75.0 Mean length of unemployment (SD): 36.3 (38.2) vs. 34.8(49.6) vs. 27.7 (22.3) vs.28.7 (27.4) months Race: NR	CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) criteria **Inclusion:** Patients 18 years or older who met the Fukuda or Oxford Criteria. **Exclusion:** Patients with other chronic conditions of co-morbidities that typically rule out a diagnosis of CFS (cancer, hepatitis, or depression, pregnancy, patents with a serious acute illness or hospital admission in the 3 months prior to entry.	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** Mean (SD): 11.3 (9.4) vs. 9.6 (6.7) vs. 9.6 (8.6) vs. 11.9 (9.9) years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Vermeulen and Scholte, 2004[96]	Number approached: NR Number screened: 114 Number eligible: 114 Number enrolled: 90 Number analyzed: 89	The Netherlands CFS clinic	24 weeks	**Overall:** 20% (18/90) **Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination:** 27% (8/30) vs. 13% (4/30) vs. 20% (6/30)	NR
Walach, *et al.,* 2008[97]	Number approached: NR Number screened: 1,400 Number eligible: 875 Number enrolled: 411 Number analyzed: 409	Germany and Austria Private practices for environmental medicine specializing in CFS	6 months treatment Followup to 18 months	**Overall:** 3.2% (13/411) **Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care**: 1.9% (2/105) vs. 5.8% (6/102) vs. 2.1% (2/94) vs. 2.8% (3/108)	Healer non-adherence to protocol and replaced: 7.4% (34/462) Healer withdrew practice: 6.7% (31/462)

Author, year	Interventions	Fatigue outcomes
Vermeulen and Scholte, 2004[96]	**Acetyl-L-carnitine:** Acetyl-L-carnitine 2 g/day **Propionyl-L-carnitine:** Propionyl-L-carnitine 2 g/day **Combination:** Acetyl-L-carnitine 2g/day + propionyl-L-carnitine 2 g/day	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** *Mean (SD) MFI-20 scores (4-20 scale, lower scores indicate better health)* General fatigue at 16 weeks: 16.5 (4.1) vs. 15.7 (4.0) vs. 16.9 (3.2) General fatigue at 24 weeks: 15.9 (4.2) vs. 16.5 (3.1) vs. 17.3 (3.3); p=0.004 for propionyl-L-carnitine change from baseline; p=0.000 for combo change from baseline Physical fatigue at 16 weeks: 15.8 (4.4) vs. 15.8 (4.0) vs. 16.1 (3.5) Physical fatigue at 24 weeks: 15.7 (4.4) vs. 16.4 (3.2) vs. 16.5 (3.4) Mental fatigue at 16 weeks: 15.0 (2.9) vs. 13.8 (4.1) vs. 14.2 (4.0) Mental fatigue at 24 weeks: 15.1 (3.6) vs. 13.9 (3.5) vs. 14.6 (4.0); p=0.015 for acetyl-L-carnitine change from baseline
Walach, *et al.,* 2008[97]	**Distant healing:** Received distant healing from 3 healers who were allowed to use whichever techniques they used in their normal practice; techniques included either prayer or imagining the transmission of 'healing energy, 'light', or 'healing power' **Usual care:** Deferred treatment for duration of treatment *Note: Patients were also randomized to being blinded or unblinded to treatment allocation*	NR

Author, year	Quality of life outcomes	Function outcomes
Vermeulen and Scholte, 2004[96]	NR	NR
Walach, *et al.,* 2008[97]	NR	**Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* 6 months: 34.69 (9.77) vs. 34.79 (10.41) vs. 35.08 (10.01) vs. 33.46 (9.68); p=NS Change from baseline: 3.66 (6.83) vs. 3.04 (7.38) vs. 3.29 (7.28) vs. 0.75 (7.85); p=NS Covariance analysis effect for blinded vs. unblinded treatment: -1.54 (SE 0.70) 95% CI -2.91 to -0.18

Author, year	Employment outcomes	Other outcomes
Vermeulen and Scholte, 2004[96]	NR	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination** *% Improved on CGI* 24 weeks: 59 (17/29) vs. 63 (16/unclear) vs. 37 (11/30)
Walach, *et al.,* 2008[97]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Vermeulen and Scholte, 2004[96]	**Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination:** 10% (3/29) vs. 7% (2/30) vs. 10% (3/30)	NR	Overstimulated feeling and sleeplessness	NR	Unclear	Fair
Walach, *et al.,* 2008[97]	NR	NR	NR	NR	NR	Good

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Weatherley-Jones, *et al.,* 2004[98]	RCT of homeopathy vs. placebo for symptoms	**Homeopathy vs. placebo** Mean age (SD): 38.9 (10.8) vs. 38.8 (11.3) years % Female: 57 (no. NR) vs. 62 (no. NR) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients over 18 years of age, meeting the Oxford criteria. **Exclusion:** Patients with primary major depression, bipolar disorders, psychosis, eating disorders, substance abuse/dependence, and somatization disorders.	**Homeopathy vs. placebo** Mean (SD): 4.8 (4.3) vs. 3.7 (2.4) years
Williams, *et al.,* 2002[99]	Crossover RCT of melatonin vs. phototherapy for symptoms	Overall, for those completing study Mean age (SD): 44.5 (11.1) years % Female: 57 (17/30) Race: NR	Oxford (Sharpe, 1991) Criteria **Inclusion:** Patients diagnosis with CFS by the Oxford criteria. **Exclusion:** Various reasons including diagnostic uncertainty and reluctance to meet the practical demands of the protocol.	Mean (SD): 3.6 (3.3) years
Cognitive and behavior therapies				
Bazelmans, *et al.,* 2005[100]	Non-randomized study of group CBT vs. wait list for symptoms	**CBT vs. wait list** Mean age (SD): 37.4 (8.6) vs. 35.8 (9.0) years % Female: 68 (21/31) vs. 78 (28/36) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Fatigue score of ≥35 on the CIS scale, score of ≥700 on the SIP-8, and willing to stop other treatments for CFS during study. **Exclusion:** NR	**CBT vs. wait list** Mean (SD): 6.2 (5.2) vs. 5.3 (4.5) years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Weatherley-Jones, *et al.,* 2004[98]	Number approached: NR Number screened: 214 Number eligible:168 Number enrolled: 103 Number analyzed: 86	United Kingdom 1 specialty clinic in CFS and 1 in infectious disease	6 months	**Overall:** 11% (11/103) **Homeopathy vs. placebo:** 10% (5/50) vs. 11% (6/53)	NR
Williams, *et al.,* 2002[99]	Number approached: NR Number screened: 62 Number eligible: 52 Number enrolled: 42 Number analyzed: 30	United Kingdom University hospital	12 weeks treatment, 12 week washout, then 12 week crossover and 12 week washout	**Overall:** 29% (12/42) **Melatonin vs. phototherapy:** 27% (6/22) vs. 30% (6/20)	Random pill counts showed no major shortfalls
Cognitive and behavior therapies					
Bazelmans, *et al.,* 2005[100]	Number approached: NR Number screened: 139 Number eligible: NR Number enrolled: 67 (31 CBT, 36 wait list) Number analyzed: 65 (29 CBT, 36 wait list)	The Netherlands 2 University hospital clinics	6 months	**CBT vs. wait list:** 6% (2/31) vs. 0% (0/36)	NR

Author, year	Interventions	Fatigue outcomes
Weatherley-Jones, *et al.,* 2004[98]	**Homeopathy:** Homeopathic prescriptions given after consultations, single remedies prescribed at each consultation, and occasionally >1 remedy; remedies changed throughout, but must be only those remedies which have been proved **Placebo:** Placebo prescribed in the same manner as homeopathy	**Homeopathy vs. placebo** *Mean change from baseline (SD) MFI-20 scores (4-20 scale, lower score indicates better health)* General fatigue: 2.70 (3.93) vs. placebo 1.35 (2.66), p=0.04 Physical fatigue: 2.13 (4.00) vs. 1.28 (2.74); p=0.21 Mental fatigue: 2.70 (4.01) vs. 2.05 (2.86); p=0.30 *Mean change from baseline (SD) FIS (0-40 scale for each subscale, except 0-80 scale for social subscale, lower score indicates better health)* Cognitive dimension: 4.88 (9.3) vs. 4.21 (7.18); p=0.61 Physical dimension: 4.98 (8.5) vs. 5.30 (6.69); p=0.98 Social dimension: 7.92 (18.02) vs. 8.20 (14.06); p=0.79
Williams, *et al.,* 2002[99]	**Melatonin:** Oral melatonin 5 mg daily **Phototherapy:** Phototherapy with 2500 Lux lightbox 30 minutes in morning	**Melatonin vs. phototherapy** *Median (IQR) visual analog scale score for How fatigued are you? (1-10 scale, lower score indicates better health)* After treatment: 6.1 (4.8 to 8.0) vs. 6.6 (5.0 to 8.0); p=NS *Median (IQR) Mental Fatigue Inventory scores (0-36 scale, lower score indicates better health)* After treatment: 23 (15.0 to 27.0) vs. 24 (21.0 to 29.0); p=NS *Median (IQR) SF-36 vitality subscale scores (0-100 scale, lower score indicates better health)* After treatment: 20 (10.0 to 40.0) vs. 20 (10.0 to 25.0); p=NS
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[100]	**Group CBT:** 12 2-hour long group CBT sessions over 6 months aimed at challenging cognitions concerning a negative self-efficacy and somatic attributions; teaching patients to behave according to their own limits and to have adequate periods of rest and relaxation, therefore a graded activity program took place. **Wait list:** Wait list for duration of assessments.	**Group CBT vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* 6 months: 45.6 (9.6) vs. 48.4 (6.2); p=0.099

Author, year	Quality of life outcomes	Function outcomes
Weatherley-Jones, *et al.,* 2004[98]	NR	**Homeopathy vs. placebo** *Mean change from baseline (SD) Functional Limitations Profile scores (scale unclear, higher score indicates better health)* Physical dimension: 5.11 (8.82) vs. 2.72 (8.40), p=0.04 Psychosocial dimension: 9.81 (14.19) vs. 6.76 (10.67); p=0.14
Williams, *et al.,* 2002[99]	NR	**Melatonin vs. phototherapy** *Median (IQR) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)* After treatment: 42.5 (16.3 to 53.8) vs. 45 (22.5 to 60.0); p=NS
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[100]	NR	**Group CBT vs. wait list** *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* 6 months: 1,736 (714) vs. 1,417 (444) Change from baseline: 29 vs. -293; p=0.004

Author, year	Employment outcomes	Other outcomes
Weatherley-Jones, *et al.,* 2004[98]	NR	NR
Williams, *et al.,* 2002[99]	NR	NR
Cognitive and behavior therapies		
Bazelmans, *et al.,* 2005[100]	**Group CBT vs. wait list** *Mean (SD) hours worked per week* 6 months: 6.4 (11.7) vs. 6.7 (10.5); p=0.958	**Responders to CBT (n=10) vs. non-responders to CBT (n=17)** *Mean (SD) baseline differences* Hours worked per week: 10.9 (12.8) vs. 2.6 (6.6); p=0.062 Functional impairment SIP-8 scores: 1,330 (417) vs. 1,985 (730); p=0.031 Daily observed fatigue: 7.4 (2.6) vs. 9.7 (2.3); p=0.023 Daily observed pain: 4.5 (2.6) vs. 7.8 (3.5); p=0.026

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Weatherley-Jones, *et al.,* 2004[98]	NR	NR	NR	NR	NR	Fair
Williams, *et al.,* 2002[99]	NR	NR	NR	NR	NR	Fair
Cognitive and behavior therapies						
Bazelmans, *et al.,* 2005[100]	NR	NR	NR	NR	National Foundation for Public Mental Health (Grant No. 4341)	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Burgess, *et al.,* 2012[101]	RCT of Face-to-face vs. telephone CBT for symptoms	**Face-to-face vs. telephone** Mean age (SD): 38.4 (9.7) vs. 36.7 (10.5) years % Female: 74 (26/35) vs. 82 (37/45) % White: 90 overall (NR per group) % With job to return to: 22 (7/35) vs. 45 (20/45)	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria **Inclusion:** Ages 18-65 years, met both CDC and Oxford criteria, had CFS for <10 years, able to attend the hospital or have telephone sessions bi-weekly. **Exclusion:** Any medical condition that may have accounted for their fatigue, had started or changed medication within 3 months, were pregnant, had psychosis, drug abuse, a somatoform disorder or melancholic depression, a subtype of major depression with specific features including anhedonia, severe weight loss, psychomotor agitation or retardation, insomnia with early morning waking, and guilt.	**Face-to-face vs. telephone** Mean (SD): 4.20 (2.21) vs. 3.80 (2.09) years
Deale, *et al.,* 1997[102] Deale, *et al.,* 2001[103]	RCT of CBT vs. relaxation for symptoms	**CBT vs. relaxation** Mean age (SD): 31 (9) vs. 38 (11) years % Female: 70 (20/30) vs. 67 (20/30) Race: NR % Unemployed: 63 (19/30) vs. 77 (23/30) % On disability benefits: 53 (16/30) vs. 67 (20/30) % Current psychiatric diagnosis: 37 (11/30) vs. 40 (12/30) % Past psychiatric diagnosis: 30 (9/30) vs. 13 (4/30)	Oxford (Sharpe, 1991) and United States (Schluederberg, 1992) criteria **Inclusion:** Main complaint of medically unexplained, disabling fatigue of ≥6 months; with impairment of physical and mental activities; those taking antidepressants or anxiolytics (dose of ≤10 mg/day of diazepam or equivalent) were included if dose was stable for 3 months before study entry and during the trial. **Exclusion:** Somatization disorder, severe depression, ongoing physical investigations, concurrent new treatment, and inability to attend all treatment sessions.	**CBT vs. relaxation** Mean (SD): 3.4 (2.1) vs. 4.6 (3.3) years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Burgess, *et al.,* 2012[101]	Number approached: NR Number screened: 410 Number eligible: 110 Number enrolled: 80 (35 face-to-face, 45 telephone) Number analyzed: 43 (23 face-to-face, 20 telephone)	United Kingdom CFS Research and Treatment Unit at the South London and Maudsley NHS Trust in London	12 months	**Face-to-face vs. telephone:** 34% (12/35) vs. 56% (25/45)	**Face-to-face vs. telephone:** 20% (7/35) vs. 33% (15/45) did not receive treatment Participants attended an average of 11.3 sessions
Deale, *et al.,* 1997[102] Deale, *et al.,* 2001[103]	Number approached: NR Number screened: 142 Number eligible: 67 Number enrolled: 60 (30 CBT, 30 relaxation) Number analyzed: 60 (30 CBT, 30 relaxation) in Deale, 1997; 53 (25 CBT, 28 relaxation) in Deale, 2001	United Kingdom Singe hospital clinic specializing in CFS	Deale, 1997: 6 months Deale, 2001: 5 years	**CBT vs. relaxation:** 10% (3/30) vs. 13% (4/30)	NR

Author, year	Interventions	Fatigue outcomes
Burgess, *et al.,* 2012[101]	**Face-to-face:** Up to 15 sessions of face-to-face CBT, first 2 sessions were 1.5 hours long with additional sessions lasting from 50-60 minutes. **Telephone:** Up to 14 sessions of CBT, first session was face-to-face and lasted up to 3 hours, with additional sessions conducted over the phone. *Note:* Both CBT interventions were aimed at helping patients to change behavioral and cognitive factors, focusing specifically on changing avoidance behavior, unhealthy sleep patterns, and unhelpful beliefs in order to improve levels of fatigue and disability. Individual sessions consisted of socialization with therapist and discussion of approach; agenda setting; homework reviewing; planning of future homework; discussion about how to mange sleep problems; ways to gradually increase activity without overdoing it; identifying and challenging unhelpful cognitions that were standing in the way of behavioral change; social factors if identified as important in perpetuating the symptoms and disability associated with their CFS; management of setbacks; and goals to work toward after treatment during followup.	**Face-to-face vs. telephone** *Mean (SD) Chalder fatigue scale scores (0-11 scale, lower scores indicate better health, score of ≥4 is cutoff for caseness); all p values are NS* 3 months: 7.08 (3.97) vs. 7.08 (3.56) 6 months: 5.75 (4.49) vs. 7.75 (3.77) 12 months: 6.83 (4.57) vs. 7.89 (3.75)
Deale, *et al.,* 1997[102] Deale, *et al.,* 2001[103]	**CBT:** 13 individual weekly or biweekly sessions over 4-6 months with the aim of showing patients that activity could be increased steadily and safely without exacerbating symptoms. **Relaxation:** 13 individual weekly or biweekly sessions over 4-6 months teaching progressive muscle relaxation, visualization, and rapid relaxation skills.	**CBT vs. relaxation** *Mean (SD) fatigue problem rating scores (0-8 scale, lower scores indicate better health)* 6 month followup: 3.4 (2.2) vs. 5.5 (1.9) p<0.001 for between group differences over time *Mean (SD) Chalder fatigue scale scores (0-11, scores of ≥4 indicate caseness or excessive fatigue, lower scores indicate better health)* 6 month followup: 4.1 (4.0) vs. 7.2 (4.0) p<0.001 for between group differences over time *% With fatigue rating by assessor at 3 months followup* Better or much better: 72 (18/25) vs. 17 (4/23); p<0.001 Unchanged or worse: 28 (7/25) vs. 83 (19/23) *% With score <4 on Chalder fatigue scale* 6 month followup: 63 (17/27) vs. 15 (4/26); p=0.001 5 year followup: 28 (7/25) vs. 25 (7/28); p=1.00

Author, year	Quality of life outcomes	Function outcomes
Burgess, *et al.*, 2012[101]	NR	**Face-to-face vs. telephone** *Mean (SD) SF-36 physical functioning scale scores (0-100 scale, higher scores indicate better health)* 3 months: 58.97 (19.38) vs. 62.89 (20.33) 6 months: 65.78 (23.61) vs. 62.96 (20.36) 12 months: 62.32 (24.96) vs. 65.83 (21.73); p=0.043 for change from baseline for both groups
Deale, *et al.*, 1997[102] Deale, *et al.*, 2001[103]	NR	**CBT vs. relaxation** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* 6 month followup: 71.6 (28.0) vs. 38.4 (26.9); p<0.03 *% With good outcome on SF-36 physical functioning scale (increase of ≥50 from baseline to 6 months, or end score of ≥ 83):* 6 months followup: 63 (19/30) vs. 17 (5/30); difference of 46 (95% CI 24 to 68) p<0.001 5 year followup: 48 (12/25) vs. 32 (9/28); p=0.27 *% With rating by assessor at 3 month followup* Better or much better: 80 (20/25) vs. 26 (6/23); p<0.001 Unchanged or worse: 20 (5/25) vs. 74 (17/23)

Author, year	Employment outcomes	Other outcomes
Burgess, *et al.*, 2012[101]	**Face-to-face vs. telephone** *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 3 months: 23.35 (8.54) vs. 21.65 (7.42) 6 months: 19.40 (10.77) vs. 23.43 (8.06) 12 months: 20.83 (12.25) vs. 19.40 (8.73); p=0.013 for change from baseline for both groups	**Face-to-face vs. telephone** *Global improvement scores (% much better or very much better)* 6 months: 60 (15/25) vs. 40 (8/20) 12 months: 57 (13/23) vs. 55 (11/20)
Deale, *et al.*, 1997[102] Deale, *et al.*, 2001[103]	**CBT vs. relaxation** *Mean (SD) Work and social adjustment scale scores (0-8 scale, lower scores indicate better health)* 6 month followup: 3.3 (2.2) vs. 5.4 (1.8) p<0.001 for between group differences over time *% With full- or part-time employment at 5 year followup:* 56 (14/25) vs. 39 (11/28); p=0.28 *Mean (SD) hours worked per week (of employed persons, n=14 vs. 11) at 5 year followup:* 35.57 (8.11) vs. 24.00 (4.97); p<0.04	**CBT vs. relaxation** *% With global improvement rating* Better or much better at 6 month followup: 70 (19/27) vs. 31 (8/26); p<0.01 Unchanged or worse at 6 month followup: 30 (8/27) vs. 69 (18/26) Better or much better at 5 year followup: 68 (17/25) vs. 36 (10/28); p=0.05 *Other outcomes at 5 year follow* % With symptoms “steadily improved” not “consistently absent’ or “mild”: 68 (17/25) vs. 43 (12/28); p=0.05 % With complete recovery (no longer met CFS criteria, employed full-time, score <4 on Chalder fatigue scale, and score >83 on SF-36): 24 (6/25) vs. 4 (1/28); p=0.04 % No longer meeting U.K. criteria for CFS: 52 (13/25) vs. 39 (11/28); p=0.42 % With no relapses: 36 (9/25) vs. 7 (2/28); p=0.02 Mean (SD) number of relapses: 2.58 (2.21) vs. 4.08 (1.55); p<0.01

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Burgess, *et al.*, 2012[101]	NR	NR	NR	NR	NR	Fair
Deale, *et al.*, 1997[102] Deale, *et al.*, 2001[103]	NR	NR	NR	NR	South East Thames Regional Health Authority Locally Organized Research Scheme	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Goudsmit, *et al.,* 2009[104]	Non-randomized trial of counseling vs. wait list for symptoms	**Counseling vs. wait list** Mean age (SD): 39.6 (13.4) vs. 37.7 (14.4) years % Female: 73 (16/22) vs. 59 (13/22) % Employed full-time: 9 (2/22) vs. 0 (0/22) % On disability benefits: 14 (3/22) vs. 24 (5/22) % Changed job/reduced hours due to illness: 86 (18/21) vs. 95 (18/19) % On medication: 45.5 (10/22) vs. 54.5 (12/22)	Oxford (Sharpe, 1991) criteria **Inclusion:** NR **Exclusion:** NR	**Counseling vs. wait list** Mean (SD): 4.93 (3.6) vs. 2.92 (2.3) years; p<0.05
Jason, *et al.,* 2010[107]	RCT of buddy counseling vs. control for symptoms	**Buddy counseling vs. control** Mean age (SD): 56.8 (16.11) vs. 58.3 (9.35) years % Female: 87 (13/15) vs. 80 (12/15) % White: 80 (12/15) vs. 87 (13/15) % Other race: 20 (3/15) vs. 13 (2/15) % On disability: 47 (7/15) vs. 60 (9/15) % Unemployed: 33 (5/15) vs. 33 (5/15) % Working part- or full-time: 20 (3/15) vs. 7 (1/15)	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosed with CFS using Fukuda, 1994 criteria and felt they could benefit from intervention. **Exclusion:** NR	NR
Knoop, *et al.,* 2008[109] Tummers, *et al.,* 2010[109]	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 37.6 (10.0) vs. 38.5 (10.6) years % Female: 82 (69/84) vs. 76 (65/85) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age ≥18 years, spoke and read Dutch, not engaged in a legal procedure concerning disability-related financial benefits, scored ≥35 on the CIS fatigue severity subscale; total score of >700 on SIP-8. **Exclusion:** NR	**Self-instruction vs. wait list** Median (range): 72 (12-420) vs. 96 (12-420) months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Goudsmit, *et al.,* 2009[104]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 44 (22 counseling, 22 wait list) Number analyzed: 44 (22 counseling, 22 wait list)	United Kingdom CFS specialist at Hospital	6 months	NR	NR
Jason, *et al.,* 2010[107]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 30 (15 buddy counseling, 15 control) Number analyzed: 30 (15 buddy counseling, 15 control)	United States, Chicago area Single site, Research Center at University	4 months	NR	NR
Knoop, *et al.,* 2008[109] Tummers, *et al.,* 2010[109]	Number approached: NR Number screened: NR Number eligible: 184 Number enrolled: 171 (85 self-instruction, 86 wait list) Number analyzed: 169 (84 self-instruction, 85 wait list)	The Netherlands Single tertiary care facility	6-12 months depending on length of treatment	**Stepped care program** **Self-instruction vs. wait list** Did not want to continue with CBT: 57% (48/84) vs. 22% (19/85)	NR

Author, year	Interventions	Fatigue outcomes
Goudsmit, *et al.,* 2009[104]	**Counseling:** Individual bi-monthly consultations consisting of diagnosis and information on CFS, daily diary completitions, advice about activity management, advice on limiting distress and increasing energy, and other advice dealing with diet, irritable bowel syndrome, and issues related to employment. **Wait list:** Wait list for duration of assessments.	**Counseling vs. wait list** *Mean (SD) Profile of fatigue-related symptoms scale scores (0-6 scale, lower scores indicate better health)* 6 months: 2.68 (1.41) vs. 3.84 (1.40); p=0.04
Jason, *et al.,* 2010[107]	**Buddy counseling:** 2-hours a week of student buddy support over 4 months consisting of emotional support, functional support (any direct help), and social support (such as working on household tasks during their visits). **Control:** No treatment for 4 months.	**Buddy counseling vs. control** *Mean (SD) FSS scores (9-63 scale, lower scores indicate better health)* 4 months: 52.9 (10.5) vs. 59.4 (3.7); p=0.04 *Mean (SD) SF-36 vitality scale scores (0-100 scale, higher scores indicate better health)* 4 months: 29.3 (13.9) vs. 24.7 (9.7); p<0.05
Knoop, *et al.,* 2008[109] Tummers, *et al.,* 2010[109]	**Self-instruction:** 16 weeks or more program of self-instruction booklet containing information about CFS and weekly assignments. **Wait list:** Wait list control for 6-12 months. ***Tummers, 2010*** **Stepped care:** Self-instruction as described above, then up to 14 sessions of individual CBT over 6 months **Care as usual:** Wait list as described above, then up to 14 sessions of individual CBT over 6 months	**Self-instruction vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (12.1) vs. 46.4 (8.7); p<0.001 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 27 (23/84; 95% CI 18 to 37) vs. 7 (6/85; 95% CI 2 to 13); OR 4.9 (95% CI 1.9 to 12.9); p<0.001 ***Tummers, 2010*** **Stepped care vs. care as usual** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Posttreatment: 35.1 (13.6) vs. 34.9 (13.8); difference 0.2 (95% CI -3.9 to 4.3); p=0.92 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 49 (41/84) vs. 48 (41/85); OR 1.0 (95% CI 0.53 to 1.89); p=1.00

Author, year	Quality of life outcomes	Function outcomes
Goudsmit, *et al.*, 2009[104]	NR	**Counseling vs. wait list** *Mean (SD) functional impairment scale scores (0-32 scale, lower scores indicate better health)* 6 months: 20.86 (6.09) vs. 22.73 (5.71); p=0.24
Jason, *et al.*, 2010[107]	NR	**Buddy counseling vs. control** *Mean (SD) SF-36 physical functioning scale scores (0-100 scale, higher scores indicate better health)* 4 months: 36.1 (14.1) vs. 36.0 (29.9); p=0.06
Knoop, *et al.*, 2008[109] Tummers, *et al.*, 2010[109]	NR	**Self-instruction vs. wait list** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.9 (23.2) vs. 60.2 (23.7); p=0.011 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Second assessment: 1,515 (545) vs. 1,319 (619); p<0.001 ***Tummers, 2010*** **Stepped care vs. care as usual** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Posttreatment: 71.6 (23.2) vs. 72.3 (24.3); difference -1.1 (95% CI -7.2 to 5.0); p=0.72 *Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)* Posttreatment: 826 (655) vs. 819 (653); difference 30.2 (95% CI -178 to 238); p=0.77

Author, year	Employment outcomes	Other outcomes
Goudsmit, *et al.,* 2009[104]	NR	NR
Jason, *et al.,* 2010[107]	NR	NR
Knoop, *et al.,* 2008[109] Tummers, *et al.,* 2010[109]	NR	***Tummers, 2010*** **Stepped care vs. care as usual** Mean (SD) number of CBT sessions: 10.9 (4.4) vs. 14.5 (5.3); p<0.01 Median minutes in sessions (range): 420 (120-1,440 vs. 720 (120-2,040); p=0.01

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Goudsmit, *et al.*, 2009[104]	NR	NR	NR	NR	Action for ME	Poor
Jason, *et al.*, 2010[107]	NR	NR	NR	NR	National Institute of Allergy and Infectious Diseases (grant numbers AI36295 and AI49720)	Poor
Knoop, *et al.*, 2008[109] Tummers, *et al.*, 2010[109]	NR	NR	NR	NR	NR	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Lopez, *et al.,* 2011[110]	RCT of group CBT vs. control for symptoms	Mean age (SD): 45.9 (9.3) years % Female: 88 (61/69) % White: 77 (53/69) % Latino: 17 (12/69) % Caribbean Islander: 1 (7/69) % Biracial: 1 (7/69) % Another ethnic group: 3 (2/69) % Working full-time: 13 (9/69) % Working part-time: 19 (13/69) % Unemployed: 16 (11/69) % Retired: 4 (3/69) % Student: 3 (2/69) % On disability: 45 (31/69)	CDC (Fukuda, 1994) criteria **Inclusion:** 18-60 years, had ≥8th grade education, fluent in English. **Exclusion:** Active or previous medical condition that would explain the presence of chronic fatigue, positive for Lyme disease, had an infection that was treated with antibiotics within 3 weeks of the study, had surgery requiring general anesthesia within the past month of the study, were on any immunomodulator, had a history of major psychiatric illness, are currently in psychotherapy, had a history of substance or drug use within 2 years of the onset of CFS, or a history of major psychiatric illness.	NR

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Lopez, *et al.,* 2011[110]	Number approached: NR Number screened: NR Number eligible: 113 Number enrolled: 69 (44 group CBT, 25 control) Number analyzed: 58 (38 group CBT, 20 control)	United States Single site, not described	12 weeks	**Overall:** 15.9% (11/69) **Group CBT vs. control:** 13.6% (6/44) vs. 20% (5/25)	NR, but group sessions, so except for the attrition, all assumed to adhere to program

Author, year	Interventions	Fatigue outcomes
Lopez, *et al.,* 2011[110]	**Group CBT**: 12 weekly 2-hour group sessions of cognitive behavioral stress management consisting of 2 parts: 1) relaxation component and 2) didactic and discussion component; main technique used was cognitive restructuring targeting cognitive appraisals of ongoing stressors. **Control:** 1 session of psychoeducation summarizing strategies from the 12 week intervention.	**Group CBT vs. control** *Mean (SD) POMS-Fatigue subscale (0-28 scale, lower scores indicate better health)* After treatment: 17.85 (7.34) vs. 20.09 (6.99); p=0.06

Author, year	Quality of life outcomes	Function outcomes
Lopez, *et al.*, 2011[110]	**Group CBT vs. control** *Mean (SD) QOLI scores* *Category score (range 1-4, lower scores indicate better health)* After treatment: 2.81 (1.15) vs. 3.26 (0.87); p=0.02 Raw score after treatment: 1.17 (1.83) vs. 0.82 (1.37); p=0.05 T score after treatment: 39.28 (14.17) vs. 36.42 (10.56); p=0.05	NR

Author, year	Employment outcomes	Other outcomes
Lopez, *et al.,* 2011[110]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Lopez, *et al.*, 2011[110]	NR	NR	NR	NR	NIH	Poor

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
O'Dowd, *et al.*, 2006[112]	RCT of group CBT vs. group support vs. usual care for symptoms	**Group CBT vs. group support vs. usual care** Mean age (SD): 41.6 (12.0) vs. 38.8 (11.8) vs. 42.9 (11.6) years % Female: 54 (28/52) vs. 76 (38/50) vs. 71 (36/51) Race: NR % Discontinued main occupation due to CFS: 77 (36/52) vs. 63 (29/50) vs. 70 (35/51)	CDC (Fukuda, 1994) criteria **Inclusion:** Presentation consistent with ME/CFS described by Fukuda; able to read and understand patient information leaflet. **Exclusion:** Concurrent severe mental illness (i.e. psychosis and allied conditions); planned or concurrent rehabilitation; inability to attend all treatment sessions; or ongoing physical investigation.	**Group CBT vs. group support vs. usual care** % With symptoms for >60 months: 42 (21/50) vs. 50 (25/50) vs. 54 (27/50) % Diagnosed >12 months before study: 57% (28/49) vs. 45% (20/44) vs. 62% (29/47)

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
O'Dowd, *et al.,* 2006[112]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 153 (52 CBT, 50 support, 51 usual care) Number analyzed: 153 (52 CBT, 50 support, 51 usual care)	United Kingdom Pain Management Hospital	12 months	**Group CBT vs. group support vs. usual care:** 25% (13/52) vs. 8% (4/50) vs. 14% (7/51)	6% (3/52) of CBT group received support; 8% (4/50) of support group received CBT

Author, year	Interventions	Fatigue outcomes
O'Dowd, *et al.,* 2006[112]	**Group CBT:** 8 2-hour group CBT sessions bi-weekly aimed at modifying thoughts and beliefs about symptoms and illness; and modifying behavioral responses to symptoms and illness, such as rest, sleep, and activity; with goal to increase adaptive coping strategies and reduce the distress and disability of CFS. **Group Support:** 8 2-hour group education and support sessions bi-weekly focusing on sharing of experiences and learning of basic relaxation skills. **Usual care:** Managed in primary care and received no other intervention.	**Group CBT vs. group support vs. usual care** *Mean (SD) Chalder fatigue scale (0-33 scale, lower scores indicate better health)* 6 months: 17.9 (8.41) vs. 21.4 (7.55) vs. 21.8 (6.90); p=0.19 12 months: 17.4 (7.32) vs. 21.4 (7.79) vs. 18.8 (7.19); p=0.19 *Difference between groups from baseline at 12 months* CBT vs. support: -3.16 (95% CI -5.59 to -0.74); p=0.011 CBT vs. usual care: -2.61 (95% CI -4.92 to -0.30); p=0.027* Support vs. usual care: 0.55 (95% CI -1.56 to 2.66); p=NR *Note: this number is -2.16 in the text and -2.61 in the table

Author, year	Quality of life outcomes	Function outcomes
O'Dowd, *et al.*, 2006[112]	**Group CBT vs. group support vs. usual care** *Mean (SD) health related quality of life utility scores (higher scores indicate better health); all p values are NS* 6 months: 0.43 (0.28) vs. 0.34 (0.32) vs. 0.41 (0.25) 12 months: 0.45 (0.34) vs. 0.34 (0.35) vs. 0.46 (0.30) *Difference between groups from baseline at 12 months* CBT vs. support: 0.023 (95% CI -0.065 to 0.11) CBT vs. usual care: 0.029 (95% CI -0.052 to 0.11) Support vs. usual care: 0.006 (95% CI -0.082 to 0.095)	**Group CBT vs. group support vs. usual care** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health); all p values are NS* 6 months: 33.4 (9.04) vs. 32.3 (9.30) vs. 34.5 (9.95) 12 months: 35.2 (8.15) vs. 32.5 (7.91) vs. 35.0 (9.93) *% Reporting SF-36 score in normal range (score was on or above the 5th centile for the distribution, estimated as the mean -1.645 × SD for the gender-specific age group)* 6 months: 40 (17/43) vs. 24 (11/45) vs. 44 (20/46) 12 months: 46 (18/39) vs. 26 (12/46) vs. 44 (19/44); OR 1.03 (95% CI 0.38 to 2.73) for support vs. CBT; OR 1.51 (95% CI 0.58 to 3.91) for usual care vs. CBT; OR 1.47 (0.56 to 3.81) for support vs. usual care *% Reporting ≥15% increase from baseline* 6 months: 24 (11/43) vs. 33 (15/45) vs. 28 (13/46) 12 months: 26 (10/39) vs. 26 (12/46) vs. 43 (19/44) 6 and/or 12 months: 32 (15/NR) vs. 40 (19/NR) vs. 49 (23/NR); OR 1.29 (95% CI 0.58 to 2.86) for support vs. CBT; OR 1.68 (95% CI 0.76 to 3.69) for usual care vs. CBT; OR 1.30 (95% CI 0.61 to 2.76) *Mean incremental shuttle walking test; shuttles walked (number of complete 10m shuttles)* 6 months: 28.5 vs. 25.6 vs. 23.6 12 months: 28.9 vs. 24.1 vs. 24.2 *Difference between groups from baseline to 12 months* CBT vs. support: 1.16 (95% CI 0.94 to 1.43) CBT vs. usual care: 1.20 (95% CI 0.99 to 1.45) Support vs. usual care: 1.04 (95% CI 0.86 to 1.24) *Mean incremental shuttle walking test; normal walking speed (number of shuttles per level per minute)* 6 months:12.1 vs. 8.76 vs. 9.39 12 months: 12.2 vs. 10.0 vs. 9.46 6 and/or 12 months: 11.58 (0.71) vs. 9.82 (0.53) vs.8.76 (0.47); p=0.006 *Difference between groups from baseline to 12 months* CBT vs. support: 1.77 (95% CI 0.025 to 3.51); p=0.0055 CBT vs. usual care: 2.83 (95% CI 1.12 to 5.53); p=0.0055 Support vs. usual care: 1.06 (-0.37 to 2.49); p=0.15

Author, year	Employment outcomes	Other outcomes
O"Dowd, *et al.,* 2006[112]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
O"Dowd, *et al.*, 2006[112]	NR	NR	NR	NR	HTA Program (project NO. 974/41/08)	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Sharpe, *et al.,* 1996[113]	RCT of CBT vs. usual care for symptoms	**CBT vs. control** Mean age (SD): 34 (9.1) vs. 38 (11.8) years % Female: 60 (18/30) vs. 77 (23/30) Race: NR % Not working or studying: 87 (26/30) vs. 50 (15/30) % Major depressive disorder: 20 (6/30) vs. 20 (6/30) % Any depressive disorder: 53 (16/30) vs. 57 (17/30) % Any anxiety disorder: 47 (14/30) vs. 50 (15/30) % Any anxiety or depression disorder: 67 (20/30) vs. 67 (20/30) % Somatization disorder: 10 (3/30) vs. 10 (3/30)	Oxford (Sharpe 1991) criteria **Inclusion:** Ages 18-60 years, with major complaint of fatigue. **Exclusion:** Currently receiving psychotherapy or antidepressant drugs; unwilling to accept randomization or unavailable for followup; met criteria for severe depression or had history of bipolar disorder, schizophrenia, or substance misuse; or at significant risk of suicide or in need of urgent psychiatric treatment.	**CBT vs. control** Mean (SD): 33.6 (9.1) vs. 29.7 (24.1) months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Sharpe, *et al.,* 1996[113]	Number approached: NR Number screened: 123 Number eligible: 62 Number enrolled: 60 (30 CBT, 30 control) Number analyzed: 60 (30 CBT, 30 control)	United Kingdom, Oxford 2 Centers	12 months	Only 1/60 did not complete 12 month followup data	All CBT patients completed their intervention

Author, year	Interventions	Fatigue outcomes
Sharpe, *et al.,* 1996[113]	**CBT:** 16 1-hour sessions of individual CBT over 4 months emphasizing cognitive techniques and tailored for patients with CFS, strategies to reduce excessive perfectionism and self criticism, and an active problem solving approach to interpersonal and occupational difficulties was also employed. **Control:** Patients were followed by their General Practitioner in their usual way.	NR

Author, year	Quality of life outcomes	Function outcomes
Sharpe, *et al.*, 1996[113]	NR	**CBT vs. control** *Achieved KPS score of ≥80* 5 months: 27% (8/30) vs. 20% (6/30); difference of 7 (95% CI -15 to 28) 8 months: 53% (16/30) vs. 30% (9/30); difference of 23 (95% CI 0 to 48) 12 months: 73% (22/30) vs. 27% (8/30); difference of 47 (95% CI 24 to 69) *Improvement of ≥10 points on KPS* 5 months: 23% (7/30) vs. 7% (2/30); difference of 17 (95% CI 0 to 34) 8 months: 60% (18/30) vs. 20% (6/30); difference of 40 (95% CI 17 to 63) 12 months: 73% (22/30) vs. 23% (7/30); difference of 50 (95% CI 28 to 72)

Author, year	Employment outcomes	Other outcomes
Sharpe, *et al.*, 1996[113]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Sharpe, et al., 1996[113]	NR	NR	NR	NR	Welcome Trust	Good

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Taylor, 2004[114]	RCT of counseling vs. wait list for symptoms	**Counseling vs. wait list** Mean age (SD): 49.0 (10.9) vs. 44.9 (9.7) years % Female: 91 (21/23) vs. 100 (24/24) % Minority: 17 (4/23) vs. 17 (4/24) % Working full-time: 9 (2/23) vs. 21 (5/24) % Working part-time: 22 (5/23) vs. 8 (2/24) % Unemployed: 70 (16/23) vs. 71 (17/24)	CDC (Fukuda, 1994) **Inclusion:** Adults with CFS by Fukuda criteria. **Exclusion:** Psychiatric illness that would rule out CFS diagnosis, untreated hypertension.	NR
Tummers, *et al.*, 2012[115]	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 36.3 (12.1) vs. 36.4 (13.6) years % Female: 74 (46/62) vs. 82 (50/61) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Age 18-65 years, were severely fatigued (≥35 on the fatigue severity subscale of the CIS), were fatigued for ≥6 months, were severely disabled (≤70 on physical and/or social functioning subscale of SF-36), reported ≥4 of 8 additional symptoms: unrefreshing sleep, post exertional malaise, headache, muscle pain, multi-joint pain, sore throat, tender lymph nodes, impairment of concentration or memory. **Exclusion:** Those with the presence of somatic diseases or psychiatric disorders and the use of medication that could explain the fatigue.	**Self-instruction vs. wait list** Median (range): 48 (6-464) vs. 60 (6-625) months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Taylor, 2004[114]	Number approached: NR Number screened: 52 Number eligible: 50 Number enrolled: 47 (23 counseling, 24 wait list) Number analyzed: 47 (23 counseling, 24 wait list)	United States, Chicago area Single site, not described	12 months	None dropped out	Stated program adherence was good, but otherwise NR
Tummers, *et al.*, 2012[115]	Number approached: NR Number screened: 181 Number eligible: 142 Number enrolled: 123 (62 self-instruction, 61 wait list) Number analyzed: 111 (55 self-instruction, 56 wait list)	The Netherlands Single tertiary care facility	6 months	**Self-instruction vs. wait list** 11% (7/62) vs. 8% (5/61)	NR

Author, year	Interventions	Fatigue outcomes
Taylor, 2004[114]	**Counseling:** 8 sessions of a group illness-management program occurring biweekly over 4 months consisting of check-ins, reporting of self-monitored goal attainment, educational lecture and discussion of self-selected, CFS-relevant topics including activity pacing using the Envelope Theory, cognitive coping skills training, relaxation and meditation training, employment issues and economic self-sufficiency, personal relationships, traditional and complementary medical approaches, and nutritional approaches. This was followed by a 1 month break and then 7 months of 1-on-1 peer counseling, which consisted of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services. **Wait list:** On waiting list for 12 months, then given program as described above. Results of this group after they received the program are NR.	NR
Tummers, *et al.,* 2012[115]	**Self-instruction:** Up to 20 weeks of guided self-instruction which included setting goals reviewing of precipitating and perpetuating factors, challenging of fatigue-related cognitions, reducing focus on fatigue, physical activity level adapted for either relatively-active person or a low-active person, gradually asked to increase activity, challenging of beliefs that activity would exacerbate symptoms, begin plan for resuming work, modifying excessive expectations regarding the response of their social environment to their symptoms, gradually increase mental and social activities, and relapse prevention. **Wait list:** Waitlist control for duration of intervention.	**Self-instruction vs. wait list** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 39.6 (14.1) vs. 48.3 (8.1); p<0.01 *% With reduction in CIS fatigue severity scores (CIS <35 and reliable change index of >1.96)* 33 (18/55) vs. 9 (5/56); OR 5.0 (95% CI 1.69 to 14.57) ***Subanalysis of baseline group with SF-36 physical functioning score ≤70*** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)* Second assessment: 38.9 (14.3) vs. 50.1 (6.2) Change from baseline: -12.4 vs. -2.4; difference: -9.9 (95% CI, -5.4 to -14.3); p<0.01

Author, year	Quality of life outcomes	Function outcomes
Taylor, 2004[114]	**Counseling vs. wait list** *Mean (SD) QLI scores (0-30 scale, higher scores indicate better outcomes)* Overall at 4 months: 13.2 (3.8) vs. 14.6 (4.8) Overall at 12 months: 15.7 (3.7) vs. 14.6 (4.1) Change in score at 12 months from baseline: 2.6 vs. 0.6; p<0.05 Health and function subscale at 4 months: 12.8 (1.8) vs. 13.6 (2.1) Health and function subscale at 12 months: 14.1 (1.7) vs. 13.6 (1.8) Social and economic subscale at 4 months: 15.2 (0.8) vs. 15.5 (1.0) Social and economic subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Psychological and spiritual subscale at 4 months: 15.0 (1.1) vs. 15.2 (1.3) Psychological and spiritual subscale at 12 months: 15.5 (1.1) vs. 15.1 (1.2) Family subscale at 4 months: 15.4 (1.0) Family subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9) Change in score at 12 months from baseline: 0.2 vs. -0.2; p<0.05	NR
Tummers, *et al.*, 2012[115]	NR	**Self-instruction vs. wait list** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 65.4 (24.9) vs. 59.3 (22.9); p=0.08 ***Subanalysis of baseline group with SF-36 physical functioning score ≤70*** **Self-instruction (n=53) vs. wait list (n=50)** *Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)* Second assessment: 63.0 (25.9) vs. 53.4 (18.7) Chnage from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05

Author, year	Employment outcomes	Other outcomes
Taylor, 2004[114]	NR	NR
Tummers, *et al.*, 2012[115]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Taylor, 2004[114]	None withdrew	NR	NR	NR	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097	Good
Tummers, *et al.*, 2012[115]	NR	NR	NR	NR	Dutch Medical Research Council ZonMW	Good

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	RCT of self-instruction therapy vs. wait list for symptoms	**Self-instruction vs. wait list** Mean age (SD): 37.2 (10.9) vs. 37.9 (12.1) years % Female: NR Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Patients included in Knoop, 2008 and Tummers, 2012 RCTs. **Exclusion:** Those who did not have complete data at the second assessment.	NR

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	See Knoop, 2008 and Tummers, 2012	The Netherlands Single tertiary care facility	6-12 months based on the RCTs	NR	NR

Author, year	Interventions	Fatigue outcomes
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	**Self-instruction:** As described in Knoop, 2008 and Tummers, 2012. **Wait list:** As described in Knoop, 2008 and Tummers, 2012.	**Interaction tests for potential moderators from linear regression models (95% CI)** Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 *Perpetuating factors* Self-efficacy: -0.06 (-1.18 to 0.56); p=0.48 Somatic attribution: 0.10 (-0.32 to 1.43); p=0.21 Avoidance of activity: 0.17 (0.03 to 1.78); p=0.04 Focus on bodily symptoms: -0.02 (-0.61 to 0.52); p=0.88 **Interaction tests for potential moderators from logistic regression models (95% CI)** Age (years): 1.06 (0.99 to 1.13); p=0.10 Depression: 1.40 (1.08 to 1.82); p=0.01 *Perpetuating factors* Self-efficacy: 0.81 (0.62 to 1.05); p=0.11 Somatic attribution: 1.13 (0.87 to 1.46); p=0.36 Avoidance of activity: 1.34 (1.03 to 1.74); p=0.03 Focus on bodily symptoms: 1.02 (0.87 to 1.20); p=0.80

Author, year	Quality of life outcomes	Function outcomes
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	NR	NR

Author, year	Employment outcomes	Other outcomes
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Tummers, *et al.,* 2013[117] Secondary analysis of Knoop, *et al.,* 2008[109] & Tummers, *et al..,* 2012[115] combined	NR	NR	NR	NR	See Knoop, 2008 and Tummers, 2012	See Knoop, 2008 and Tummers, 2012

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	RCT of pragmatic rehab vs. supportive listening vs. usual care for symptoms	**Pragmatic rehab vs. supportive listening vs. usual care** Mean age: 43.74 vs. 45.13 vs. 44.92 years % Female: 78 (74/95) vs. 79 (80/101) vs. 76 (76/100) Race: NR % Ambulatory: 90 (85/95) vs. 87 (88/101) vs. 88 (88/100) % Met London ME criteria: 30 (28/95) vs. 31 (31/101) vs. 33 (33/100) % Any anxiety diagnosis: 27 (21/95) vs. 20 (17/101) vs. 26 (22/100) % Any depression diagnosis: 19 (18/95) vs. 15 (15/101) vs. 20 (20/100) % With ≥2 comorbidities: 34 (32/95) vs. 32.7 (33/101) vs. 43 (43/100) % With 1 comorbidity: 22 (21/95) vs. 28 (29/101) vs. 24 (24/100) % With no comorbidities: 44 (42/95) vs. 39 (39/101) vs. 33 (33/100)	Oxford (Sharpe ,1991) criteria **Inclusion:** Ages ≥18 years, scored ≤70% on SF-36 physical functioning scale, scored ≥4 on Chalder fatigue scale. **Exclusion:** Fit criteria for antisocial, borderline, or paranoid personality disorders; active suicidal ideation; unable to read or write English; currently under taking systemic psychological therapies for CFS/ME; had received pragmatic rehabilitation in the past year.	Median (range): 7 (0.5-51.7) years

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	Number approached: 449 Number screened: 338 Number eligible: NR Number enrolled: 296 (95 pragmatic rehab, 101 supportive listening, 100 usual care) Number analyzed: 257 (81 pragmatic rehab, 90 supportive listening, 86 usual care)	United Kingdom 186 general practitioners referred patients	18 weeks treatment; 70 weeks total followup	**Overall:** 13.2% (39/296) **Pragmatic rehab vs. supportive listening vs. usual care:** 14.7% (14/95) vs. 10.9% (11/101) vs. 14.0% (14/100) 1 in supportive listening group subsequently received diagnosis of multiple sclerosis (misdiagnosis)	**Pragmatic rehab:** 3/95 didn't receive intervention **Supportive listening:** 10/101 didn't receive intervention 1/101 received pragmatic rehab instead

Author, year	Interventions	Fatigue outcomes
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	**Pragmatic rehab:** 10 sessions over an 18-week period of a program of graded return to activity; designed collaboratively by the patient and therapist, which encourages patients to regularize their sleep patterns and includes relaxation exercises to address somatic symptoms of anxiety. An additional component to address concentration and memory problems was also included. **Supportive listening:** 10 sessions over an 18-week period of listening therapy based on non-directive counseling, with therapist aiming to provide an empathic and validating environment in which the patient can discuss his or her concerns and work towards resolution of whichever problems the patient wishes to prioritize. **Usual care:** Practitioners managed their patients as they saw fit, but were not referred for systematic psychological therapies for CFS/ME during the 18-week treatment period.	**Pragmatic rehab vs. supportive listening vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored dichotomously; lower scores indicate better outcomes)* 20 weeks: 8.39 (3.67) vs. 9.67 (2.76) vs. 9.32 (3.18); treatment effect estimate -1.18, 95% CI -2.18 to -0.18; p=0.021 for pragmatic rehab vs. usual care 70 weeks: 8.72 (3.65) vs. 9.39 (3.21) vs. 9.48 (2.71); p=NS **Pragmatic rehab vs. usual care** *Mean (SD) Chalder fatigue scale scores (items scored 0-3 and summed to total of 0-33; lower scores indicate better outcomes)* 20 weeks: 22.78 (8.56) vs. 26.27 (7.68) 70 weeks: 23.90 (8.34) vs. 26.02 (7.11) **Significant regression coefficients for interaction between putative moderators and treatment (pragmatic rehab vs. usual care)** HADS baseline depression score: -0.67 (95% CI -1.25 to -0.10); p=0.022 HADS baseline total score: -0.30 (95% CI -0.58 to -0.02); p=0.039 EQ-5D self-care scale, those with severe problems: -28.72 (95% CI -32.14 to -25.31); p<0.001 **Significant regression coefficients to predict change in Chalder fatigue scale scores (pragmatic rehab vs. usual care)** Age: -0.10 (95% CI -0.19 to -0.003); p=0.044 Duration of illness: -0.01 (95% CI -0.02 to -0.003); p=0.008 EQ-5D mobility scale; those with severe problems: -2.95 (95% CI -5.51 to -0.40); p=0.024

Author, year	Quality of life outcomes	Function outcomes
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	NR	**Pragmatic rehab vs. supportive listening vs. usual care** *Mean percentage scores (SD) on SF-36 physical functioning scale (0-100 scale, higher scores indicate better outcomes)* 20 weeks: 39.94 (25.21) vs. 33.28 (22.94) vs. 40.27 (26.45); treatment effect estimate -7.54, 95% CI -2.96 to -0.11; p=0.035 for supportive listening vs. usual care 70 weeks: 43.27 (27.38) vs. 35.72 (25.94) vs. 39.83 (27.77); p=NS

Author, year	Employment outcomes	Other outcomes
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Wearden, *et al.,* 2010[118] ***FINE Trial*** Wearden, *et al.,* 2012[119] Wearden and Emsley, 2013[120]	Unclear, 1 each in pragmatic rehab and supportive listening withdrew due to nurse therapist safety concern, not otherwise described	None reported	See Total adverse events	Overall: 4 (herpes simplex infection, attempted suicide, bleeding peptic ulcer, and recurrence of cancer; all deemed unrelated to interventions)	United Kingdom Medical Research Council (G200212) and the United Kingdom Department of Health; and the University of Manchester	Good

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Exercise				
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	RCT of qigong exercise vs. no qigong exercise for symptoms	**Exercise vs. control** Mean age: 42.4 vs. 42.5 years % Female: 72 (52/72) vs. 82 (53/65) Race: NR % Employed full-time: 76 (55/72) vs. 80 (52/65) % Employed part-time: 4.2 (3/72) vs. 1.5 (1/65) % Unemployed: 5.6 (4/72) vs. 1.5 (1/65) % Housewife: 13 (9/72) vs. 15 (10/65) % Regularly exercise: 26 (19/72) vs. 26 (17/65) Mean number of reported fatigue symptoms (SD): 6.3 (1.4) vs. 6.3 (1.4)	CDC (Fukuda, 1994) criteria **Inclusion:** Unexplained fatigue over 6 months which was of new onset, with 4 of 8 following symptoms: impaired memory or concentration, PEM, unrefreshing sleep, muscle pain, multijoint pain, new headaches, sore throat, and tender lymph nodes. **Exclusion:** Medical condition that may explain the presence of chronic fatigue.	≥6 months
Fulcher and White, 1997[109]	RCT (with control treatment crossover after the first followup examination) of graded aerobic exercise vs. flexibility exercises and relaxation therapy for symptoms	Mean age (SD): 37.2 (10.7) years % Female: 74 (49/66) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Patients meeting the Oxford criteria. **Exclusions:** Patients excluded for psychiatric disorders, not including simple phobias, using the clinical interview for the DSM-III-R or for co-morbid symptomatic insomnia.	Median (range): 2.7 years (0.6-19.0)

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Exercise					
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	Number approached: NR Number screened: 1,441 Number eligible: 236 Number enrolled: 154 Number analyzed: 137 (72 exercise, 65 control)	Hong Kong Special Administrative Region of China	4 months (5 weeks training in qigong exercise and 12 weeks of qigong exercise at home)	**Overall:** 28% (43/154) **Exercise vs. control:** 31% (24/77) vs. 25% (19/77)	NR
Fulcher and White, 1997[109]	Number approached: NR Number screened: 167 Number eligible: 66 Number enrolled: 66 Number analyzed: 59 (29 exercise, 30 control)	United Kingdom, London Department of Psychological Medicine, St Bartholomew's and the Royal London Medical School	12 weeks, 1 year followup	**Overall:** 12% (7/59) **Exercise vs. control:** 14% (4/29) vs. 10% (3/30)	NR

Author, year	Interventions	Fatigue outcomes
Exercise		
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	**Exercise:** Qigong exercise 30 minutes every day, at home. **Control:** Refrained from qigong exercise.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale total fatigue scores (0-56 scale, lower score indicates better health)* 4 months: 26.6 (13.6) vs. 33.2 (6.3); p<0.001 *Mean (SD) Chalder fatigue scale physical fatigue scores (0-32 scale, lower score indicates better health)* 4 months: 15.9 (8.0) vs. 20.8 (5.7); p<0.001 *Mean (SD) Chalder fatigue scale mental fatigue scores 0-24 scale, lower score indicates better health)* 4 months: 10.6 (6.1) vs. 12.4 (4.9); p=0.05
Fulcher and White, 1997[109]	**Exercise:** Exercise treatment, weekly for 12 weeks of supervised treatment. **Control:** 12 weeks of flexibility and relaxation sessions.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale scores (0-56 scale, lower score indicates better health)* 12 weeks: 20.5 (8.9) vs. 27.4 (7.4); p=0.004 *Mean (SD) Visual analog scale total fatigue score (unclear scale, 200 noted as 'normal', lower scores indicate better health)* 12 weeks: 253 (48) vs. 286 (67); p=0.04 *Mean (SD) Visual analog scale physical fatigue score (unclear scale, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 130 (28) vs. 154 (34); p=0.006 *Mean (SD) Visual analog scale mental fatigue score (unclear scale, 100 noted as 'normal', lower scores indicate better health)* 12 weeks: 124 (31) vs. 132 (39); p=0.38

Author, year	Quality of life outcomes	Function outcomes
Exercise		
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	NR	**Exercise vs. control** *Mean (SD) QOL SF-12 mental functioning score (6 items scored from 0 to 100, higher scores indicate better health)* 4 months: 42.7 (7.2) vs. 35.7 (9.5); p=0.001 *Mean (SD) QOL SF-12 physical functioning score (6 items scored from 0 to 100, higher scores indicate better health)* 4 months: 40.1 (6.9) vs. 37.8 (5.6); p=0.484
Fulcher and White, 1997[109]	NR	**Exervise vs. control** *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69 (18.5) vs 55 (21.8); p=0.01

Author, year	Employment outcomes	Other outcomes
Exercise		
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	NR	**Exercise vs. control** *Mean (SD) telomerase activity (arbitrary unit)* 4 months: 0.178 (0.201) vs. 0.104 (0.059) p=0.029, between groups over time
Fulcher and White, 1997[109]	**Exercise vs. all participants** (due to control allowed to crossover to exercise) Working full- or part-time at 1 year followup: 66% (31/47) vs. 39% (26/66); 95% CI 9% to 44%; p=NR	**Exercise vs. control** *Self-rated CGI score after 12 weeks* % Very much better: 31 (9/29) vs. 7 (2/30) % Much better: 24 (7/29) vs. 20 (6/30) % A little better: 38 (11/29) vs. 60 (18/30) % No change: 3 (1/29) vs. 10 (3/30) % A little worse: 3 (1/29) vs.0 (0/30) % Much worse: 0 (0/29) vs. 3 (1/30) % Very much worse: 0 (0/29) vs. 0 (0/30) p=0.05 for between groups comparison *Median (IQR) peak O_2 consumption (ml/kg/minute)* After 12 weeks: 35.8 (30.8-40.7) vs. 29.8 (24.7 (34.9); p=0.03 Median increase in peak O2 consumption: 13% vs. 6% Median increase in isometric strength: 26% vs. 15%; p=0.20 *Rated self as better at 1 year followup:* 74% (35/47)

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Exercise						
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	NR	NR	NR	None	Centre on Behavioral Health Research Fund, University of Hong Kong	Fair
Fulcher and White, 1997[109]	NR/unclear (“minimal adverse effects” but no number reported)	NR	NR	NR	Linbury Trust, a Sainsbury charitable trust	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Moss-Morris, *et al.,* 2005[127]	RCT of graded exercise vs. standard medical care for symptoms	**Exercise vs. control** Mean age (SD): 36.7 (11.8) vs. 45.5 (10.4) years % Female: 60 (15/25) vs. 79 (19/24) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages 18-65 years and meeting Fukuda criteria. **Exclusion:** Patients unable to exercise for medical reasons or patients already performing regular exercise.	Median (range): 3.08 years (0.5-45 years)
Sutcliffe, *et al.,* 2010[128]	RCT of orthostatic training vs. placebo for symptoms	**Orthostatic training vs. control** Mean age: 48 vs. 48 years % Female: 79 (15/19) vs. 84 (16/19) Race: NR	CDC (Fukuda, 1994) criteria **Inclusion:** Ages ≥18 years with diagnosis of CFS under Fukuda criteria. **Exclusion:** Use of drugs which can affect the autonomic nervous system that cannot be safely discontinued, inability to stand up for 40 minutes, or pregnancy.	NR

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Moss-Morris, *et al.,* 2005[127]	Number approached: NR Number screened: 51 Number eligible: 49 Number enrolled: 49 Number analyzed: 49 (25 exercise, 24 control)	Auckland, New Zealand CFS private general practice centers	12 weeks, 6 month followup	**Overall:** 12% (6/49) **Exercise vs. control:** 12% (3/25) vs. 13% (3/24)	**Overall:** 88% (43/49) **Exercise vs. control:** 88% (22/25) vs. 88% (21/24)
Sutcliffe, *et al.,* 2010[128]	Number approached: 59 Number screened: 52 Number eligible: 49 Number enrolled: 38 Number analyzed: 36 (18 orthostatic training, 18 control)	Newcastle, United Kingdom UK NIHR Biomedical Research Centre in Ageing, Royal Victoria Infirmary, Newcastle University	6 months	**Overall:** 26% (10/38) **Orthostatic training vs. control:** NR	**Overall completion of fatigue questionnaires:** 24 **Orthostatic training vs. control:** 12 vs. 12

Author, year	Interventions	Fatigue outcomes
Moss-Morris, *et al.,* 2005[127]	**Exercise:** Graded exercise therapy, 30 minutes per day 5 days per week. **Control:** Standard medical care.	**Exercise vs. control** *Mean (SD) Chalder fatigue scale total fatigue scores (0-56 scale, lower scores indicate better health)* 12 weeks: 13.91 (10.88) vs. 24.41(9.69); p=0.02 *Mean (SD) Chalder fatigue scale physical fatigue subscale scores (0-32 scale, lower score indicates better health)* 12 weeks: 7.91 (7.06) vs. 14.27 (5.75); p=0.02 *Mean (SD) Chalder fatigue scale mental fatigue subscale scores (0-24 scale, lower score indicates better health)* 12 weeks: 6.00 (4.06) vs. 10.14 (4.27); p=0.03
Sutcliffe, *et al.,* 2010[128]	**Orthostatic training**: Standing with upper back against a wall, heels 15 cm from the wall with a cushioned 'drop zone', maintained position without movement for 40 minutes or until symptoms of CFS occur. **Control:** Standing against a wall as described above for only 10 minutes, also taught to perform gentle flexion and extension exercises with their calf muscles while standing against the wall, to enhance believability, counter venous pooling and prevent any possible orthostatic training effect.	**Orthostatic training vs. control** Improvement of ≥10 points on FIS at 6 months: 50% (7/14) vs. 38% (5/13); p=NR

Author, year	Quality of life outcomes	Function outcomes
Moss-Morris, *et al.,* 2005[127]	NR	**Exercise vs. control** *Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)* 12 weeks: 69.05 (21.94) vs. 55.00 (22.94); p=0.49
Sutcliffe, *et al.,* 2010[128]	NR	**Orthostatic training vs. control** Difference in mean (SD) blood pressure drop with active stand at 6 months: 6 mmHg; 95% CI, 0.0 to 12.6; p=0.05

Author, year	Employment outcomes	Other outcomes
Moss-Morris, *et al.,* 2005[127]	NR	**Exercise vs. control** *Self-rated CGI at 6 months* % Much or very much improved: 54 (12/22) vs. 24 (5/21); p=0.04
Sutcliffe, *et al.,* 2010[128]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Moss-Morris, *et al.,* 2005[127]	1 patient withdrew due to injured calf	NR	10 of 25 patients refused to repeat fitness test as felt initial test harmful	2% (1/49)	University of Auckland Staff Grants	Fair
Sutcliffe, *et al.,* 2010[128]	NR	NR	NR	NR	Northern Regional CFS/ME Clinical Network	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Combination therapies and Head-to-Head Comparisons				
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105]	RCT of CBT vs. COG vs. ACT vs. relaxation for symptoms	Mean age: 43.8 years % Female: 83 (no. NR) % White: 88 (no. NR) % Black: 4 (no. NR) % Latino: 4 (no. NR) % Asian-American: 4 (no. NR) % On disability: 25 (no. NR) % Unemployed: 24 (no. NR) % Working part-time: 20 (no. NR) % Working full-time: 19 (no. NR) % Retired: 6 (no. NR) % Part-time student: 4 (no. NR) % Full-time student: 1 (no. NR) % Working part-time and on disability: 2 (no. NR) % Lifetime axis I diagnosis: 62 (no. NR) % Current axis I diagnosis: 39 (no. NR)	CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment **Inclusion:** Ages ≥18 years, not pregnant, able to read and speak English, considered to be physically capable of attending the scheduled sessions. **Exclusion:** Persons who used wheelchairs and who were bedridden or housebound; lifelong fatigue; >4 secondary symptoms of CFS; BMI >45 kg/m^2; melancholic depression or bipolar depression; alcohol or substance abuse disorder; autoimmune thyroiditis; cancer; lupus; or rheumatoid arthritis.	NR

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Combination therapies and Head-to-Head Comparisons					
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105]	Number approached: NR Number screened: NR Number eligible: NR Number enrolled: 114 (29 CBT, 28 COG, 29 ACT, 28 Relaxation) Number analyzed: 114 (29 CBT , 28 COG, 29 ACT, 28 Relaxation) in Jason, 2007; 81 (49 staying within their energy envelope, 32 going beyond their energy envelope) in Jason, 2009; 82 (22 CBT, 22 COG, 18 ACT, 20 Relaxation) in Hlavaty, 2011	United States, Chicago area Single site, not described	12 months	Average drop out rate: 25%, but NR per group	Participants attended an average of 10 out of 13 sessions (range: 1-13) Hlavaty, 2011 focuses on subgroup analysis based on homework compliance, groups defined by amount of homework completed as follows: Minimum (0-25% completed) vs. moderate (25.1%-75% completed) vs. maximum (75.1%-100% completed)

Author, year	Interventions	Fatigue outcomes
Combination therapies and Head-to-Head Comparisons		
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105]	**CBT:** 13 sessions of individual CBT, held once every 2 weeks, with graded activity developed in collaboration with the participant; beginning modestly, with activity and rest pre-planned and time-contingent rather than symptom-driven; negative automatic thoughts were reviewed and cognitive strategies were introduced to develop new ways of thinking. **Cognitive therapy (COG):** 13 sessions, held once every 2 weeks, of broad-based cognitive approach focused on developing cognitive strategies to better tolerate and reduce stress and symptoms, and to lessen self-criticism. **Anaerobic activity therapy (ACT):** 13 sessions, held once every 2 weeks, of anaerobic activity therapy focused on developing individualized, constructive and pleasurable activities with reinforcement. **Relaxation:** 13 sessions, held once every 2 weeks, focusing on progressive muscle relaxation techniques, breathing, yoga form stretching, and thematic imagery relaxation; participants were shown how to use relaxation techniques in stressful situations.	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) FSS scores (9-63 scale, lower score indicates better health)* 12 months: 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 5.7 vs. 6.1; p=NR 12 months: 5.3 vs. 6.3 Change at 12 months from baseline: -0.9 vs. 0.1; p<0.01 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR

Author, year	Quality of life outcomes	Function outcomes
Combination therapies and Head-to-Head Comparisons		
Jason, *et al.*, 2007[108] Jason, *et al.*, 2009[106] Hlavaty, *et al.*, 2011[105]	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) QLS scores (16-112 scale, higher score indicates better health)* 12 months: 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR	**CBT vs. COG vs. ACT vs. Relaxation** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)* 12 months: 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70) p<0.01 for CBT and COG over time vs. ACT over time % Achieving clinically significant improvement: 18.2 vs. 30.4 vs. 11.1 vs. 21.7; p=NS ***Jason, 2009 data: comparison by energy envelope (data estimated from figure)*** **Stayed within envelope vs. outside envelope** 6 months: 58 vs. 48;p=NR 12 months: 65 vs. 43 Change at 12 months from baseline: 17 vs. 0; p=0.03 ***Hlavaty, 2011 data: comparison by homework compliance level*** **Minimum vs. moderate vs. maximum** Change in score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR

Author, year	Employment outcomes	Other outcomes
Combination therapies and Head-to-Head Comparisons		
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105]	**CBT vs. COG vs. ACT vs. Relaxation** % Employed at 12 month followup: 62 vs. 56 vs. 33 vs. 43; p=NS	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Combination therapies and Head-to-Head Comparisons						
Jason, *et al.,* 2007[108] Jason, *et al.,* 2009[106] Hlavaty, *et al.,* 2011[105]	NR	NR	NR	NR	NIAID (Grant No. AI 49720)	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Núñez, *et al.,* 2011[111]	RCT of CBT + GET vs. usual care for symptoms	**CBT + GET vs. usual care** Mean age: 42.7 vs. 44.3 years % Female: 93 (53/58) vs. 86 (48/57) Race: NR % Actively working: 16 (9/58) vs. 20 (11/57) % Unemployed: 9 (5/58) vs. 4 (2/57) % Temporary work disability: 31 (18/58) vs. 23 (13/57) % Permanent work disability: 33 (19/58) vs. 45 (25/57) % Retired: 0 (0/58) vs. 2 (1/57) % Other: 11 vs. 7 Mean number of co-morbidities: 1.60 vs. 1.46 % Fibromyalgia: 75 (43/58) vs. 63 (37/57) % Sicca syndrome: 9 (5/58) vs. 20 (11/57) % Dysthymia: 35 (20/58) vs. 23 (13/57) % Thyroid disturbances: 12 (7/58) vs. 16 (9/57) % Dysmenorrhea/endometriosis: 0 vs. 0 % Chemical sensitivity: 5 (3/58) vs. 7 (4/57) % Other co-morbidities: 23 (13/58) vs. 18 (10/57) Mean HADS-anxiety score: 11 vs. 11 Mean HADS-depression score: 12 vs 11	CDC (Fukuda, 1994) criteria **Inclusion:** Diagnosed with CFS using Fukuda, 1994 criteria. **Exclusion:** Past or current diagnosis of a major depressive disorder with psychotic or melancholic features according to Fukuda criteria; physical diseases that could cause fatigue, including morbid obesity, hypothyroidism, Cushing syndrome, anemia (blood hemoglobin <10 g/L), diabetes, active neoplastic or infectious disease, inflammatory rheumatic disease, and patients unable to participate fully in study procedures; involved in ongoing legal or occupational conflicts.	**CBT + GET vs. usual care** Mean: 32 vs. 33 months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Núñez, *et al.,* 2011[111]	Number approached: NR Number screened: 276 Number eligible: 134 Number enrolled: 120 (60 each group) Number analyzed: 115 (58 CBT + GET vs. 57 usual care)	Spain 1 University hospital clinic	2.5-3 months of treatment, 12 months followup after treatment	**Overall:** 4.2% (5/120) **CBT vs. usual care** 3.3% (2/60) vs. 5.0% (3/60)	NR, but group sessions, so except for the attrition, all assumed to adhere to program

Author, year	Interventions	Fatigue outcomes
Núñez, *et al.,* 2011[111]	**CBT + GET:** Group CBT, 9 twice weekly 90-minute sessions during 2.5-3 months; content included: psychoeducational interventions to explain the multi-factorial character of CFS, progressive muscle relaxation procedures, sleep hygiene patterns, detection and control of verbal and non-verbal pain-inducing attitudes, cognitive thought patterns, information about the relationship between vegetative and anxiety symptoms, modification of type A behavioral patterns, improvement in assertiveness, patterns to increase attention and memory, sensorial focalization for sexual inhibition, and disease relapse prevention. Group GET, 3 times a week 1-hour sessions, over intermittent periods of 10 minutes for 3 months, with gradual increases in aerobic exercise at a rate of 5 minutes per session and complementary activities such as flexibility exercise and relaxation therapy were included. Total exercise load was maintained or increased to a maximum of 40 minutes per day according to tolerance. **Usual care:** Usual CFS therapy including exercise counseling and conventional pharmacological symptomatic treatment. *Note:* Symptomatic pharmacological treatment was the same in both groups: paracetamol 1-3 g/day and ibuprofen 600-1,800 mg/day if reported inflammation and zolpidem 10 mg/night if reported insomnia.	**CBT + GET vs. usual care** *Mean FIS (0-160 scale, higher score indicates better health)* 12 months: 139.2 vs. 137.4; p=NS

Author, year	Quality of life outcomes	Function outcomes
Núñez, *et al.*, 2011[111]	NR	**CBT + GET vs. usual care** *Mean SF-36 physical function subscale (0-100 scale, higher score indicates better health)* 12 months: 32.63 vs. 38.28; p=NS

Author. year	Employment outcomes	Other outcomes
Núñez, *et al.*, 2011[111]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Núñez, *et al.*, 2011[111]	NR	NR	NR	NR	Generalitat of Catalonia, SGR 2009-1158 and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
Wearden, *et al.,* 1998[90]	RCT of GET + fluoxetine vs. GET alone vs. fluoxetine alone vs. control for symptoms	**Overall, GET + fluoxetine vs. GET vs. fluoxetine vs. control** Mean age: 38.7, 38.2 vs. 40.4 vs. 38.8 vs. 37.6 years % Female: 71 (97/136), 67 (22/33) vs. 79 (27/34) vs. 77 (27/35) vs. 62 (21/34) Race: NR	Oxford (Sharpe, 1991) criteria **Inclusion:** Ages ≥18 years, meeting Oxford criteria, principle complaint of fatigue, impairment in 3 out of 4 areas of activity. **Exclusion** Medical cause of fatigue.	≥6 months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
Wearden, *et al.,* 1998[90]	Number approached: NR Number screened: 227 Number eligible: 165 Number enrolled: 136 Number analyzed: ITT: 136 (33 GET + fluoxetine, 34 fluoxetine, 35 GET, 34 control) Completed trial: 96 (19 GET + fluoxetine, 23 fluoxetine, 25 GET, 29 control)	Northwest England and North Wales University department of medicine out-patient clinic	26 weeks	**Overall:** 29% (40/136) **GET + fluoxetine vs. fluoxetine vs. GET vs. control** 42% (14/33) vs. 32% (11/34) vs. 29% (10/35) vs. 17% (5/29)	NR

Author, year	Interventions	Fatigue outcomes
Wearden, *et al.,* 1998[90]	**GET + fluoxetine**: Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3/week, with low initial intensity that was gradually increased based on hear rate plus fluoxetine 20 mg daily. **Fluoxetine**: Fluoxetine 20 mg daily plus placebo exercise program of being told to keep doing what they were doing and no other advice. **GET:** Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3/week, with low initial intensity that was gradually increased based on hear rate plus placebo drug. **Control:** Placebo drug plus placebo exercise program of being told to keep doing what they were doing and no other advice.	**GET + fluoxetine vs. GET vs. fluoxetine vs. control** *Mean (95% CI) Chalder fatigue scale scores (unclear scale, lower scores indicate better health)* 0-12 weeks: -5.7 (-9.2 to -2.2) vs. -2.1 (-4.9 to 0.6) vs. -1.6 (-4.4 to 1.2) vs. -2.0 (-4.1 to 0.1) 26 weeks: -6.0 (-9.7 to -2.3) vs. -5.7 (-9.5 to -1.9) vs. -3 (-5.9 to -0.2) vs. -2.7 (-5.4 to 0.01) *% non-cases of fatigue (Chalder fatigue scale score <4)* 12 weeks: 18 (6/33) vs. 3 (1/34) vs. 1 (3/35) vs. 6 (2/34) 26 weeks: 18 (6/33) vs. 18 (6/34) vs. 6 (2/ 35) vs. 6 (2/34) p=0.025 for exercise interventions combined vs. others *Exercise improved fatigue scale scores* 0-12 weeks: mean change=2.l (95% CI -0.6 to 4.8), p=0.13 26 weeks: mean change=2.9 (95% CI -0.2 to 6.1), p=0.07

Author, year	Quality of life outcomes	Function outcomes
Wearden, *et al.*, 1998[90]	NR	**GET + fluoxetine vs. GET vs. fluoxetine vs. control** *Mean (SD) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight)* Mean change (95% CI) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight) 0-12 weeks: 2.2 (1.0 to 3.4) vs. 2.6 (1.0 to 43) vs. 0.4 (-1.2 to 2.0) vs. 0.4 (-0.9 to 1.7) 26 weeks: 2.0 (0.4 to 3.5) vs. 2.8 (0.8 to 4.8) vs. 1.0 (-0.9 to 3.0) vs. -0.1 (-1.7 to 1.6) *Effect of exercise on functional work capacity* Mean change 0-12 weeks: 2.0 (95% CI 0.60 to 3.49), p=0.00 Mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03

Author. year	Employment outcomes	Other outcomes
Wearden, *et al.,* 1998[90]	NR	NR

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
Wearden, *et al.*, 1998[90]	11 medication side-effects (2 reported with placebo)	NR	NR	Unclear, only reported those who dropped out due to AEs	Lansbury Trust	Fair

Author, year	Objective	Population characteristics (age, sex, race, co-morbidities)	Diagnostic criteria Eligibility criteria	Duration of illness
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	RCT of CBT vs. GET vs. APT vs. usual care for symptoms	**APT vs. CBT vs. GET vs. control** Mean age (SD): 39 (11) vs. 39 (12) vs. 39 (12) vs. 37 (11) years % Female: 76 (121/159) vs. 80 (129/161) vs. 77 (123/160) vs. 76 (122/160) % White: 92 (146/159) vs. 94 (151/161) vs. 93 (148/160) vs. 94 (150/160) % Any depressive disorder: 35 (55/159) vs. 34 (55/161) vs. 34 (54/160) vs. 34 (55/160) % Any psychiatric disorder: 47 (75/159) vs. 47 (75/161) vs. 46 (73/160) vs. 48 (77/160)	Oxford (Sharpe, 1991) criteria **Inclusion:** Bimodal score of ≥6 out of 11 on Chalder fatigue scale and score of ≤60 on SF-36 physical function subscale (after 11 months this was changed to ≤65). **Exclusion:** Ages <18 years, at significant risk of self-harm, unable to attend hospital appointments, unable to speak and read English, had medical needs that made participation inappropriate, had previously received a trial treatment for their present illness at a PACE trial clinic.	**APT vs. CBT vs. GET vs. control** Median (IQR): 33 (16-69) vs. 36 (16-104) vs. 35 (18-67) vs. 25 (15-57) months

Author, year	Number approached, screened, eligible, enrolled, analyzed	Country & setting	Duration of followup	Attrition	Adherence
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	Number approached: NR Number screened: 3,158 Number eligible: NR Number enrolled: 641 (160 APT, 161 CBT, 160 GET, 160 control) Number analyzed: 630 (159 APT, 155 CBT, 159 GET, 157 control)	United Kingdom 6 specialist CFS clinics	52 weeks	**Overall:** 1.7% (11/641) **APT vs. CBT vs. GET vs. control:** 0.6% (1/160) vs. 3.7% (6/161) vs. 0.6% (1/160) vs. 1.9% (3/160)	NR

Author, year	Interventions	Fatigue outcomes
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	**Adaptive pacing therapy (APT):** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual adaptive pacing therapy with the aim of achieving optimum adaptation to the illness, this was done by helping the participant to plan and pace activity to reduce or avoid fatigue, achieve prioritized activities and provide the best conditions for natural recovery. Strategies consisted of: identifying links between activity and fatigue; encouragement to plan activity to avoid exacerbation; developing awareness of early warnings of exacerbation; limiting demands and stress; regularly planning rest and relaxation; and alternating different types of activities; with advice not to undertake activities that demand >70% of participant's perceived energy envelopes. **CBT:** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual CBT with the aim of changing the behavioral and cognitive factors assumed to be responsible for perpetuation of the participant's symptoms and disability. Strategies guided participants to address unhelpful cognitions, including fears about symptoms or activity by testing them in behavioral experiments, consisting of gradual increases in both physical and mental activity. **GET:** Up to 14 sessions in 23 weeks, with booster session offered at 36 weeks, of individual GET with the aim of helping the participant gradually return to appropriate physical activities, reverse the deconditioning, and thereby reduce fatigue and disability. Strategies consisted of establishment of baseline achievable exercise or physical activity, followed by a negotiated, incremental increase in the duration of time spent physically active; target heart rate ranges set when necessary to avoid overexertion; which aimed at 30 minutes of light exercise 5 times a week; with mutually agreed upon gradual increases in intensity and aerobic nature of exercises. **Control:** Usual care.	**APT vs. CBT vs. GET vs. control** *Mean (SD) Chalder fatigue scale scores (0-33 scale, lower scores indicate better health)* 12 weeks: 24.2 (6.4) vs. 23.6 (6.5) vs. 22.8 (7.5) vs. 24.3 (6.5) 24 weeks: 23.7 (6.9) vs. 21.5 (7.8) vs. 21.7 (7.1) vs. 24.0 (6.9) 52 weeks: 23.1 (7.3) vs. 20.3 (8.0) vs. 20.6 (7.5) vs. 23.8 (6.6) Mean difference (95% CI) from control at 52 weeks: -7.0 (-2.3 to 0.9) p=NS vs. -3.4 (-5.0 to -1.8) p=0.0001 vs. -3.2 (-4.8 to -1.7) p=0.0003 vs. NR Mean difference (95% CI) from APT at 52 weeks: NR vs. -2.7 (-4.4 to -1.1) p=0.0027 vs. -2.5 (-4.2 to -0.9) p=0.0059 vs. NR % Improved from baseline (by ≥2 points): 65 (99/153) vs. 76 (113/148) vs. 80 (123/154) vs. 65 (98/152) % Within normal range (score ≤18): 22 (34/153) vs. 41 (60/148) vs. 33 (51/154) vs. 21 (32/152)

Author, year	Quality of life outcomes	Function outcomes
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	NR	**APT vs. CBT vs. GET vs. control** *Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher scores indicate better health)* 12 weeks: 41.7 (19.9) vs. 51.0 (20.7) vs. 48.1 (21.6) vs. 46.6 (20.4) 24 weeks: 43.2 (21.4) vs. 54.2 (21.6) vs. 55.4 (23.3) vs. 48.4 (23.1) 52 weeks: 45.9 (24.9) vs. 58.2 (24.1) vs. 57.7 (26.5) vs. 50.8 (24.7) Mean difference (95% CI) from control at 52 weeks: -3.4 (-8.4 to 1.6) p=NS vs. 7.1 (2.0 to 12.1) p=0.0068 vs. 9.4 (4.4 to 14.4) p=0.0005 vs. NR Mean difference (95% CI) from APT at 52 weeks: NR vs. 10.5 (5.4 to 15.6) p=0.0002 vs. 12.8 (7.7 to 17.9) p<0.0001 vs. NR % Improved from baseline (by ≥8 points): 49 (75/153) vs. 71 (105/148) vs. 70 (108/154) vs. 58 (88/152) % Within normal range (score ≥60): 35 (53/153) vs. 52 (77/148) vs. 53 (81/154) vs. 41 (62/152)

Author, year	Employment outcomes
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	**APT vs. CBT vs. GET vs. control** *Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)* 52 weeks: 24.5 (8.8) vs. 21.0 (9.6) vs. 20.5 (9.4) vs. 23.9 (9.2); p=0.0001 for CBT vs. control p=0.0006 for GET vs. control; p=0.0001 for CBT vs. APT; p=0.0004 for GET vs. APT

Author, year	Other outcomes
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	**APT vs. CBT vs. GET vs. control** *Patients with self-rated CGI changes* 12 weeks % Positive change: 13 (20/153) vs. 21 (32/153) vs. 25 (37/151) vs. 5 (7/151) % Minimum change: 82 (126/159) vs. 74 (113/161) vs. 74 (111/151) vs. 88 (133/160) % Negative change: 5 (7/153) vs. 5 (8/153) vs. 2 (3/151) vs. 7 (11/151) 24 weeks % Positive change: 24 (37/155) vs. 38 (56/149) vs. 37 (54/148) vs. 19 (28/151) % Minimum change: 72 (111/155) vs. 55 (82/149) vs. 60 (89/148) vs. 71 (107/151) % Negative change: 5 (7/155) vs. 7 (11/149) vs. 3 (5/148) vs. 11 (16/151) 52 weeks % Positive change: 31 (47/153) vs. 41 (61/147) vs. 41 (62/152) vs. 25 (38/152) % Minimum change: 63 (96/153) vs. 52 (77/147) vs. 53 (80/152) vs. 66 (100/152) % Negative change: 7 (10/153) vs. 6 (9/147) vs. 7 (10/152) vs. 9 (14/152) OR (95% CI) positive change vs. negative change Compared with control: 1.3 (0.8 to 2.1) p=NS vs. 2.2 (1.2 to 3.9) p=0.011 vs. 2.0 (1.2 to 3.5) p=0.013 vs. NR Compared with APT: NR vs. 1.7 (1.0 to 2.7) p=0.034 vs. 1.5 (1.0 to 2.3) p=0.028 vs. NR *Recovery based on different criteria at 52 weeks* % Within the normal range on both the Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60): 16 (25/153) vs. 30 (44/148) vs. 28 (43/154) vs. 15 (22/152) *% No longer meeting case definitions* CDC (Fukuda, 1994) criteria: 49 (74/150) vs. 67 (97/144) vs. 65 (93/144) vs. 51 (76/149) Oxford (Sharpe, 1991) criteria: 43 (64/149) vs. 54 (77/143) vs. 56 (81/144) vs. 41 (62/150) London ME criteria: 68 (100/147) vs. 76 (107/140) vs. 77 (106/138) vs. 66 (97/148) *Cumulative criteria for recovery at 52 weeks* Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), and not meeting Oxford (Sharpe, 1991) criteria: 15 (23/149) vs. 28 (40/143) vs. 28 (41/144) vs. 14 (21/150) Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), not meeting Oxford (Sharpe, 1991) criteria, and CGI of very much better or much better (this cumulative criteria considered meeting “trial recovery criteria”): 8 (12/149) vs. 22 (32/143) vs. 22 (32/143) vs. 7 (11/150) Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), not meeting Oxford (Sharpe, 1991) criteria, CGI of very much better or much better, and not meeting CDC (Fukuda, 1994) criteria: 8 (12/149) vs. 22 (32/143) vs. 22 (32/143) vs. 7 (11/149) Normal range on both Chalder fatigue scale (score ≤18) and SF-36 physical functioning subscale (score ≥60), not meeting Oxford (Sharpe, 1991) criteria, CGI of very much better or much better, not meeting CDC (Fukuda, 1994) criteria, and not meeting London ME criteria: 8 (12/147) vs. 21 (29/193) vs. 21 (29/138) vs. 7 (11/147) *Meeting “trial recovery criteria” in subgroups meeting alternate definitions of CFS or ME at baseline* CDC (Fukuda, 1994) criteria: 9 (9/102) vs. 19 (17/89) vs. 22 (20/93) vs. 6 (6/98) London ME criteria: 11 (8/75) vs. 21 (15/70) vs. 21 (16/75) vs. 10 (7/73) OR (95% CI) for composite “trial recovery” CBT vs. APT: 3.36 (1.64 to 6.88); p=0.001 CBT vs. control: 3.69 (1.77 to 7.69); p<0.001 GET vs. APT: 3.38 (1.65 to 6.93); p=0.001 GET vs. control: 3.71 (1.78 to 7.74); p<0.001 APT vs. control: 1.10 (0.47 to 2.58); p=NS

Author, year	Withdrawals due to adverse event	Serious harms	Other harms	Total harms	Sponsor	Quality rating
White, *et al.,* 2011[121] ***PACE Trial*** White, *et al.,* 2013[123] Dougall, *et al.,* 2014[122]	NR	**APT vs. CBT vs. GET vs. control** % With ≥1 SAE*: 9 (15/159) vs. 4 (7/161) vs. 8 (13/160) vs. 4 (7/160); p=NS Number of SAEs: 16 vs. 8 vs. 17 vs. 7, p=0.04 for GET vs. control SAEs per 100 person-years (95% CI): 10.1 (5.8 to 16.3) vs. 5.0 (2.2 to 9.8) vs. 10.6 (6.2 to 17.0) vs. 4.4 (1.8 to 9.0) % With ≥1 serious adverse reactions†: 1 (2/159) vs. 2 (3/161) vs. 1 (2/160) vs. 1 (2/160); p=NS Number of serious adverse reactions†: 2 vs. 4 vs. 2 vs. 2 Serious adverse reactions† per 100 person-years (95% CI): 1.3 (0.2 to 4.5) vs. 2.5 (0.7 to 6.4) vs. 1.3 (0.2 to 4.5) vs. 1.3 (0.2 to 4.5)	**APT vs. CBT vs. GET vs. control** % with physical function worse: 25 (39/159) vs. 9 (15/161) vs. 11 (18/160) vs. 18 (28/160); p=0.0007 % with worse fatigue: 13 (21/159) vs. 9 (14/161) vs. 7 (11/160) vs. 14 (22/160); p=NS % with worse function and fatigue: 7 (11/159) vs. 2 (4/161) vs. 3 (5/160) vs. 5 (8/160); p=NS	**APT vs. CBT vs. GET vs. control** % With ≥1 non-serious AE‡: 96 (152/159) vs. 89 (143/161) vs. 93 (149/160) vs. 93 (149/160); p=NS Number of non-serious AEs‡: 949 vs. 848 vs. 992 vs. 977, p=0.0081 for CBT vs. APT and p=0.0016 for CBT vs. control Median (quartiles) non-serious AEs‡ per person-year: 4 (2, 9) vs. 4 (2, 7) vs. 5 (2, 8) vs. 4 (3, 8); p=NS	United kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions	Good

*Serious AEs were defined in the PACE trial as an event that resulted in one of the following outcomes: a) death, b) threat to life (i.e., an immediate, not hypothetical, risk of death at the time of the event), c) required hospitalization except for elective treatment of a pre-existing condition, d) increased severity and persistent disability, defined as: (i) severe, i.e. significant deterioration in the participant's ability to carry out their important activities of daily living (e.g. employed person no longer able to work, caregiver no longer able to give care, ambulant participant becoming bed bound); and (ii) symptom and disability persistent, i.e. of at least 4 weeks continuous duration, e) any other important medical condition which, though not included in the above, might require medical or surgical intervention to prevent one of the outcomes listed, and f) any episode of deliberate self-harm.
†Serious adverse reactions were considered in the PACE trial to be a reaction to one of the supplementary therapies or a drug prescribed as part of usual care.
‡Non-serious AEs were defined in the PACE trial as 'any clinical change, disease or disorder experienced by the participant during their participation in the trial, whether or not considered related to the use of treatments being studied in the trial.'
Abbreviations: ACT= anaerobic activity therapy; ADL= activities of daily living; AE= adverse event; APT= adaptive pacing therapy; BMI= body mass index; CBT= cognitive behavioral therapy; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical global impression change score; CI= confidence interval; CIBEROBN= Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion; CIS= Checklist of individual strength; cm= centimeters; COG= cognitive therapy; DBPC= double blind placebo controlled; DSM-III-R= Diagnostic and Statistical Manual third edition revised; DSM-IV= Diagnostic and Statistical Manual fourth edition; FINE= Fatigue Intervention by Nurses Evaluation; FIQ= Fibromyalgia Impact Questionnaire; FIS= Fatigue Impact Score; FSS= Fatigue Severity Scale; g= gram; GET= graded exercise therapy; HADS= hospital anxiety and depression score; HTA= Health Technology Assessment; IGF1= insulin like growth factor 1; IGFBP3= insulin like growth factor binding protein 3; IgG= immunoglobulin G; IQR= interquartile range; ITT= intention to treat; IV= intravenous; kg= kilogram; KPS= Karnofsky performance score; L= liter; Ltd.= limited; m= meter; ME= Myalgic encephalomyelitis; MFI-20= Multidimensional Fatigue Inventory; mg= milligram; ml= milliliter; mmHG= millimeters mercury; SF-12= Short-form 12-item Health Survey; n= sample size; NHS= National Health Services; NIAID= National Institute of Allergy and Infectious Diseases; NIH= National Institutes of Health; NIHR= National Institute for Health Research; no.= number; NR= not reported; NS= not significant; NSAID= non-steroidal anti-inflammatory drug; OR= odds ratio; PACE= Pacing, graded Activity and Cognitive behavior therapy: a randomized Evaluation; POMS= Profile of Mood States; QLI= Quality of Life Index; QLS= Quality of life scale; QOLI= Quality of Life Inventory; RCT= randomized control trial; SAE= serious adverse event; SD= standard deviation; SEM= standard error of the mean; SF-36= 36-item Short Form Survey; SFQ= Abbreviated fatigue questionnaire; SGR = support the activities of research groups; SIP-8= Sickness Impact Profile 8-item; SSRI= selective serotonin reuptake inhibitor; U.S.= United States; µg= microgram; UK= United Kingdom; vs.= versus; XRCT= cross sectional control trial; ZonMW= ZorgOnderzoek Nederland and Medische wetenschappen.

Appendix H. Quality Assessment Tables

Table H1. Quality assessment table of diagnostic accuracy/concordance studies

Study, Year	Was the test applied to an appropriate spectrum of patients (with and without disease)? Avoid case-control?	Was the population tested random (not consecutive)?	Adequate sample size?	Eligibility criteria specified? Was there a rigorous assessment of the CFS population?	Reporting of attrition? Minimal loss to followup?
Davenport, *et al.,* 2011[60]	Unclear - CFS group and a non-disabled sedentary control group	Unclear - physician referral	No: n=30 100% female	Yes: 2 physicians referred patients meeting criteria	Unclear
Davenport, *et al.,* 2011[61]	Unclear - CFS group and a non-disabled sedentary control group	Unclear - physician referral	No: n=30 100% female	Yes: 2 physicians referred patients meeting criteria	Unclear
Gaab, *et al.,* 2004[66]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=42 52% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Gaab, *et al.,* 2002[67]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=35 43% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Gaab, *et al.,* 2005[68]	Unclear - CFS group and a randomly selected control group were matched for age/sex	Unclear for CFS (subjects were recruited from a self-help organization); yes for controls	No: n=41 51% female	Yes: all underwent psychiatric evaluation in addition to fulfilling the CFS criteria	Unclear
Hadzi-Pavlovic, *et al.,* 2000[64]	Unclear - CFS controls recruited a non-CFS control	Yes, population-based recruitment of the CFS and control groups	Yes: n=798 66% female	Yes/unclear: assessed diagnostic confidence; analyzed with and without those for whom there was less diagnostic confidence	Yes: began with 770 subjects; final sample 368

Study, Year	Is the test adequately described and reproducible? Reliable and valid measurements?	Validation of test protocol in a second group?	Standard case definition?	Evaluate all patients for the outcome?	Were the outcome assessors blinded to the reference standard (CFS diagnosis)?	Quality rating
Davenport, *et al.,* 2011[60]	Yes: described cardiopulmonary exercise tests in detail and it is reproduced from prior studies No reliability/validity results presented	No	Yes: CDC (Fukuda, 1994)	Yes	Unclear	Fair
Davenport, *et al.,* 2011[61]	Yes: used standardized measures	Unclear (reproducibility assessed statistically and construct validity also assessed)	Yes: CDC (Fukuda, 1994)	Yes	Unclear	Fair
Gaab, *et al.,* 2004[66]	Yes: detailed descriptions of salivary cortisol testing No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria	Yes	Unclear	Fair
Gaab, *et al.,* 2002[67]	Yes: detailed description of insulin tolerance test, ACTH, cortisol No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda 1994) and Oxford (Sharpe 1991) criteria	Yes	Unclear	Fair
Gaab, *et al.,* 2005[68]	Yes: detailed description of ACTH, cortisol, cytokine No reliability/validity results presented	No	Yes: CFS patients fulfilled both CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria	Yes	Unclear	Fair
Hadzi-Pavlovic, *et al.,* 2000[64]	Yes: used standardized measures	No	Yes: had physician rating of diagnostic confidence regarding CFS diagnosis	No: 92 of 798 subjects were excluded because of incomplete data (70/368 CFS and 22/430 controls)	Unclear	Fair

Study, Year	Was the test applied to an appropriate spectrum of patients (with and without disease)? Avoid case-control?	Was the population tested random (not consecutive)?	Adequate sample size?	Eligibility criteria specified? Was there a rigorous assessment of the CFS population?	Reporting of attrition? Minimal loss to followup?
Jason, 2010[56]	Yes - community-based recruitment of CFS population	Yes - recontact of subjects from community-based CFS recruitment	Unclear: n=108 % Female: NR	Yes: 2 physicians independently rated	Yes Loss to follow up: began with 213 from the community sample; data available on 84 without CFS and 24 with CFS
Jason, 2011[65]	Yes - had 2 groups of CFS patients (tertiary care and community sample) and control from community	Yes - community samples recruited from stratified random sample of Chicago neighborhoods; tertiary care CFS group also recruited from variety of sources (physician, newspaper, CFS support groups)	No: n=79 58% female	Yes: 4 physicians and 1 psychiatrist responsible for final decision about diagnosis of community sample; tertiary sample had psychiatric interview	Unclear
Linder, *et al.,* 2002[63]	Yes - CFS population with fibromyalgia and lupus patients as controls	Unclear - recruited by study physicians	Unclear: n=198 68% female	Unclear: few details about how patients were assessed; excluded primary psychiatric disorders	Unclear
Tiev, *et al.,* 2003[62]	Unclear - case-control study; recruitment not reported	Unclear (NR)	No: n=25 64% female	Unclear	Unclear
Watson, *et al.,* 2014[69]	Yes - had 3 groups including some CFS subjects recruited from community/internet forums	Yes/unclear - CFS subjects recruited from various sources including internet and some physician referral	Yes: n=691 % female: NR	Unclear: all subjects had diagnosed by licensed physician; those with exclusionary diagnoses were removed.	Yes, reported missing values and procedure for replacement.

Study, Year	Is the test adequately described and reproducible? Reliable and valid measurements?	Validation of test protocol in a second group?	Standard case definition?	Evaluate all patients for the outcome?	Were the outcome assessors blinded to the reference standard (CFS diagnosis)?	Quality rating
Jason, 2010[56]	Used Reeves 2005 criteria as the diagnostic test	No	Yes: screening questionnaire, then DSM-IV interview, medical history/exam and symptom inventory; all met CDC (Fukuda, 1994) criteria	Unclear	Unclear	Fair
Jason, 2011[65]	Yes: used standardized measures	No	Yes: 2 physicians independently rated each file using the CDC (Fukuda, 1994) criteria	Yes	Unclear	Fair
Linder, *et al.,* 2002[63]	Yes: used prospective assessment of 26 symptoms taken from CFS, FMS and SLE diagnostic criteria	Yes: study sample randomly divided into development and validation cohorts	Yes: Oxford (Sharpe, 1991)	Unclear	Unclear	Good
Tiev, *et al.,* 2003[62]	Yes: laboratory test for Rnase L levels described in detail No reliability/validity presented	No	Yes: CDC (Fukuda 1994)	Yes	Unclear	Poor
Watson, *et al.,* 2014[69]	Yes: unsupervised thresholding algorithm	No	Yes: CDC (Fukuda, 1994), Canadian and ME-ICC	Yes: for those included, all data were used.	Unclear	Fair

Abbreviations: ACTH = adrenocorticotropic hormone; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; DSM-IV= Diagnostic and Statistical Manual, fourth edition; FMS= fibromyalgia; n= sample size; NR= not reported; RCT= randomized, controlled trial; Rnase L= latent ribonuclease; SLE=systemic lupus erythematosus; UK= United Kingdom.

Table H2. Quality assessment of randomized controlled trials

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bazelmans, *et al.,* 2005[100]	No	No	Yes	Yes	Yes	No	No	No
Blacker, *et al.,* 2004[82]	Yes	NR	Yes	Yes	Yes	Unclear	Unclear	Yes
Blockmans, *et al.,* 2003[84]	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
Burgess, *et al.,* 2012[101]	Yes	Yes	Yes	Yes	Yes	No	No	No
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	Yes	NR	Yes	Yes	Yes	No	No	No
Deale, *et al.,* 1997[102]	Yes	Yes	No	Unclear	Yes	Yes - VAS on fatigue and disability No - all other self-report measures	No	No
Diaz-Mitoma, *et al.,* 2003[89]	NR	NR	Unclear	Unclear	No	No	No	Yes
Fulcher and White, 1997[125]	Yes	Yes	No	No (exercise group younger)	Yes	Unclear	Unclear	No

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Bazelmans, *et al.,* 2005[100]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	2 (3%) patients excluded from analysis	No	Yes	National Foundation for Public Mental Health (Grant No. 4341)	Fair
Blacker, *et al.,* 2004[82]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Shire Pharmaceutical Development Ltd.	Fair
Blockmans, *et al.,* 2003[84]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No	Yes	Yes	NR	Fair
Burgess, *et al.,* 2012[101]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes 34% (12/35) vs. 56% (25/45)	Yes	No	Yes	NR	Fair
Chan, *et al.,* 2013[129] Ho, *et al.,* 2012[126]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes (28% dropped overall)	Yes	No	Yes	Center of Behavioral Research fund	Fair
Deale, *et al.,* 1997[102]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	South East Thames Regional Health Authority Locally Organized Research Scheme	Fair
Diaz-Mitoma, *et al.,* 2003[89]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	Grants from Enterprise Ireland (130590/D)	Poor
Fulcher and White, 1997[125]	Attrition: Yes Crossovers: Yes (22) Adherence: No Contamination: No	No (11%)	Yes	No	Yes	Linbury Trust, a Sainsbury charitable trust	Fair

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Goudsmit, *et al.,* 2009[104]	No	No	No	Unclear	Yes	No	No	No
Hobday, *et al.,* 2008[93]	Yes	No	Yes	Yes	Yes	Yes	No	No
Jason, *et al.,* 2007[108]	Yes	NR	Yes	Yes	Yes	Unclear	Unclear	No
Jason, *et al.,* 2010[107]	NR	NR	Yes	Unclear	Briefly	No	No	No
Knoop, *et al.,* 2008[109]	Yes	Yes	Yes	Unclear	Yes	No	No	No
Lopez, *et al.,* 2011[110]	NR	NR	NR	NR	Yes	Unclear	Unclear	No
McKenzie, *et al.,* 1998[83]	Yes	NR	Yes	Yes	Yes	unclear	unclear	Yes
Montoya, *et al.,* 2013[86]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Moss-Morris, *et al.,* 2005[127]	Yes	Yes	No - exercise group younger	No	Yes	Unclear	Unclear	Unclear

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Goudsmit, *et al.,* 2009[104]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	NR	No	Yes	Action for ME	Poor
Hobday, *et al.,* 2008[93]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes (25% of patients did not complete)	No	Yes	Yes	NR	Fair
Jason, *et al.,* 2007[108]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	Unclear	No	Yes	NIAID (Grant No. AI 49720)	Fair
Jason, *et al.,* 2010[107]	Attrition: No Crossovers: No Adherence: No Contamination: No	NR	NR	No	Yes	National Institute of Allergy and Infectious Diseases (grant numbers AI36295 and AI49720)	Poor
Knoop, *et al.,* 2008[109]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	NR	Fair
Lopez, *et al.,* 2011[110]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No (ITT not utilized “due to the fact that it was a pilot study”)	No	Yes	NIH	Poor
McKenzie, *et al.,* 1998[83]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	NR	Fair
Montoya, *et al.,* 2013[86]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Hoffman-La Roche (Basel, Switzerland)	Fair
Moss-Morris, *et al.,* 2005[127]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	University of Auckland Staff Grants	**Fair**

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Núñez, *et al.,* 2011[111]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No
Öckerman, 2000[94]	NR	Unclear/NR	Unclear	Unclear	No	Unclear	Yes	Yes
O'Dowd, *et al.,* 2006[112]	Yes	Yes	Yes, except for sex	Unclear	Yes	Yes	No	Yes
Peterson, *et al.,* 1990[85]	Yes	Yes	Yes, except for age	Yes	Yes	Yes	Unclear	Yes
Sharpe, *et al.,* 1996[113]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	No
Sutcliffe, *et al.,* 2010[128]	Yes	Yes	Yes	yes	Yes	Unclear	Yes	Yes
Strayer, *et al.,* 2012[88]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Strayer, *et al.,* 1994[87]	Unclear	Yes	Yes, except for sex	Yes	Yes	Yes	Unclear	Yes
Taylor, 2004[114]	Yes	Unclear	Yes	Yes	Yes	No	No	No

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
Núñez, *et al.,* 2011[111]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Unclear	No	Yes	Generalitat of Catalonia, SGR 2009-1158 and CIBEROBN, Carlos III Health Institute, Majadahonda, Madrid	Fair
Öckerman, 2000[94]	Attrition: Yes Crossovers: Yes Adherence: No Contamination: No	No	Yes	No	Yes	NR	Poor
O'Dowd, *et al.,* 2006[112]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: Yes	No/No	Yes	No	Yes	HTA Programme (project NO. 974/41/08)	Fair
Peterson, *et al.,* 1990[85]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Baxter Healthcare Corp.	Fair
Sharpe, *et al.,* 1996[113]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	Wellcome Trust	Good
Sutcliffe, *et al.,* 2010[128]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	Yes (28%)	No	No	Yes	Research grant from the Northern Regional CFS/ME Clinical Network	**Fair**
Strayer, *et al.,* 2012[88]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Hemispherx Biopharma	Fair
Strayer, *et al.,* 1994[87]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	No	No	Yes	Hemispherx Biopharma	Fair
Taylor, 2004[114]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097	Good

Author, year	Randomization adequate?	Allocation con-cealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
The, *et al.,* 2007[95]	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Tummers, *et al.,* 2012[115]	Yes	Yes	Yes	Yes	Yes	No	No	No
Vermeulen and Scholte, 2004[96]	Yes	Yes	Yes	Unclear	Yes	Unclear	No	No
Weatherley-Jones, *et al.,* 2004[98]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Walach, *et al.,* 2008[97]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes (50%) No (50%)
Wearden, *et al.,* 1998[90]	Yes	NR	Yes	Yes	Yes	Yes	Unclear	Yes
Wearden, *et al.,* 2010[118] ***FINE Trial***	Yes	Yes	Yes	Yes	Yes	Yes	No	No

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
The, *et al.,* 2007[95]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Grant from Optipharma	Fair
Tummers, *et al.,* 2012[115]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Dutch Medical Research Council ZonMW	Good
Vermeulen and Scholte, 2004[96]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	No	Yes	No	Yes	Sigma-Tau Ethifarma Assen	Fair
Weatherley-Jones, *et al.,* 2004[98]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes	No	No	Yes	Linbury Trust	Fair
Walach, *et al.,* 2008[97]	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	Maurice Lang Foundation Grant	Good
Wearden, *et al.,* 1998[90]	Attrition: Yes Crossovers: No Adherence: No Contamination: No	Yes	Yes	No	Yes	Linbury Trust	Fair
Wearden, *et al.,* 2010[118] ***FINE Trial***	Attrition: Yes Crossovers: No Adherence: Yes Contamination: Yes	No	Yes	No	Yes	UK Medical Research Council (G200212) and the UK Department of Health; and the University of Manchester	Good

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
White, et al., 2011[121] **PACE Trial**	Yes	Yes	Yes	Yes	Yes	Yes - statistician No - self-report measures	No	No
Williams, et al., 2002[99]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes pre-specified	Funding source	Quality rating
White, et al., 2011[121] **PACE Trial**	Attrition: Yes Crossovers: No Adherence: Yes Contamination: No	No	Yes	No	Yes	UK Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions	Good
Williams, et al., 2002[99]	Attrition: Yes Crossovers: No Adherence: Yes Contamination : No	Yes	No	No	Yes	Linbury Trust	Fair

Abbreviations: CFS= chronic fatigue syndrome; CIBEROBN= Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion; Corp.=corporation; FINE= Fatigue Intervention by Nurses Evaluation; HTA= Health Technology Assessment; ITT= intetion-to-treat; Ltd.= limited; ME= myalgic encephalomyelitis; NIAID= National Institute of Allergy and Infectious Diseases; NIH = National Institutes of Health; No.= number; NR= not reported; PACE= Pacing, graded Activity and Cognitive behavior therapy: a randomized Evaluation; SGR= support the activities of research groups; U.S.= United States; UK= United Kingdom; VAS= visual analogue scale; vs.= versus; ZonMW= ZorgOnderzoek Nederland and Medische wetenschappen.

Appendix I. Published Case Definition Criteria

Table I1. Published case definition criteria

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
CDC, Holmes, et al., 1988[10]	Requires each of the following: 1. New onset of ≥6 months of persistent or relapsing, debilitating fatigue not resolved with bed rest 2. ≥8 of the symptom criteria, or 6 of the symptom criteria + ≥2 of following: low grade fever, nonexudative pharyngitis, palpable, or tender lymph nodes 3. ≥50% impairment of daily functioning as compared to premorbid levels	6-8 of the symptoms in any category: generalized fatigue after levels of exercise that would have been easily tolerated previously	None noted	6-8 of the symptoms in any category: Sleep disturbance
Oxford Sharpe, et al., 1991[46] CFS	Requires each of the following: 1. Fatigue as principal symptom 2. Definite onset of syndrome (not lifelong) 3. Syndrome must be severe, disabling have an effect on physical and mental (cognitive) functioning; 4. Present for >6 months, or >50% of the time 5. May include other symptoms: myalgias, mood and sleep disturbance	Fatigue is required to be complained of, significantly affect the patient's functioning, be disproportionate to exertion, represent a clear change from a previous state and be present >50% of the time.	None noted	Sleep disturbances are required to be complained of, not a response to external disturbances, changes from previous states, and persistent.
London Dowsett, et al., 1994[47] ME/CFS	Must meet all 3 criteria: 1. Exercise-induced fatigue, see fatigue criteria. 2. Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances, see neuroglogic/cognitive criteria. 3. Fluctuation of symptoms, usually precipitated by either physical or mental exercise.	Exercise-induced fatigue precipitated by trivially small exertion (physical or mental) relative to the patient's previous exercise tolerance.	Nothing noted	Nothing noted

Case Definition Statements	**Pain**	**Neurological/cognitive**
CDC, Holmes, *et al.,* 1988[10]	6-8 of the symptoms in any category: Myalgia Migratory arthralgia without joint swelling or redness Painful lymph notes Muscle discomfort	6-8 of the symptoms in any category: Neuropsychological complaints Prolonged (>24 hours) generalized headaches
Oxford Sharpe, *et al.,* 1991[46] CFS	Myalgia should be complained of, disproportionate to exertion, a change from a previous state, persistent or recurrent, and should be distinguished from joint pain or weakness.	Mood disturbances should be complained of, significant changes from previous state and should be relatively persistent or recurrent. This may include depression, loss of interest or pleasure, anxiety, emotional liability or irritability.
London Dowsett, *et al.,* 1994[47] ME/CFS	Nothing noted	Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances such as emotional lability (being upset by things that would not normally cause distress), nominal dysphasia (difficulty finding the right word), disturbed sleep patterns, dysequilibrium (imbalance or unsteadiness rather than vertigo/spinning round) or tinnitus (noises in the ear).

Case Definition Statements	Other Criteria	Additional Considerations
CDC, Holmes, *et al.,* 1988[10]	6-8 of the symptoms in any category: Mild fever, sore throat, or description of the main symptom complex as initially developing over a few hours to a few days	None
Oxford Sharpe, *et al.,* 1991[46] CFS	Disability refers to any restriction or lack of ability to perform an activity within the range considered normal for a human being, it should be distinguished from impairment of function and handicap.	None
London Dowsett, *et al.,* 1994[47] ME/CFS	Fluctuation of symptoms, usually precipitated by either physical or mental exercise.	None

Case Definition Statements	**General Diagnostic Criteria**	**Fatigue**	**Post-Exertional Malaise**	**Sleep**
CDC ≥6 months Fukuda, *et al.,* 1994[4] CFS	2 of the fatigue criteria and ≥4 of the criteria in any category	Unexplained, persistent fatigue ≥6 months not due to ongoing exertion, not substantially relieved by rest, of new onset, and results in a significant reduction in previous activity levels.	Post-exertional malaise	Unrefreshing sleep
Canadian ≥ 6 months Carruthers, *et al.,* 2003[2] ME/CFS	<u>All of the following:</u> Fatigue Post-exertional fatigue Sleep dysfunction Pain <u>≥2 of the following:</u> Neurological/cognitive manifestations <u>≥1 symptoms from ≥2 of the following categories:</u> Autonomic Neuroendocrine Immune	New onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.	Loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a slow recovery period, usually ≥24 hours.	Unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.*

Case Definition Statements	**Pain**	**Neurological/cognitive**
CDC ≥6 months Fukuda, *et al.,* 1994[4] CFS	Muscle pain Multi-joint pain without swelling or redness Headaches of new type or severity Recurrent sore throat Tender cervical or axillary lymph nodes	Impaired memory of concentration
Canadian ≥ 6 months Carruthers, *et al.,* 2003[2] ME/CFS	Significant myalgia and/or arthralgia, is often widespread and migratory in nature. Often there are significant headaches of new type, pattern or severity.**	≥2 of the following: Confusion, impaired concentration and short-term memory, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances (e.g., spatial instability and disorientation and inability to focus vision). Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory (e.g., photophobia and hypersensitivity to noise); and/or emotional overload, which may lead to crash periods and/or anxiety.

Case Definition Statements	Other Criteria	Additional Considerations
CDC ≥6 months Fukuda, *et al.,* 1994[4] CFS	Recurrent sore throat Tender cervical or axillary lymph nodes	Diagnosis of CFS-like illness if ≥6 months fatigue but doesn't meet other criteria
Canadian ≥ 6 months Carruthers, *et al.,* 2003[2] ME/CFS	<u>≥1 symptoms from ≥2 of the following categories:</u> 1. Autonomic manifestations: orthostatic hypotension, neurally mediated, postural orthostatic tachycardia syndrome, delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea. 2. Neuroendocrine manifestations: loss of thermostatic stability. subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change. anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress. 3. Immune manifestations: tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.	*There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. **Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
Reeves, *et al.,* 2005[49] CFS	Follows Fukuda, 1994 criteria, meant to define how to apply criteria	Fatigue (must satisfy all): - Lasting >6 months - Not relieved by rest (by answering "a little or not at all" to the question "is your fatigue relieved by rest?) - Causing substantial reduction in occupational, educational, social, or recreational activities (by answering "a lot" to "Does fatigue interfere with...") Severe fatigue as >medians of the MFI-20 general fatigue (>13) or reduced activity (>10) scales.	Nothing noted	Nothing noted
Revised Canadian ≥6 months Jason, *et al.,* 2010[48] ME/CFS	<u>All of the following :</u> ≥ 6 months of persistent fatigue Post-exertional malaise and/ or post-exertional fatigue Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance ≥1 of myofascial and/or joint pain ≥2 neurological/cognitive manifestations <u>≥1 symptom from 2 of the following 3 categories:</u> 1. Autonomic manifestations, 2. Neuroendocrine manifestations 3. Immune manifestation	≥6 months, persistent or recurring chronic fatigue that is not lifelong and results in substantial reductions in previous levels of occupational, educational, social, and personal activities.	Post-exertional malaise and/ or post-exertional fatigue. With activity there must be a loss of physical or mental stamina, rapid/sudden muscle or cognitive fatigability, post-exertional malaise and/or fatigue and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 2-24 hours or longer.	Unrefreshing sleep or disturbance of sleep quantity or rhythm disturbance. May include unrefreshing sleep, prolonged sleep (including frequent naps), disturbed sleep (e.g., inability to fall asleep or early awakening) and/or day/night reversal.

Case Definition Statements	Pain	Neurological/cognitive
Reeves, *et al.,* 2005[49] CFS	Nothing noted	Nothing noted
Revised Canadian ≥6 months Jason, *et al.,* 2010[48] ME/CFS	Pain (or discomfort) that is often widespread and migratory in nature. <u>≥1 symptom from any of the following:</u> Myofascial and/or joint pain, myofascial pain can include deep pain, abdomen/stomach pain, or achy and sore muscles. Pain, stiffness, or tenderness may occur in any joint but must be present in ≥1 joint and lacking edema or other signs of inflammation. Abdominal and/or head pain. May experience stomach pain or chest pain. Headaches often described as localized behind the eyes or in the back of the head. May include headaches localized elsewhere, including migraines. Headaches would need to be more frequent than they were before, which would indicate new pattern, of a new type as compared to headaches previously experienced, or different in severity type as compared to headaches previously experienced by the patient.	<u>≥2 neurological/cognitive manifestations:</u> Impaired memory (self-reported or observable disturbance in ability to recall information or events on a short-term basis); difficulty focusing vision and attention (disturbed concentration may impair ability to remain on task, to screen out extraneous/excessive stimuli); loss of depth perception; difficulty finding the right word; frequently forget what wanted to say; absent mindedness; slowness of thought; difficulty recalling information; need to focus on one thing at a time; trouble expressing thought; difficulty comprehending information; frequently lose train of thought; sensitivity to bright lights or noise; muscle weakness/muscle twitches

Case Definition Statements	Other Criteria	Additional Considerations
Reeves, *et al.,* 2005[49] CFS	-Presence of 4 of 8 case-defining symptoms (by answering “all of the time or most of the time” to questions about symptoms, e.g. “during the past month how often have you had a sore throat?)” -Functional impairment defined as score <25th percentile of the SF-36 on the physical function (<70), or role physical (<50), or social function (<75), or role emotional (<66.7) -Reporting >4 symptoms and scoring >25 on the Symptom Inventory Case Definition Subscale	None
Revised Canadian ≥6 months Jason, *et al.,* 2010[48] ME/CFS	≥1 symptom from 2 of the following 3 categories: 1. Autonomic manifestations: neurally mediated hypotension, postural orthostatic tachycardia, delayed postural hypotension, palpitations with or without cardiac arrhythmias, dizziness or fainting, feeling unsteady on the feet--disturbed balance, shortness of breath, nausea, bladder dysfunction, or irritable bowel syndrome. 2. Neuroendocrine manifestations recurrent feelings of feverishness and cold extremities, subnormal body temperature and marked diurnal fluctuations, sweating episodes, intolerance of extremes of heat and cold, marked weight change-loss of appetite or abnormal appetite. 3. Immune manifestations: recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation--generally minimal swelling noted, new sensitivities to food, odors, or chemicals.	None

Case Definition Statements	General Diagnostic Criteria	Fatigue	Post-Exertional Malaise	Sleep
International Consensus Statement Carruthers, *et al.,* 2011[3] ME	A. Post-exertional neuroimmune exhaustion: cardinal B. Neurological impairments ≥ 1 from 3 of the 4 symptom categories: 1. Neurocognitive impairments 2. Pain 3. Sleep disturbance 4. Neurosensory, perceptual, and motor disturbances C. Immune, gastrointestinal, and genitourinary impairments ≥1 symptom from ≥3 of the following: 1.Flu-like symptoms 2. Susceptibility to viral infections 3.Gastrointestinal symptoms 4.Gentourinary symptoms 5. Sensitivities to food, medications, odors or chemicals D. Energy production/ transportation impairments: ≥1 1. Cardiovascular – orthostatic, etc. 2. Respiratory – shortness of breath, etc. 3. Thermostatic instability 4. Temperature intolerance	≥1 Symptom: 1. Cardiovascular: e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic Tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/ dizziness 2. Respiratory: e.g. air hunger, labored breathing, fatigue of chest wall muscles 3. Loss of thermostatic stability: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities 4. Intolerance of extremes of temperature	1. Marked, rapid physical and/ or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse 2. Post-exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms. 3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days. 4. Recovery period is prolonged, usually taking 24 hour longer. A relapse can last days, weeks or longer. 5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.	≥1 from Sleep, Pain, or Neurological/cognitive categories: Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams /nightmares b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness

Case Definition Statements	Pain	Neurological/cognitive
International Consensus Statement Carruthers, et al., 2011[3] ME	≥1 from Sleep, Pain, or Neurological/cognitive categories: Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is non-inflammatory in nature and often migrates. e.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain	≥1 from Sleep, Pain, or Neurological/cognitive categories: 1. Neurocognitive impairments: a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory 2. Neurosensory, perceptual and motor disturbances a. Neurosensory and perceptual: e.g. inability to focus vision, sensitivity to light, noise, vibration, odor, taste and touch; impaired depth perception b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia

Case Definition Statements	Other Criteria	Additional Considerations
International Consensus Statement Carruthers, et al., 2011[3] ME	Immune, gastrointestinal and genitourinary impairments; ≥1 symptom from ≥3 of the following: 1. Flu-like symptoms typically worsen with exertion e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation 2. Susceptibility to viral infections with prolonged recovery periods 3. Gastro-intestinal tract: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome 4. Genitourinary: e.g. urinary urgency or frequency, nocturia 5. Sensitivities to food, medications, odors or chemicals	None

Abbreviations: CDC= Centers for Disease control and Prevention; CFS= chronic fatigue syndrome; e.g.= example; etc.= etcetera; ME= myaligic encephalomyelitis; MFI-20=Multidimensional Fatigue Inventory, 20-item; SF-36= 36-item Short Form Survey.

Appendix J. Standardized Measures Tables

Table J1. Standardized measures used in evaluation of case definitions of ME/CFS

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Beck Depression Inventory[1]	BDI	Self-reported multiple-choice inventory of 21-questions for measuring the severity of depression. Scores of 0-9 indicate minimal depression, 10-18 mild depression, 19-29 moderate depression, 30-63 severe depression.	Validated in population receiving treatment for CFS[2]
Brief Coping Orientation to Problems Experienced Scale[3]	bCOPE	28 questions that cover 14 coping strategies as potential responses to stressors: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. Each item scored on 1-4 scale (1=haven't been doing this at all and 4=have been doing this a lot), each coping strategy is scored 2-8.	None
Chronic Fatigue Syndrome Medical Questionnaire[4]		Single item of questionnaire: rate the severity of your post-exertional malaise over the past 6 months using scale of 0-100, with lower scores indicating less severity.	Developed for CFS population
Chronic Fatigue Symptoms Checklist[5,6]	CFSC	Self-reported set of 40 symptoms, 30 thought to be typical of CFS symptoms and 10 considered atypical. Each item is scored 0-4, with 0=never suffer from it; 1=mild or rare symptoms during the last month causing minor disruption; 2=moderate or frequent symptoms during the last month causing major disruption; 3=severe or very frequent symptoms during the last month unable to perform usual activities; and 4=suffered from it previously for ≥1 month but not now.	Designed for CFS patients
Cognitive Failures Questionnaire[7]	CFQ	The CFQ measure self-reported failures in perception, memory and motor function over the previous 6-months. It consists of 25 items, each graded on a scale of 5 point Likert-scale, total scores are calculated by adding the individual item scores. Final scores range from 0-100, lower scores indicate better health.	None
Fatigue Impact Scale [8]	FIS	Self- reported instrument of fatigue impact on 40-items subdivided into 3 subscales, cognitive functioning (10-items), physical functioning (10-items), and psychosocial functioning (20-items). Each item is rated from 0 (no problem) to 4 (extreme problem), with a maximum score of 160.	Validated in population who had experienced ≥6 months of fatigue[8]
General Health Questionnaire[9]	GHQ	A 60-item questionnaire to screen individuals for psychiatric disorders, scores are given as means and scores above 3 indicate disorders; a 30-item version of the same questionnaire uses a threshold of 6 to indicate general psychological distress.	None
Hospital Anxiety and Depression Scale[10]	HADS	Self-reported scale of 14-items for the detection of depression and anxiety in hospitalized patients. Scores range from 1-21 interpreted as: normal (0-7), mild (8-10), moderate (11-14), severe (15-21). Subscales for anxiety (HADS-A) and depression (HADS-D).	Validated in patients identified using CDC (Fukuda, 1994) criteria[11]

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Karnofsky Performance Scale[12]	KPS	Descriptive ordinal scale that measures the patient's ability to carry on normal activities/the degree of assistance required. The scale range is comprised of 10-point intervals from 0-100, where 0=dead and 100=normal, no complaints or evidence of disease. Score thresholds: 80-100=normal health; 50-80=an inability to work, with a varying amount of assistance needed at home; 10-40=an inability for self care requiring the equivalence of institutional care	Validated in patients with chronic pain, but not specifically CFS[13]
Multidimensional Fatigue Inventory[14]	MFI-20	Self-reported instrument used to measure fatigue consisting of 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each subscale has 4 statements regarding levels of fatigue experienced in the previous days (20 total) rated on a Likert-type scale from 1-5 for a final subscale score of 4-20, lower scores indicate less fatigue.	Validated in those with >12 months of fatigue[14] Validated in population self-reporting symptoms meeting CDC (Fukuda, 1994) criteria[15]
Modified Somatic Perception Questionnaire[16]	MSPQ	Self-reported 13-item scale for patients with chronic pain or disabilities, it is used to identify somatic complaints that may be associated with psychological responses such as anxiety or depression. Each item is scored 0-3 (0=not at all and 3=extremely could not have been worse) for a total score of 0-39 with lower scores indicated lower general somatic symptoms.	None
Orthostatic Grading Scale[17]	OGS	Self-reported 5-item scale assessing for symptoms of orthostatic intolerance because of orthostatic hypotension. Each item is scored 0-4, with total score of 0-20, with lower scores indicated better health.	None
Pennebaker Inventory of Limbic Languidness[18]	PILL	Self-reported 54-item questionnaire measures the tendency for someone to notice and report a broad array of physical symptoms and sensations. Each item scored from 0-4 (0=never or almost never experienced and 4=more than once a week) for a total score of 0-216 interpreted as: 0-21 below normal range; 22-66 well within normal range; 67-84slighly above average, within normal range; and ≥85 top 25%.	None
Sickness Impact Profile 8-items[19,20]	SIP-8	Self-reported measure of perceived impact of illness or disease on physical and psychosocial functioning, it can be self or interviewer administered. The 8 subscales used are home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work and recreation and pastimes. A total score is calculated by addition of the weights of items (range 0–5,799). Lower scores indicate better health.	None
36-item Short Form survey[21]	SF-36	Self-reported survey of 36 questions of patient health on 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The scale has a range from 0-100, with higher scores indicating better health.	Validated in those identified using CDC (Holmes, 1988) criteria[22,23]
Somatization Checklist [24]	None	Self-reported set of 39 physical symptoms derived from diagnostic interview schedule for making a DSM-III/III-R diagnosis of somatization disorder. Items were answered yes or no for current and lifetime symptoms.	None

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Symptom Checklist-90[25]	SCL-90	Self-reported checklist of 90 questions to assess psychological status in the following categories: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism.	None
Zung Self-Rating Depression Scale[26]	ZDS	Self-reported questionnaire of 20-items that rate affective, psychological, and somatic symptoms associated with depression. Each item is rated from 1 (a little of the time) to 4 (most of the time) with final scores ranging from 20-80, interpreted as: 20-44 normal, 45-59 mildly depressed, 60-69 moderately depressed, ≥70 severely depressed.	None

Abbreviations: BDI = Beck Depression Inventory; bCOPE = brief Coping Orientation to Problems Experienced scale; CDC = Centers for Disease Control and Prevention; CFS = Chronic Fatigue Syndrome; CFSC = chronic fatigue symptoms checklist; CFQ= Cognitive Failures Questionnaire; DSM III/III-R= Diagnostic and Statistical Manual third edition/third edition revised; GHQ = General Health Questionnaire; HADS = Hospital Anxiety and Depression Scale; HADS-A = anxiety subscale of HADS; HADS-D = depression subscale of HADS; KPS = Karnofsky Performance Scale; MFI-20 = Multidimensional Fatigue Inventory 20-Item; MSPQ = Modified Somatic Perception Questionnaire; PILL= Pennebaker Inventory of Limbic Languidness; SIP-8 = Sickness Impact Profile 8-Item; SF-36 = Short Form-36; SCL-90 = Symptom Checklist; ZDS = Zung Self-Rating Depression Scale.

Table J2. Standardized measures used to assess outcomes after interventions for ME/CFS

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Abbreviated Fatigue Questionnaire[27]	SFQ	Self-reported measure of fatigue consisting of 4 questions answered on a 7-point Likert-type scale. Final scores range from 4-28, with higher scores indicate lower levels of fatigue.	None
Clinical global impression change score[28]	CGI	Clinician-rated clinical global impression of change. Levels of improvement after intervention is rated on a 7 point Likert-type scale where 1=very much better and 7=very much worse. Note: Several studies had the patients self-report their ratings instead of a clinician.	None
Chalder Fatigue Scale[29]	None	Self-reported, 14- or 11-item fatigue scale. Items scored dichotomously on a 4-point scale (0,0,1,1), lower scores indicate better outcomes, total scores ≥4 designate clinically significant levels of fatigue. Note: Several different scoring methods are used for this scale.	Validated in those identified using Oxford (Sharpe, 1991) criteria[30] Validated in CFS patient meeting either Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) criteria[31]
Checklist of Individual Strength[19]	CIS	Self-reported questionnaire measuring several aspects of fatigue, 20-items, separated into 4 subscales: severity of fatigue (8-items), concentration problems (5-items), decrease motivation (4-items), and decreased physical activity (3-items). Each item is rated on a 7-point Likert-type scale for final scores of 20- 140. Lower scores indicate better health.	Validated in patients with >1 year self-reported fatigue unexplained by other diagnosis[19]
EuroQol Scale [32]	None	Measures health status, with scores ranging from 0=worst health status to 100=best health status.	Validated in population meeting Oxford (Sharpe, 1991) criteria[33]
Fatigue Impact Scale [8]	FIS	Self- reported instrument of fatigue impact on 40-items subdivided into 3 subscales, cognitive functioning (10-items), physical functioning (10-items, and psychosocial functioning (20-items). Each item is rated from 0 (no problem) to 4 (extreme problem), with a maximum score of 160.	Validated in population who had experienced ≥6 months of fatigue[8]
Fatigue Severity Scale[34]	FSS	Self-reported measure of fatigue, composed of 9-items rated on 7-point Likert-type scales, where 1=no fatigue-related impairment and 7=high impairment. Final scores range from 9-63, lowers scores indicate lower fatigue impairment.	Validated in patients with CFS like symptoms, but not formally diagnosed[35]
Fibromyalgia Impact Questionnaire[36]	FIQ	Self-reported 10-item measure that assesses the current health status of patients with fibromyalgia on physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and wellbeing. Each item has multiple questions scored on Likert-type scales, for a final score ranging from 0-100. Lower scores indicate better health.	None

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Karnofsky Performance Scale[12]	KPS	Descriptive ordinal scale that measures the patient's ability to carry on normal actives/the degree of assistance required. The scale range is comprised of 10-point intervals from 0-100, where 0=dead and 100=normal, no complaints or evidence of disease. Score thresholds: 80-100=normal health; 50-80=an inability to work, with a varying amount of assistance needed at home; 10-40=an inability for self care requiring the equivalence of institutional care	Validated in patients with chronic pain, but not specifically CFS[13]
Medical Outcome Study Short Form[37]	MOS-SF	Measures functioning and well being of 6 health concepts: physical functioning, social functioning role functioning, mental health, health perceptions, and bodily pain. Each area has varying numbers of items and are scored on scales from 1-100, with higher scores indicating better health.	Validated in patients with chronic conditions[38] Validated in those identified using Oxford (Sharpe, 1991) criteria[39]
Modified barthel's Activities of Daily Living index[40]	ADL	Self-reported measure that measures the patient's ability to preform 83 discrete activities of daily living. The maximum score is 100, higher scores indicate better health.	None
Multidimensional Fatigue Inventory[14]	MFI-20	Self-reported instrument used to measure fatigue consisting of 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each subscale has 4 statements regarding levels of fatigue experienced in the previous days (20 total) rated on a Likert-type scale from 1-5 for a final subscale score of 4-20, lower scores indicate less fatigue.	Validated in those with >12 months of fatigue[14] Validated in population self-reporting symptoms meeting CDC (Fukuda, 2004) criteria[15]
Profile of Mood States[41]	POMS	Self-reported scale used to assess transient mood states, consisting of 65 adjectives, separated into 6 subscales: tension-anxiety, depression-dejection, anger-hostility, fatigue, vigor, confusion. Each item is rated on a 5-point Likert-type scale, items for the subscales are combined with vigor scores subtracted for an overall score ranging from 0-200. For this review, only the fatigue and vigor subscales were included. The maximum score for the fatigue subscale is 28, and the maximum score for the vigor subscale is 32.	None
Quality of Life Index[42,43]	QLI	Self-reported questionnaire covering 34-items related to quality of life overall and in 4 subscales: health and functioning, social and economic, psychological/spiritual, and family. The first part of the questionnaire rates satisfaction with 34-items on a 6-point Likert-type scale ranging from very dissatisfied to very satisfied (-2.5 to 2.5 for analysis). The second part of the questionnaire rates the importance of these items from 1=very unimportant to 6=very important. Final scores for each subscales and the total scale range from 0-30 and are computed by weighting satisfaction responses with paired importance responses. Higher scores indicate higher life quality.	Used in CFS populations, but unclear if validated[44]

Measure	Abbreviation	Description	Validation studies in ME/CFS population
Quality of Life Inventory[45,46]	QOLI	Inventory of patient satisfaction and happiness in 17 (16 in the more recent version) areas of life potentially relevant to overall life satisfaction. Each area is first rated in terms of importance to overall happiness where 0=not at all important, 1=important, and 2=very important. The items are then rated in terms of the patient satisfaction with that area on a scale ranging from -3 (very dissatisfied) to 3 (very satisfied). The 2 scores are multiplied to produce weighted satisfaction ratings ranging from -6 to 6 and the overall life satisfaction score is obtained by averaging all weighted satisfaction ratings that have nonzero importance ratings. Higher scores indicate better health.	None
Quality of Life Scale[47]	QLS	16-items answered on a 7-point Likert-type scale which measures 6 conceptual domains of quality of life: material and physical well-being; relationships with other people; social, community and civic activities; personal development and fulfillment; recreation; and independence. Scored on a 16-113 scale, higher scores indicate better quality of life.	None
36-item Short Form Survey [21]	SF-36	Self-reported survey of 36 questions of patient health on 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The scale has a range from 0-100, with higher scores indicating better health. For this review, only the physical functioning and vitality subscales were included.	Validated in those identified using CDC (Holmes, 1988) criteria[22,23]
Short Form 12-Item Health Survey[48]	SF-12	A health survey with 12-items assessing physical and mental health. The survey yields 2 summary scores: the mental component summary and the physical component summary. Each summary score ranges from 0-100, higher scores indicate better health.	None
Sickness Impact Profile 8-items [19,20]	SIP-8	Self-reported measure of perceived impact of illness or disease on physical and psychosocial functioning, it can be self or interviewer administered. The 8 subscales used are home management, mobility, alertness behavior, sleep/rest, ambulation, social interactions, work and recreation and pastimes. A total score is calculated by addition of the weights of items (range 0–5,799). Lower scores indicate better health.	None
Work and social adjustment scale[49]	None	A 5-item questionnaire that measures impairment in in work, home management, social activities, and private leisure. Each item is measured on a 0-8 Likert-type scale where 8=maximum impairment. The scale is scored from 0-45.	Validated in CFS populations receiving treatment[50]

Abbreviations: ADL = Activities of Daily Living; CDC= Centers for Disease Control and Prevention; CFS= chronic fatigue syndrome; CGI= Clinical Global Impression Change Score; CIS= Checklist of Individual Strength; FIQ= Fibromyalgia Impact Questionnaire; FIS= Fatigue Impact Scale; FSS= Fatigue Severity Scale; KPS = Karnofsky Performance Scale; MFI-20=Multidimensional Fatigue Inventory; POMS= Profile of Mood States; QLI= Quality of Life Index; QLS= Quality of Life Scale; QOLI= Quality of Live Inventory; SF-36= Short Form-36; SF-12= Short-Form 12-Item Survey; SFQ= Abbreviated Fatigue Questionnaire; SIP-8= Sickness Impact Profile 8 items.

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Appendix K. Strength of Evidence

Table K1. Strength of evidence

Key Question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Treatment and harms								
a) What are the benefits of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?								
Galantamine vs. placebo								
Decreased fatigue	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Global improvement	1 RCT (n=423)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Hydrocortisone vs. placebo								
Improved overall function	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=65)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Hydrocortisone + fludrocortisone vs. placebo								
Improved overall function	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient

Key Question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Improved quality of life	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Immunoglobulin G vs. placebo								
Improved overall function	1 RCT (n=28)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Rintatolimod vs. placebo								
Improved overall function	1 RCT (n=84)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Increased exercise work capacity	2 RCT (n=316)	Medium	Direct	Consistent	Precise	Undetected	+	Low
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Valganciclovir vs. placebo								
Improved overall function	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Isoprinosine vs. placebo								
Improved overall function	1 RCT (n=15)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=15)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Key Question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Fluoxetine vs. placebo								
Improved overall function	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Acclydine vs. placebo								
Improved overall function	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Increased physical activity (actometer)	1 RCT (n=57)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination								
Decreased fatigue	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Global improvement	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved overall function and quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Pollen extract vs. placebo								
Decreased fatigue	1 RCT (n=22)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life	1 RCT (n=22)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient

Key Question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Low sugar/low yeast diet vs. healthy eating								
Decreased fatigue	1 RCT (n=39)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life	1 RCT (n=39)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved overall function, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Distant healing vs. no treatment								
Improved overall function	1 RCT (n=409)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>[ll]	Insufficient
Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Homeopathy vs. placebo								
Improved overall function	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	-	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
Melatonin vs. phototherapy								
Improved overall function	1 RCT crossover design (n=30)	High	Direct	Consistency unknown (single study)	imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT crossover design (n=30)	High	Direct	Consistency unknown (single study)	imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing								
Improved overall function	11 RCT (n=1,441) 8 pooled	Medium	Direct	Inconsistent	Precise	Undetected	SF-36 physical function WMD 7.73 (95% CI 3.58 to 11.87)	Low
Decreased fatigue	11 RCT (n=1,439)	Medium	Direct	Consistent	Precise	Undetected	+[†]	Low
Improved quality of life	4 RCT (n=343)	Medium	Direct	Inconsistent	Imprecise	Undetected	<>[‡]	Low
Increased proportion working full- or part-time	2 RCT (n=145)	Medium	Direct	Consistent	Imprecise	Undetected	<>	Low
Increased hours worked	2 RCT (n=125)	Medium	Direct	Inconsistent	Imprecise	Undetected	<>[§]	Low
Decreased work impairment	2 RCT (n=531)	Medium	Direct	Consistent	Precise	Undetected	+	Low
Global improvement	2 RCT (n=531)	Medium	Direct	Consistent	Precise	Undetected	+	Moderate
Face-to-face CBT vs. telephone CBT								
Improved overall function	1 RCT (n=43)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased fatigue	1 RCT (n=43)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased work impairment	1 RCT (n=43)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Global improvement	1 RCT (n=43)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing								
Improved overall function	4 RCT (n=619) 3 pooled	Medium	Direct	Consistent	Precise	Undetected	SF-36 physical function WMD 10.29 (95%CI, 6.71 to 13.88)	Moderate
Decreased fatigue	4 RCT (n=619)	Medium	Direct	Consistent	Imprecise	Undetected	+[††]	Low
Increased proportion working full- or part-time	1 RCT (n=59)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased work impairment	1 RCT (n=475)	Low	Direct	Consistency unknown (single study)	Precise	Undetected	+	Low
Global improvement	3 RCT (n=583) 3 pooled	Medium	Direct	Consistent	Precise	Undetected	Mean CGI scores RR 1.58 (95% CI, 1.25 to 1.98)	Moderate
Recovery (Chalder fatigue score <18, SF-36 physical function score >60, no longer meeting Oxford case definition criteria, and reporting much or very much improvement on CGI)	1 RCT (n=475)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school	No studies							Insufficient
Home orthostatic training vs. sham home orthostatic training								
Improved overall function	1 RCT (n=36)	High	Imprecise	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Decreased fatigue	1 RCT (n=36)	High	Imprecise	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Qigong exercise vs. no qigong exercise								
Improved overall function	1 RCT (n=52)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+[¶]	Insufficient
Decreased fatigue	1 RCT (n=52)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
GET vs. fluoxetine vs. combination or placebo								
Improved overall function	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Precise	Undetected	+	Insufficient
Decreased fatigue	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Precise	Undetected	+	Insufficient
Increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
CBT + GET vs. usual care								
Improved overall function	1 RCT (n=115)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Decreased fatigue	1 RCT (n=115)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Improved quality of life, increased days spent at work/school and proportion working full- or part-time	No studies							Insufficient
b) What are the harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?								
Galantamine vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals, serious harms, and total harms	1 RCT (n=434)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Hydrocortisone vs. placebo								
Withdrawals due to harms, serious harms, other harms	1 RCT (n=70)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	-	Insufficient
Rates of harms, total withdrawals, total harms	No studies							Insufficient
Hydrocortisone + fludrocortisone vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=80)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies	No studies						Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Immunoglobulin G vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=28)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>‡‡	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Rintatolimod vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	2 RCT (n=324)	Medium	Direct	Inconsistent	Imprecise	Undetected	Mixed[§§]	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Valganciclovir vs. placebo								
Withdrawals due to harms, serious harms, other harms, total harms	1 RCT (n=30)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Isoprinosine vs. placebo								
Withdrawals due to harms	1 RCT (n=15)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Fluoxetine vs. placebo								
Total withdrawals	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Withdrawal due to harms	1 RCT (n=68)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Acclydine vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination								
Withdrawals due to harms	1 RCT (n=89)	High	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms, total withdrawals	No studies							Insufficient
Pollen extract vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Low sugar/low yeast diet vs. healthy eating								

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Distant healing vs. no treatment								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
Homeopathy vs. placebo								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Melatonin vs. phototherapy								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
CBT/counseling vs. no treatment or support or relaxation or adaptive pacing								
Withdrawals due to harms	1 RCT (n=47)	Low	Indirect	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Rates of harms	1 RCT (n=257)	Low	Indirect	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Total harms	2 RCT (n=728)	Low	Direct	Consistent	Imprecise	Undetected	<>	Low
Serious harms	2 RCT (n=728)	Low	Direct	Inconsistent	Imprecise	Undetected	<>	Low
Face-to-face CBT vs. telephone CBT								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing								
Withdrawals due to harms	1 RCT (n=49)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Total harms	2 RCT (n=524)	Medium	Direct	Consistent	Imprecise	Undetected	<>	Insufficient
Serious harms	1 RCT (n=475)	Low	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Home orthostatic training vs. sham home orthostatic training								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
Qigong exercise vs. no qigong exercise								
Total harms	1 RCT (n=52)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	<>	Insufficient
Withdrawals due to harms and rates of harms	No studies							Insufficient

Key question outcome	Study design/ number of studies (n)	Study limitations	Directness	Consistency	Precision	Reporting bias	Overall effect	Strength of evidence/ grade
GET vs. fluoxetine vs. combination or placebo								
Total withdrawals	1 RCT (n=136)	Medium	Direct	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Rates of harms and total harms	No studies							Insufficient
CBT + GET vs. usual care								
Withdrawals due to harms, rates of harms, total withdrawals	No studies							Insufficient
c) What are the characteristics of responders and non-responders to interventions?								
CBT vs. no treatment								
Baseline differences	1 RCT (n=27)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
GET vs. usual care								
Mediating factors affecting response to GET	1 RCT (n=49)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
CBT vs. cognitive therapy, vs. anaerobic therapy vs. relaxation								
Energy envelope comparisons	1 RCT (n=81)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient
Pragmatic rehabilitations vs. supportive listening								
Baseline differences	1 RCT (n=257)	Medium	Indirect	Consistency unknown (single study)	Imprecise	Undetected	+	Insufficient

Key: + = positive effect; <> = no effect; - = negative effect.

*5 studies showed overall positive effect, while 2 showed mixed effects using different measures, 1 showed negative effect, and 4 showed no effect.

†9 studies showed positive effects, while 3 showed no effect.

‡2 studies showed positive effects, 2 showed no effect, and 1 showed a positive effect vs. support but not vs. no treatment.

§Significant increase in 1 of 3 trials, 1trial reported a significant increase vs. support but not vs. no treatment.

‖ For those blinded to treatment only, not for comparison of intervention groups.

¶Intervention scored better on mental functioning subscale, but not physical functioning subscale.

**2 of 4 studies showed a benefit, for the intervention group, while 2 showed no differences.

[††]3 of 4 studies showed a benefit for the intervention group, while 1 showed no differences.

[‡‡]More headaches in intervention group, but no other differences.

[§§]Some harms more frequent in intervention group, insomnia more frequent in placebo group, see Appendix G4 for details.

Abbreviations: CBT= cognitive behavioral therapy; CFS= chronic fatigue syndrome; CI= confidence interval; CGI= Clinical Global Impression of Change score; GET= graded exercise treatment; ME= myaligc encephalomyelitis; n= sample size; RCT= randomized controlled trial; RR= relative risk; SF-36= 36-item Short Form Survey; WMD= weighted mean difference; vs.= versus.