

Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): An Updated Systematic Evidence Review

A DRAFT Systematic Evidence Review prepared for:
Centers for Disease Control and Prevention
December 7, 2020

Investigators:

Roger Chou, MD, FACP
Marian McDonagh, Pharm.D.
Jessica C. Griffin, MS
Sara Grusing, BA



Pacific Northwest Evidence-based Practice Center

Roger Chou, MD, Director

Marian McDonagh, PharmD, Co-Director

Copyright © 2020 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

Structured Abstract

Objectives. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) can have profound effects on function and quality of life. This report updates a 2014 Agency for Healthcare Research Quality (AHRQ)-funded review in order to synthesize the evidence on evaluation and management of ME/CFS. It also expands upon the prior AHRQ review by including children as well as adults, evaluating harms as well as benefits of diagnosis, and evaluating effects of treatment on depression, anxiety, sleep quality, pain, and other symptoms associated with ME/CFS in addition to fatigue, function, and quality of life.

Data Sources. MEDLINE (1988 to January 2019), PsycINFO (1988 to January 2019), Embase (through January 2019) and the Cochrane Library (through January 2019); supplemented by review of reference lists and the 2014 AHRQ review.

Review Methods. Articles were selected for review if they included: 1) evaluation of patients with fatigue, 2) diagnosis of ME/CFS, or 3) treatments (pharmacological, nonpharmacological, dietary, or complementary and alternative therapies) of ME/CFS. We abstracted data on the frequency of non-ME/CFS conditions in patients presenting with fatigue; benefits and harms of diagnosis of ME/CFS versus non-diagnosis; and benefits and harms of treatments. Two investigators reviewed abstracts and full-text articles for inclusion based on predefined criteria. Risk of bias was assessed using predefined criteria. Discrepancies were resolved through discussion and consensus, with a third investigator if needed. Random effects meta-analyses were conducted on trials of exercise and cognitive therapy; where evidence was unsuitable for combining, it was synthesized qualitatively. The strength of evidence was assessed using methods recommended by the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.

Results. We identified 4,951 potentially relevant articles, selected 636 for full-text review, and included 72 studies in 91 publications (1 systematic review and 5 observational studies on diagnosis and 66 trials of treatments). A systematic review of patients with fatigue or tiredness in primary care settings found that the most common non-ME/CFS conditions were depression (18.5%), serious somatic diseases (4.3%), anemia (2.8%), and malignancy (0.6%). In specialty settings of patients referred for evaluation of possible ME/CFS, the most common non-ME/CFS conditions were psychological (15% to 51%) and sleep disorders (6% to 30%). No study evaluated benefits or harms of ME/CFS diagnosis versus non-diagnosis.

Sixty-six trials evaluated treatments for ME/CFS. Thirty-three trials were included in the prior AHRQ report and 33 trials were new since the prior report. CBT and exercise therapy were associated with improved fatigue, function, and other outcomes versus inactive control therapies, but the magnitude of effects based on average benefits was small to moderate. These trials demonstrated unexplained statistical heterogeneity in pooled estimates and contained methodological limitations. Additionally, the applicability of findings to patients with severe ME/CFS diagnosed using more current, specific case definitions was uncertain. Other pharmacological, nonpharmacological, dietary, and complementary and alternative therapies were ineffective, or evidence of effectiveness was too limited to guide clinical practice. Reporting of harms across trials was suboptimal, with limited evidence that exercise and CBT were not associated with increased risk of serious adverse events or worsening of symptoms. In

adolescents with ME/CFS, limited evidence found CBT (family based or involving parents) associated with improved function and school attendance versus inactive therapies, but differences were not statistically significant.

Limitations. Treatment trials had methodological limitations. Most interventions and comparisons were evaluated in few trials, most trials used older ME/CFS case definitions, and there was limited information on how key characteristics and subgroups of patients impacted outcomes. There was unexplained statistical heterogeneity in meta-analyses, study inclusion was restricted to English language publications and formal methods for determining small sample effects were not performed due to small numbers of studies.

Conclusions. Evidence on effective treatments for ME/CFS remains limited. Although graded exercise and CBT were more effective than inactive control therapies (usual care, usual specialist care, or an attention control) in improving fatigue, function, and other outcomes, the magnitude of effects was small to moderate and methodological and other limitations (imprecision, inconsistency, uncertain generalizability) precluded strong conclusions. Other therapies were not shown to be effective or require additional evidence to verify effectiveness. Non-ME/CFS conditions were common in patients presenting with fatigue.

Contents

Introduction.....	1
Background.....	1
Purpose.....	5
Methods.....	5
Topic Development and Refinement	5
Data Sources and Searches	6
Process for Study Selection	6
Inclusion criteria	6
Data Extraction and Data Management	7
Risk of Bias of Individual Studies Assessment	7
Assessing Research Applicability.....	8
Data Synthesis.....	8
Grading the Body of Evidence for Each Key Question.....	10
Peer Review and Public Commentary	10
Results.....	11
Results of Literature Searches	11
Key Question 1. In patients undergoing evaluation for possible ME/CFS, what is the frequency of non-ME/CFS conditions?	12
Key Points.....	12
Detailed Synthesis.....	12
Key Question 2. What are the benefits and harms of diagnosing ME/CFS vs. non-diagnosis?	16
Key Points.....	16
Detailed Synthesis.....	16
Key Question 3. What are the benefits and harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?.....	17
Key Question 3a. Interventions for treating ME/CFS Key Question 3b. Interventions for treating symptoms commonly present in persons with ME/CFS (poor sleep, orthostatic intolerance, pain, fatigue, cognitive problems, depression, multiple chemical sensitivity, gastrointestinal symptoms, urinary symptoms, etc.).....	17
Key Points.....	17
Exercise Therapy	18
Cognitive behavioral therapy.....	17
Other behavioral approaches.....	18
Medications.....	18
Dietary interventions, herbal supplements or homeopathy.....	18
Complementary and alternative therapies.....	19
Detailed Synthesis.....	19
Exercise therapy.....	19
Exercise versus inactive controls.....	30
Exercise versus active interventions	40
Other exercise therapies	61
Cognitive behavioral therapy.....	61
Cognitive behavioral therapy versus inactive controls	71
CBT versus active interventions	82

One method of CBT delivery versus another	101
Other behavioral approaches in adults	101
CBT in adolescents	106
CBT versus inactive controls in adolescents	110
Cognitive behavioral therapy plus biofeedback versus biofeedback	114
Cognitive therapy and education versus pacing.....	114
Other behavioral approaches in adolescents	115
Other therapies	115
Medications.....	115
Immune Modulators.....	126
Antidepressants	129
Other Drugs.....	131
Subgroup effects	133
Complementary and alternative therapies.....	133
Dietary interventions, herbal supplements, or homeopathy.....	133
Qigong, yoga, or abdominal tuina.....	143
Distant healing versus no treatment.....	144
Discussion	149
Limitations	159
Future Research	160
Conclusions.....	160
References.....	161
Abbreviations and Acronyms	169
Key Informants	172

List of Tables

Table 1. Commonly used case definitions or diagnostic criteria	3
Table 2. Studies reporting diagnosis rates for ME/CFS and non-ME/CFS conditions	14
Table 3. Exercise therapy RCTs: Study characteristics	20
Table 4. Exercise therapy RCTs: Study results	25
Table 5. Exercise vs. inactive controls: Summary of stratified results	38
Table 6. Exercise versus active interventions: Summary of stratified results	44
Table 7. Cognitive Behavioral Therapy RCTs: Study Characteristics	63
Table 8. Cognitive Behavioral Therapy RCTs: Study Results	67
Table 9. Cognitive behavioral therapy vs. inactive controls.....	80
Table 10. CBT versus active interventions: Summary of stratified results	85
Table 11. RCTs of behavioral approaches in adults: Study characteristics	103
Table 12. RCTs of behavioral approaches in adults: Study results	105
Table 13. RCTs of CBT and behavioral approaches in adolescents: Study Characteristics.....	107
Table 14. RCTs of CBT and behavioral approaches in adolescents: Study results.....	109
Table 15. CBT versus inactive controls in adolescents: Summary of results	114
Table 16. Medication RCTs: Study Characteristics.....	117
Table 17. Medication RCTs: Study results	121
Table 18. RCTs of dietary interventions, herbal supplements, or homeopathy: Study Characteristics	135
Table 19. RCTs of dietary interventions, herbal supplements, or homeopathy: Study Results .	138

Table 20. RCTs of Qigong, yoga, abdominal tuina, or distant healing: Study Characteristics ..	145
Table 21. RCTs of Qigong, yoga, abdominal tuina, or distant healing: Study Results	147
Table 22. Summary of Evidence.....	153

List of Figures

Figure 1. Literature flow diagram.....	11
Figure 2. Fatigue severity: Graded exercise versus inactive control at end of intervention.....	31
Figure 3. Fatigue severity: Graded exercise versus inactive control at post-intervention follow-up	31
Figure 4. Functional impairment: Graded exercise versus inactive control at end of intervention	33
Figure 5. Functional impairment: Graded exercise versus inactive control at post-intervention follow-up	33
Figure 6. Likelihood of functional improvement: Graded exercise versus inactive control	34
Figure 7. Depression severity: Graded exercise versus inactive control at end of intervention...	35
Figure 8. Anxiety severity: Graded exercise versus inactive control at end of intervention	35
Figure 9. Sleep quality: Graded exercise versus inactive controls at end of intervention	36
Figure 10. Sleep quality: Graded exercise versus controls at post-intervention follow-up.....	36
Figure 11. Likelihood of recovery: Graded exercise versus inactive control	37
Figure 12. Fatigue severity: Graded exercise versus active intervention at end of intervention ..	47
Figure 13. Fatigue severity: Graded exercise versus active intervention at post-intervention follow-up.....	48
Figure 14. Functional impairment: Graded exercise versus active intervention at end of intervention	49
Figure 15. Functional impairment: Graded exercise versus active intervention at post-intervention follow-up	50
Figure 16. Depression severity: Graded exercise versus active intervention at end of intervention	51
Figure 17. Depression severity: Graded exercise versus active intervention at post-intervention follow-up	52
Figure 18. Anxiety severity: Graded exercise versus active intervention at end of intervention .	53
Figure 20. Sleep: Graded exercise versus active intervention at end of intervention.....	54
Figure 21. Sleep: Graded exercise versus active intervention at post-intervention follow-up	54
Figure 22. Pain: Graded exercise versus active intervention at post-intervention follow-up.....	55
Figure 25. Likelihood of functional improvement: Graded exercise versus active interventions	58
Figure 26. Likelihood of recovery: Graded exercise versus active interventions.....	59
Figure 27. Likelihood of serious adverse event: Graded exercise versus active intervention	60
Figure 28. Likelihood of withdrawal due to adverse event: Graded exercise versus active intervention.....	60
Figure 29. Likelihood of function worsening: Graded exercise versus active intervention	61
Figure 30. Fatigue severity: CBT versus inactive controls at end of treatment.....	72
Figure 31. Fatigue severity: CBT versus inactive controls at post-intervention follow-up.....	73
Figure 32. Likelihood of fatigue improvement: CBT versus inactive controls	73
Figure 33. Functional impairment: CBT versus inactive controls at end of treatment.....	75
Figure 34. Functional impairment: CBT versus inactive controls at post-intervention follow-up	75

Figure 35. Likelihood of functional improvement: CBT versus inactive controls	76
Figure 36. Depression severity: CBT versus inactive controls at end of treatment.....	77
Figure 37. Depression severity: CBT versus inactive controls at post-intervention follow-up....	77
Figure 38. Anxiety severity: CBT versus inactive controls at post-intervention follow-up.....	78
Figure 39. Likelihood of recovery: CBT versus inactive controls.....	79
Figure 40. Six-minute walk test: CBT versus inactive controls at post-intervention follow-up ..	80
Figure 41. Fatigue severity: CBT versus active interventions at end of treatment.....	87
Figure 42. Fatigue severity: CBT versus active interventions at post-intervention follow-up.....	88
Figure 43. Functional impairment: CBT versus active interventions at end of treatment	89
Figure 44. Functional impairment: CBT versus active interventions at post-intervention follow-up	90
Figure 45. Depression severity: CBT versus active interventions at end of treatment.....	91
Figure 46. Depression severity: CBT versus active interventions at post-intervention follow-up	91
Figure 47. Anxiety severity: CBT versus active interventions at post-intervention follow-up	92
Figure 48. Sleep: CBT versus active interventions at post-intervention follow-up.....	93
Figure 49. Pain: CBT versus active interventions at post-intervention follow-up	94
Figure 50. Six-minute walk test: CBT versus active interventions at end of treatment	95
Figure 51. Likelihood of fatigue improvement: CBT versus active interventions	95
Figure 52. Likelihood of functional improvement: CBT versus active interventions	97
Figure 53. Likelihood of recovery: CBT versus active interventions.....	98
Figure 54. Likelihood of serious adverse event: CBT versus active interventions	99
Figure 55. Likelihood of withdrawal due to adverse event: CBT versus active interventions ...	100
Figure 56. Likelihood of worsening function: CBT versus active interventions.....	100
Figure 57. Fatigue severity in adolescents: CBT versus inactive controls	111
Figure 58. Likelihood of functional improvement in adolescents: CBT versus inactive controls	112
Figure 59. Likelihood of school attendance: CBT versus inactive controls.....	113

List of Appendices

- Appendix A. Search Strategies
- Appendix B. Inclusion and Exclusion Criteria
- Appendix C. List of Included Studies
- Appendix D. List of Excluded Studies
- Appendix E. Evidence Tables
- Appendix F. Risk of Bias Tables
- Appendix G. Abbreviations and Acronymns

Introduction

This report was commissioned by the Centers for Disease Control and Prevention (CDC) to inform the development of a guideline on evaluation and management of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). It builds upon and updates a 2014 Agency for Healthcare Research and Quality (AHRQ) review that was conducted to support a National Institutes of Health Pathways to Prevention conference.¹

Background

ME/CFS is a condition characterized by a constellation of symptoms; hallmarks of ME/CFS are post-exertional malaise and/or persistent and disabling fatigue, as well as various additional manifestations, including pain, sleep disturbance, orthostatic intolerance, motor impairment, neurological and cognitive manifestations (i.e., impaired concentration, mental processing, and memory), and altered immune and autonomic responses.²⁻⁵ ME/CFS often follows a relapsing and remitting course and may result in reduced quality of life and loss of independence.¹ In 2015, the Institute of Medicine (IOM) recommended renaming the condition to systemic exertion intolerance disease.⁵ However, the terms ME and CFS continue to be used, and will be used in this report.

Although similar symptom clusters were reported as early as the 1930s, the term “myalgic encephalomyelitis (ME)” was first used to describe the condition in the 1950s and ME was recognized by the World Health Organization as a disease entity in the 1960s.⁶ The term “chronic fatigue syndrome (CFS)” was coined in the 1980s after research failed to identify a clear viral association in what was previously labeled chronic Epstein-Barr virus syndrome.⁷⁻¹⁰ Although the terms ME and CFS are often used together or interchangeably, ME may be considered a subset of CFS or its own distinct disease.

Many case definitions for ME and CFS have been proposed (Table 1 shows commonly used case definitions and the names we used to refer to them in this report). The first case definition for ME/CFS was published in 1988.⁸ Other case definitions have been introduced over the years, including the 1994 Fukuda criteria,⁴ the 2003 Canadian clinical case definition,² and the 2011 international consensus criteria.³ The 2011 international consensus report advocates for use of the term ME over CFS, to better reflect an underlying pathophysiology involving widespread inflammation and neuropathology, though this position has not been accepted by all.³ The proposed IOM definition for systemic exertion intolerance disease requires substantial reduction or impairment in ability to engage in pre-illness levels of activity; post-exertional malaise; unrefreshing sleep; and either cognitive impairment or orthostatic intolerance.⁵ The use of multiple case definitions for ME/CFS is an ongoing challenge in the field, as it has resulted in heterogeneous populations in the research literature. For example, a systematic review found that median ME/CFS prevalence was fifteen times higher in studies that used the earlier Oxford case definition (1.5%) compared with those that used the Canadian case definition.¹¹ As noted in the prior AHRQ report, studies have not been able to determine the accuracy of different ME/CFS case definitions, due to the lack of a reliable and universally accepted reference (“gold”) standard.^{1,11}

The IOM report estimates ME/CFS prevalence in the U.S. between 836,000 and 2.5 million.⁵ However, the prevalence of ME/CFS is difficult to estimate given the uncertainty and variability in case definitions and differences in study methodology. Even with these challenges in

estimating ME/CFS prevalence, it is estimated that as many as 84 to 91 percent of persons with ME/CFS have not been diagnosed.⁵ ME/CFS is more common among women than men, with an average age at diagnosis of between 30 and 40 years of age.¹² The prevalence of ME/CFS and pattern of symptoms in children appears similar to adults, though in children an antecedent acute flu- or mononucleosis-like syndrome is more frequently present and the prognosis appears to be more favorable.¹³⁻¹⁵ Data suggest that about 40 percent (8 to 63%) of adult patients with ME/CFS improve but only 5 percent (0 to 31%) fully recover,¹⁶ compared to recovery in over 50 percent of children within 6 months.¹⁴

The goal of treatment for ME/CFS is to reduce symptoms and improve function. Although a number of medications have been used to treat ME/CFS, no medication is approved by the U.S. Food and Drug Administration (FDA) for ME/CFS. Treatments for ME/CFS fall into two broad categories: those intended to treat the underlying cause of the disease (pathogenesis-based therapies) and those targeting ME/CFS symptoms (symptom-based therapies).¹⁷ The first category includes immune modulators (e.g., rintatolimod, immunoglobulin, rituximab, and corticosteroids), antiviral and antibiotic medications, and other medications. Symptom-based therapies include medications to treat fatigue, sleep dysfunction, pain, mood disorders, and other symptoms associated with ME/CFS, as well as non-drug therapies such as yoga, stretching and relaxation techniques, mindfulness based training, graded exercise, pacing strategies, cognitive behavioral and other psychological therapies, dietary supplements and interventions, and various complementary and alternative therapies.¹⁷ In practice, there are wide variations in the clinical management of patients with ME/CFS, and many patients receive multiple therapies in various combinations and sequences.

The prior AHRQ report found limited evidence that graded exercise therapy (GET) and counseling therapies (primarily cognitive behavioral therapy [CBT]) were associated with beneficial effects on fatigue and function in some patients, but found that these therapies had not been adequately tested in patients with more severe ME/CFS identified by more current case definitions.¹ It also found limited evidence that rintatolimod was associated with improved exercise performance in some patients. There was insufficient evidence to determine the effectiveness of other therapies. The CDC commissioned a review to incorporate new research and address research gaps identified in the 2014 AHRQ report.

Table 1. Case definitions or diagnostic criteria

Case Definition Or Diagnostic Criteria	Reference	Population
Holmes, 1988 ⁸	Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. <i>Ann Intern Med.</i> 1988;108(3):387-9.	Adults
Oxford Sharpe, 1991 ¹⁸	Sharpe MC, Archard LC, Banatvala JE, et al. A report-chronic fatigue syndrome: guidelines for research. <i>J R Soc Med.</i> 1991;84(2):118-21.	Adults
London ME Dowsett, 1994 ¹⁹	Dowsett E, Goudsmit E, Macintyre A, et al. Report from the national task force on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME). <i>Westcare.</i> 1994.	Adults
Fukuda, 1994 ⁴	Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. <i>Ann Intern Med.</i> 1994;121(12):953-9.	Adults
Canadian ME/CFS Carruthers, 2003 ²	Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. <i>J Chronic Fatigue Syndr.</i> 2003;11(1):7-115.	Adults Children
NICE, 2007 ²²	National Institute for Clinical Excellence. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and management of CFS/ME in adults and children. NHS National Institute for Health and Clinical Excellence, 7.	Adults Children

	2007; NICE clinical guideline 53; 2007.	
International Pediatric Jason, 2006 ²³	Jason LA, Bell DS, Rowe K, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. <i>Journal of Chronic Fatigue Syndrome</i> . 2006;13(2-3):1-44.	Children
Revised Canadian ME/CFS Jason, 2010 ²⁴	Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. <i>Am J Biochem Biotechnol</i> . 2010;6(2):120-35.	Adults
International ME Carruthers, 2011 ³	Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. <i>J Intern Med</i> . 2011;270(4):327-38.	Adults Children
IOM ME/CFS criteria 2015 ⁵	Institute of Medicine. <i>Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness</i> . Washington, DC: National Academies Press; US; 2015.	Adults Children

Abbreviations: CFS = chronic fatigue syndrome; IOM = Institute of Medicine; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence;

Purpose

The purpose of this systematic review is to synthesize the evidence on benefits and harms of treatment for ME/CFS; benefits and harms of diagnosing ME/CFS; and the prevalence of non-ME/CFS conditions in persons presenting for evaluation of potential ME/CFS.

Methods

This systematic review follows the methods of the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.²⁵

Topic Development and Refinement

The scope and key questions used to guide the current review were developed by the Pacific Northwest Evidence-based Practice Center (EPC) with input from the CDC and eight Key Informants representing clinical, research, or patient perspectives in ME/CFS. The protocol for this review was registered in the PROSPERO international database of prospectively registered systematic reviews.²⁶ The following key questions were used to guide this report:

Key Question 1: In patients undergoing evaluation for possible ME/CFS, what is the frequency of non-ME/CFS conditions?

Key Question 2: What are the benefits and harms of diagnosing ME/CFS, versus non-diagnosis?

Key Question 3: What are the benefits and harms of therapeutic interventions for patients with ME/CFS, and how do they vary by patient subgroups?

Key Question 3a: Interventions for treating ME/CFS

Key Question 3b: Interventions for treating symptoms commonly present in persons with ME/CFS (fatigue, poor sleep, orthostatic intolerance, pain, cognitive problems, depression, multiple chemical sensitivity, gastrointestinal symptoms, urinary symptoms, etc.)

The scope of this report differs from the prior report in several ways. Whereas the prior report focused on adults with ME/CFS, this update also includes children within its scope. The prior report included questions on the accuracy and concordance of case definitions and diagnostic criteria used to diagnosis ME/CFS. This update does not address diagnostic accuracy of case definitions for ME/CFS, due to the lack of a reliable, universally accepted reference standard, which is necessary to estimate diagnostic accuracy. Instead, this report addresses a new Key Question on the frequency of non-ME/CFS conditions (without a diagnosis of ME/CFS) in persons presenting for evaluation for possible ME/CFS (Key Question 1). The prior report included a question on the harms of diagnosing ME/CFS and included qualitative and noncomparative studies. This update addresses both the benefits and harms of diagnosis (Key Question 2), in order to present a more balanced perspective, and is restricted to comparative studies that assessed outcomes in persons diagnosed and not diagnosed with ME/CFS. Finally, for evaluation of ME/CFS treatments the prior report focused on effects on fatigue, function, and quality of life. This update also evaluates effects of treatments on other outcomes (depression, anxiety, sleep quality, pain, and others [e.g., cognitive functioning, gastrointestinal symptoms, orthostatic intolerance, and symptoms associated with multiple chemical sensitivity]). Because numerous trials evaluated outcomes addressed in Key Questions 3a and 3b, we report results for both sub-questions in the same section. This report also seeks to determine how effects of

ME/CFS treatments varied in subgroups defined by patient characteristics, including the ME/CFS case definition used, severity of symptoms, duration of symptoms, type of onset (e.g., sudden versus gradual), demographic factors, and others.

Data Sources and Searches

A research librarian conducted searches in Ovid MEDLINE (1988 to January 9, 2019), PsycINFO (1988 to January Week 1 2019), the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through January 9, 2019), and Embase (through January 11, 2019) (search strategies shown in **Appendix A**). We supplemented searches of electronic databases with review of reference lists of relevant studies. We also reviewed the excluded studies list of the prior AHRQ report to identify studies potentially relevant to the revised scope of this update. Searches were updated on August 24, 2020 and new studies will be incorporated prior to finalizing systematic review.

Process for Study Selection

Criteria for inclusion and exclusion of studies were developed for the Key Questions using the populations, interventions, comparators, outcomes, timing, and setting/study design (PICOTS) framework (**Appendix B**). Articles were selected for review if they were about evaluation of patients with fatigue, diagnosis of ME/CFS, or treatment of ME/CFS in adults or children; were relevant to a Key Question; and met the prespecified inclusion criteria. Studies of nonhuman subjects and studies without original data were excluded. Abstracts were independently reviewed by two investigators and full-text articles were obtained for all studies that either investigator classified as potentially meeting inclusion criteria. Discrepancies were resolved through discussion and consensus, with a third investigator to resolve discrepancies if necessary. 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**.

Inclusion criteria

For Key Question 1, we included systematic reviews and cohort studies of adults or children presenting with possible ME/CFS due to fatigue or post-exertional malaise that reported the proportion of patients with non-CFS symptoms/conditions. We excluded studies on the prevalence of symptoms in patients diagnosed with ME/CFS, which was not the topic of this Key Question.

For Key Question 2, we included randomized trials and cohort studies of patients presenting with fatigue or post-exertional malaise. The studies compared those diagnosed with ME/CFS versus those not given an ME/CFS diagnosis and reported any potential benefit or harm from diagnosis (including access to treatment, psychological harms, labeling, risk from diagnostic testing, misdiagnosis, or other). We also included studies that evaluated these outcomes before and after diagnosis of ME/CFS.

For Key Question 3, we included randomized trials of patients diagnosed with ME/CFS using published case definitions. Included interventions were various forms of counseling and behavioral therapy (e.g., CBT, cognitive therapy, relaxation, mindfulness-based stress reduction, biofeedback), exercise (e.g., graded exercise or anaerobic exercise), adaptive pacing, orthostatic

training, complementary and alternative therapies (e.g., acupuncture, massage, tuina, Qigong, distant healing, and others), pathogenesis-based medications (e.g., immune modulators, antivirals, or antibiotics), and symptom-based medications (beta blockers, antidepressants, anxiolytics, stimulants, mineralocorticoids, ivabradine, and others). Trials compared an included intervention versus inactive treatment (defined as placebo, no treatment, usual care/usual specialist care, wait list, or an attention control) or versus another included intervention. Wait list refers to trials in which the inactive treatment is delayed initiation of the studied intervention. Attention controls are not intended to have an important therapeutic effect but control for some of the attentional and time aspects of active therapy (e.g., in a trial with CBT as the active intervention, simple education or advice without a cognitive behavioral component). We also included trials that evaluated combinations of included interventions. Outcomes were continuous measures of fatigue, function, quality of life, school attendance (children), sleep, depression, anxiety, and other outcomes associated with specific ME/CFS-associated symptoms (gastrointestinal, autonomic dysfunction, orthostatic intolerance, urinary symptoms, symptoms associated with multiple chemical sensitivity). We also included dichotomous measures for improvement in fatigue, improvement in function, overall efficacy, and recovery, as defined in the trials. Harms were serious adverse events, withdrawals due to harms, withdrawal due to symptom worsening, post-exertional malaise, worsening of function, and specific drug-related adverse events.

For all Key Questions, inclusion was restricted to studies that utilized a formal, published case definition for diagnosis of ME/CFS. We included only studies of patients that met criteria for ME/CFS, and not those that only had conditions often present in patients with ME/CFS (e.g., fibromyalgia, irritable bowel syndrome, orthostatic intolerance). No duration or timing restriction was applied, other than that treatment trials had to assess outcomes at least 12 weeks after initiation of therapy, because short-term outcomes may not be maintained and may be less meaningful than longer-term outcomes, given the chronic and fluctuating nature of ME/CFS.²⁷ Studies conducted in inpatient settings or in institutionalized individuals were excluded, to increase applicability to outpatient management, where ME/CFS is typically treated.

Data Extraction and Data Management

The following information was extracted from included studies into evidence tables: study design, setting, ME/CFS case definition, inclusion and exclusion criteria, population characteristics (including sex, age, race, duration of ME/CFS, baseline fatigue, baseline function, presence and severity of depression, and other co-morbidities), sample size, duration of follow-up, attrition, characteristics of treatments and control interventions, funding source, and results, including outcomes at baseline and at follow-up. For studies that reported population characteristics by treatment arm, mean values and standard deviations were calculated for the overall sample from the data provided. For each study, data extraction was performed by two investigators: the first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

Risk of Bias of Individual Studies Assessment

The 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.²⁵ Two investigators

independently assessed the risk of bias of each study. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

For randomized trials of interventions, risk of bias assessment was based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; attrition; and use of intent-to-treat analysis.^{25,28} For observational studies, risk of bias assessment was based on the methods for selecting patients, ascertaining exposures and outcomes, attrition, and analysis, including control for confounders (when applicable). Based on these factors, each study was assigned an overall “low,” “medium,” or “high” risk of bias.^{25,28}

Low risk of bias studies are considered likely to be valid. Low risk of bias studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocating patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods to control for confounders (observational studies); blind patients and care providers to treatments (randomized trials); assess outcomes blinded to intervention status; and appropriately measure outcomes and fully report results.

Medium risk of bias 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 medium risk of bias category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some medium risk of bias studies are likely to be valid, while others are probably invalid.

High risk of bias 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 at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. High risk of bias studies were not excluded a priori but were considered highly unreliable.

Assessing Research Applicability

Applicability is 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.²⁵ It indicates the extent to which research included in a review might be useful for informing clinical decisions in specific situations. We recorded factors relevant for understanding applicability, such as the characteristics of the patients (e.g., severity or duration of ME/CFS, ME/CFS case definition used, presence and severity of associated conditions and symptoms, and demographic characteristics), interventions, and settings.²⁹ To interpret the magnitude of benefits, we defined a minimum clinically important difference for fatigue as 2.3 points on the 11-item 0 to 33 Chalder scale, 0.6 points on the 1 to 7 Fatigue Severity Scale, or 11.5 points on the 1 to 50 Multidimensional Assessment of Fatigue;³⁰ for function as 10 points on the 0 to 100 Short Form (SF)-36 physical function subscale;³¹ and for psychiatric outcomes as 1.7 points on the 0 to 21 Hospital Anxiety and Depression Scale (HADS) depression or anxiety scales.³² For pooled standardized mean difference (SMD) estimates for outcomes reported using different scales, we defined an SMD of 0.2 to <0.5 as small, 0.5 to <0.8 as moderate, and ≥ 0.8 as large.³³

Data Synthesis

Meta-analysis was performed for exercise and CBT, the treatments evaluated in the largest number of trials, using the Dersimonian-Laird random-effects models in RevMan 5.3 (the Nordic

Cochrane Centre, Copenhagen).³⁴ Separate meta-analyses were performed for exercise versus inactive controls, exercise versus active treatments, CBT versus inactive controls, and CBT versus active treatments. We pooled results separately for each active treatment comparator, due to clinical heterogeneity and potential differences in effects; stratified results are presented for each active treatment comparator without pooling results across comparators.

Meta-analyses were also conducted on continuous measures for fatigue, functional impairment, depression, anxiety, sleep quality, pain, and the six-minute walk test. Separate analyses were performed for outcomes assessed at the end of treatment and for outcomes assessed after the completion of therapy (post-intervention follow-up). Analyses of continuous outcomes were based on the raw (unadjusted) mean difference or SMD (for outcomes assessed using different scales) in follow-up scores.³⁵ To enable calculation of pooled raw mean differences, continuous pain scales were converted to a common 0 to 10 scale. For function, results using the SF-36 physical function subscale were converted to the standard 0 to 100 scale if necessary. Estimates based on the difference in change from baseline were similar or slightly larger than the difference in follow-up scores and are not discussed further. We utilized the difference in change from baseline when follow-up scores were not reported. Studies that reported adjusted estimates reported results similar to the raw mean differences. When fatigue or function were reported using different scales, we reported the results as the SMD; we also reported stratified results based on each of the original scales. When standard deviations for follow-up scores were not reported, we imputed them based on the average from the other studies in the analysis. Unless indicated otherwise, for all continuous outcomes except for functional impairment, lower scores indicate a better outcome; for functional impairment, lower scores indicate a worse outcome. If necessary, for the purpose of meta-analysis we reversed the scale so that the direction of effects (e.g., higher scores indicating worse outcomes) was the same for all studies in an analysis. Although some trials reported results at long-term, post-trial follow-up, we restricted meta-analyses to outcomes assessed during the trial, due to potential crossover and contamination following trial completion.

We also conducted meta-analyses on dichotomous measures for improvement in fatigue, improvement in function, recovery, serious adverse events, withdrawal due to adverse events, withdrawal due to worsening, post-exertional malaise, and school attendance (for studies of children), based on the pooled relative risk (RR). If necessary, RR's were calculated from data reported in the trial publication. For the Pacing, graded Activity, Cognitive behavior therapy (PACE) trial, the primary analyses of dichotomous outcomes were based on data reported in the main trial publication,³⁶ which utilized definitions modified from the original protocol.³⁷ We conducted sensitivity analyses using data based on the original protocol definitions.³⁸

For studies with more than two treatment arms relevant for an analysis, we combined the arms for the main analysis, so that each study was represented once, in order to avoid overweighting. However, one study could be represented in multiple subgroups in stratified analyses. Heterogeneity was assessed using the I-squared statistic (the proportion of variation in study estimates due to heterogeneity).^{39,40} We conducted subgroup analyses based on the inactive control type (usual care, specialist care, attention control, wait list, or placebo), ME/CFS case definition, and CBT type (individual/face-to-face, individual/web or telephone, group/face-to-face) and evaluated for the subgroup differences with a statistical test (fixed effect analysis based on the inverse-variance method in RevMan 5.3). We also performed sensitivity analyses in which high risk of bias and outlier trials (trials that qualitatively differed substantially from others in the analysis) were excluded. We did not evaluate for potential publication bias using

graphical or statistical methods for small sample effects, because no analysis had at least 10 trials.⁴¹

Grading the Body of Evidence for Each Key Question

We assessed the strength of evidence for treatment comparisons and outcomes addressed in Key Question 3, in accordance with the AHRQ Methods Guide.^{25,42} The strength of evidence was based on risk of bias/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). We did not evaluate the strength of evidence for Key Question 1 because it provided descriptive information regarding the prevalence of non-CFS conditions and we did not evaluate the strength of evidence for Key Question 2 because no studies met inclusion criteria for this question.

The strength of evidence was rated using the four categories recommended in the AHRQ Methods Guide:^{25,42} 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 is unlikely to 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 there is some uncertainty. 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 to determine that the findings are stable or that the estimate of effect is close to the true effect. An “insufficient” grade indicates that evidence is too limited to estimate an effect, there is no confidence in the effect estimate, no evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Peer Review and Public Commentary

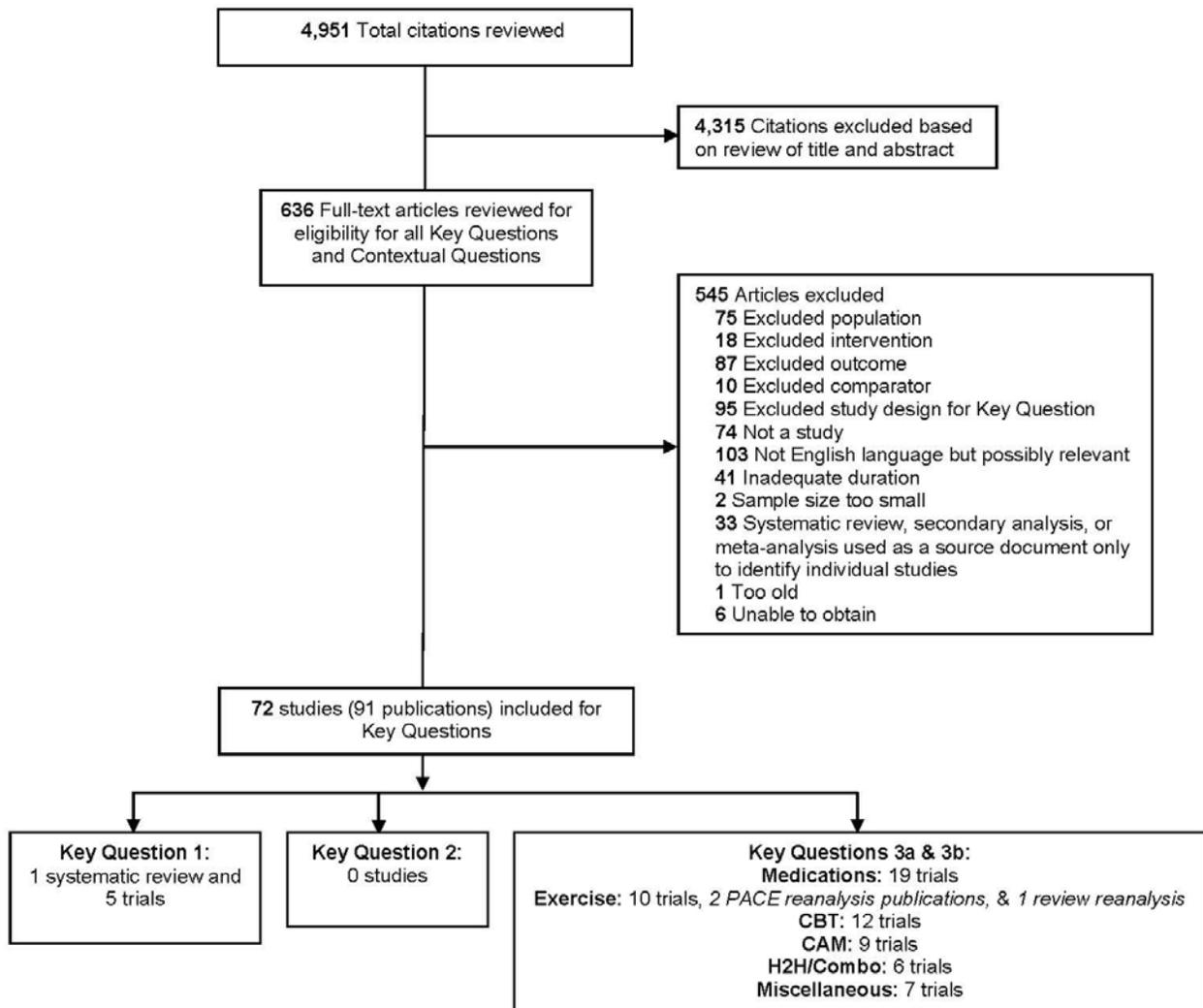
Experts in ME/CFS and Key Informants will be invited to provide external peer review of the draft report. The draft report will also be posted on the CDC ME/CFS website for facilitating the 90-day public comment through Federal Register Notice and Regulations.gov. The draft report will be further edited in response to peer review and public comment, prior to finalization.

Results

Results of Literature Searches

Results of the literature search and selection process are summarized in the literature flow diagram (Figure 1). Database searches and searches of reference lists resulted in 4,951 potentially relevant citations. After dual review of abstracts and titles, 636 articles were selected for full-text review. After dual review of full text articles, 72 studies (in 91 publications) were included. Thirty-three studies were included in the prior AHRQ report and 39 studies were added for this update. The new studies include one systematic review and five observational studies for Key Question 1 and 33 studies for Key Question 3 (treatments for ME/CFS). No study met inclusion criteria for Key Question 2. Detailed evidence tables with data abstraction and risk of bias assessment tables for included studies by Key Question are available in **Appendices E** and **F**.

Figure 1. Literature flow diagram



Note: Some studies included multiple interventions or were reported in multiple publications.

Abbreviations: CBT = cognitive behavioral therapy; RCT = randomized controlled trial

Key Question 1. In patients undergoing evaluation for possible ME/CFS, what is the frequency of non-ME/CFS conditions?

Key Points

- A systematic review of studies of patients presenting with tiredness/fatigue found a pooled prevalence of anemia of 2.8% (95% CI 1.6% to 4.8%; 3 studies, N=1091), malignancy 0.6% (0.3% to 1.3%; 3 studies, N=1091), depression 18.5% (16.2% to 21.0%; 6 studies, N=1000), and serious somatic diseases 4.3% (2.7% to 6.7%; 3 studies, N=436).
- A study of primary care adult patients with a primary symptom of fatigue (n=571) found that the most frequent diagnostic categories (present in >5% of patients) were musculoskeletal (19.4%), infection (18.0%), psychological or social (16.5%, most commonly depression, strain/burnout, or anxiety), gastrointestinal (8.1%), and neurologic (6.7%, most commonly headache or dizziness).
- Three European studies of adult patients with fatigue (total N = 789) undergoing evaluation for possible ME/CFS in specialty settings found that the most common non-ME/CFS conditions were psychiatric (15% to 51%) and sleep disorders (6% to 30%). A U.S. study (N=104) found that the most common non-ME/CFS conditions were alcohol abuse (8.2%), anemia (6.1%), diabetes mellitus (16%), high C-reactive protein (20%), hypothyroidism (20%), depression (8.2%), urinary tract infection (8.2%), restless legs syndrome (6.1%), and substance abuse (6.1%).

Detailed Synthesis

We included a systematic review⁴³ and five additional studies⁴⁴⁻⁴⁸ on the prevalence of non-ME/CFS conditions in adult patients presenting with fatigue and possible ME/CFS. The systematic review addressed the differential diagnosis of tiredness/fatigue and included 26 studies⁴³ (**Evidence Table Appendix E1**). The review restricted inclusion to studies conducted in primary care settings in which patients sought care for tiredness or fatigue (i.e., tiredness symptoms were not elicited from patients through a review of symptoms or other method). Although all patients had fatigue, they did not necessarily present specifically for evaluation of ME/CFS. The review pooled prevalence data for common causes of tiredness based on all studies that met inclusion criteria, as well as a more rigorous subset of studies that used precisely defined diagnostic criteria and described an appropriate diagnostic work-up. Based on this subset of studies in the review, the pooled prevalence of anemia was 2.8% (1.6% to 4.8%; 3 studies, N=1091), malignancy 0.6% (0.3% to 1.3%; 3 studies, N=1091), depression 18.5% (16.2% to 21.0%; 6 studies, N=1000), and serious somatic diseases 4.3% (2.7% to 6.7%; 3 studies, N=436). The serious somatic disease category overlapped with the other categories and included diabetes, anemia, hypothyroidism, and malignancy. The systematic review also included three studies on the prevalence of CFS. The rates were 1.9% and 0.7% in two studies and 31.2% in the third. The higher prevalence in the latter study could be related to the inclusion criteria: it restricted inclusion to patients with tiredness for at least 6 months without a diagnosis associated with the tiredness (2 of the criteria in the 1994 Fukuda case definition for CFS that was utilized in the study). The review did not pool estimates of prevalence of CFS, due to the small number of studies, in addition to the inconsistency across studies.

A prospective Dutch study of primary care patients (N=571) evaluated diagnoses following a new episode in which fatigue was the main symptom (duration >6 months in 58%) (**Table 2**).⁴⁸ It found that 0.7% of patients were diagnosed with CFS. The most frequent diagnostic categories were musculoskeletal (19.4%), psychological or social (16.5%, most commonly depression, strain/burnout, or anxiety), gastrointestinal (8.1%), neurologic (6.7%, most commonly headache or dizziness), general conditions (4.2%, including anemia, adverse drug effects, pain, and allergies), infection (18%), respiratory (4.9%), endocrine (2.8%, most commonly hypothyroidism), cardiovascular (1.9%), climacteric symptoms (1.1%), malignancy (0.7%), and dermatological (0.5%).

Four studies (N=893) reported the prevalence of CFS in patients evaluated in specialty settings for possible CFS⁴⁴⁻⁴⁷ (**Evidence Table Appendix E1**). One study⁴⁴ was conducted in the U.S. and three studies⁴⁵⁻⁴⁷ in Europe. In these studies, the proportion of patients who met criteria for CFS ranged from 36% to 60% (**Table 2**). In the three European studies, the most common non-ME/CFS conditions among patients who did not meet criteria for CFS were psychiatric (15% to 51%) and sleep disorders (6% to 30%). Other diagnoses included cardiovascular, pain, endocrine, nutritional, musculoskeletal, gastrointestinal, and neurological conditions (<5% for each of these categories); one study⁴⁷ found that 47% of patients had chronic diseases but did not specify the conditions further. The U.S. study (N=104) enrolled patients who were self-referred or referred by a clinician for evaluation of possible ME/CFS.⁴⁴ A diagnosis of ME/CFS was excluded in 47% due to the presence of non-ME/CFS conditions. The most common non-ME/CFS conditions were alcohol abuse (8.2%), anemia (6.1%), diabetes mellitus (16%), high C-reactive protein (20%), hypothyroidism (20%), depression (8.2%), restless legs syndrome (6.1%), substance abuse (6.1%), and urinary tract infection (8.2%). Less common conditions (diagnosed in <5% of the sample) were active inflammation, anorexia, autoimmune disorder, bipolar disorder, spinal disease, hepatitis C virus infection, high blood urea, hypertension, mitochondrial myopathy, obesity, obstructive sleep apnea, osteoarthritis, narcolepsy, rheumatoid arthritis, sleep problems, schizophrenia, sickle cell disease, and uncontrolled high blood pressure.

We identified no studies on the prevalence of non-ME/CFS conditions in children presenting with fatigue symptoms.

Table 2. Studies reporting diagnosis rates for ME/CFS and non-ME/CFS conditions

Author, year	Presentation	Setting Country	N	ME/CFS (%)	Non-ME/CFS conditions (%)
Brimmer, 2013 ⁴⁴	Self-referred from CFS support group or referred by clinician for evaluation of fatigue	Healthcare settings: primary care and multiple specialties United States	104	36%	Non-CFS due to insufficient fatigue or number of symptoms: 17.3% Non-CFS due to presence of other conditions: 47.1%* Active inflammation: 4.1% Alcohol abuse: 8.2% Anemia: 6.1% Anorexia: 2.0% Autoimmune disorder: 2.0% Bipolar: 4.1% Spinal disease: 2.0% Diabetes mellitus: 16.3% Hepatitis C virus: 2.0% High blood urea: 4.1% High C-reactive protein: 20.4% Hypertension: 2.0% Hypothyroidism: 20.4% Depression: 8.2% Mitochondrial myopathy: 2.0% Obesity: 4.1% Obstructive sleep apnea: 4.1% Osteoarthritis: 4.1% Narcolepsy: 2.0% Restless legs syndrome: 6.1% Rheumatoid arthritis: 2.0% Sleep problems: 2.0% Schizophrenia: 2.0% Sickle cell: 2.0% Substance abuse: 6.1% Uncontrolled high blood pressure: 2.0% Urinary tract infection: 8.2%
Devasahayam, 2012 ⁴⁵	Referral to CFS service	ME/CFS specialty United Kingdom	250 (assessed)	54%	Psychiatric: 22% Sleep disorder: 6% Pain: 2% Endocrine: 3% Nutritional: 3% Musculoskeletal: 1% Gastrointestinal: 2% Neurological: 1% Others: 2% Miscellaneous/other: 2.4%
Mariman, 2013 ⁴⁶	Presumed CFS	Multidisciplinary setting Belgium	279	Unequivocal CFS: 23% CFS with comorbidity: 21% Psychiatric disorder: 2.5% Sleep disorder: 16% Both: 2.5%	≥4 minor Fukuda criteria, CFS excluded: 35.8% Psychiatric disorder: 12.5% Sleep disorder: 6.5% Both: 14.7% Internal disease: 1.4% Other: 0.7% <4 minor Fukuda criteria: 19.7% Psychiatric: 6.5% Sleep: 3.2% Both: 6.1% Other: 4.0%

Author, year	Presentation	Setting Country	N	ME/CFS (%)	Non-ME/CFS conditions (%)
Newton, 2010 ⁴⁷	Referral to CFS service	ME/CFS Specialty United Kingdom	260	60%	Chronic disease: 47% Sleep disorder: 20% Psychological: 15% Idiopathic: 13% Cardiovascular: 4% Other: 1%
Nijrolder, 2009 ⁴⁸	Fatigue	Primary care The Netherlands	571	0.7% (4/571)	Musculoskeletal: 19.4% Psychological or social: 16.5% Gastrointestinal: 8.1% Neurologic: 6.7% General (anemia, adverse drug event, pain, allergies): 4.2% Infection: 18% Respiratory: 4.9% Endocrine: 2.8% Cardiovascular: 1.9% Menopause: 1.1% Cancer: 0.7% Skin: 0.5%

*Individual could have more than one exclusion condition and the exclusion could be based on one or multiple conditions

Abbreviations: CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis

Key Question 2. What are the benefits and harms of diagnosing ME/CFS vs. non-diagnosis?

Key Points

No study measured benefits or harms of diagnosing ME/CFS versus non-diagnosis.

Detailed Synthesis

We identified no study that measured benefits or harms of diagnosing ME/CFS versus non-diagnosis. The prior AHRQ report included fourteen studies on the consequences of the diagnostic process or diagnosis of ME/CFS.¹ The studies primarily used descriptive or qualitative methods, and did not meet inclusion criteria for this review because no study measured patient outcomes (e.g., quality of life, function, mood) using validated measures or compared outcomes in persons diagnosed with ME/CFS compared with those not diagnosed with ME/CFS. The AHRQ report included five studies that found that patients with ME/CFS feel stigmatized by their diagnosis in multiple aspects of their life. Two studies in the AHRQ report described prejudices and stereotypes in medical trainees and mental health practitioners related to the diagnosis assigned to an identical case presentation (CFS, ME, or other). The AHRQ report also included six studies that indicated a substantial burden due to failure to diagnosis ME/CFS, due to misdiagnosis or not meeting case definitions for ME/CFS due to presence of an exclusionary condition. Although the prior AHRQ report focused on harms of ME/CFS diagnosis, it included one study in which patients reported that a CFS diagnosis reduced uncertainty and provided social and medical legitimacy by providing a coherent diagnosis for their symptoms.

Key Question 3. What are the benefits and harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?

Key Question 3a. Interventions for treating ME/CFS

Key Question 3b. Interventions for treating symptoms commonly present in persons with ME/CFS (poor sleep, orthostatic intolerance, pain, fatigue, cognitive problems, depression, multiple chemical sensitivity, gastrointestinal symptoms, urinary symptoms, etc.)

Key Points

Cognitive behavioral therapy (CBT)

- In adults diagnosed with ME/CFS, CBT was associated with decreased fatigue severity and improved function versus inactive controls at the end of therapy and at post-intervention follow-up, but the magnitude of benefits was small to moderate, the trials had methodological limitations, some trials used the Oxford case definition, and there was unexplained statistical heterogeneity (low strength of evidence).
- CBT was associated with greater likelihood of improvement in fatigue and recovery, based on the modified or original PACE trial definitions for these outcomes; however, the definition for recovery did not exclude patients with persistent symptoms. There was no difference in likelihood of improvement in function (low strength of evidence).
- CBT was associated with decreased depression severity, decreased anxiety severity, and improved sleep quality versus inactive controls, but the magnitude of benefit was small (low strength of evidence).
- Harms of CBT versus inactive controls were not well reported, but two trials found no difference in risk of serious adverse events, withdrawal due to worsening, or physical function worsening, though estimates were imprecise. One trial (PACE) found CBT associated with decreased risk of post-exertional malaise versus usual specialist care (low strength of evidence).
- Comparisons of CBT versus other active therapies (relaxation, adaptive pacing, cognitive therapy, or mirtazapine) were limited to 1 or 2 trials each, with no differences for most outcomes but imprecise estimates. One trial (PACE) found CBT associated with improved outcomes versus adaptive pacing (low strength of evidence).
- In adolescents diagnosed with ME/CFS, CBT (family focused or with parental involvement) was associated with decreased fatigue severity at the end of the intervention; effects on severity of functional impairment and school attendance favored CBT but differences were not statistically significant.
- One trial found an intensive but brief osteopathy, life coaching, and neurolinguistics programming intervention (“Lightning Process”) in adolescents diagnosed with ME/CFS associated with improved function versus usual specialist care, but there were no statistically significant effects on fatigue, pain, anxiety, depression, or quality of life.

School attendance was improved at 12 months but not at 6 months (low strength of evidence).

Other behavioral approaches

- There was insufficient evidence to determine effects of other behavioral approaches in adults (illness management and peer counseling, mindfulness-based cognitive therapy, or self-management interventions) due to small numbers of trials, imprecise estimates, methodological limitations, and inconsistency in findings (for self-management interventions).

Medications

- The immune modulating biologic drug rintatolimod was associated with small improvements in exercise ability and overall function, with greater frequency of infusion-related headache, flu-like symptoms, chills, vasodilation and dyspnea versus placebo (low strength of evidence). Fatigue was not measured.
- Immunoglobulin G (IgG) infusions were not associated with improvements in fatigue or function versus placebo in 2 trials of adults (low strength of evidence). A small trial of adolescents found no difference between IgG versus placebo in overall improvement in function, but significantly more patients had >25% improvement 3-months post treatment using an unvalidated method (insufficient strength of evidence). IgG infusions were associated with increased likelihood of withdrawal due to adverse events and headache versus placebo.
- Small placebo-controlled trials of other drugs, including other immune modulators, antidepressants, corticosteroids, and single studies of an antiviral, an acetylcholinesterase inhibitor, an alpha-adrenergic agonist, and a stimulant, did not find statistically significant effects on fatigue or function outcomes (low strength of evidence).

Exercise Therapy

- In adults diagnosed with ME/CFS, graded exercise therapy (GET) was associated with decreased fatigue severity and improved function versus inactive controls at the end of therapy and at post-intervention follow-up, but the magnitude of benefits was small to moderate. The trials had methodological limitations, most trials used the Oxford case definition, and there was unexplained statistical heterogeneity (low strength of evidence).
- Graded exercise was associated with increased likelihood of improvement in fatigue, improvement in function, and recovery versus inactive controls, based on the modified or original PACE trial definitions for these outcomes; however, the definition for recovery did not exclude patients with persistent symptoms (low strength of evidence).
- Graded exercise was associated with decreased depression severity, decreased anxiety severity, and improved sleep quality versus inactive controls, but the magnitude of benefit was small (low strength of evidence).
- Harms of graded exercise versus inactive controls were not well reported, but two trials found no difference in risk of serious adverse events, withdrawal due to worsening of symptoms, or physical function worsening, though estimates were imprecise. One trial found graded exercise associated with decreased risk of post-exertional malaise versus usual specialist care (low strength of evidence).

- There were no differences between GET versus CBT in fatigue, function, depression, anxiety, sleep quality, pain, or likelihood of recovery, but findings were based on 1 or 2 trials and most estimates were imprecise (low strength of evidence).
- Comparisons of exercise therapy versus other (non-CBT) active therapies (relaxation, adaptive pacing, biofeedback, or fluoxetine) were limited to 1 or 2 trials each with no differences for most outcomes; however, estimates were frequently imprecise. One trial found graded exercise associated with improved outcomes versus adaptive pacing (low strength of evidence).
- One small trial found no difference between home orthostatic training versus sham training in fatigue severity. Home orthostatic training was associated with a small improvement in blood pressure changes with standing, but orthostatic symptoms were not reported.

Dietary interventions, herbal supplements or homeopathy

- There was insufficient evidence to determine the effects of dietary interventions/herbal supplements (insulin-like growth factor, antioxidant, acetyl-carnitine, homeopathy, melatonin, low-sugar/low-yeast diet).

Complementary and alternative therapies

- There was insufficient evidence to determine the effects of yoga, abdominal tuina, or distant healing.
- Although single small studies found qigong exercise associated with decreased fatigue severity, the evidence was insufficient due to small sample sizes and methodological limitations of the studies.

Detailed Synthesis

Exercise therapy

Ten trials evaluated exercise therapy in adult patients with ME/CFS (**Tables 3 and 4, Evidence Table Appendix E2**).^{36,49-57} Sample sizes ranged from 24 to 630 (total N=1688). Six trials compared exercise versus inactive controls (usual care, usual specialist care, or an attention control [advice or supportive listening]) and six trials compared exercise versus an active intervention (CBT, adaptive pacing, relaxation, biofeedback, or fluoxetine). Six trials were included in the prior AHRQ report^{36,50-52,55,56} and four trials were added for this update.^{49,53,54,57} Of the new trials, two trials compared exercise versus inactive controls^{49,53} and two trials compared exercise versus active therapies (relaxation⁵⁴ and biofeedback⁵⁷).

One trial was conducted in the United States, seven trials in Europe, and 1 trial each in New Zealand and Australia. The mean age of participants ranged from 28 to 51 years and the proportion female ranged from 69% to 100%. The case definition for ME/CFS was the Oxford criteria in five trials, the Fukuda criteria in four trials, and the National Institute for Clinical Excellence (NICE) criteria in one trial. The duration of ME/CFS ranged from 28 to 52 months in four trials that reported this information. Baseline fatigue was measured using a variety of scales (**Table 3**). One trial⁴⁹ required patients to have post-exertional fatigue; in the other trials, the proportion of patients with post-exertional fatigue was not described and none of the trials described the severity of post-exertional fatigue. Two trials excluded patients with major

depression.^{50,57} In the other trials, the proportion of patients with depression or an axis I psychiatric diagnosis ranged from 10% to 39%. Depression severity was most commonly reported using the HADS depression score (0 to 21 scale, higher scores indicate more severe depression). In eight trials, mean HADS depression scores ranged from 6.2 to 9.6. Functional impairment was most commonly reported using the SF-36 physical function subscale (0 to 100 scale, lower scores indicate more functional impairment). In eight trials, mean SF-36 physical function subscale scores ranged from 30.0 to 49.4.

The exercise intervention was graded exercise in all of the trials except for one,⁵¹ which evaluated anaerobic exercise. The duration of the exercise therapy intervention ranged from 8 to 26 weeks. In most trials, the frequency of exercise was weekly or biweekly. The session length and exercise intensity varied, with details not reported in some trials (Table 3). Outcomes were assessed at 12 to 70 weeks; eight trials evaluated patients at the end of the intervention and seven trials evaluated patients 13.5 to 52 weeks following the completion of therapy.

Eight trials were rated medium risk of bias and two trials^{54,57} were rated high risk of bias (**Risk of Bias Table Appendix F**). In all trials, blinding of patients and care providers to the exercise intervention was not feasible. Other methodological limitations included high attrition, failure to report attrition, inadequate description of randomization or allocation concealment methods, and failure to blind or unclear blinding status of outcomes assessors and data analysts.

Table 3. Exercise therapy RCTs: Study characteristics

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Clark, 2017 ⁴⁹ GETSET United Kingdom Medium	n: 199 Age: 38.4 % Female: 79	Criteria: NICE Duration: Median 46 and 42 months	Chalder Fatigue Scale 11-item (0 to 33): Baseline: 26.2 (SD 4.7) Post-exertional fatigue: Post- exertional fatigue or malaise required	Major depression: 10% Baseline depression: HADS depression (0 to 21): 8.9 (SD 4.0) Baseline function: SF-36 physical function (0 to 100): 48.7 (SD 22.4)	A: Graded exercise (guided graded exercise self-help) plus specialist medical care B: Specialist medical care Frequency: Once, then up to 3 more sessions Session length: 30 minutes (initial), 20 minutes (follow- up) Exercise intensity: Not specified Duration of treatment: ~8 weeks Duration of follow-up: 12 weeks

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Fulcher, 1997 ⁵⁰ United Kingdom Medium	n: 59 Age: 37.2 % Female: 74	Criteria: Oxford Duration, median: 2.7 years	Chalder Fatigue Scale 14-item (0 to 42) Baseline, mean: 29.7 (SD 6.4) Post-exertional fatigue: not reported	Major depression: Excluded Baseline depression: HADS depression (0 to 21), median: 5.0 (range 1.5 to 8.5) Baseline function: SF-36 physical function (0 to 100), mean: 47.8 (SD 20.5)	A: Graded exercise B: Flexibility/relaxation Frequency: Weekly visits, plus home exercise 5-days per week Session length: Visit length not reported, at home practice increased to maximum of 30 minutes Exercise intensity: maximum 30 minutes daily at 60% of peak oxygen consumption Duration of treatment: 12 weeks Duration of follow-up: 12 weeks/1 year. Flexibility group was permitted to cross over to exercise treatment after 12-week follow-up
Jason, 2007 ⁵¹ United States Medium	n: 114 Age: 43.8 % Female: 83	Criteria: Fukuda Duration: not reported	Fatigue Severity Scale 9-item (1 to 7) Baseline: 6.1 (SD 0.71) Post-exertional fatigue: not reported	Major depression: Current axis I diagnosis: 39% Baseline depression: Beck Depression Inventory (0 to 63): 18.7 (SD 9.9) Baseline function: SF-36 physical function (0 to 100): 46.2 (SD 23.8)	A: Anaerobic Exercise (Anaerobic Activity Therapy [ACT]/progressive relaxation) B: Relaxation (RELAX) C: Cognitive-behavioral therapy D. Cognitive therapy Frequency: Biweekly Session length: 45 minutes Exercise intensity: Not specified Duration of treatment: 6 months Duration of follow-up: 1 year
Moss-Morris, 2005 ⁵² New Zealand Medium	n: 43 Age: 41.0 % Female: 69	Criteria: Fukuda Duration: Median 2.67 and 5.00 (unclear if months or years)	Chalder Fatigue Scale 14-item (0 to 42) Baseline: 24.9 (SD 8.4) Post-exertional fatigue: not reported	Major depression: not reported Baseline depression: HADS depression (0 to 21): 6.2 (SD 19.8) Baseline function: SF-36 physical function (0 to 100): 49.4 (SD 19.8)	A: Graded exercise B: Usual care Frequency: Weekly Session length: 1-hour initial session, length of follow-up sessions not reported Exercise intensity: Goal 30 minutes 5 days a week at 80% of maximum heart rate Duration of treatment: 12 weeks Duration of follow-up: 12 weeks

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Powell, 2001 ⁵³ Powell, 2004 ⁵⁸ United Kingdom Medium	n: 148 Age: 33.2 % Female: 78	Criteria: Oxford Duration: median 51.7 months	Chalder Fatigue Scale 11-item (0 to 11) Baseline: 10.3 (SD 1.4) Post-exertional fatigue: not reported	On antidepressants: 18% Baseline depression: HADS depression (0 to 21): 9.4 (SD 3.9) Baseline function: SF-36 physical function (10 to 30): 16.0 (SD 3.5)	A: Graded exercise (maximum intervention) B: Graded exercise (minimum intervention) C: Graded exercise (minimum intervention + telephone contacts) D. Standardized medical care (assessment, advice, and booklet) Frequency: 9 sessions over 3 months (maximum intervention), 2 initial sessions only (minimum intervention), 2 initial sessions plus 7 telephone contacts over 3 months (minimum intervention + telephone contacts) Session length: 2 initial sessions totaled 3 hours in all groups; 1-hour follow-up (maximum intervention), or 20-minute follow-up (telephone follow-up) Exercise intensity: not specified Duration of treatment: 3 months Duration of follow-up: 12 months/24 months
Wallman, 2004 ⁵⁴ Australia High	n: 61 Age: not reported (range 16 to 74 years) % Female: not reported	Criteria: Fukuda Duration: not reported	Chalder Fatigue Scale 11-item (0 to 33) Baseline: Mental fatigue: 6.0 (SD 1.8) Physical fatigue: 11.5 (SD 3.5) Post-exertional fatigue: not reported	Major depression: 12% Baseline depression: HADS depression (0 to 21): 6.8 (SD 3.2) Baseline function: not reported	A: Graded exercise B: Flexibility/relaxation Frequency: Biweekly Session length: not described Exercise intensity: not described Duration of treatment: 12 weeks Duration of follow-up: 12 weeks

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Wearden, 1998 ⁵⁶ United Kingdom Medium	n: 136 Age: 38.7 % Female: 71	Criteria: Oxford Duration of fatigue: median 28.0 months	Chalder Fatigue Scale 14-item (0 to 42) Baseline: 34.5 (SD 5.7) Post-exertional fatigue: not reported	Major depression: 10% Baseline depression: HADS depression (0 to 21): 8.8 (SD 3.5) Baseline function: not reported	A: Graded exercise B: Attention control (advice) C. Fluoxetine D. Graded exercise + fluoxetine Frequency: at weeks 0, 1, 2, 4, 8, 12, 20, and 26 Session length: 20 minutes Exercise intensity: At least 3 times a week, at 75% of maximum oxygen uptake. Increased after reduction of 10 bpm in post-exercise heart rate for one week and two points on the perceived exertion scale. Duration of treatment: 26 weeks Duration of follow-up: 26 weeks
Wearden, 2010 ⁵⁵ FINE United Kingdom Medium	n: 274 Age: 44.6 % Female: 78	Criteria: Oxford Duration: 7 years	Chalder Fatigue Scale 11-item (0 to 11) Baseline: 10.5 (SD 1.1) Post-exertional fatigue: not reported	Any depression diagnosis: 18% Baseline depression: HADS depression (0 to 21): 9.6 (SD 4.1) Baseline function: SF-36 physical function (0 to 100): 30.1 (SD 18.9)	A: Graded exercise (pragmatic rehabilitation, including relaxation exercises) B: Usual care C. Supportive listening Frequency: 10 sessions over 18 weeks Session length: 90 minutes (initial session), 1 hour (home visits weeks 2, 4, 10, and 19), 30 minutes (telephone calls weeks 3, 6, 8, 12, and 15) Exercise intensity: not specified Duration of treatment: 18 weeks Duration of follow-up: 20 weeks/70 weeks

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
White, 2011 ³⁶ PACE United Kingdom Medium	n: 630 Age: 28 % Female: 77	Criteria: Oxford Duration: median 32 months	Chalder Fatigue Scale 11-item (0 to 33) Baseline: 28.2 (SD 3.8) Post-exertional fatigue: not reported	Any depressive disorder: 34% Baseline depression: HADS depression (0 to 21) 8.2 (SD 3.8) Baseline function: SF-36 physical function (0 to 100): 38.0 (SD 15.8)	A: Graded exercise + specialist medical care B: Specialist medical care C: CBT + specialist medical care D. Adaptive pacing therapy + specialist medical care Frequency: Weekly x 4 weeks, then biweekly, plus one booster at 36 weeks Session length: not described Exercise intensity: Target 30 minutes 5 times weekly Duration of treatment: 23 weeks (booster at 36 weeks) Duration of follow-up: 52 weeks
Windthorst, 2017 ⁵⁷ Germany High	n: 24 Age: 50.7 % Female: 100	Criteria: Fukuda Duration of symptoms: >2 years in 92%	MFI 20-item (20 to 100) Baseline: 64.8 (SD 9.9) Post-exertional fatigue: not reported	Major depression: Excluded Baseline depression: PHQ-9 (0 to 27): mean: 8.2 (SD 4.3) Baseline function: SF-36 physical function (0 to 100): 40.4 (SD 8.8)	A: Graded exercise B: Heart rate variability biofeedback therapy Frequency: weekly Session length: 50 minutes Exercise intensity: Target 20 to 30 minutes 2 to 3 times weekly at 70% of maximum heart rate Duration of treatment: 8 weeks Duration of follow-up: 5 months

Abbreviations: ACT = anaerobic activity therapy; CFS = chronic fatigue syndrome; FINE = Fatigue Intervention by Nurses Evaluation; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; HADS-D = Hospital Anxiety and Depression Scale-depression; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence; PACE = pacing, graded activity, cognitive behavior therapy; PHQ = patient health questionnaire; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Table 4. Exercise therapy RCTs: Study results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes* (fatigue and post- exertional fatigue)	Depression Outcomes*	Function Outcomes*
Clark, 2017 ⁴⁹ GETSET NICE	A: Graded exercise (guided graded exercise self-help) plus specialist medical care (107) B: Specialist medical care (104) Duration of Treatment: ~8 weeks Duration of follow-up: 12 weeks	Fatigue at end of intervention, mean (SD): Chalder Fatigue Scale 11-item (0 to 33): 19.1 (7.6) vs. 22.9 (6.9), AMD: -4.2 (95% CI, -6.1 to -2.3) p<0.0001 Meeting Fukuda criteria (n=138), mean difference in Chalder fatigue scale score at end of intervention: -4.1 (95% CI, -6.5 to -1.7) p=0.001 Meeting Oxford criteria (n=141), mean difference in Chalder fatigue scale score: -3.5 (95% CI, -5.7 to -1.3) p=0.002	HADS depression (0 to 21), mean (SD): 7.4 (4.3) vs. 8.6 (4.7), mean difference: -1.1 (-2.0 to -0.3), p=0.006	Physical Function at end of intervention, mean (SD) SF-36 physical function (0 to 100): Overall: 55.7 (23.3) vs. 50.8 (25.3), AMD: 6.3 (95% CI, 1.8 to 10.8) p=0.006 Meeting Fukuda criteria (n=141), mean difference in SF-36: 6.3 (95% CI, 1.1 to 11.6) p=0.019 Meeting Oxford criteria (n=159), mean difference in SF-36: 5.6 (95% CI, 0.8 to 10.4) p=0.024
Fulcher, 1997 ⁵⁰ Oxford	A: Graded exercise (33) B: Flexibility/relaxation (33) Duration of Treatment: 12 weeks Duration of follow-up: 12 weeks/1 year	Fatigue at end of intervention, mean (SD): Chalder Fatigue Scale 14-item (0 to 42): 20.5 (8.9) vs. 27.4 (7.4); p=0.004 VAS total fatigue (sum of subscales, (200=normal): 253 (48) vs. 286 (67); p=0.04 VAS physical fatigue subscale (, 100=normal): 130 (28) vs. 154 (34); p=0.006 VAS mental fatigue subscale (100=normal): 124 (31) vs. 132 (39); p=0.38	HADS depression at end of intervention (0 to 21), median (IQR): 5.5 (2.9 to 8.1) vs. 4 (0.6 to 7.4), p=0.92	Physical Function at end of intervention, mean (SD) SF-36 physical function (0 to 100): 69 (18.5) vs 55 (21.8); p=0.01

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes* (fatigue and post- exertional fatigue)	Depression Outcomes*	Function Outcomes*
Jason, 2007 ⁵¹ Fukuda	A: Anaerobic exercise (Anaerobic Activity Therapy [ACT]/progressive relaxation (29) B: Relaxation (RELAX) (28) C: Cognitive- behavioral therapy (29) D: Cognitive therapy (28) Duration of Treatment: 6 months Duration of follow- up: 1 year	Fatigue at follow up, mean (SD): Fatigue Severity Scale scores 9- item (1 to 7): 5.77 (1.43) vs. 5.62 (1.06) vs. 5.37 (1.19) vs. 5.87 (1.01); p=NR	Beck Depression Inventory (0 to 63) at follow up: 16.94 (11.82) vs. 13.50 (9.97) vs. 13.95 (13.08) vs. 11.86 (7.36), p<0.001	Physical Function at follow up, mean (SD) SF-36 physical function (0 to 100): 39.72 (27.63) vs. 61.20 (27.70) vs. 58.64 (30.44) vs. 61.09 (23.74) p<0.01 for cognitive-behavioral therapy and cognitive therapy over time vs. ACT over time % Achieving clinically significant improvement: 11.1 vs. 21.7 vs. 18.2 vs. 30.4; p=0.49
Moss-Morris, 2005 ⁵² Fukuda	A: Graded exercise (25) B: Usual care (24) Duration of Treatment: 12 weeks Duration of follow- up: 12 weeks	Fatigue at end of intervention, mean (SD): Chalder Fatigue Scale 14-item (0 to 42): 13.91 (10.88) vs. 24.41 (9.69); p=0.02 Chalder Fatigue Scale physical fatigue: 7.91 (7.06) vs. 14.27 (5.75); p=0.02 Chalder Fatigue Scale mental fatigue: 6.00 (4.06) vs. 10.14 (4.27); p=0.03	Not reported	Physical Function at end of intervention, mean (SD) SF-36 physical function (0 to 100): 69.05 (21.94) vs. 55.00 (22.94); p=0.49

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes* (fatigue and post- exertional fatigue)	Depression Outcomes*	Function Outcomes*
Powell, 2001 ⁵³ Powell, 2004 ⁵⁸ Oxford	A: Graded exercise (maximum intervention) (38) B: Graded exercise (minimum intervention) (37) C: Graded exercise (minimum intervention + telephone contacts) (39) D: Standardized medical care (assessment, advice, and booklet) (34) Duration of Treatment: 3 months Duration of follow-up: 12 months/24 months	Fatigue, mean (95% CI): Chalder Fatigue Scale 11-item (0 to 11): 3 months: 4.3 (2.9 to 5.8) vs. 5.0 (3.4 to 6.6) vs. 3.7 (2.3 to 5.2) vs. 10.4 (10.1 to 10.8) 6 months: 3.4 (2.2 to 4.6) vs. 3.8 (2.5 to 5.2) vs. 4.0 (2.5 to 5.5) vs. 9.9 (9.1 to 10.8) 1 year: 3.1 (1.8 to 4.4) vs. 3.2 (1.8 to 4.7) vs. 3.5 (2.1 to 4.9) vs. 10.1 (9.3 to 10.8), p<0.001 (initial scores and depression scores used as covariates) 2 year, Mean score, (SD): 2.84 (3.67) vs. 4.46 (4.78) vs. 3.59 (4.69) vs. 6.07 (4.60)	Depression, mean (95% CI) HADS depression (0 to 21) 3 months: 5.8 (4.8 to 6.9) vs. 6.1 (4.7 to 7.4) vs. 5.9 (4.5 to 7.3) vs. 11.2 (9.6 to 12.9) 6 months: 5.0 (3.8 to 6.2) vs. 5.4 (3.9 to 6.9) vs. 5.6 (4.3 to 6.9) vs. 11.0 (9.2 to 12.9) 12 months: 4.2 (2.9 to 5.5) vs. 4.2 (3.0 to 5.5) vs. 4.6 (3.2 to 6.0) vs. 10.1 (8.4 to 11.7), p<0.001 (initial scores used as a covariate) 2-year Mean score, (SD): 4.08 (4.33) vs. 5.11 (5.12) vs. 4.77 (4.67) vs. 8.37 (5.75)	Physical Function, mean (95% CI) SF-36 physical function (10 to 30): 3 months: 22.8 (21.2 to 24.3) vs. 22.8 (21.1 to 24.4) vs. 22.3 (20.6 to 24.0) vs. 16.3 (14.9 to 17.7) 6 months: 24.1 (22.6 to 25.6) vs. 24.0 (22.4 to 25.6) vs. 23.0 (21.2 to 24.7) vs. 17.2 (15.6 to 18.7) 1 year: 24.9 (23.4 to 26.4) vs. 25.1 (23.3 to 26.8) vs. 24.3 (22.5 to 26.0) vs. 16.9 (15.4 to 18.4), p<0.001 (initial scores and depression scores used as covariates) 2-year Mean score, (SD): 25.45 (4.72) vs. 24.11 (5.94) vs. 23.64 (6.39) vs. 22.47 (7.02)
Wallman, 2004 ⁵⁴ Fukuda	A: Graded exercise (32) B: Flexibility/relaxation (29) Duration of Treatment: 12 weeks Duration of follow-up: 12 weeks	Mental fatigue at end of intervention, maximum score 12, average score (range): 4.5 (3.9 to 5.2) vs. 4.8 (4.2 to 5.5) Chalder Fatigue Scale physical fatigue, average score (range): 8.1 (6.9 to 9.4) vs. 9.6 (8.3 to 10.9)	HADS depression (0 to 21) at end of intervention, mean (95% CI): 4.8 (3.6 to 5.9) vs. 6.5 (5.5 to 7.6), p=0.041	Overall Function at end of intervention: Ratings of perceived exertion (estimated from figure): 1.3 vs. 1.8 (p=0.013)

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes* (fatigue and post- exertional fatigue)	Depression Outcomes*	Function Outcomes*
Wearden, 1998 ⁵⁶ Oxford	A: Graded exercise + fluoxetine (33) B: Graded exercise (34) C: Fluoxetine (35) D: Attention control (advice) (34) Duration of Treatment: 26 weeks Duration of follow- up: 26 weeks	Fatigue, mean (95% CI): Chalder Fatigue Scale 14-item (0 to 42) 0-12 weeks: -5.7 (-9.2 to -2.2) vs. -2.0 (-4.1 to 0.1) vs. -1.6 (-4.4 to 1.2) vs. -2.1 (-4.9 to 0.6) 26 weeks: -6.0 (-9.7 to - 2.3) vs. -2.7 (-5.4 to 0.01) vs. -3 (-5.9 to -0.2) vs. -5.7 (-9.5 to -1.9) % non-cases of fatigue (Chalder fatigue scale score <4 positive items on 14-item scale) 12 weeks: 18 (6/33) vs. 6 (2/34) vs. 3 (1/35) vs. 3 (1/34) 26 weeks: 18 (6/33) vs. 6 (2/34) vs. 6 (2/ 35) vs. 18 (6/34) p=0.025 for exercise interventions combined vs. others Exercise improved Chalder Fatigue Scale scores Mean change 0 to12 weeks: 2.1 (95% CI -0.6 to 4.8), p=0.13 Mean change 26 weeks: 2.9 (95% CI -0.2 to 6.1), p=0.07	HADS-Depression, mean change (95% CI) at 26 weeks: -2.0 (3.3 to -0.7) vs. -1.2 (-2.5 to 0.2) vs. -1.7 (-3.0 to -0.5) vs. -1.3 (-2.3 to -0.3)	Overall Function, mean (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 4.3) 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=0.005 Mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03
Wearden, 2010 ⁵⁵ FINE Oxford	A: Graded exercise (pragmatic rehabilitation, including relaxation exercises) (95) B: Usual care (100) C: Supportive listening (101) Duration of Treatment: 18 weeks Duration of follow- up: 20 weeks/70 weeks	Fatigue, mean (SD): Chalder Fatigue Scale 11-item (0 to 11) 20 weeks: 8.39 (3.67) vs. 9.32 (3.18) vs. 9.67 (2.76); treatment effect estimate -1.18, 95% CI - 2.18 to -0.18; p=0.021 for graded exercise vs. usual care 70 weeks: 8.72 (3.65) vs. 9.48 (2.71) vs. 9.39 (3.21). Graded exercise vs. usual care Chalder Fatigue Scale 11-item (0 to 33) (20 weeks: 22.78 (8.56) vs. 26.27 (7.68) 70 weeks: 23.90 (8.34) vs. 26.02 (7.11)	HADS-Depression, mean (SD): 20 weeks: 7.28 (4.02) vs. 8.48 (4.47) vs. 8.85 (4.01) 70 weeks: 7.88 (4.45) vs. 8.06 (4.75) vs. 8.67 (4.51)	SF-36 physical function (0 to 100), mean (SD) 20 weeks: 39.94 (25.21) vs. 40.27 (26.45) vs. 33.28 (22.94) Treatment effect: -7.54, 95% CI -12.96 to -2.33; p=0.005 for supportive listening vs. usual care 70 weeks: 43.27 (27.38) vs. 39.83 (27.77) vs. 35.72 (25.94); p=NS

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes* (fatigue and post- exertional fatigue)	Depression Outcomes*	Function Outcomes*
White, 2011 ³⁶ PACE Oxford	A: Adaptive pacing therapy + specialist medical care (160) B: CBT + specialist medical care (161) C: Graded exercise + specialist medical care (160) D: Specialist medical care (160) Duration of Treatment: 23 weeks (booster at 36 weeks) Duration of follow- up: 12 months	Mean (SD) Chalder Fatigue Scale 11-item (0 to 33) 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) 52 weeks: CBT vs. control: p=0.0001 APT vs. control: p=NS GET vs. control: p=0.0003 CBT vs. APT: p=0.0027 GET vs. APT: p=0.0059 % Improved from baseline by ≥2 points: 65 (99/153) vs. 76 (113/148) vs. 80 (123/154) vs. 65 (98/152) % Within normal range: 22 (34/153) vs. 41 (60/148) vs. 33 (51/154) vs. 21 (32/152)	HADS-Depression (0 to 21), mean (SD) 52 weeks: 7.2 (4.5) vs. 6.2 (3.7) vs. 6.1 (4.1) vs. 7.2 (4.7); CBT vs. control: p=0.0003; GET vs. control: p=0.0035; CBT vs. APT: p=0.382, GET vs. APT: p=0.23	Mean (SD) SF-36 physical function (0 to 100) 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) 52 weeks: APT vs. control: p=NS CBT vs. control: p=0.0068 GET vs. control: p=0.0005 CBT vs. APT: p=0.0002 GET vs. APT: p<0.0001 % Improved from baseline by ≥8 points: 49 (75/153) vs. 71 (105/148) vs. 70 (108/154) vs. 58 (88/152) % Within normal range: 35 (53/153) vs. 52 (77/148) vs. 53 (81/154) vs. 41 (62/152)
Windthorst, 2017 ⁵⁷ Fukuda	A: Graded exercise (11) B: Heart rate variability biofeedback therapy (13) Duration of Treatment: 8 weeks Duration of follow- up: 5 months	MFI 20-item (20 to 100) total baseline vs. end of treatment vs. 5-month follow-up, mean(SD): GET: 68.8 (10.1) vs. 56.6 (18.8) vs. 55.6 (21.3), p=0.319 Biofeedback: 61.5 (9.7) vs. 48.2 (15.9) vs. 43.6 (15.9), p<0.001	PHQ-9 (0 to 27) baseline vs. end of treatment vs. 5-month follow-up, mean (SD): GET: 8.9 (5.4) vs. 8.3 (4.6) vs. 8.8 (6.0), p=0.656 Biofeedback: 7.5 (3.1) vs. 4.3 (3.0) vs. 4.2 (3.1), p=0.006	Overall Function: SF-36 Physical baseline vs. end of treatment vs. 5- month follow-up, mean (SD): GET: 37.7 (7.8) vs. 44.8 (9.7) vs. 46.6 (7.1), p=0.011 Biofeedback: 42.6 (9.2) vs. 45.2 (9.9) vs. 47.1 (12.2), p=0.292

*A vs. B vs. C vs. D, unless otherwise noted

Abbreviations: ACT = anaerobic activity therapy; AMD = adjusted mean difference; APT = adaptive pacing therapy; CBT = cognitive behavioral therapy; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; GET = graded exercise therapy; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence; NS = not significant; PACE = pacing, graded activity, cognitive behavior therapy; RCT = randomized controlled trial; SD = standard deviation; SES = standardized effect sizes; SF-36 = 36-item Short Form Health Survey

Exercise versus inactive controls

Six trials (N=1,430)^{36,49,52,53,55,56} compared graded exercise versus usual care (3 trials),^{52,53,55} usual specialist care (2 trials),^{36,49} or an attention control (advice or supporting listening, 2 trials)^{55,56} (**Tables 3 and 4**). One trial⁴⁹ was published subsequent to the AHRQ report and one older trial⁵³ not included in the prior AHRQ report were added for this update; both trials used the Oxford case definition. The duration of the exercise intervention ranged from eight to 26 weeks across the trials. All of the trials evaluated patients at the end of the intervention and four trials also evaluated patients four weeks to 24 months following the end of the intervention. All of the trials were rated medium risk of bias.

Fatigue

Graded exercise was associated with decreased fatigue severity versus usual care, specialist care, or an attention control at the end of the exercise intervention, though statistical heterogeneity was high (6 trials, N=1,034, SMD -0.55, 95% CI -0.91 to -0.19, $I^2=85\%$; **Figure 2**).^{36,49,52,53,55,56} Fatigue severity was measured using the Chalder fatigue scale, but the trials used different versions and scoring methods. Mean differences were -2.91 (95% CI -4.36 to -1.47, $I^2=91\%$) in two trials (N=501) that used the 11-item 0 to 33 Chalder scale,^{36,49} -6.47 (95% CI -13.80 to 0.86, $I^2=72\%$) in two trials (N=111) that used the 14-item 0 to 42 Chalder scale,^{52,56} and -3.60 (95% CI -8.49 to 1.29, $I^2=98\%$) in two trials (N=422) that used the 11-item 0 to 11 Chalder scale^{53,55} (**Table 5**). Estimates consistently favored exercise when trials were stratified by the control type or ME/CFS case definition and there were no statistically significant subgroup differences; however, stratification on these factors did not reduce heterogeneity (**Table 5**). The most commonly used case definition was the Oxford criteria (4 trials, N=792, SMD -0.59, 95% CI -1.05 to -0.14, $I^2=88\%$).^{36,53,55,56}

An outlier trial by Powell et al. reported substantially greater effects on fatigue (SMD -1.46, 95% CI -1.88 to -1.04) than the other trials (SMD range -0.07 to -1.00).⁵³ The methods used to select patients (the Oxford case definition), severity of ME/CFS symptoms at baseline (mean 10.3 on the 11-item 0 to 11 Chalder scale and 30.0 on the 0 to 100 SF-36 physical function subscale) and intensity of the exercise intervention (2 to 9 sessions) did not appear to explain the difference in results between this trial and the others. Excluding this trial reduced statistical heterogeneity and attenuated the pooled estimate (5 trials, N=886, SMD -0.32, 95% CI -0.52 to -0.12, $I^2=46\%$).

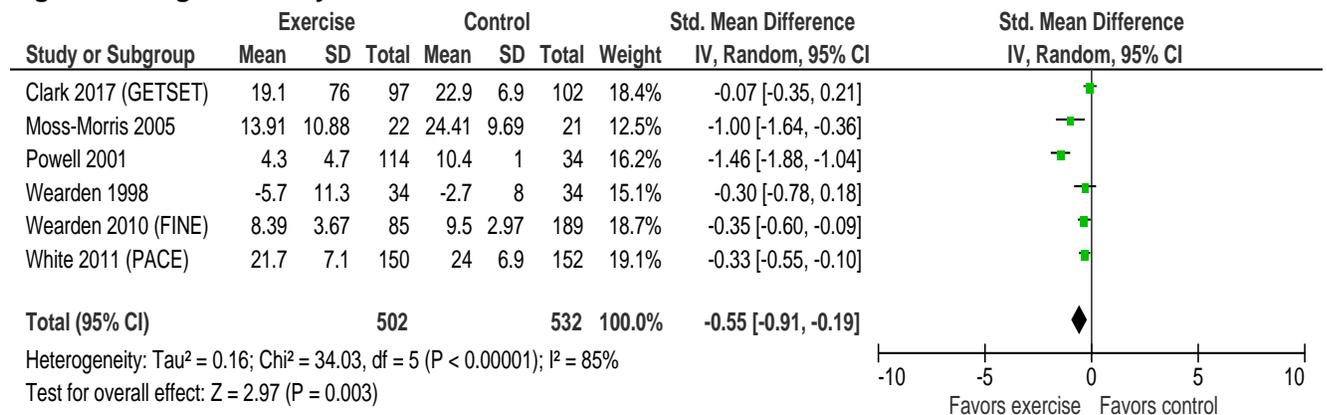
Graded exercise was also associated with decreased fatigue severity versus controls at post-intervention follow-up (29 to 52 weeks following the completion of therapy), though the estimate was based on fewer studies (3 trials, N=625, SMD -0.76, 95% CI -1.48 to -0.05, $I^2=94\%$;^{36,53,55} **Figure 3**). Statistical heterogeneity was very high. The outlier trial by Powell et al.⁵³ reported substantially greater effects on fatigue (SMD -1.69) than the other two trials (SMD -0.21 and -0.45). Excluding this trial reduced statistical heterogeneity and attenuated the pooled estimate (2 trials, N=477, SMD -0.35, 95% CI -0.58 to -0.12, $I^2=35\%$).

The PACE trial evaluated improvement in fatigue as a dichotomous outcome. The main PACE publication found graded exercise associated with an increased likelihood of experiencing a ≥ 2 point improvement on the 11-item 0 to 33 Chalder scale versus specialist care (80% vs. 65%, RR 1.23, 95% CI 1.07 to 1.42; adjusted risk difference [ARD] 15%, 95% CI 5% to 25%).³⁶ However, this differed from the original protocol, which defined improvement in fatigue as a score of ≤ 3 on the 11-item 0 to 11 Chalder fatigue scale or improvement of >50 percent from baseline.³⁷ Using the original protocol definition, graded exercise remained associated with

increased likelihood of improvement in fatigue (24% vs. 13%, RR 1.81, 95% CI 1.11, to 2.94; ARD 15%, 95% CI 2% to 19%).³⁸

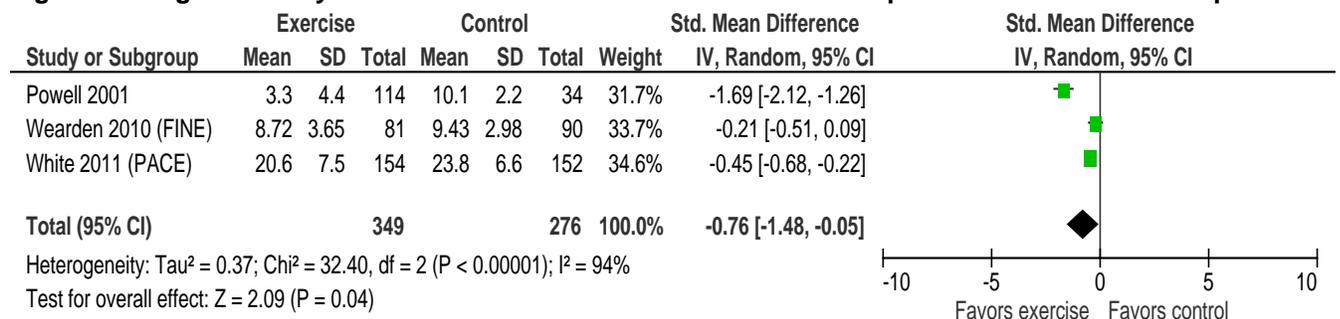
The PACE trial also evaluated longer-term, post-trial outcomes of graded exercise versus specialist care (N=320, median duration from randomization 31 months).⁵⁹ 32 percent of patients in the exercise group and 63 percent in the specialist care group received non-randomly allocated therapies between the end of the trial (1 year) and long-term follow-up. Fatigue severity on the 11-item 0 to 33 Chalder fatigue scale was improved at long-term follow-up compared with end-of-trial scores in the exercise (mean change -1.3 points, 95% CI -2.7 to -0.1) and specialist care (-3.9 points, 95% CI -5.3 to -2.6) groups. At long-term post-trial follow-up, there was no difference between graded exercise vs. specialist medical care in fatigue severity (mean difference -0.8, 95% CI -2.8 to 1.2), based on mixed model analyses.

Figure 2. Fatigue severity: Graded exercise versus inactive control at end of intervention



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 3. Fatigue severity: Graded exercise versus inactive control at post-intervention follow-up



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Function

Graded exercise was associated with less severe functional impairment versus usual care, usual specialist care, or an attention control (5 trials, N=965, mean difference 11.73, 95% CI 2.33 to 21.14 on the 0 to 100 SF-36 physical function subscale, I²=88%; **Figure 4**), but statistical heterogeneity was high.^{36,49,52,53,55} Estimates consistently favored exercise when trials were stratified according to the control type or ME/CFS and there were no statistically significant

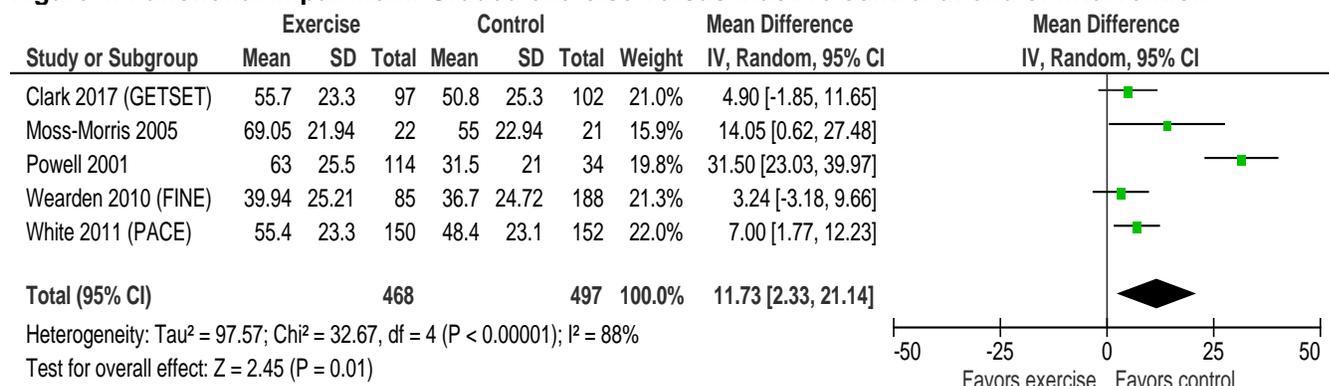
subgroup differences (**Table 5**). However, stratification on these factors did not reduce heterogeneity. The most commonly used ME/CFS case definition was the Oxford criteria (3 trials, N=723, mean difference 13.60, 95% CI -1.18 to 28.37, $I^2=93\%$).^{36,53,55} An outlier trial by Powell et al.⁵³ reported substantially greater effects on SF-36 physical function scores (mean difference 31.50, 95% CI 23.03 to 39.97) than the other trials (mean differences ranged from 3.24 to 14.05 points). Excluding this outlier trial eliminated statistical heterogeneity and attenuated the pooled estimate (4 trials, N=817, mean difference 5.89, 95% CI 2.52 to 9.25, $I^2=0\%$).

Graded exercise was associated with decreased functional impairment versus controls at post-intervention follow-up, but the difference was not statistically significant (3 trials, N=711, mean difference 17.07, 95% CI -2.02 to 36.16 on the 0 to 100 SF-36 physical function subscale, $I^2=95\%$).^{36,53,55} **Figure 5**. Excluding the outlier trial by Powell et al.⁵³ attenuated the estimate, eliminated statistical heterogeneity, and resulted in a statistically significant effect (2 trials, N=563, mean difference 6.37, 95% CI 1.89 to 10.85, $I^2=0\%$).

Three trials evaluated functional improvement as a dichotomous outcome. Functional improvement was defined in one trial⁵³ as ≥ 50 point improvement from baseline on SF-36 physical function (standardized to a 0 to 100 scale) or score ≥ 75 and in one trial⁵⁵ as a $\geq 50\%$ improvement from baseline or score > 70 . In PACE, the third trial, the main study publication defined improvement in fatigue as ≥ 8 point improvement on the SF-36 physical function score from baseline (proportion meeting this definition 70% vs. 58%).³⁶ However, this differed from the study protocol, which defined functional improvement as an SF-36 physical function score ≥ 75 or $\geq 50\%$ improvement from baseline (proportion meeting this definition 61% vs. 44%), similar to the definition used in the other trials.³⁷ Using the data from the main PACE publication, exercise was associated with increased likelihood of functional improvement versus usual care or specialist care (3 trials, N=618, RR 2.48, 95% CI 0.77 to 7.97, $I^2=89\%$; ARD 28%, 95% CI -7% to 63%) (**Figure 6**).^{36,53,55} The pooled estimate was very similar when data based on the original (protocol) PACE definition for functional improvement were used (3 trials, N=632, RR 2.52, 95% CI 0.90 to 7.02, $I^2=85\%$; ARD 30%, 95% CI -4% to 63%).³⁸ The trial by Powell et al.⁵³ reported a much stronger effect on likelihood of functional improvement (RR 11.78, 95% CI 3.05 to 45.45) than the other two trials (RR 1.39 and 1.74). Excluding this outlier trial from the analysis attenuated the pooled estimate and eliminated statistical heterogeneity, but results were based on only two trials (N=484, RR 1.41, 95% CI 1.15 to 1.74, $I^2=0\%$; ARD 13%, 95% CI 5% to 21%).^{36,55}

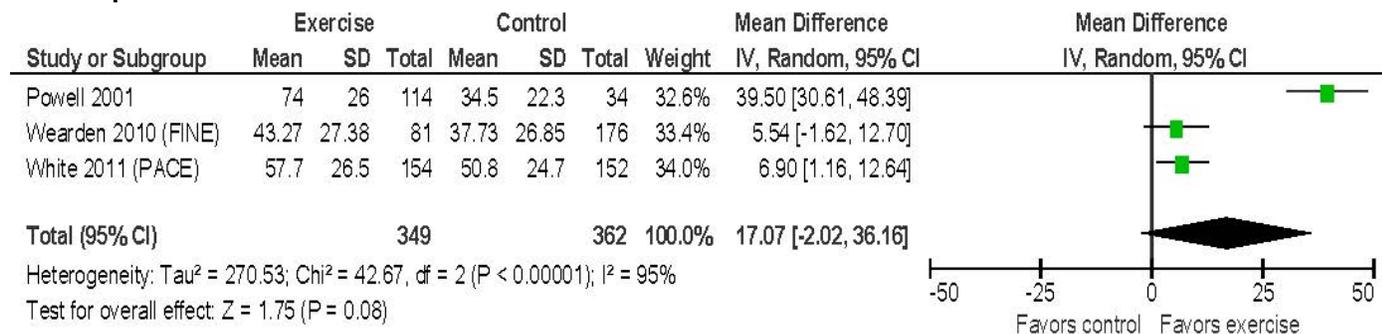
The PACE trial also evaluated longer-term (median duration from randomization 31 months), post-trial outcomes.⁵⁹ There was no change in SF-36 physical function at long-term follow-up compared with the end of the trial for exercise (mean change 0.5 point, 95% CI -2.7 to 3.6 on a 0 to 100 scale), but function improved in the specialist care group (mean change 7.1 points, 95% CI 4.0 to 10.3). At long-term post-trial follow-up, there was no difference between graded exercise versus specialist medical care (mean difference 2.0, 95% CI -4.0 to 7.9), based on mixed model analyses.

Figure 4. Functional impairment: Graded exercise versus inactive control at end of intervention



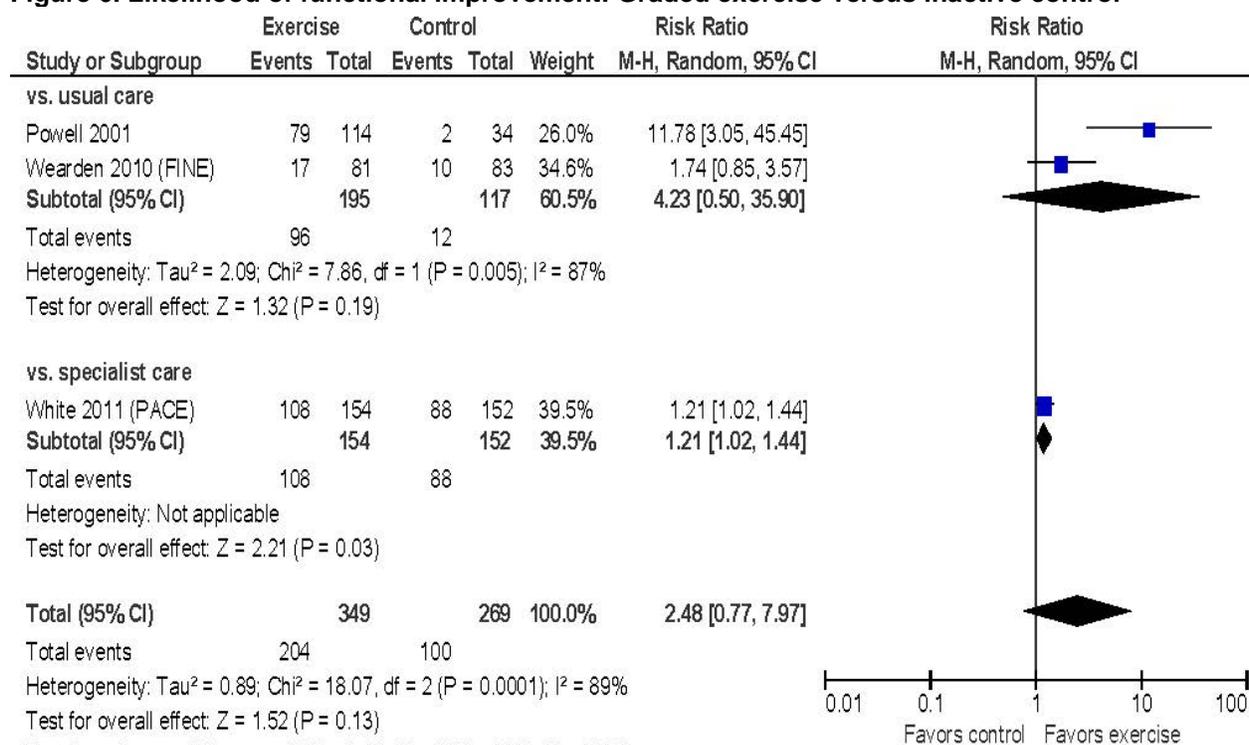
Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 5. Functional impairment: Graded exercise versus inactive control at post-intervention follow-up



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 6. Likelihood of functional improvement: Graded exercise versus inactive control



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

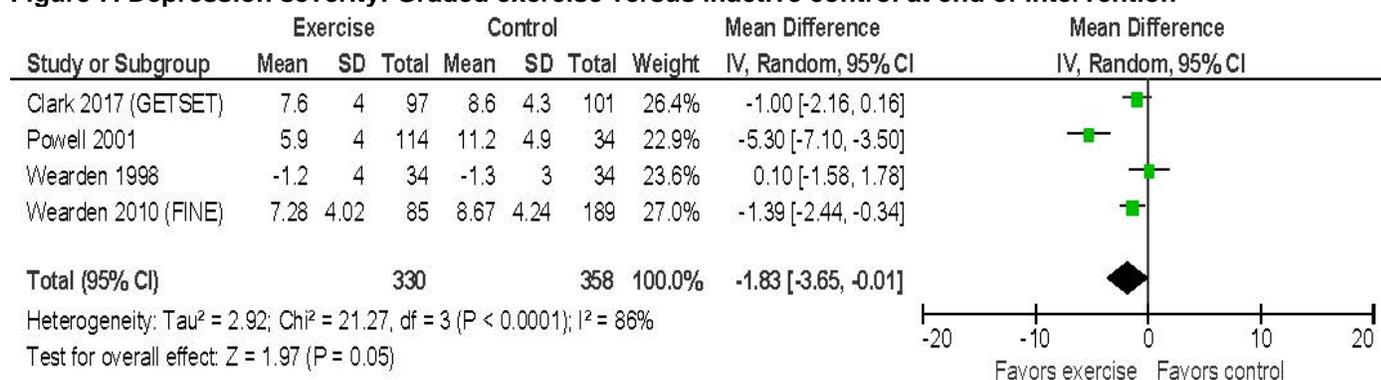
Depression and anxiety

Graded exercise was associated with less severe depression versus usual care, usual specialist care, or an attention control at the end of the intervention (4 trials, N=688, mean difference -1.83, 95% CI -3.65 to -0.01 on the 0 to 21 HADS depression scale, I²=86%;^{49,53,55,56} **Figure 7**). The estimate was similar at post-intervention follow-up, but the difference was not statistically significant (3 trials, N=699, mean difference -2.36, 95% CI -4.98 to 0.27, I²=92%).^{36,53,55} Statistical heterogeneity was high. Excluding the trial by Powell et al. attenuated the estimates and accounted for almost all statistical heterogeneity (3 trials, N=540, mean difference -0.97, 95% CI -1.71 to -0.23, I²=8%) at end of intervention and (2 trials, N=551, mean difference -0.85, 95% CI -1.61 to -0.08, I²=0%) at post-intervention follow-up.

Graded exercise was also associated with less severe anxiety versus usual care, usual specialist care, or an attention control at the end of the intervention (3 trials, N=620, mean difference -1.59, 95% CI -2.41 to -0.77 on the 0 to 21 HADS anxiety scale, I²=16%;^{49,53,55} **Figure 8**). There was no difference between graded exercise versus controls in anxiety at post-intervention follow-up (3 trials, N=697, mean difference -1.07, 95% CI -2.64 to 0.49, I²=75%).^{36,53,55} Excluding the trial by Powell et al. slightly attenuated the estimate at the end of the intervention (2 trials, N=372, mean difference -1.31, 95% CI -2.12 to -0.51, I²=0%) and had little effect on the estimate for anxiety at post-intervention follow-up (2 trials, N=566, mean difference -0.38, 95% CI -1.52 to 0.76, I²=49%).

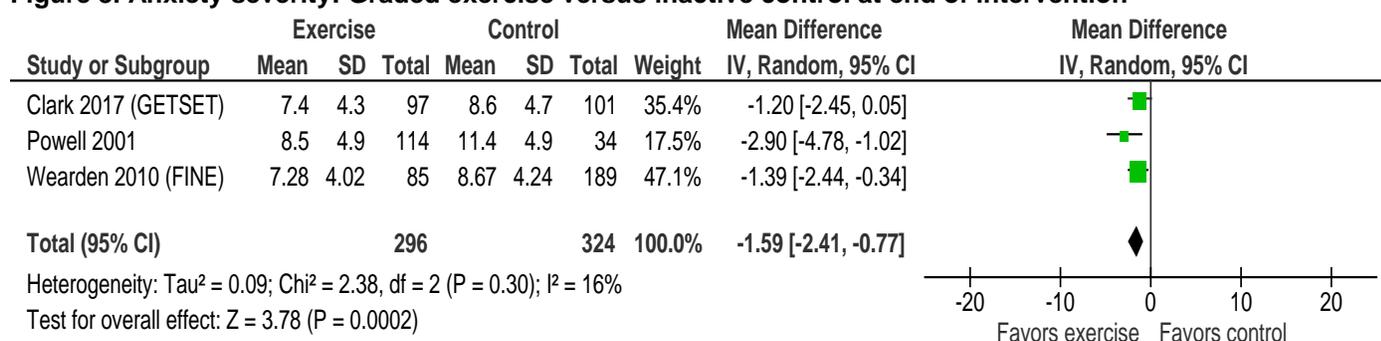
Stratified analyses based on control type and ME/CFS criteria were limited by the small number of trials but indicated no statistically significant subgroup effects (**Table 5**)

Figure 7. Depression severity: Graded exercise versus inactive control at end of intervention



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; IV = instrumental variable; SD = standard deviation

Figure 8. Anxiety severity: Graded exercise versus inactive control at end of intervention

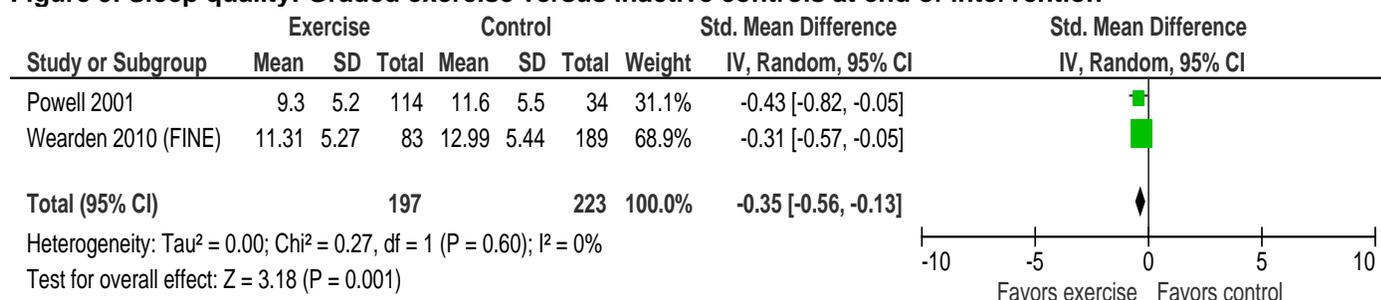


Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; GETSET = guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome; IV = instrumental variable; SD = standard deviation

Sleep

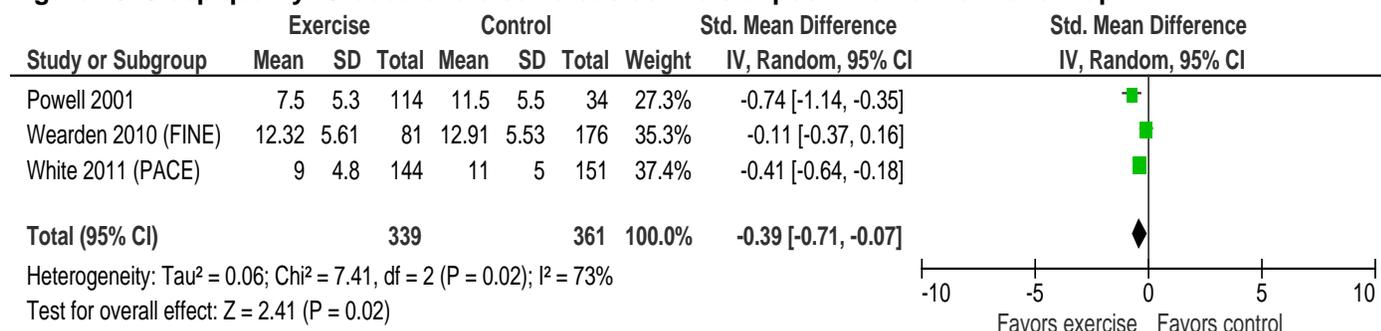
Three trials evaluated effects of graded exercise on sleep quality using the Sleep Problem Questionnaire or the Jenkins Sleep Questionnaire.^{36,53,55} Graded exercise was associated with improved sleep quality versus controls at the end of the intervention (2 trials, N=420, SMD -0.35, 95% CI -0.56 to -0.13, I²=0%;^{53,55} **Figure 9**) and at post-intervention follow-up (3 trials, N=700, SMD -0.39, 95% CI -0.71 to -0.07, I²=73%;^{36,53,55} **Figure 10**). On the original 0 to 20 scales, the pooled differences were about 2 points. Subgroup analyses based on the control type or ME/CFS criteria used showed no statistically significant subgroup differences but were limited by the small numbers of trials (**Table 5**). Excluding the trial by Powell et al. had little effect on the estimates at the end of the intervention (1 trial, N=272, SMD -0.31, 95% CI -0.57 to -0.05)⁵⁵ or at post-intervention follow-up (2 trials, N=552, SMD -0.26, 95% CI -0.56 to 0.03, I²=65%).^{36,55}

Figure 9. Sleep quality: Graded exercise versus inactive controls at end of intervention



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 10. Sleep quality: Graded exercise versus controls at post-intervention follow-up



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; IV = instrumental variable; PACE = pacing, graded activity, cognitive behavior therapy; SD = standard deviation; Std = standard

Pain

A post-hoc analysis from the PACE trial found exercise associated with decreased severity of muscle pain (mean difference -0.42, 95% CI -0.11 to -0.73) and joint pain (mean difference -0.25, 95% CI -0.70 to -0.57) at post-intervention follow-up (each measured on a 0 to 4 scale).⁶⁰

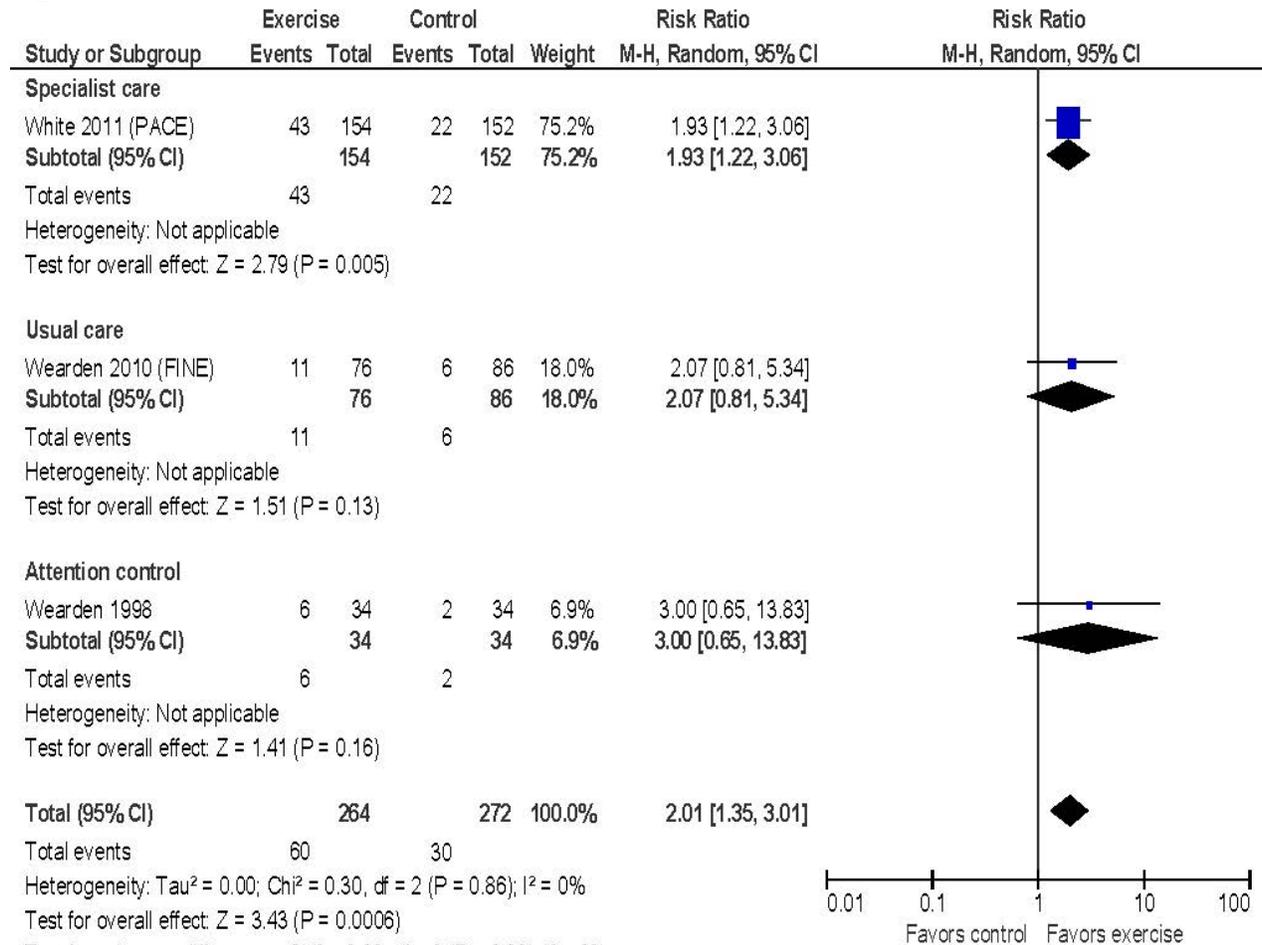
Recovery

Three trials evaluated effects of exercise on likelihood of recovery.^{36,55,56} In two trials, recovery was defined as a score of <4 on the 11-item 0 to 11 Chalder fatigue scale.^{55,56} The third trial, PACE, reported results for recovery based on the following definition: SF-36 physical function score ≥ 60 , 11-item 0 to 33 Chalder fatigue score ≤ 18 , Clinical Global Impression rating of better or very much better, and failure to meet one or more case definitions for CFS (the Oxford case definition, SF-36 score ≤ 65 , or positive response on at least 6 of 11 items on the Chalder fatigue scale).³⁶ This recovery definition has been criticized because the SF-36 physical function threshold includes patients with significant functional impairment; in addition, some patients met the SF-36 physical function and Chalder fatigue scale thresholds for recovery at study entry.⁶¹ Also, the definition used in the main PACE publication differed from the definition for recovery in the original trial protocol: SF-36 physical function score ≥ 85 , 11-item 0 to 11 Chalder score ≤ 3 , Clinical Global Impression rating of very much better, and failure to meet Oxford, CDC, and London case definitions for CFS.³⁷

Based on the published results from PACE (proportion meeting definition for recovery 28% for graded exercise vs. 14% for usual specialist care), graded exercise was associated with

increased likelihood of recovery versus usual care, usual specialist care, or attention control (3 trials, N=536, RR 2.01, 95% 1.35 to 3.01, $I^2=0\%$; ARD 11%, 95% CI 5% to 17%,^{36,55,56} **Figure 11**). Replacing the data from PACE with results based on the original definition for recovery (proportion meeting definition 4% vs. 3%), resulted in an attenuated, imprecise estimate that was no longer statistically significant (3 trials, N=550, RR 1.86, 95% CI 0.96 to 3.61, $I^2=0\%$).^{38,55,56}

Figure 11. Likelihood of recovery: Graded exercise versus inactive control



Abbreviations: CI = confidence interval; FINE = Fatigue Intervention by Nurses Evaluation; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Overall improvement

In the PACE trial, a composite outcome for overall improvement (defined as an 11-item 0 to 11 Chalder fatigue scale score ≤ 3 or $>50\%$ improvement from baseline and SF-36 physical function score ≥ 75 or $>50\%$ improvement from baseline at 52 weeks), was described as the primary outcome in the study protocol but not reported in the main publication.³⁷ In a subsequent publication, the authors reported that graded exercise associated with greater likelihood of overall improvement than usual specialist care alone, using the protocol definition (N=320, 21% vs. 10%, RR 2.16, 95% CI 1.34 to 3.47).³⁸

The Graded Exercise Therapy guided Self-help Treatment (GETSET) trial found guided graded exercise self-help associated with greater likelihood of self-rated Clinical Global Impression of “much better” or “very much better” versus specialist medical care alone, but the

difference was not statistically significant (N=198, 14% vs. 5.9%, RR 2.43, 95% CI 0.97 to 6.07).⁴⁹

6-minute walk test

The PACE trial (N=228) found graded exercise associated with longer distance on the 6-minute walk test versus usual specialist care at the end of the intervention, though the difference was small (31.00 meters, 95% CI 4.00 to 58.00).³⁶

Harms

Data on harms were available from two trials of graded exercise plus usual specialist care versus usual specialist care alone (PACE and GETSET).^{36,49} There was no statistically significant difference in the pooled risk of serious adverse events (2 trials, N=518, RR 1.59, 95% CI 0.69 to 3.66, $I^2=0\%$),^{36,49} but the estimate was imprecise, with 20 of 23 events reported in one trial (PACE).³⁶ For withdrawal due to worsening, the PACE trial³⁶ reported three cases and the GETSET trial⁴⁹ reported none, resulting in a very imprecise estimate (1 trial, N=320, RR 2.00, 95% CI 0.18 to 21.84). Exercise was not associated with increased likelihood of physical function worsening, though the pooled estimate was imprecise (2 trials, N=518, RR 0.83, 95% CI 0.52 to 1.34, $I^2=0\%$).^{36,49} The PACE trial found graded exercise associated with decreased likelihood of post-exertional malaise versus usual specialist care (N=320, 44% vs. 63%, RR 0.70, 95% CI 0.57 to 0.87).³⁶

Table 5. Exercise vs. inactive controls: Summary of stratified results

Outcome	Number of studies (N)	Estimate (95% CI)	I^2	p for subgroup difference
<i>Fatigue, end of intervention</i>	6 (1034)	SMD -0.55 (-0.91 to -0.19)	85%	--
By control type: vs. usual care	3 (368)	SMD -0.90 (-1.71 to -0.08)	91%	0.48
vs. usual specialist care	2 (501)	SMD -0.41 (-0.59 to -0.22)	9%	--
vs. attention control	2 (250)	SMD -0.37 (-0.62 to -0.12)	0%	--
On original scale: Chalder (11-item, 0 to 33)	2 (501)	MD -2.91 (-4.36 to -1.47)	24%	--
Chalder (14-item, 0 to 42)	2 (111)	MD -6.47 (-13.80 to 0.86)	72%	--
Chalder (11-item, 0 to 11)	2 (422)	MD -3.60 (-8.49 to 1.29)	98%	--
By ME/CFS criteria: Oxford	4 (792)	SMD -0.59 (-1.05 to -0.14)	88%	0.41
Fukuda	1 (43)	SMD -1.00 (-1.64 to -0.36)	--	--
NICE	1 (199)	SMD -0.52 (-0.80 to -0.24)	--	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	5 (886)	SMD -0.32 (-0.52 to -0.12)	46%	--
Using difference in change from baseline	6 (1034)	SMD -0.68 (-1.01 to -0.35)	82%	--
<i>Fatigue, post-intervention</i>	3 (625)	SMD -0.76 (-1.48 to -0.05)	94%	--
By control type: vs. usual care	2 (315)	SMD -0.95 (-2.38 to 0.47)	97%	0.29
vs. usual specialist care	1 (306)	SMD -0.45 (-0.68 to -0.22)	--	--
vs. attention control	1 (171)	SMD -0.19 (-0.50 to 0.11)	--	--
On original scale: Chalder (11-item, 0 to 33)	1 (306)	MD -3.20 (-4.78 to -1.62)	--	--
Chalder (11-item, 0 to 11)	2 (319)	MD -3.75 (-9.72 to 2.22)	98%	--
By ME/CFS criteria Oxford	3 (625)	SMD -0.76 (-1.48 to -0.05)	94%	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (477)	SMD -0.35 (-0.58 to -0.12)	35%	--
Using difference in change from baseline	3 (625)	SMD -0.83 (-1.58 to -0.09)	94%	--

Outcome	Number of studies (N)	Estimate (95% CI)	I ²	p for subgroup difference
<i>Fatigue improvement (dichotomous)</i>	1 (305)	RR 1.23 (1.07 to 1.42)	--	--
Using original PACE definition	1 (320)	RR 1.81 (1.11 to 2.94)	--	--
<i>SF-36 physical function (0 to 100), end of intervention</i>	5 (965)	MD 11.73 (2.33 to 21.14)	88%	--
By control type: vs. usual care	3 (368)	MD 15.04 (-6.13 to 36.22)	93%	0.72
vs. usual specialist care	2 (501)	MD 6.21 (2.08 to 10.35)	0%	--
vs. attention control	1 (181)	MD 6.66 (-0.40 to 13.72)	--	--
By ME/CFS criteria:	3 (723)	MD 13.60 (-1.18 to 28.37)	93%	0.34
Oxford				
Fukuda	1 (43)	MD 14.05 (0.62 to 27.48)	--	--
NICE	1 (199)	MD 4.90 (-1.85 to 11.65)	--	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	4 (817)	MD 5.89 (2.52 to 9.25)	0%	--
Using difference in change from baseline	5 (969)	MD 12.23 (2.54 to 21.91)	90%	--
<i>SF-36 physical function (0 to 100), post-intervention</i>	3 (711)	MD 17.07 (-2.02 to 36.16)	95%	--
By control type: vs. usual care	2 (315)	MD 21.44 (-13.90 to 56.78)	97%	0.73
vs. usual specialist care	1 (306)	MD 6.90 (1.16 to 12.64)	--	--
vs. attention control	1 (171)	MD 7.55 (-0.47 to 15.57)	--	--
By ME/CFS criteria:	3 (711)	MD 17.07 (-2.02 to 36.16)	95%	--
Oxford				
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (563)	MD 6.37 (1.89 to 10.85)	0%	--
Using difference in change from baseline	3 (711)	MD 17.91 (-2.00 to 37.81)	97%	--
<i>Functional improvement</i>	3 (618)	RR 2.48 (0.77 to 7.97)	89%	--
Using original PACE definition	3 (632)	RR 2.52 (0.90 to 7.02)	85%	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (484)	RR 1.41 (1.15 to 1.74)	0%	--
<i>HADS depression (0 to 21), end of intervention</i>	4 (688)	MD -1.83 (-3.65 to -0.01)	86%	--
By control type: vs. usual care	2 (325)	MD -3.20 (-7.21 to 0.82)	93%	0.56
vs. usual specialist care	1 (198)	MD -1.00 (-2.16 to 0.16)	--	--
vs. attention control	2 (250)	MD -0.85 (-2.47 to 0.77)	61%	--
By ME/CFS criteria:	3 (398)	MD -2.16 (-4.97 to 0.65)	90%	0.45
Oxford				
NICE	1 (198)	MD -1.00 (-2.16 to 0.16)	--	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	3 (540)	MD -0.97 (-1.71 to -0.23)	8%	--
<i>HADS depression (0 to 21), post-intervention</i>	3 (699)	MD -2.36 (-4.98 to 0.27)	92%	--
By control type: vs. usual care	2 (314)	MD -2.96 (-8.47 to 2.55)	96%	0.74
vs. usual specialist care	1 (295)	MD -1.10 (-2.11 to -0.09)	--	--
vs. attention control	1 (171)	MD -0.79 (-2.13 to 0.55)	--	--
By ME/CFS criteria:	3 (699)	MD -2.36 (-4.98 to 0.27)	92%	--
Oxford				
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (551)	MD -0.85 (-1.61 to -0.08)	0%	--
<i>HADS anxiety (0 to 21), end of intervention</i>	3 (620)	MD -1.59 (-2.41 to -0.77)	16%	--
By control type: vs. usual care	2 (325)	MD -1.90 (-3.54 to -0.26)	54%	--
vs. usual specialist care	1 (198)	MD -1.20 (-2.45 to 0.05)	--	--
vs. attention control	1 (182)	MD -1.57 (-2.74 to -0.40)	--	--
By ME/CFS criteria:	2 (422)	MD -1.94 (-3.36 to -0.51)	47%	0.45
Oxford				
NICE	1 (198)	MD -1.20 (-2.45 to 0.05)	--	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (472)	MD -1.31 (-2.12 to -0.51)	0%	--

Outcome	Number of studies (N)	Estimate (95% CI)	I ²	p for subgroup difference
<i>HADS anxiety (0 to 21), post-intervention</i>	3 (697)	MD -1.07 (-2.64 to 0.49)	75%	--
By control type: vs. usual care	2 (314)	MD -1.14 (-4.71 to 2.44)	89%	0.64
vs. usual specialist care	1 (293)	MD -0.90 (-1.92 to 0.12)	--	--
vs. attention control	1 (171)	MD -0.08 (-1.52 to 1.36)	--	--
By ME/CFS criteria Oxford	3 (697)	MD -1.07 (-2.64 to 0.49)	75%	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (549)	MD -0.38 (-1.52 to 0.76)	49%	--
<i>Sleep, end of intervention</i>	2 (420)	SMD -0.35 (-0.56 to -0.13)	0%	--
By control type: vs. usual care	2 (323)	SMD -0.27 (-0.53 to -0.00)	19%	0.33
vs. attention control	1 (180)	SMD -0.46 (-0.76 to -0.17)	--	--
By ME/CFS criteria: Oxford	2 (420)	SMD -0.35 (-0.56 to -0.13)	0%	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	1 (272)	SMD -0.31 (-0.57 to -0.05)	--	--
<i>Sleep, post-intervention</i>	3 (700)	SMD -0.39 (-0.71 to -0.07)	73%	--
By control type: vs. usual care	2 (315)	SMD -0.39 (-1.06 to 0.29)	86%	0.41
vs. usual specialist care	1 (295)	SMD -0.41 (-0.64 to -0.18)	--	--
vs. attention control	1 (171)	SMD -0.15 (-0.45 to 0.15)	--	--
By ME/CFS criteria: Oxford	3 (700)	SMD -0.39 (-0.71 to -0.07)	73%	--
Sensitivity analysis: Outlier trial (Powell 2001) excluded	2 (552)	SMD -0.26 (-0.56 to 0.03)	65%	--
<i>Recovery</i>	3 (536)	RR 2.01 (1.35 to 3.01)	0%	--
Original PACE definition	3 (550)	RR 1.86 (0.96 to 3.61)	0%	--
6-minute walk test (meters)	1 (228)	MD 31.00 (4.00 to 58.00)	--	--
<i>Serious adverse events</i>	2 (518)	RR 1.59 (0.69 to 3.66)	0%	--
<i>Withdrawal due to worsening</i>	1 (320)	RR 2.00 (0.18 to 21.84)	--	--
<i>Physical function worsening</i>	2 (518)	RR 0.83 (0.52 to 1.34)	0%	--
<i>Post-exertional malaise</i>	1 (320)	RR 0.70 (0.57 to 0.87)	--	--

Abbreviations: CFS = chronic fatigue syndrome; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; MD = mean difference; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence; PACE = pacing, graded activity, cognitive behavior therapy; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference

Exercise versus active interventions

Six trials (N=1,024) compared exercise versus active interventions (**Tables 3 and 4, Evidence Table Appendix E2**).^{36,50,51,54,56,57} The active interventions were CBT (2 trials),^{36,51} relaxation (3 trials),^{50,51,54} adaptive pacing (1 trial),³⁶ heart rate variability biofeedback (1 trial),⁵⁷ and fluoxetine (1 trial).⁵⁶ Of these, one trial of relaxation⁵⁴ and one trial of biofeedback⁵⁷ were added for this update. Five trials evaluated graded exercise and one trial⁵¹ evaluated anaerobic exercise. The duration of the exercise intervention ranged from six to 26 weeks. Four trials evaluated patients at the end of the intervention and five trials evaluated patients 26 to 70 weeks following the end of the intervention. Four trials were rated medium risk of bias and two trials were rated high risk of bias. One high risk of bias trial⁵⁴ evaluated exercise versus relaxation and the other⁵⁷ evaluated exercise versus biofeedback. Results stratified by the active comparator are summarized in **Table 6** and shown in **Figures 12 to 29**.

Exercise versus CBT

Two trials compared graded³⁶ or anaerobic⁵¹ exercise versus CBT in patients who met the Oxford case definition. The duration of the interventions was 5 to 6 months in both trials. One trial³⁶ evaluated outcomes at the end of the intervention and both trials evaluated outcomes approximately 6 months following the completion of therapy (**Table 6**).

There were no differences between exercise versus CBT in fatigue severity at the end of the intervention (1 trial, N=298, mean difference 0.20, 95% CI -1.49 to 1.89, **Figure 12**)³⁶ or between exercise versus CBT in fatigue at post-intervention follow-up (2 trials, N=360, SMD 0.08, 95% CI -0.13 to 0.29, $I^2=0\%$).^{36,51} There were also no differences between exercise versus CBT in severity of functional impairment at the end of the intervention (1 trial, N=298, mean difference 1.20, 95% CI -3.90 to 6.30 on the 0 to 100 SF-36 physical component scale, **Figure 14**)³⁶ or severity of functional impairment (2 trials, N=360, mean difference -8.36, 95% CI -26.21 to 9.50),^{36,51} depression (2 trials, N=345, SMD 0.02, 95% CI -0.19 to 0.23, $I^2=0\%$, **Figure 17**),^{36,51} anxiety (2 trials, N=345, SMD 0.07, 95% CI -0.14 to 0.28, $I^2=0\%$, **Figure 19**),^{36,51} sleep quality (2 trials, N=345, SMD -0.17, 95% CI -0.39 to 0.04, $I^2=0\%$, **Figure 21**),^{36,51} pain interference (1 trial, N=58, mean difference -0.35, 95% CI -2.02 to 1.32 on the 0 to 10 Brief Pain Inventory [BPI]),⁵¹ or 6-minute walk test distance (2 trials, N=291, mean difference -4.23 meters, 95% CI -75.99 to 67.52, $I^2=71\%$, **Figure 23**)^{36,51} at post-intervention follow-up. One trial found no differences between exercise versus CBT in severity of sore throat, tender lymph nodes, impaired memory, or headaches.⁵¹ The PACE trial found no difference between exercise versus CBT in likelihood of having poor concentration or memory (N=321, 48% vs. 45%, RR 1.05, 95% CI 0.83 to 1.33)³⁶ and a post-hoc analysis from PACE found no difference between exercise versus CBT in severity of muscle or joint pain.⁶⁰

There were no differences between exercise versus CBT in the likelihood of improvement in fatigue using the definition reported in the main PACE publication (1 trial, N=303, 80% vs. 76%, RR 1.05, 95% CI 0.93 to 1.19)³⁶ or the PACE protocol definition (1 trial, N=321, 24% vs. 26% RR 0.91, 95% CI 0.62 to 1.33)³⁸ (see earlier Results for details regarding PACE outcome definitions). There were also no differences in the likelihood of improvement in function using the definition reported in the main PACE definition (2 trials, N=360, RR 0.98, 95% CI 0.85 to 1.14, $I^2=0\%$)^{36,51} or the PACE protocol definition (2 trials, N=379, RR 1.17, 95% CI 0.81 to 1.70)^{38,51} or in the likelihood of overall improvement (the primary outcome in the PACE protocol), a composite of improvement in fatigue and function (1 trial, N=321, 21% vs. 20%, RR 1.04, 95% CI 0.67 to 1.60).³⁸ There was no difference between exercise versus CBT in the likelihood of recovery (2 trials, N=360, RR 0.91, 95% CI 0.65 to 1.29, $I^2=0\%$).^{36,51} As previously noted, the definition for recovery in the PACE trial was modified from the original protocol; there was also no difference in the likelihood of recovery using the original PACE definition for this outcome (2 trials, N=379, RR 1.13, 95% CI 0.33 to 3.84, $I^2=45\%$).^{51,62}

Data on harms of exercise versus CBT were largely limited to the PACE trial.³⁶ It found exercise associated with increased likelihood of serious adverse events, but the difference was not statistically significant (N=321, RR 1.87, 95% CI 0.77 to 4.56). The estimate for withdrawal due to adverse events was based on only 2 cases and very imprecise (RR 5.03, 95% CI 0.24 to 104.0). There was no difference in the likelihood of worsening of function (RR 1.01, 95% CI 0.30 to 3.41) or post-exertional malaise (RR 0.90, 95% CI 0.72 to 1.14). However, one other trial found exercise associated with increased severity of post-exertional malaise versus CBT (N=58, mean difference 18.6, 95% CI -31.6 to 7.1 on the 0 to 100 CFS Questionnaire).⁵¹

The PACE trial also evaluated longer-term, post-trial outcomes (median duration from randomization 31 months).⁵⁹ About 30% of patients in both the exercise and CBT groups received non-randomly allocated therapies between the end of the trial at 1 year and long-term follow-up. Fatigue on the 11-item 0 to 33 Chalder scale was slightly improved at long-term follow-up compared with end-of-trial scores in both the exercise (mean change -1.3 points, 95% CI -2.7 to -0.1) and CBT arms (-2.2 points, 95% CI -3.7 to -0.6). For SF-36 physical function (0 to 100 scale), there was no change at long-term follow-up compared with the end of the trial in the exercise group (mean change 0.5 point, 95% CI -2.7 to 3.6 on a 0 to 100 scale), but function slightly improved in the CBT group (mean change 3.3 points, 95% CI 0.02 to 6.7). At long-term post-trial follow-up, there were no difference between graded exercise or CBT versus specialist medical care in fatigue (N=246, mean difference 0.7, 95% CI -1.4 to 2.8) or function (N=246, mean difference -2.4, 95% CI -9.3 to 4.5), based on mixed model analyses.

Exercise versus cognitive therapy

One trial included a comparison of exercise versus cognitive therapy (N=57) in patients who met the Fukuda case definition.⁵¹ Outcomes were evaluated 6 months following completion of 6 months of treatment. There were no differences between CBT versus cognitive therapy in severity of fatigue, depression, anxiety or pain; sleep quality; or distance on the 6-minute walking test (**Table 6**). CBT was associated with greater severity of functional impairment (mean difference -21.37, 95% CI -34.73 to -9.01 on the 0 to 100 SF-36 physical function scale) and greater severity of post-exertional malaise (mean difference 20.1, 95% CI 3.0 to 37.3 on the 0 to 100 CFS Questionnaire). There were no differences in severity of sore throat (mean difference 3.6, 95% CI -7.2 to 14.4), tender lymph nodes (mean difference 4.7, 95% CI -8.5 to 17.9), impaired memory (mean difference 1.5, 95% CI -13.4 to 16.5), or headaches (mean difference -0.64, 95% CI -20.7 to 19.4). There was also no difference in likelihood of functional improvement or recovery, but estimates were imprecise (**Table 6**).

Exercise versus relaxation

Three trials compared exercise versus relaxation in patients who met the Oxford⁵⁰ or Fukuda^{51,54} case definition. Two of the trials included a flexibility intervention along with relaxation.^{50,54} Two trials^{50,54} evaluated graded exercise (treatment duration 12 weeks) and one trial⁵¹ evaluated anaerobic exercise (treatment duration 6 months). One trial⁵⁰ evaluated outcomes at the end of the intervention and two trials^{51,54} evaluated outcomes 4 weeks and 6 months following the end of the intervention. One trial was rated high risk of bias⁵⁴ and the other two were medium risk of bias; conclusions did not change when the high risk of bias trial was excluded.

Exercise was associated with decreased fatigue severity versus relaxation at the end of the intervention (1 trial, N=66, mean difference -6.9, 95% CI -10.85 to 2.95 on the 14-item 0 to 42 Chalder fatigue scale, **Figure 12**)⁵⁰ but there was no difference at post-intervention follow-up (2 trials, N=118, SMD -0.16, 95% CI -0.71 to 0.38, I²=56%).^{51,54} Exercise was associated with decreased functional impairment at the end of the intervention (1 trial, N=66, mean difference 14.00, 95% CI 4.24 to 23.76 on the 0 to 100 SF-36 physical function subscale)⁵⁰ but greater functional impairment at post-intervention follow-up (1 trial, N=57, mean difference -21.48, 95% CI -35.85 to -7.11);⁵¹ only 1 trial evaluated this outcome at each of these timepoints. There were no differences between exercise versus relaxation in depression, anxiety, sleep, pain, or the 6-minute walk test, at the end of the intervention or at post-intervention follow-up (**Table 6**).

One trial found no difference between exercise versus relaxation in severity of sore throat, tender lymph nodes, impaired memory, or headaches.⁵¹ Exercise was associated with increased likelihood of a self-rated Clinical Global Impression rating of much better or very much better (2 trials, N=120, RR 1.64, 95% CI 1.09 to 2.48, I²=0%).^{50,54} There was no difference in the likelihood of functional improvement, defined as improvement in the SF-36 physical function subscale greater than the age adjusted reliable change index and within 1 standard deviation of the normative mean (1 trial, N=57, RR 0.48, 95% CI 0.13 to 1.74).⁵¹ The estimate for recovery was very imprecise (1 trial, N=57, RR 4.83, 95% CI 0.24 to 96.42).⁵¹

One trial found exercise associated with increased severity of post-exertional malaise versus relaxation (1 trial, N=57, mean difference 22.0, 95% CI 5.7 to 38.4).⁵¹ The trials did not report serious adverse events, withdrawal due to adverse events, or other harms.

Exercise versus adaptive pacing

The PACE trial included a comparison of graded exercise versus adaptive pacing (N=319) in patients who met the Oxford case definition. Outcomes were reported at the end of therapy at 24 weeks and 28 weeks following the completion of therapy.³⁶ Exercise was associated with decreased fatigue severity versus adaptive pacing at the end of the intervention (mean difference -2.0, 95% CI -3.6 to -0.4 on the 11-item 0 to 33 Chalder scale) and at post-intervention follow-up (mean difference -2.5, 95% CI -4.2 to -0.84). Exercise was also associated with decreased depression severity (mean difference -1.1, 95% CI -2.0 to -0.15 on the 0 to 21 HADS depression scale), better sleep quality (mean difference -1.6, 95% CI -2.7 to -0.54 on the 0 to 20 Jenkins sleep scale), and longer 6-minute walk test (mean difference 45 meters, 95% CI 21 to 69) at post-intervention follow-up, with no difference in anxiety (mean difference -0.4, 95% CI -1.4 to 0.6 on the 0 to 21 HADS anxiety scale).

Exercise was associated with increased likelihood of improvement in fatigue (80% vs. 65%, RR 1.23, 95% CI 1.07 to 1.41), improvement in function (70% vs. 49%, RR 1.43, 95% CI 1.18 to 1.73), and recovery (28% vs. 16%, RR 1.71, 95% CI 1.10 to 2.65) versus adaptive pacing, based on the definitions used in the main PACE publication.³⁶ Results were similar using the original PACE protocol definitions for improvement in fatigue (24% vs. 14%, RR 1.64, 95% CI 1.03 to 2.62), improvement in function (61% vs. 40%, RR 1.51, 95% CI 1.20 to 1.89), and overall improvement (composite of improvement in fatigue and function, 21% vs. 9%, RR 2.19, 95% CI 1.24 to 3.86).³⁸ Exercise was also associated with lower likelihood of post-exertional malaise (44% vs. 63%, RR 0.71, 95% CI 0.57 to 0.87). There were no differences between exercise therapy versus adaptive pacing in risk of serious adverse events, withdrawal due to adverse events, or worsening of function, but estimates were imprecise (**Table 6**). In a post-hoc analysis, exercise was associated with decreased severity of muscle pain (mean difference -0.37, 95% CI -0.69 to -0.05) and joint pain (mean difference -0.36, 95% CI -0.69 to -0.05) at post-intervention follow-up (each assessed on a 0 to 4 scale).⁶⁰

The PACE trial also evaluated longer-term, post-trial outcomes (median duration from randomization 31 months).⁵⁹ About 30% of patients in the exercise group and 50% in the adaptive pacing group received non-randomly allocated therapies between the end of the trial at 1 year and long-term follow-up. Fatigue severity based on the 11-item 0 to 33 Chalder scale was improved at long-term follow-up compared with end-of-trial scores in both the exercise (mean change -1.3, 95% CI -2.7 to -0.1) and adaptive pacing groups (mean change -3.0, 95% CI -4.4 to -1.6). For SF-36 physical function, there was no change at long-term follow-up compared with the end of the trial for exercise (mean change 0.5 point, 95% CI -2.7 to 3.6 on a 0 to 100 scale),

but the severity of functional impairment improved in the adaptive pacing group (mean change 8.5 points, 95% CI 4.5 to 12.5). At long-term follow-up, mixed models showed no differences between graded exercise versus adaptive pacing in fatigue (mean difference -1.1, 95% CI -3.0 to 0.9) or function (mean difference 5.6, 95% CI -0.3 to 11.5), though estimates favored graded exercise.

Exercise versus biofeedback

One small (n=24), high risk of bias trial compared graded exercise versus heart rate variability biofeedback therapy in patients who met the Fukuda case definition.⁵⁷ The duration of the intervention was 8 weeks and outcomes were assessed at the end of treatment and at 5 months. Results favored exercise therapy over biofeedback for fatigue at the end of the intervention and at post-intervention follow-up, but differences were small and not statistically significant, and the estimates were imprecise (**Table 6**). Exercise was associated with greater depression severity at the end of treatment (mean difference 4.0, 95% CI 0.72 to 1.14 on the 0 to 27 Patient Health Questionnaire, 95% CI 0.72) and at post-intervention follow-up (mean difference 4.6, 95% CI 0.65 to 8.55) compared with biofeedback. The trial did not report harms.

Exercise versus fluoxetine

One trial (n=69) compared graded exercise versus fluoxetine (a selective serotonin reuptake inhibitor [SSRI]) in patients who met the Oxford case definition.⁵⁶ Outcomes were evaluated at the completion of 12 weeks of treatment and 14 weeks following the end of treatment. There were no differences between exercise versus fluoxetine in fatigue or depression at the end of the intervention or at post-intervention follow-up (**Table 6**). There was also no difference in the likelihood of recovery (defined as a score <4 on the 11-item 0 to 11 Chalder fatigue scale), but the estimate was imprecise (RR 3.09, 95% CI 0.67 to 14.25). The trial did not evaluate harms.

Exercise plus medication (fluoxetine) versus exercise or fluoxetine alone

One trial (N=102) compared graded exercise plus fluoxetine versus exercise or fluoxetine alone in patients who met the Oxford case definition.⁵⁶ Outcomes were evaluated at the completion of 12 weeks of treatment and 14 weeks following the end of treatment. The combination of exercise and fluoxetine was associated with less fatigue severity at the end of the intervention versus either exercise (mean difference -3.6, 95% CI -8.1 to 0.9 on the 14-item 0 to 42 Chalder fatigue scale) or fluoxetine (mean difference -4.1, 95% CI -8.6 to 0.4) alone, but the differences were not statistically significant. At post-intervention follow-up, differences in fatigue severity between the combination versus either therapy alone were smaller and remained non-statistically significant. Differences in depression scores were small and not statistically significant at the end of the intervention and at post-intervention follow-up (mean differences on the 0 to 21 HADS depression scale ranged from -1.0 to 0.5 points). The trial did not evaluate harms.

Table 6. Exercise versus active interventions: Summary of stratified results

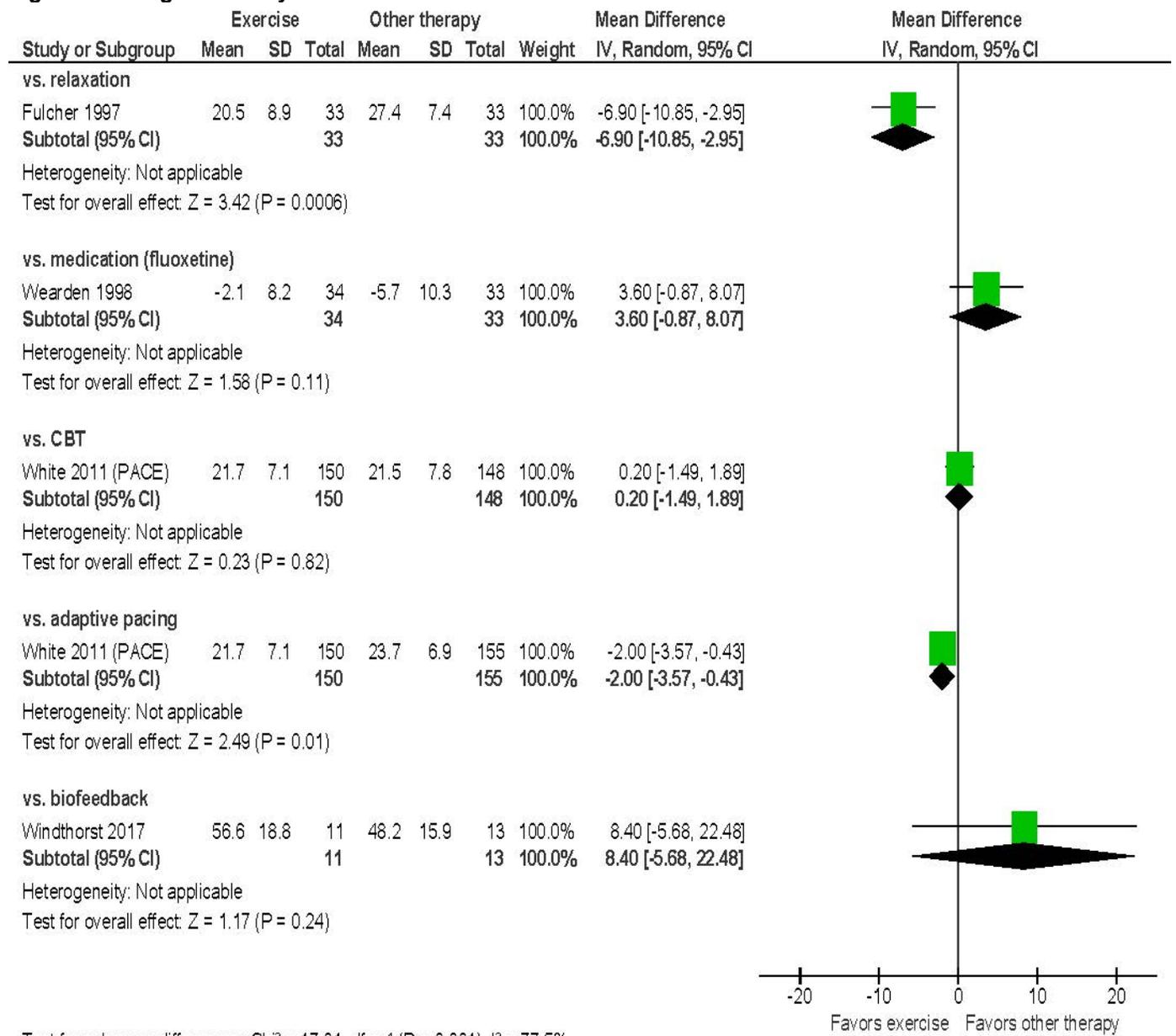
Outcome	Number of studies (N)	Estimate (95% CI)	I ²
<i>Fatigue, end of intervention</i>			
vs. CBT	1 (298)	SMD 0.03 (-0.20 to 0.25)	--
vs. relaxation	1 (66)	SMD -0.83 (-1.34 to -0.33)	--
vs. adaptive pacing	1 (305)	SMD -0.29 (-0.51 to -0.06)	--
vs. biofeedback	1 (24)	SMD 0.47 (-0.35 to 1.29)	--
vs. fluoxetine	1 (67)	SMD 0.38 (-0.10 to 0.87)	--

Outcome	Number of studies (N)	Estimate (95% CI)	I ²
<i>Fatigue, post-intervention</i>			
vs. CBT	2 (360)	SMD 0.08 (-0.13 to 0.29)	0%
vs. relaxation	2 (118)	SMD -0.16 (-0.71 to 0.38)	56%
vs. cognitive therapy	1 (57)	SMD -0.08 (-0.60 to 0.44)	--
vs. adaptive pacing	1 (307)	SMD -0.34 (-0.56 to -0.11)	--
vs. biofeedback	1 (24)	SMD 0.62 (-0.20 to 1.45)	--
vs. fluoxetine	1 (69)	SMD -0.27 (-0.74 to 0.21)	--
<i>SF-36 physical function subscale or physical component score (0 to 100), end of intervention</i>			
vs. CBT	1 (298)	MD 1.20 (-3.90 to 6.30)	--
vs. relaxation	1 (66)	MD 14.00 (4.24 to 23.76)	--
vs. adaptive pacing	1 (305)	MD 12.20 (7.17 to 17.23)	--
vs. biofeedback	1 (24)	MD -0.40 (-8.26 to 7.46)	--
<i>SF-36 physical function subscale or physical component score (0 to 100), post-intervention</i>			
vs. CBT	2 (360)	MD -8.36 (-26.21 to 9.50)	80%
vs. relaxation	1 (57)	MD -21.48 (-35.85 to -7.11)	--
vs. cognitive therapy	1 (57)	MD -21.37 (-34.73 to -8.01)	--
vs. adaptive pacing	1 (207)	MD 11.80 (6.05 to 17.55)	--
vs. biofeedback	1 (24)	MD -0.50 (-8.35 to 7.35)	--
<i>Depression, end of intervention</i>			
vs. relaxation	1 (66)	SMD 0.33 (-0.15 to 0.82)	--
vs. biofeedback	1 (24)	SMD 1.01 (0.15 to 1.88)	--
vs. fluoxetine	1 (69)	SMD 0.44 (-0.04 to 0.91)	--
<i>Depression, post-intervention</i>			
vs. CBT	2 (345)	SMD 0.02 (-0.19 to 0.23)	0%
vs. relaxation	2 (118)	SMD -0.12 (-0.95 to 0.72)	81%
vs. cognitive therapy	1 (57)	SMD 0.51 (-0.02 to 1.04)	--
vs. adaptive pacing	1 (293)	SMD -0.25 (-0.48 to -0.02)	--
vs. biofeedback	1 (24)	SMD 0.96 (0.10 to 1.81)	--
vs. fluoxetine	1 (80)	SMD 0.13 (-0.32 to 0.57)	--
<i>HADS anxiety (0 to 21), end of intervention</i>			
vs. relaxation	1 (66)	MD -1.50 (-3.68 to 0.68)	--
<i>Anxiety, post intervention</i>			
vs. CBT	2 (345)	SMD 0.07 (-0.14 to 0.28)	0%
vs. relaxation	2 (118)	SMD -0.25 (-0.88 to 0.37)	66%
vs. cognitive therapy	1 (57)	SMD 0.36 (-0.16 to 0.88)	--
vs. adaptive pacing	1 (293)	SMD -0.09 (-0.32 to 0.14)	--
<i>Pittsburgh Sleep Quality Index (0 to 21), end of intervention</i>			
vs. relaxation	1 (66)	MD -1.00 (-2.21 to 0.212)	--
<i>Sleep, post intervention</i>			
vs. CBT	2 (345)	SMD -0.17 (-0.39 to 0.04)	0%
vs. relaxation	1 (57)	SMD 0.14 (-0.38 to 0.66)	--
vs. cognitive therapy	1 (57)	SMD -0.04 (-0.56 to 0.48)	--
vs. adaptive pacing	1 (294)	SMD -0.33 (-0.56 to -0.10)	--
<i>Brief Pain Inventory (0 to 10), post intervention</i>			
vs. CBT	1 (58)	MD -0.35 (-2.02 to 1.32)	--
vs. relaxation	1 (57)	MD -0.69 (-2.23 to 0.85)	--
vs. cognitive therapy	1 (57)	MD 0.39 (-1.14 to 1.92)	--
<i>6-minute walk test (meters), end of intervention</i>			
vs. CBT	2 (291)	MD -4.23 (-75.99 to 67.52)	71%
vs. relaxation	1 (57)	MD -15.53 (-55.32 to 24.26)	--
vs. cognitive therapy	1 (57)	MD -41.21 (-79.61 to -2.80)	--
vs. adaptive pacing	1 (221)	MD 45.00 (16.31 to 73.69)	--
<i>Recovery</i>			
vs. CBT	2 (360)	RR 0.91 (0.65 to 1.29)	0%
vs. relaxation	1 (57)	RR 4.83 (0.24 to 96.42)	--
vs. cognitive therapy	1 (57)	RR 0.48 (0.10 to 2.43)	--
vs. adaptive pacing	1 (307)	RR 1.71 (1.10 to 2.65)	--
vs. fluoxetine	1 (69)	RR 3.09 (0.67 to 14.25)	--

Outcome	Number of studies (N)	Estimate (95% CI)	I ²
<i>Fatigue improvement</i>			
vs. CBT	1 (303)	RR 1.05 (0.93 to 1.19)	--
vs. adaptive pacing	1 (306)	RR 1.23 (1.07 to 1.41)	--
<i>Functional improvement</i>			
vs. CBT	2 (360)	RR 0.98 (0.85 to 1.14)	0%
vs. relaxation	1 (57)	RR 0.48 (0.13 to 1.74)	--
vs. cognitive therapy	1 (57)	RR 0.32 (0.10 to 1.07)	--
vs. adaptive pacing	1 (307)	RR 1.43 (1.18 to 1.73)	--
<i>Serious adverse events</i>			
vs. CBT	1 (321)	RR 1.87 (0.77 to 4.56)	--
vs. adaptive pacing	1 (319)	RR 0.86 (0.42 to 1.75)	--
<i>Withdrawal due to worsening</i>			
vs. CBT	1 (321)	RR 5.03 (0.24 to 103.97)	--
vs. adaptive pacing	1 (319)	RR 0.66 (0.11 to 3.91)	--
<i>Physical function worsening</i>			
vs. CBT	1 (321)	RR 1.01 (0.30 to 3.41)	--
vs. adaptive pacing	1 (319)	RR 0.71 (0.23 to 2.19)	--
<i>Post-exertional malaise</i>			
vs. CBT	1 (321)	RR 0.90 (0.72 to 1.14)	--
vs. adaptive pacing	1 (319)	RR 0.71 (0.57 to 0.87)	--

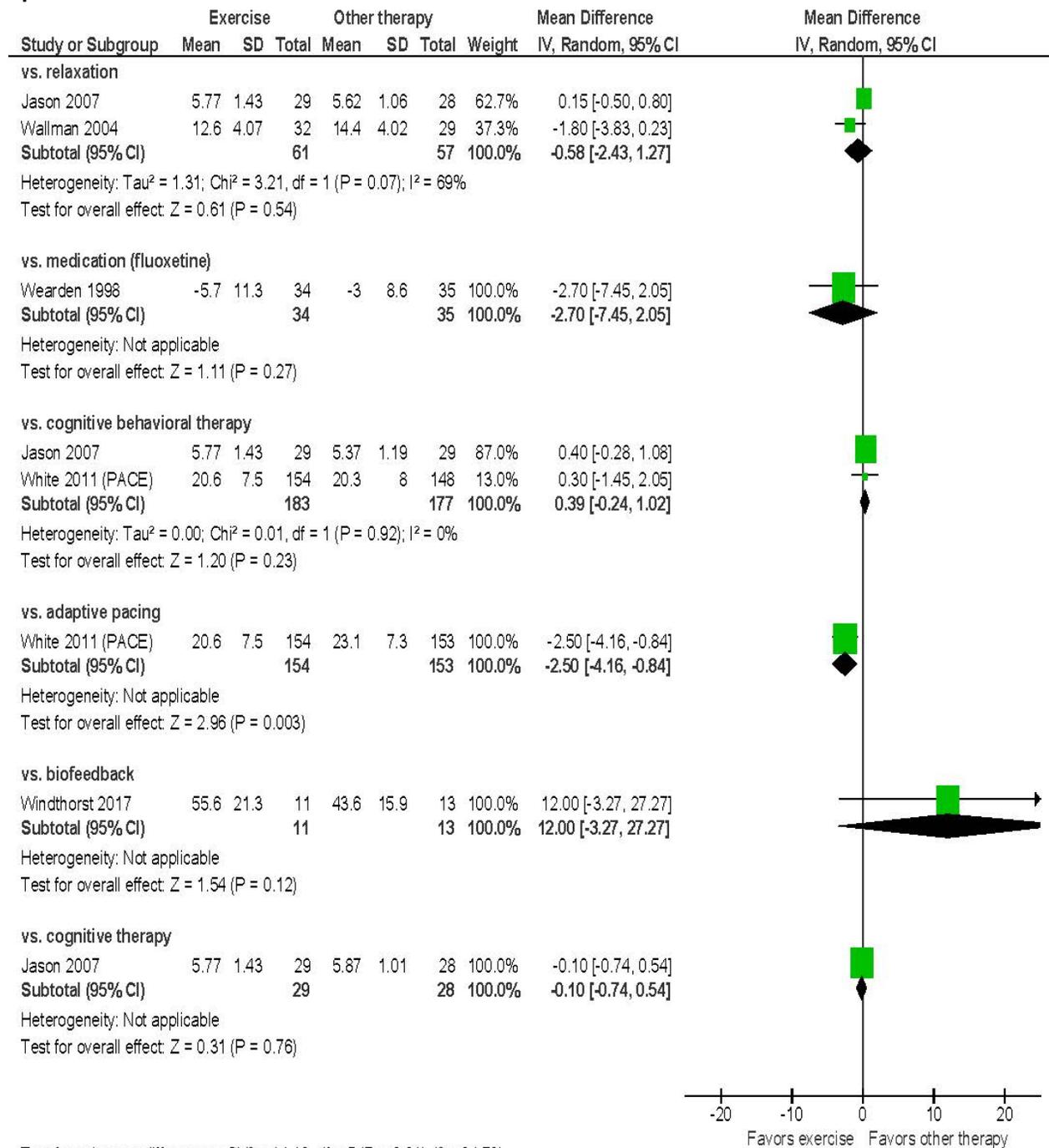
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; MD = mean difference; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference

Figure 12. Fatigue severity: Graded exercise versus active intervention at end of intervention



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

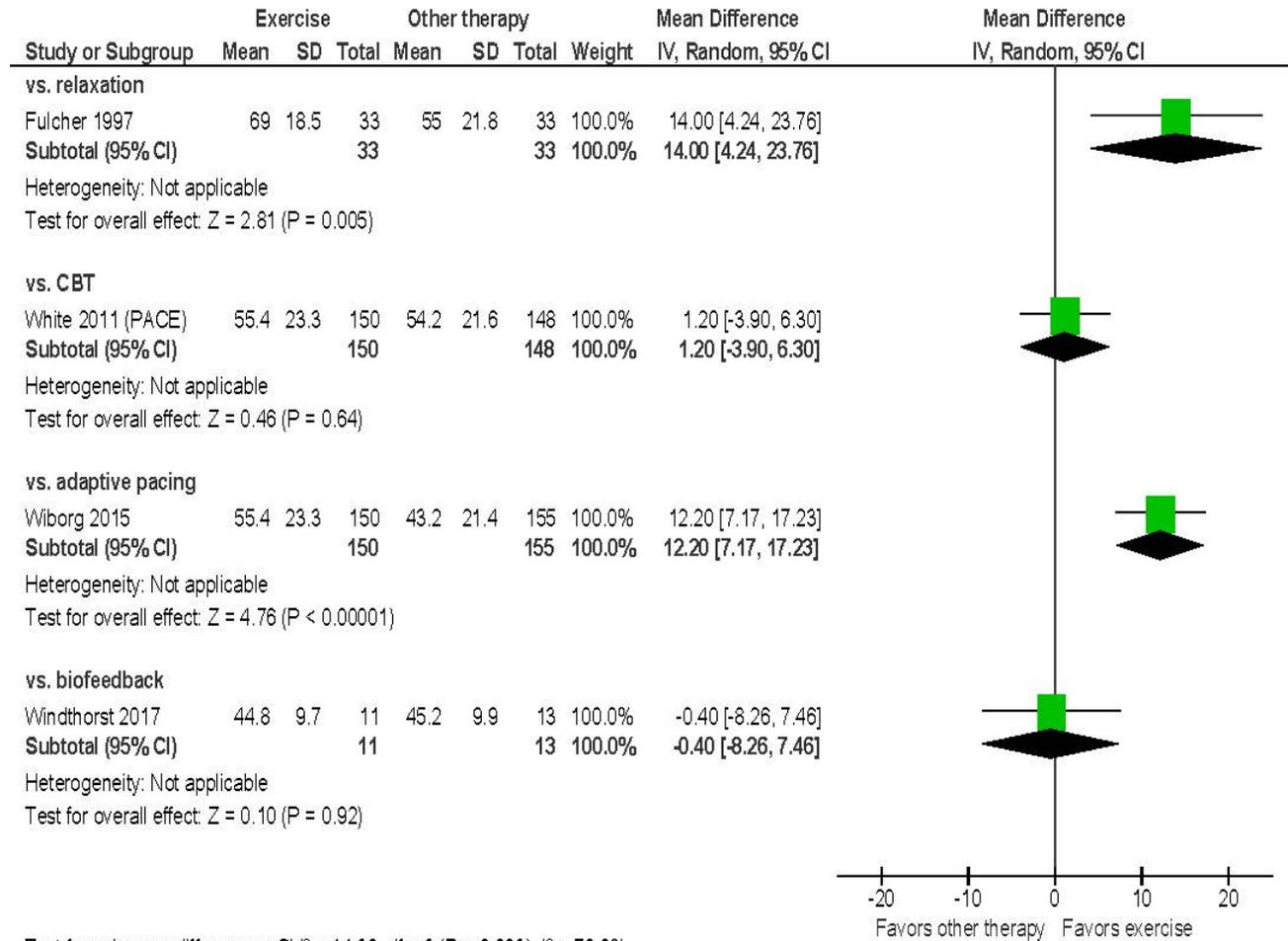
Figure 13. Fatigue severity: Graded exercise versus active intervention at post-intervention follow-up



Test for subgroup differences: Chi² = 14.16, df = 5 (P = 0.01), I² = 64.7%

Abbreviations: CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

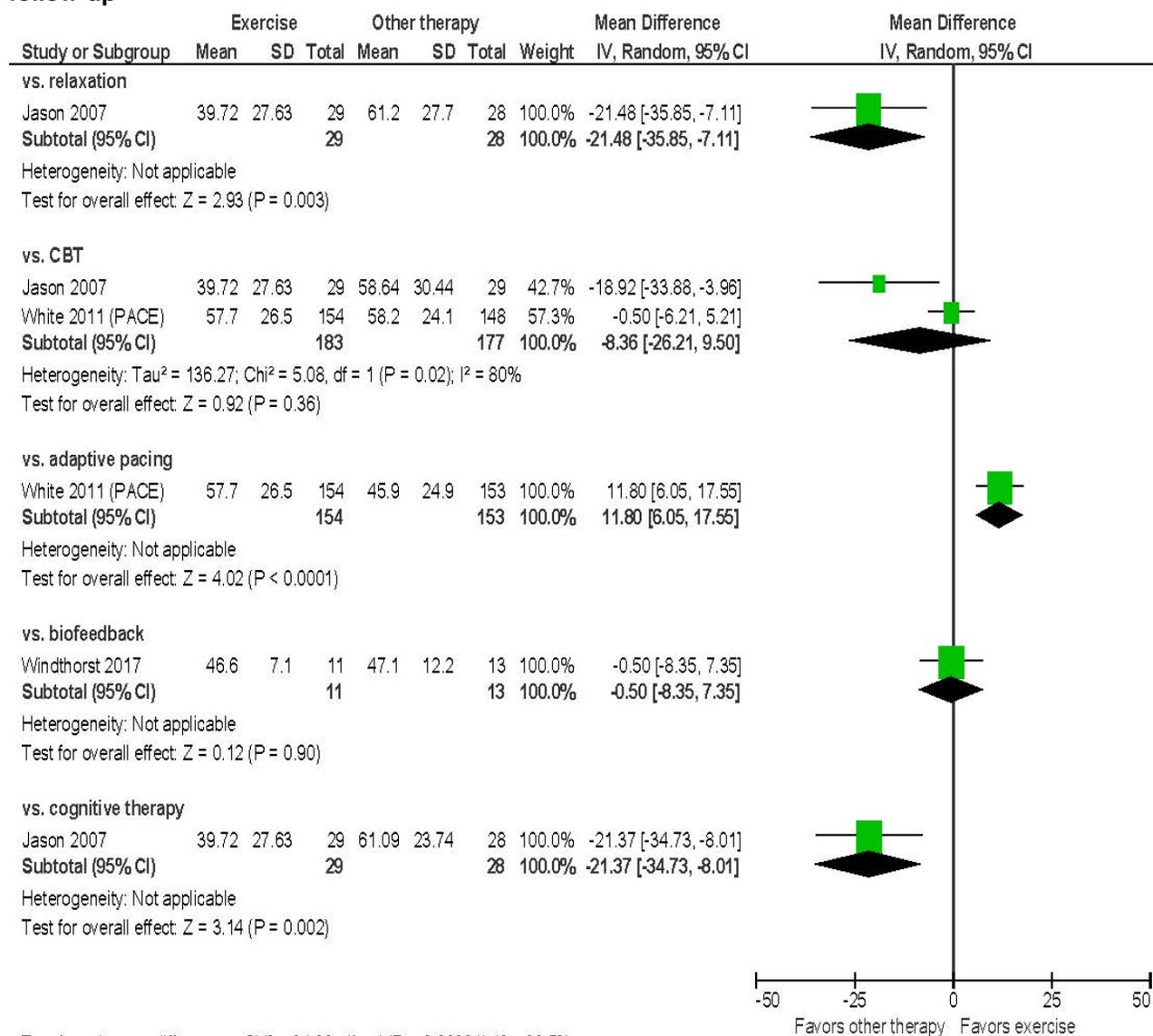
Figure 14. Functional impairment: Graded exercise versus active intervention at end of intervention



Test for subgroup differences: Chi² = 14.32, df = 3 (P = 0.003), I² = 79.0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

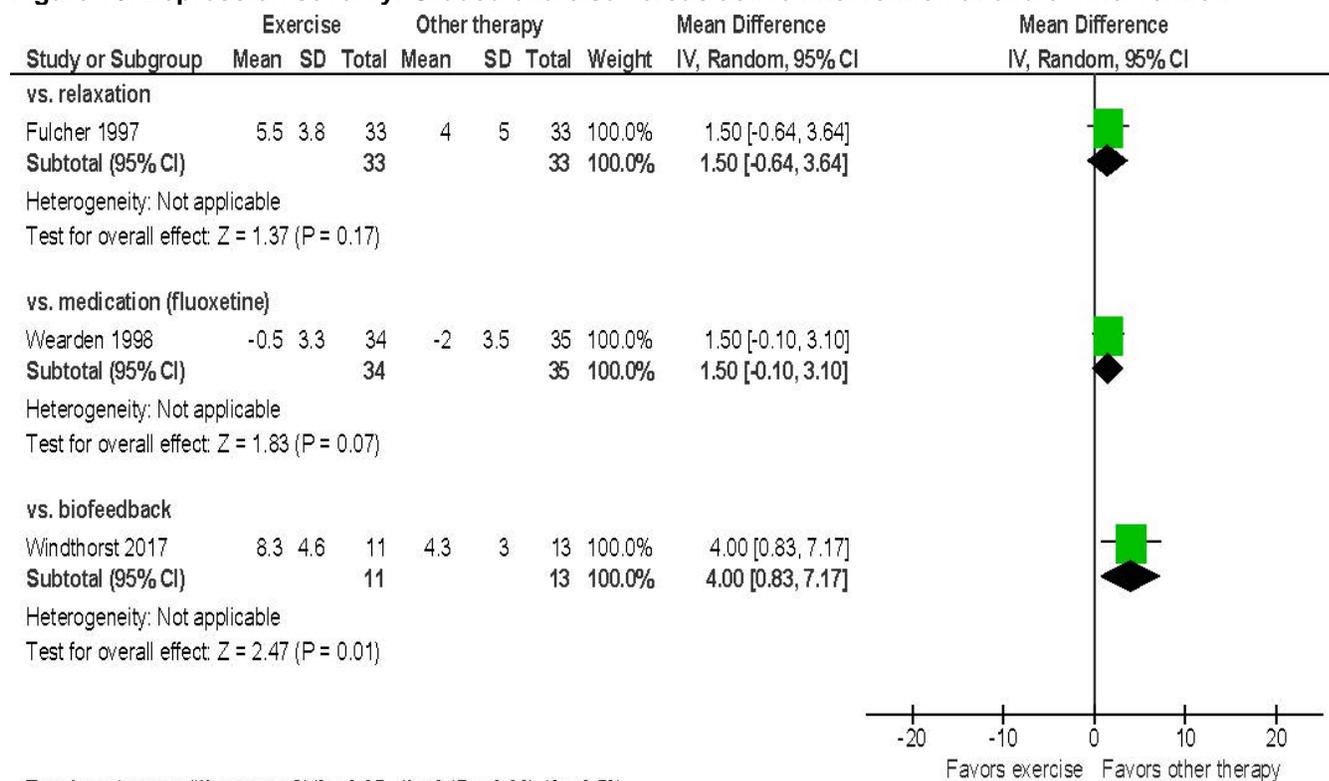
Figure 15. Functional impairment: Graded exercise versus active intervention at post-intervention follow-up



Test for subgroup differences: Chi² = 34.82, df = 4 (P < 0.00001), I² = 88.5%

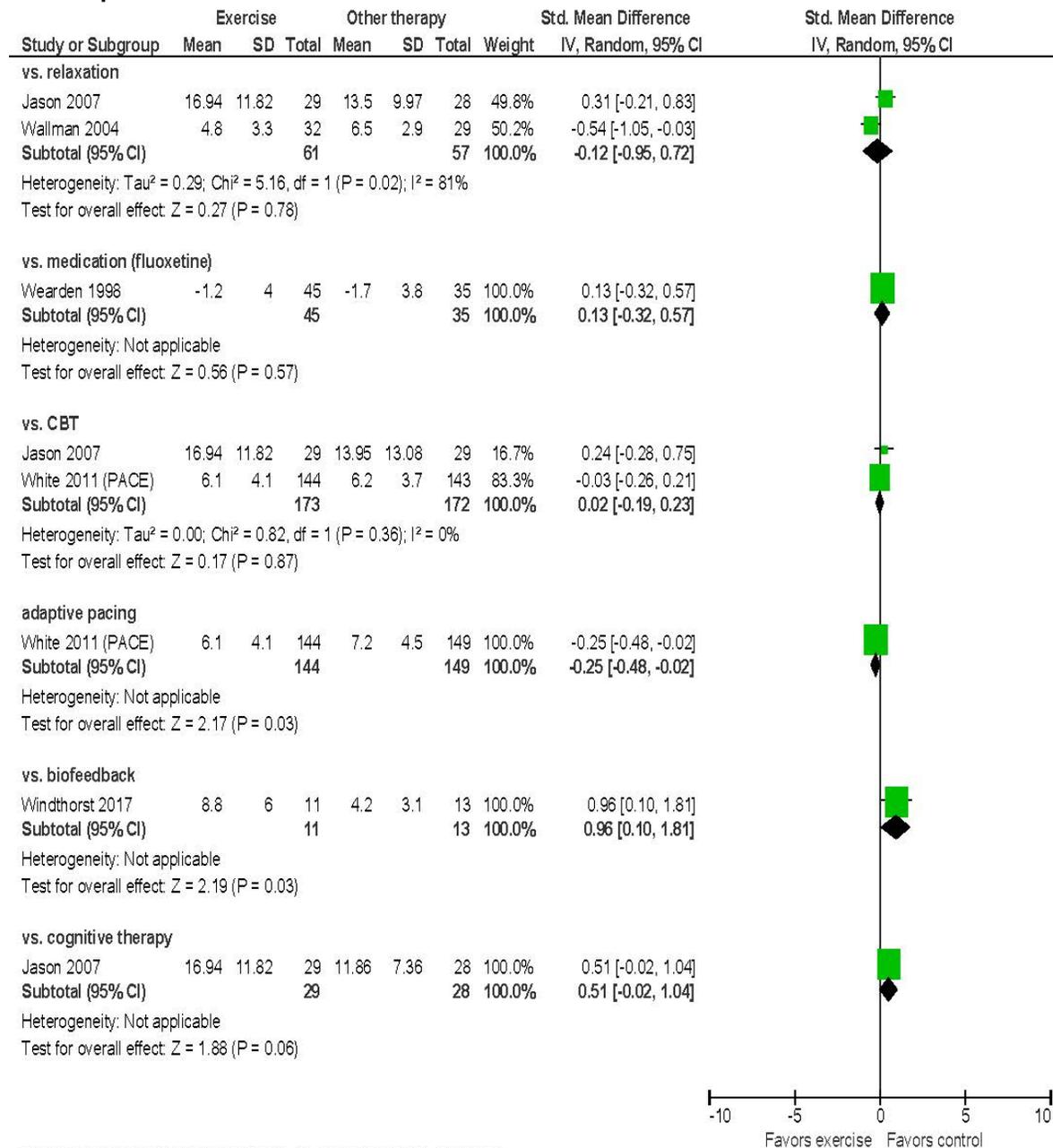
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 16. Depression severity: Graded exercise versus active intervention at end of intervention



Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.5%
 Abbreviations: CI = confidence interval; IV = instrumental variable; SD = standard deviation

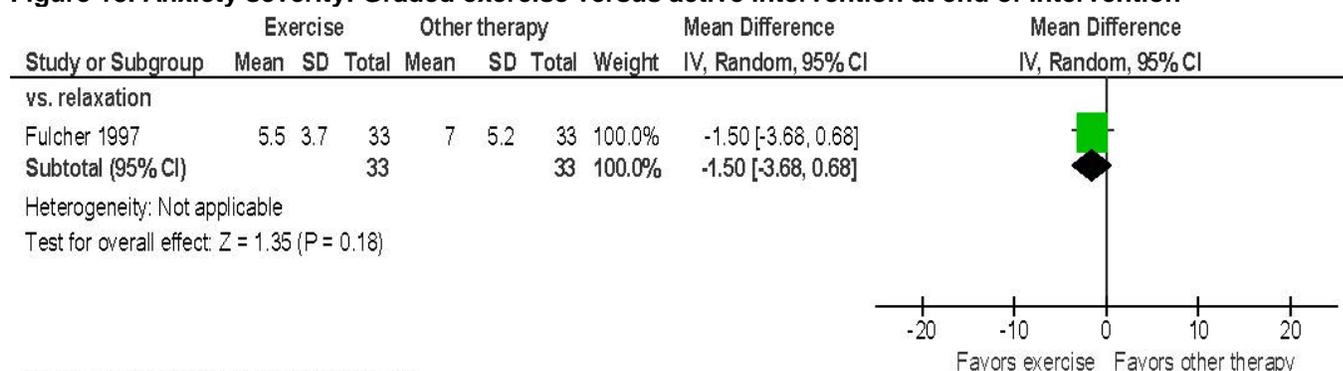
Figure 17. Depression severity: Graded exercise versus active intervention at post-intervention follow-up



Test for subgroup differences: Chi² = 13.41, df = 5 (P = 0.02), I² = 62.7%

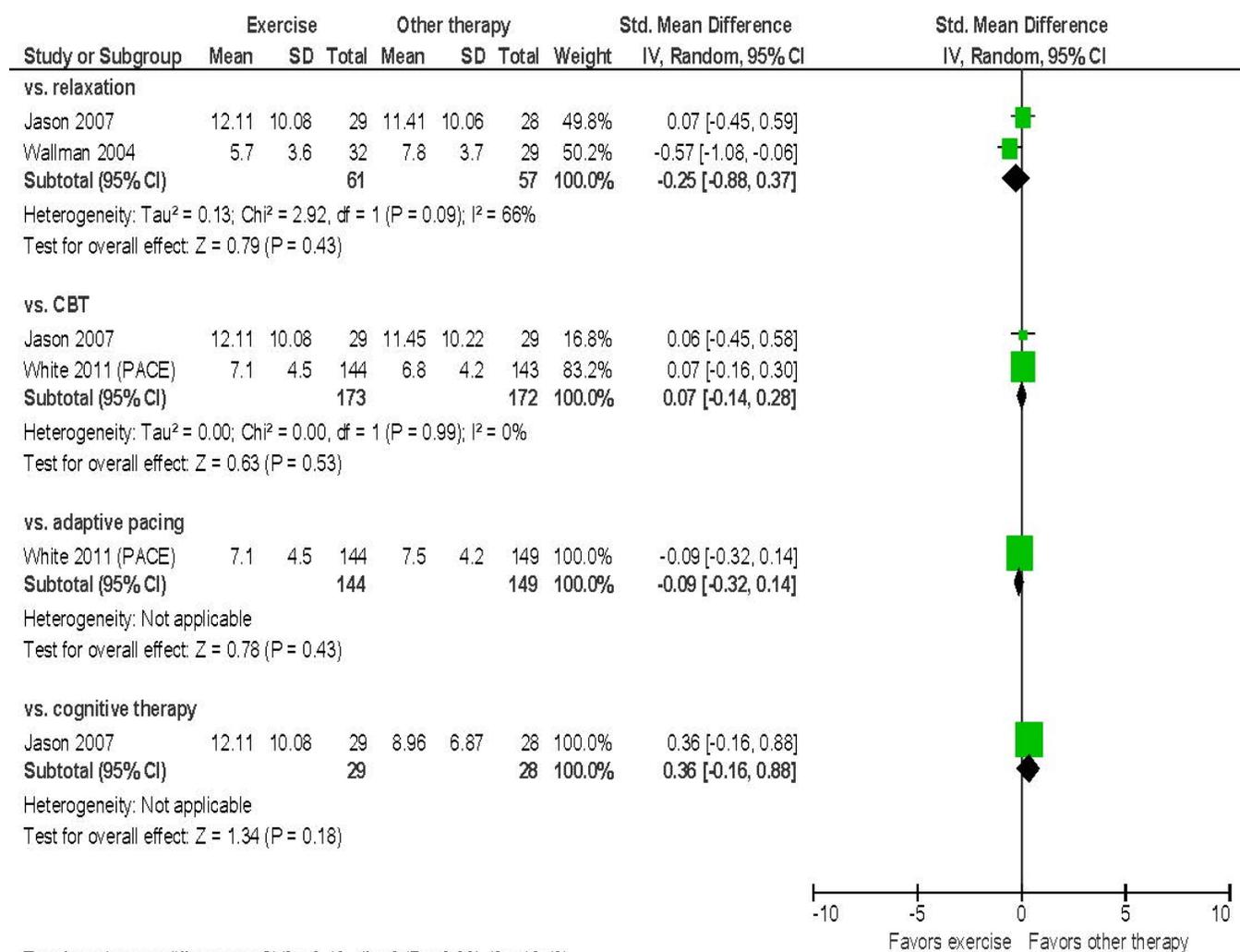
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 18. Anxiety severity: Graded exercise versus active intervention at end of intervention



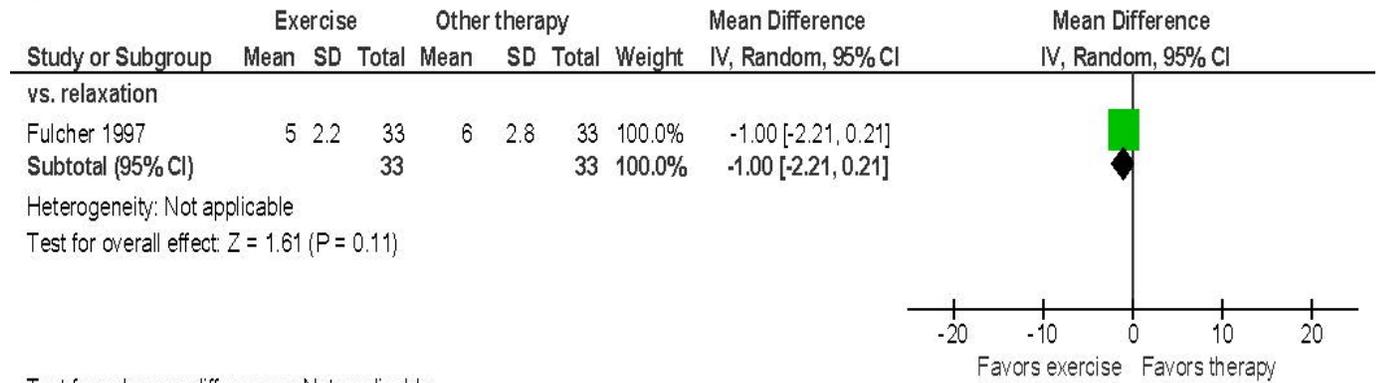
Test for subgroup differences: Not applicable
Abbreviations: CI = confidence interval; IV = instrumental variable; SD = standard deviation

Figure 19. Anxiety severity: Graded exercise versus active interventions at post-intervention follow-up



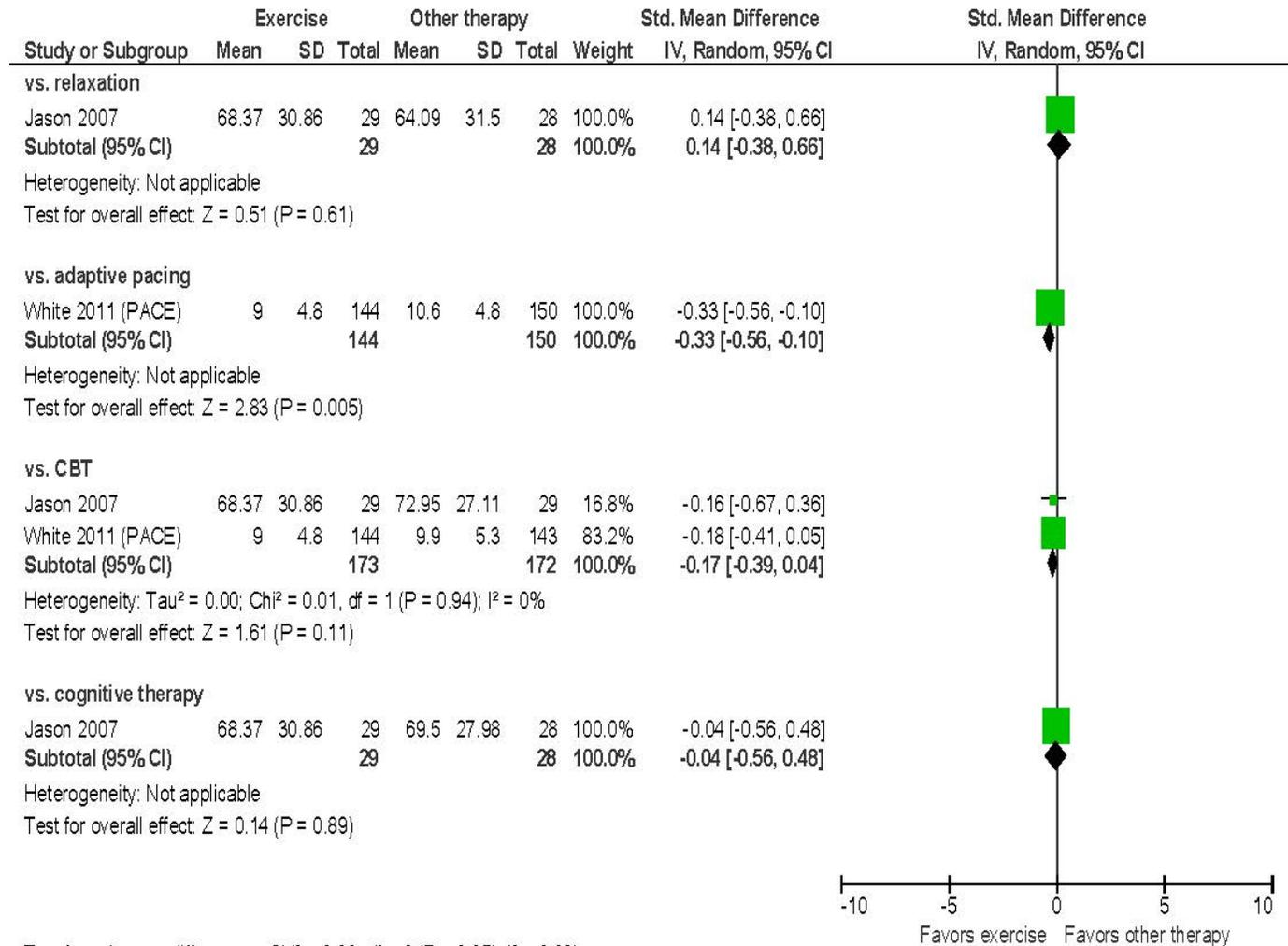
Test for subgroup differences: Chi² = 3.42, df = 3 (P = 0.33), I² = 12.4%
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 20. Sleep: Graded exercise versus active intervention at end of intervention



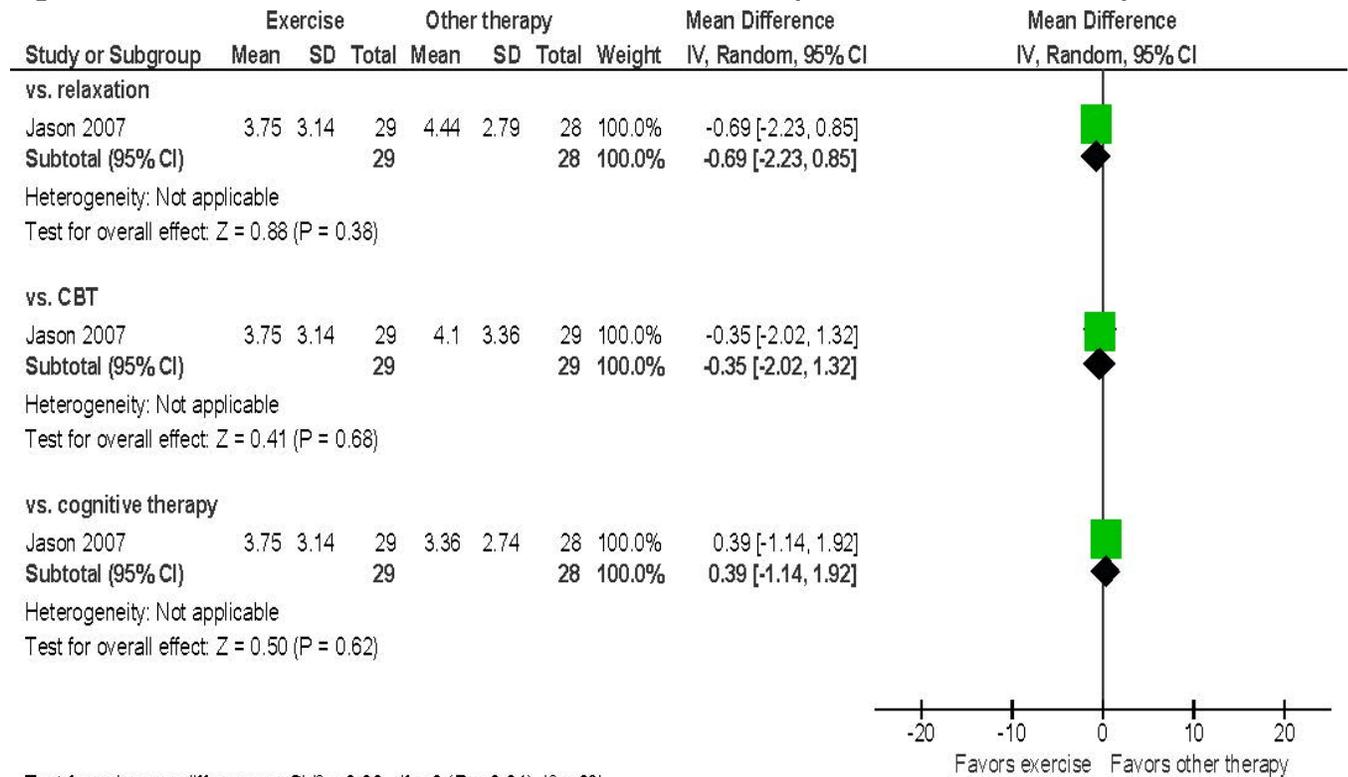
Test for subgroup differences: Not applicable
 Abbreviations: CI = confidence interval; IV = instrumental variable; SD = standard deviation

Figure 21. Sleep: Graded exercise versus active intervention at post-intervention follow-up



Test for subgroup differences: Chi² = 3.30, df = 3 (P = 0.35), I² = 9.2%
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

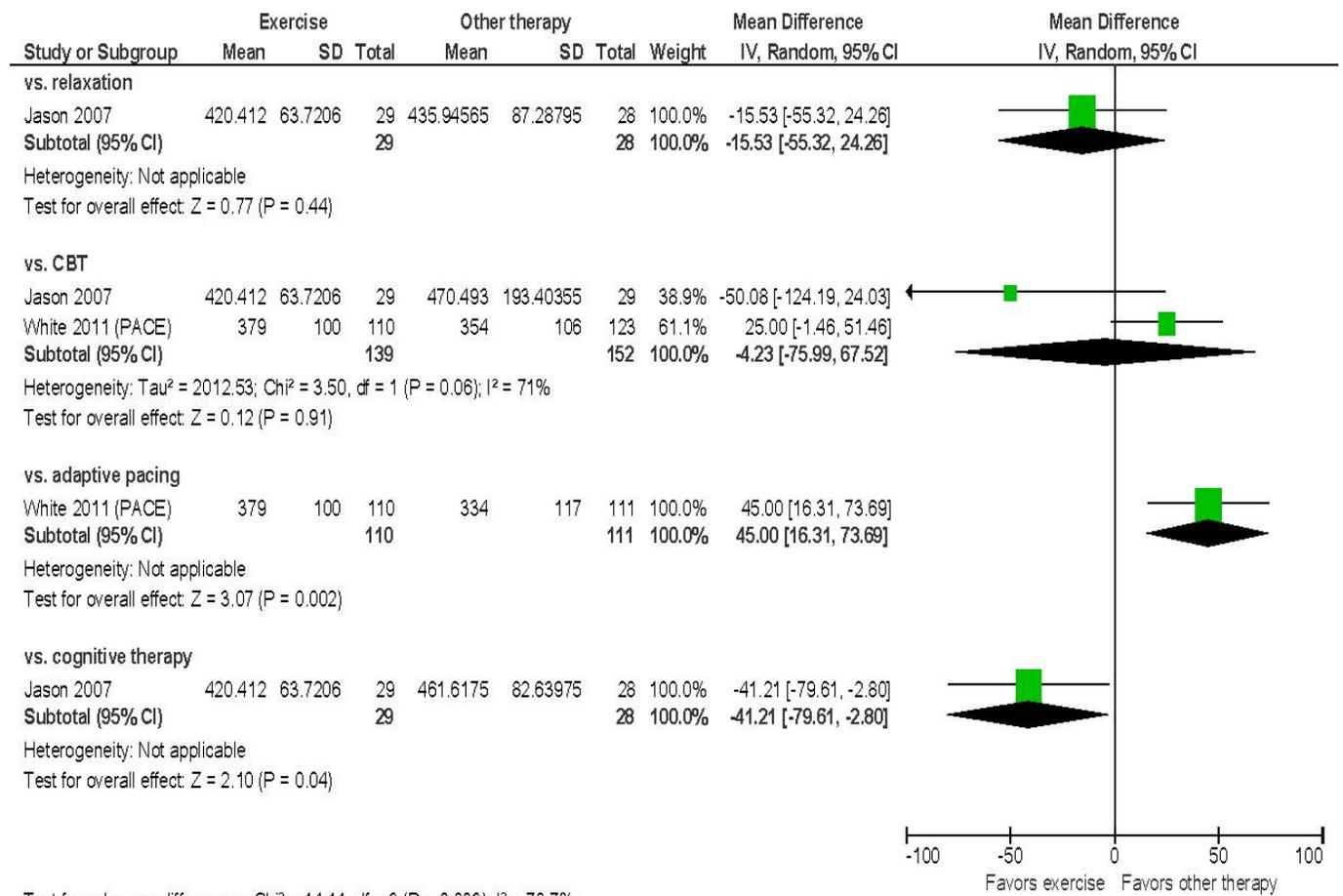
Figure 22. Pain: Graded exercise versus active intervention at post-intervention follow-up



Test for subgroup differences: Chi² = 0.99, df = 2 (P = 0.61), I² = 0%

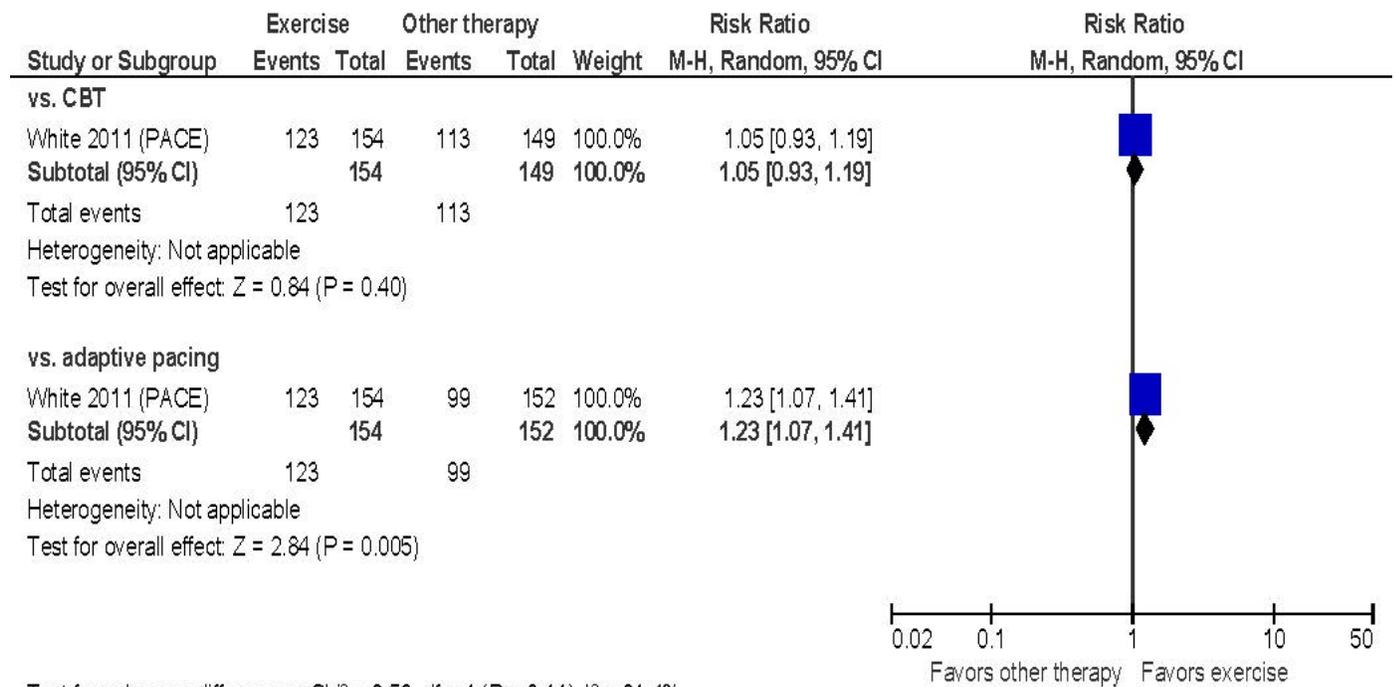
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; IV = instrumental variable; SD = standard deviation

Figure 23. Six-minute walk test: Graded exercise versus active intervention at end of intervention



Test for subgroup differences: Chi² = 14.11, df = 3 (P = 0.003), I² = 78.7%
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

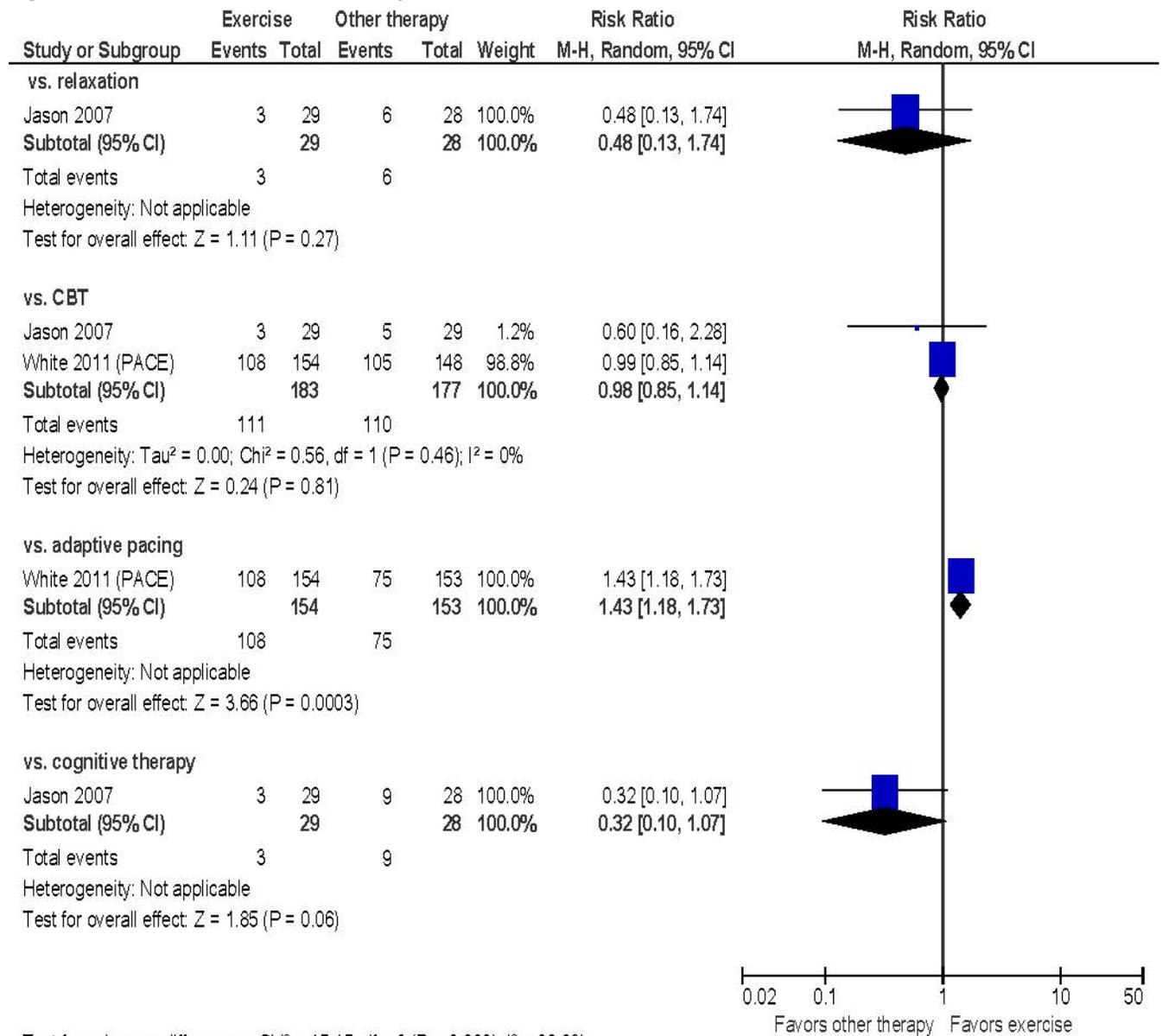
Figure 24. Likelihood of fatigue improvement: Graded exercise versus active interventions



Test for subgroup differences: $\text{Chi}^2 = 2.59$, $\text{df} = 1$ ($P = 0.11$), $I^2 = 61.4\%$

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

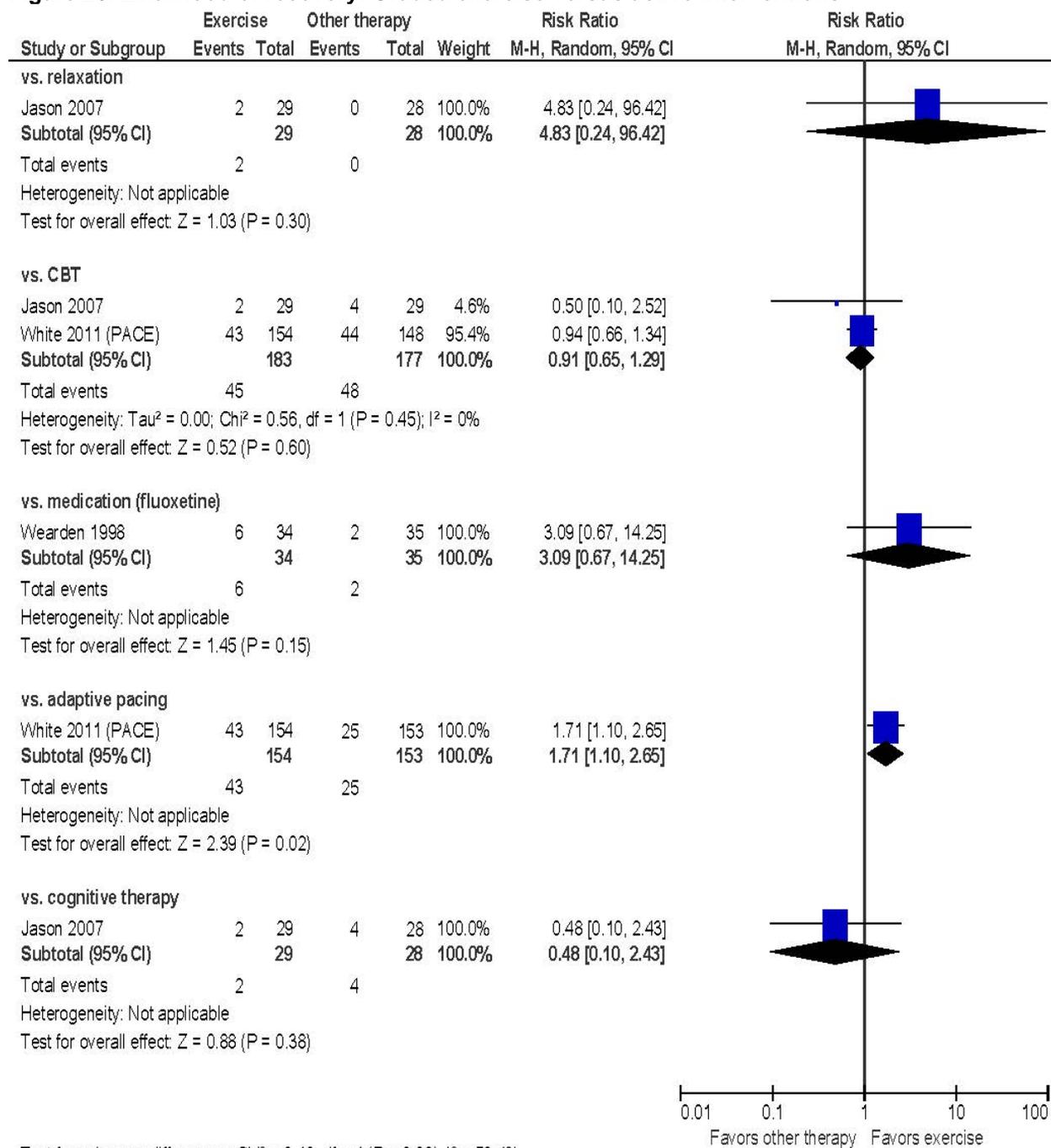
Figure 25. Likelihood of functional improvement: Graded exercise versus active interventions



Test for subgroup differences: Chi² = 15.15, df = 3 (P = 0.002), I² = 80.2%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

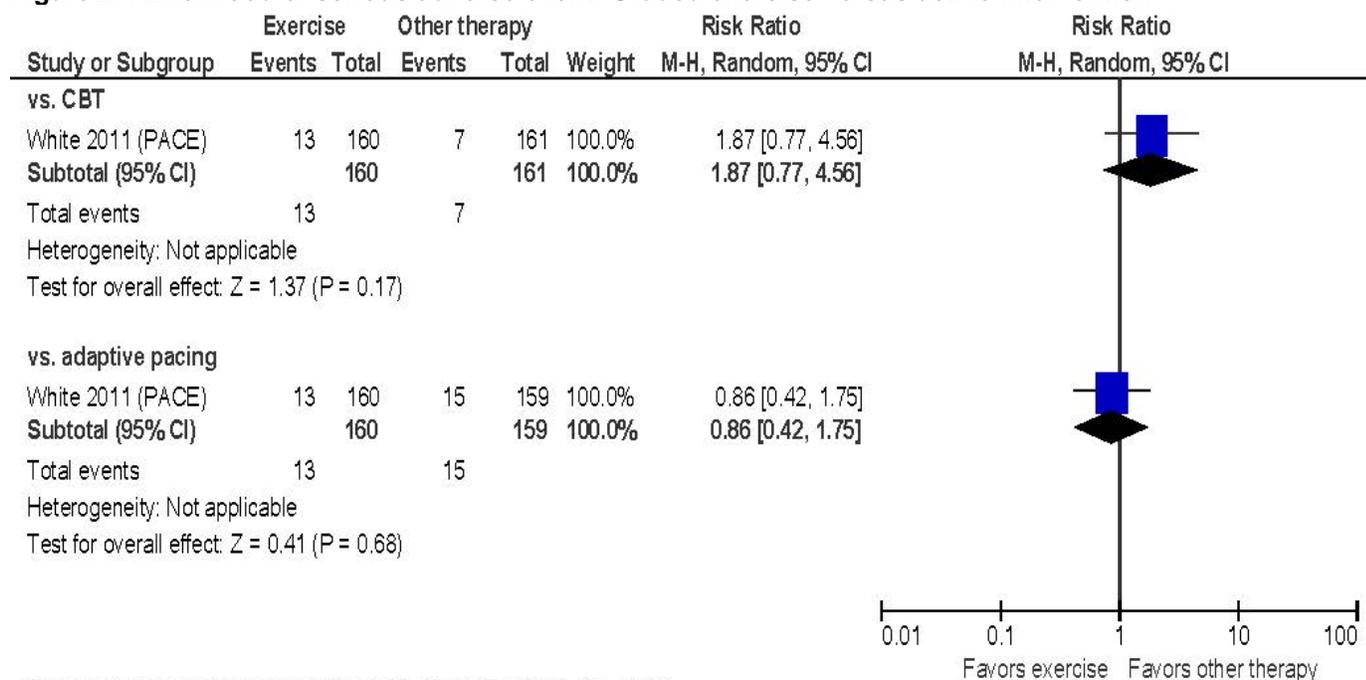
Figure 26. Likelihood of recovery: Graded exercise versus active interventions



Test for subgroup differences: Chi² = 8.40, df = 4 (P = 0.08), I² = 52.4%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

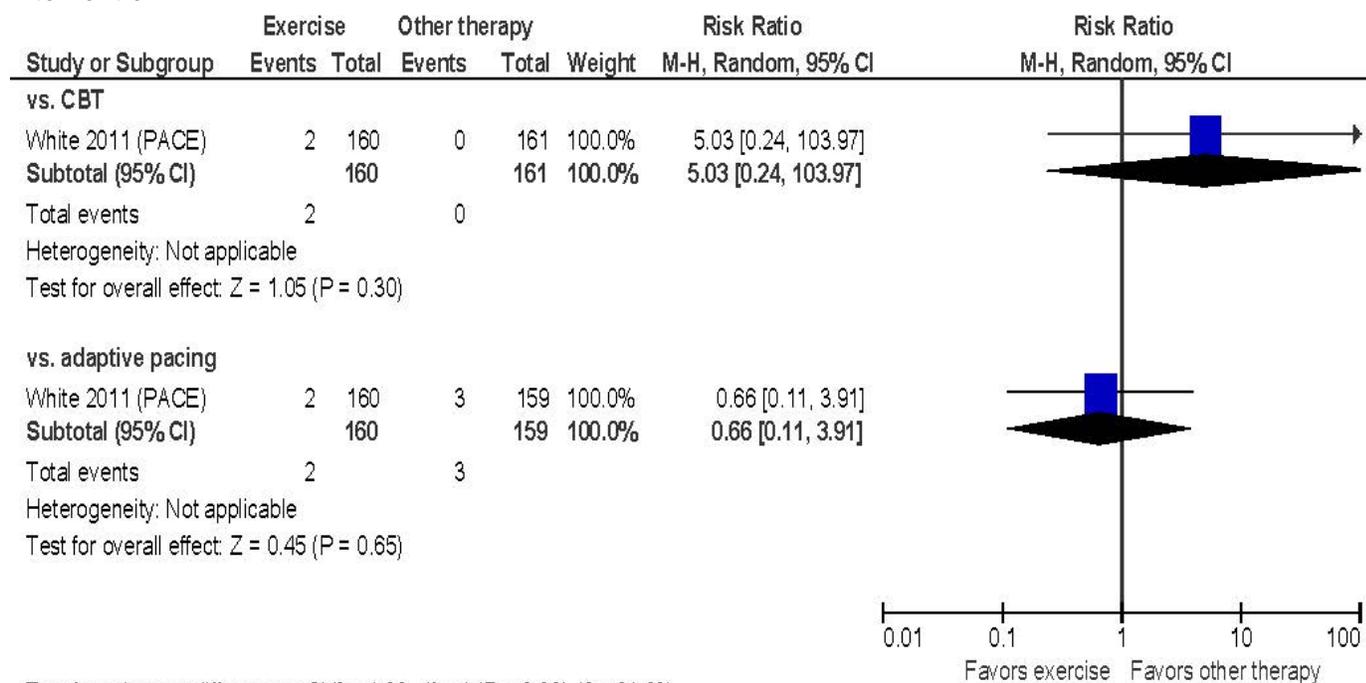
Figure 27. Likelihood of serious adverse event: Graded exercise versus active intervention



Test for subgroup differences: Chi² = 1.77, df = 1 (P = 0.18), I² = 43.6%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

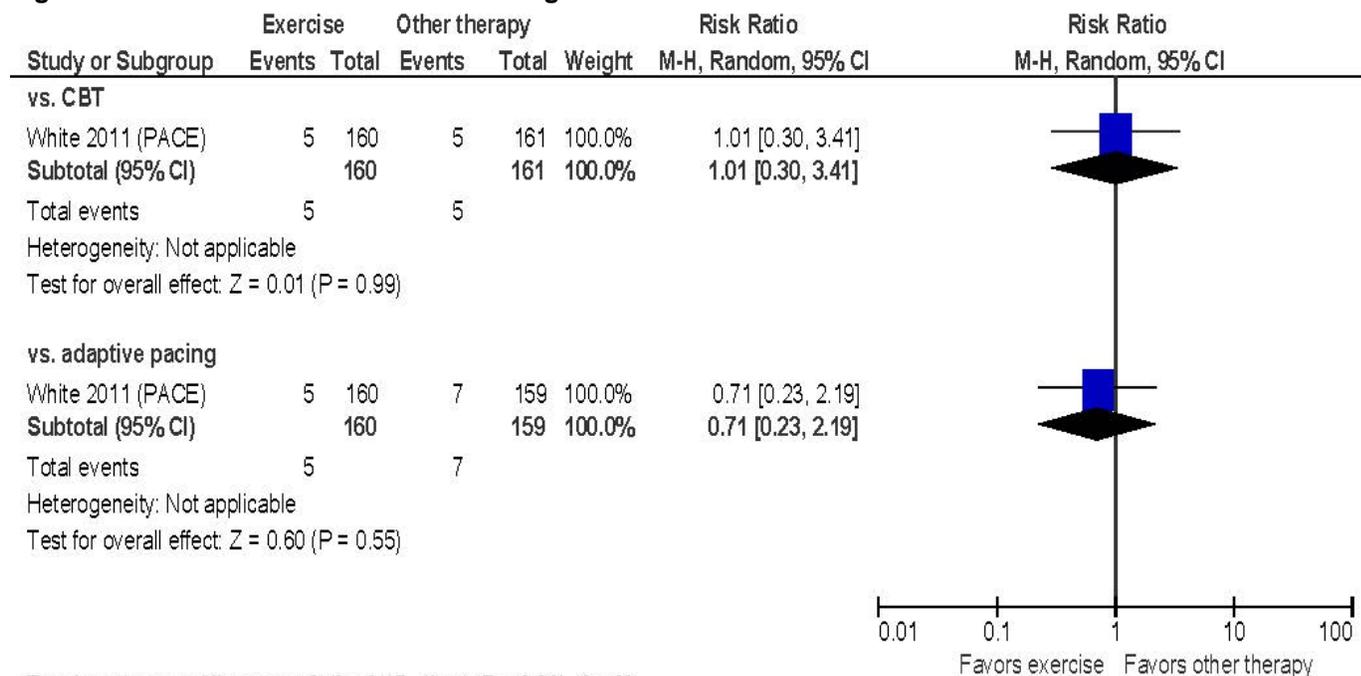
Figure 28. Likelihood of withdrawal due to adverse event: Graded exercise versus active intervention



Test for subgroup differences: Chi² = 1.28, df = 1 (P = 0.26), I² = 21.9%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Figure 29. Likelihood of function worsening: Graded exercise versus active intervention



Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Other exercise therapies

Orthostatic training versus sham training

One medium risk of bias trial (N=25, Evidence Table Appendix E2) included in the prior AHRQ report compared home orthostatic training versus sham treatment in patients who met the Fukuda case definition.⁶³ Home orthostatic training consisted of standing with the upper back against the wall and heels approximately 15 cm from the base of the wall once daily for 30 minutes. Sham training consisted of the same position for 10 minutes and gentle calf flexion and extension exercises. The mean Fatigue Impact Severity score at baseline was 95.3 (0 to 160 scale). At the end of 6 months of therapy, there was no difference between orthostatic training versus no orthostatic training in fatigue severity (mean difference -8.00, 95% CI -33.5 to 1.75 on the Fatigue Impact scale; estimate includes data from two non-adherent patients). Orthostatic training was associated with reduced drop in blood pressure with standing (mean difference 6 mm Hg, 95% CI 00 to 12.6). The trial did not report orthostatic symptoms or harms.

Cognitive behavioral therapy

Twelve trials evaluated CBT in adult patients with ME/CFS (**Tables 7 and 8**).^{36,51,64-73} Sample sizes ranged from 58 to 630 (total N=1888). Nine trials compared CBT versus usual care, usual specialist care, an attention control (education and support), or wait list (advice or supportive listening);^{36,66-73} four trials compared CBT versus an active intervention (exercise, adaptive pacing, relaxation, cognitive therapy, or fluoxetine);^{36,51,65,71} and one trial compared different CBT modes of delivery (face-to-face or telephone).⁶⁴ Nine trials were included in the

prior AHRQ report^{36,51,64,65,67-70,72} and three trials were added for this update.^{66,71,73} All three new trials compared CBT versus inactive controls and one⁷¹ also compared CBT versus active therapy (mirtazapine).

Two trials were conducted in the United States and 10 trials in Europe. The mean age of participants ranged from 35 to 46 years and the proportion female ranged from 60% to 88%. The case definition for ME/CFS was the Oxford criteria in two trials, the Fukuda criteria in seven trials (including one trial⁶⁶ that used Dutch criteria in accordance with Fukuda), or both in three trials. The duration of ME/CFS ranged from 37 to 104 months in eight trials that reported this information. Baseline fatigue was measured using a variety of scales (**Table 7**). One trial⁶⁶ reported that 90% of patients had post-exertional fatigue at baseline and one trial⁷² reported that 38% of patients were “low active” and 62% “relative active” at baseline. Otherwise, details regarding the presence of post-exertional fatigue and activity patterns were lacking. One trial⁶⁴ excluded patients with melancholic depression, the proportion of patients with depression or treated for depression ranged from 10% to 39% in six trials,^{36,51,65,66,69,70} and five trials^{67,68,71-73} did not report the proportion of patients with depression. Two trials excluded patients with major depression. In the other trials, the proportion of patients with depression or an axis I psychiatric diagnosis ranged from 10% to 39%. Depression severity was most commonly assessed with the HADS depression score (0 to 21 scale, higher scores indicate more severe depression). In three trials, mean HADS depression scores at baseline ranged from 8.2 to 9.1. Functional impairment was most commonly reported using the SF-36 physical function subscale (0 to 100 scale, lower scores indicate more functional impairment). In 10 trials, mean SF-36 physical function subscale scores ranged from 26.6 to 62.5.

CBT was administered individually in 10 trials; of these, the mode of delivery was face-to-face in seven trials and another mode of delivery (web-based, telephone, or self-guided) was used in three trials. CBT was administered in group, face-to-face sessions in two trials. The duration of the CBT intervention ranged from 12 weeks to 6 months. In most trials, the frequency of CBT was weekly or biweekly. The session length varied, with details not reported in some trials (**Table 7**). Outcomes were assessed at 16 weeks to 18 months; nine trials^{36,64-68,71-73} evaluated patients at the end of the intervention and five trials^{36,51,64,69,70} evaluated patients 29 weeks to 12 months following the completion of therapy.

Eleven trials were rated medium risk of bias and one trial⁶⁸ was rated high risk of bias (**Risk of Bias Table Appendix F**). In all trials, blinding of patients and care providers to CBT was not feasible. Other methodological limitations included high attrition, failure to report attrition, inadequate description of randomization or allocation concealment methods, and failure to blind or unclear blinding status of outcomes assessors and data analysts.

Table 7. Cognitive Behavioral Therapy RCTs: Study Characteristics

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Burgess, 2012 ⁶⁴ United Kingdom Medium	n: 58 Age: 37.4 % Female: 79	Criteria: Fukuda and Oxford Duration: 3.97 years	Fatigue Scale: Chalder (11-item, 0 to 11) Baseline: 10.2 (SD 1.9) Post-exertional fatigue: not reported	Major depression: Excluded for melancholic depression Baseline depression: HADS depression (0 to 21): 9.1 (SD 1.7) Baseline function: SF-36 physical function (0 to 100): 51.4 (SD 1.7)	A: Face-to-face CBT B: Telephone CBT Frequency: Face-to-face: 2 initial sessions and 15 follow-up sessions over 6 months Telephone: 1 initial session and 13 follow- up sessions over 6 months Session length: Face-to-face: 1.5 hours for initial sessions and 50 minutes to 1 hour for follow-up sessions Telephone: 3 hours for initial session and 30-minute follow- up sessions Duration of Treatment: 6 months Duration of follow-up: 18 months
Deale, 1997 ⁶⁵ United Kingdom Medium	n: 60 Age: 34.5 % Female: 68	Criteria: Oxford and Fukuda Duration: 4 years	Fatigue Scale: Chalder (11-item, 0 to 11) Baseline: 9.8 (SD 2.1) Post-exertional fatigue: Not reported	Major depression: 15% Baseline depression: Beck Depression Inventory (0 to 63): 14.1 (SD 6.7) Baseline function: SF-36 physical function (0 to 100): 26.6 (SD 23.4)	A: CBT B: Relaxation (10 sessions with twice daily practice) Frequency: 13 sessions weekly or biweekly over 4 to 6 months Session length: Not described (mean total time 15 hours) Duration of Treatment: 4 to 6 months Duration of follow-up: 10 to 12 months
Janse, 2018 ⁶⁶ The Netherlands Medium	n: 240 Age: 37.6 % Female: 60	Criteria: National Dutch guidelines (in accordance with Fukuda) Duration: 4 to 6.5 years	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 50.0 (SD 5.2) Post-exertional fatigue: 90%	Major depression: Any depressive disorder: 10% Baseline depression: SCL-90 (90 to 450): 156.5 (SD 35.3) Baseline function: SF-36 physical function (0 to 100): 62.5 (SD 19.4)	A: 1: Web-based CBT, protocol driven feedback B: Web-based CBT, feedback on demand C: Wait list Frequency: At least biweekly (protocol driven) or individualized (feedback on demand) Session length: Diagnostic sessions 2 hours, otherwise not specified Duration of Treatment: 6 months Duration of follow-up: 6 months

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Jason, 2007 ⁵¹ United States Medium	n: 114 Age: 43.8 % Female: 83	Criteria: Fukuda Duration: Not reported	Fatigue Scale: Fatigue Severity Scale 9-item (1 to 7) Baseline: 6.1 (SD 0.71) Post-exertional fatigue: not reported	Major depression: Current axis I diagnosis: 39% Baseline depression: Beck Depression Inventory (0 to 63), mean: 18.7 (SD 9.9) Baseline function: SF-36 physical function (0 to 100): 46.2 (SD 23.8)	A: CBT B: Cognitive therapy C: Relaxation (RELAX) D: Anaerobic exercise (Anaerobic Activity Therapy [ACT]/progressive rehabilitation) Frequency: Biweekly Session length: 45 minutes Duration of Treatment: 6 months Duration of follow-up: 1 year
Knoop, 2008 ⁶⁷ The Netherlands Medium	n: 159 Age: 38.0 % Female: 79	Criteria: Fukuda Duration: Median 72 vs. 96 months	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 49.5 (SD 5.4) Post-exertional fatigue: Not reported	Major depression: Not reported Baseline depression: Not reported Baseline function: SF-36 physical function (0 to 100): 53.2 (SD 20.7)	A: Self-guided CBT B: Wait list Frequency: Not specified for self-guided sessions. Email contact with therapist at least every 2 weeks for at least 16 weeks Session length: Not described Duration of Treatment: At least 16 weeks Duration of follow-up: At least 16 weeks
Lopez, 2011 ⁶⁸ United States High	n: 58 Age: 45.9 % Female: 88	Criteria: Fukuda Duration: Not reported	Fatigue Scale: Profile of Mood States fatigue/inertia subscale (0 to 28) Baseline: 17.8 (SD 6.3) Post-exertional fatigue: Not reported	Major depression: Not reported Baseline depression: POMS total mood disturbance (0 to 200): 36.3 (SD 30.8) Baseline function: Not reported	A: Group cognitive behavioral stress management B: Psycho-educational seminar (half day) Frequency: Intervention: Weekly for 12 weeks Control: single session Session length: Intervention: 2 hours (20 to 30 minutes relaxation, 90 minutes didactic and discussion) Control: half-day Duration of Treatment: 12 weeks Duration of follow-up: 12 weeks

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
O'Dowd, 2006 ⁶⁹ United Kingdom Medium	n: 122 Age: 41.1 % Female: 67	Criteria: Fukuda Duration: Mean/median not reported (48% >60 months)	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 24.6 (SD 6.4) Post-exertional fatigue: Not reported	Major depression: Treated for depression: 16% Baseline depression: HADS depression (0 to 21): 8.7 (SD 3.5) Baseline function: SF-36 physical function (0 to 100): 32.2 (SD 7.8)	A: CBT B: Education and support (8 sessions every other week, 2 hours each) C: Usual care Frequency: 8 sessions every other week Session length: 2 hours Duration of Treatment: 16 weeks Duration of follow-up: 12 months
Sharpe, 1996 ⁷⁰ United Kingdom Medium	n: 60 Age: 36.0 % Female: 68	Criteria: Oxford Duration: Mean 31.6 months	Fatigue Scale: 0 to 10 Likert scale Baseline: 7.8 (SD 1.7) Post-exertional fatigue: Not reported	Major depression: Excluded for severe depression or bipolar disorder Major depression: 20% Baseline depression: HADS depression (0 to 21): 6.8 (SD 3.6) Baseline function: KPS (0 to 100): 71.5 (SD 3.4)	A: CBT B: Usual medical care Frequency: 16 sessions over 4 months Session length: 1 hour Duration of Treatment: 4 months Duration of follow-up: 12 months
Stubhaug, 2008 ⁷¹ Norway Medium	n: 72 Age: 46.3 % Female: 82	Criteria: Oxford (90%) or Fukuda (40%) Duration: not reported	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 25.0 (SD 4.5) Post-exertional fatigue: not reported	Major depression: Not reported Baseline depression: Hamilton Rating Scale for Depression (0 to 52): 14.5 (SD 3.9) Baseline function: SF-36 physical function (0 to 100): 28.9 (SD 11.3)	A: CBT B: Mirtazapine 15 to 45 mg/day C: Placebo Frequency: 2 sessions per week for 12 weeks Session length: 1.5 hours Duration of Treatment: 12 weeks (initial therapy) Duration of follow-up: 24 weeks (after crossover)
Tummers, 2012 ⁷² The Netherlands Medium	n: 111 Age: 36.4 % Female: 78	Criteria: Fukuda Duration: 48 vs. 60 months	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 51.3 (SD 5.4) Post-exertional fatigue: Not reported Low active: 38% Relative active: 62%	Major depression: Proportion with depression not reported Baseline depression: Brief Symptom Inventory psychological distress (0 to 4): 1.02 (SD 0.63) Baseline function: SF-36 physical function (0 to 100): 50.8 (SD 22.3)	A: Self-guided CBT B: Wait list Frequency: Not specified for self-guided sessions. Email contact with therapist at least every 2 weeks for at least 20 weeks Session length: Not described Duration of Treatment: At least 20 weeks Duration of follow-up: At least 20 weeks

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
White, 2011 ³⁶ United Kingdom Medium	n: 630 Age: 38.0 % Female: 77	Criteria: Oxford Duration: Median 32 months	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 28.2 (SD 3.8) Post-exertional fatigue: Not reported	Major depression: Any depressive disorder: 34% Baseline depression: HADS depression (0 to 21), mean: 8.2 (SD 3.8) Baseline function: SF-36 physical function (0 to 100): 38.0 (SD 15.8)	A: Adaptive pacing therapy + specialist medical care B: CBT + specialist medical care C: Graded exercise + specialist medical care D: Specialist medical care Frequency: Weekly x 4 weeks, then biweekly, plus one booster at 36 weeks Session length: Not described Duration of Treatment: 23 weeks (booster at 36 weeks) Duration of follow-up: 12 months
Wiborg, 2015 ⁷³ The Netherlands Medium	n: 204 Age: 37.7 % Female: 77	Criteria: Fukuda Duration: Mean 8.7 years	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 50.6 (SD 4.7) Post-exertional fatigue: Not reported	Major depression: Proportion with depression not reported Baseline depression: SCL-90 (90 to 450): 163.7 (SD 37.6) Baseline function: SF-36 physical function (0 to 100): 56.9 (SD 19.2)	A: Group CBT, 8 patients per group B: Group CBT 4 patients per group C: Wait list Frequency: 14 session over 6 months Session length: 2 hours Duration of Treatment: 6 months Duration of follow-up: 6 months

Abbreviations: ACT = anaerobic activity therapy; CBT = cognitive behavioral therapy; CFS = chronic fatigue syndrome; HADS = Hospital Anxiety and Depression Scale; ME = myalgic encephalomyelitis; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Table 8. Cognitive Behavioral Therapy RCTs: Study Results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)*	Depression Outcomes*	Function Outcomes*
Burgess, 2012 ⁶⁴ Fukuda and Oxford	A: Face-to-face CBT (35) B: Telephone CBT (45) Duration of Treatment: 6 months Duration of follow-up: 18 months	Fatigue: Chalder Fatigue Scale 11-item (0-11, score of ≥4 is cutoff for caseness), mean (SD); 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)	Not reported	Overall Function: MOS-SF physical function (0 to 100), mean (SD) 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, all other p-values NS
Deale, 1997 ⁶⁵ Oxford and Fukuda	A: CBT (30) B: Relaxation (10 sessions with twice daily practice) (30) Duration of Treatment: 4 to 6 months Duration of follow-up: 10 to 12 months	Fatigue: Fatigue Problem Rating (0-8 scale), mean (SD): Posttreatment: 4.1 (1.9) vs. 5.5 (1.4) 6-month follow-up: 3.4 (2.2) vs. 5.5 (1.9), p<0.001 for between group differences over time Chalder Fatigue Scale 11- item (0 to 11), score of ≥4 is cutoff for caseness, mean (SD) Posttreatment: 7.2 (4.0) vs. 7.5 (4.1) 6-month follow-up: 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-month follow- up 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 follow-up: 63 (17/27) vs. 15 (4/26); p=0.001 5-year follow-up: 28 (7/25) vs. 25 (7/28); p=1.00	Beck Depression Inventory, mean (SD) Posttreatment: 8.9 (5.6) vs. 11.9 (7.4) 6-month follow up: 10.1 (6.9) vs. 12.3 (8.5), p>0.30	Overall Function: SF-36 physical function (0 to 100), mean (SD) Posttreatment: 56.2 (26.2) vs. 34.6 (28.3) 6-month follow-up: 71.6 (28.0) vs. 38.4 (26.9); p<0.03 % With good outcome on SF-36 physical function (increase of ≥50 from baseline to 6 months, or end score of ≥83): 6 months follow-up: 63 (19/30) vs. 17 (5/30); difference of 46 (95% CI 24 to 68) p<0.001 5-year follow-up: 48 (12/25) vs. 32 (9/28); p=0.27 % With rating by assessor at 3- month follow-up 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 ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)*	Depression Outcomes*	Function Outcomes*
Janse, 2018 ⁶⁶ National Dutch guidelines (in accordance with Fukuda)	A: 1: Web-based CBT, protocol driven feedback (80) B: Web-based CBT, feedback on demand (80) C: Wait list (80) Duration of Treatment: 6 months Duration of follow-up: 6 months	Fatigue: Checklist Individual Strength, fatigue severity subscale (8 to 56), mean (SD): 36.3 (14.6) vs. 37.0 (13.1) vs. 43.9 (10.5) Mean difference compared with control (97.5% CI): iCBT with protocol feedback: -8.3 (-12.7 to -3.9), p<0.0001; iCBT with feedback on demand: -7.2 (-11.3 to -3.1), p<0.0001	Not reported	Overall Function: SF-36 physical function (0 to 100), mean (SD): 73.3 (25.9) vs. 77.0 (21.3) vs. 70.8 (21.0) Difference compared with control: iCBT with protocol feedback: 2.4 (-3.6 to 8.4), p=0.44; iCBT with feedback on demand: 5.8 (0.6 to 11.0), p=0.030
Jason, 2007 ⁵¹ Fukuda	A: CBT (29) B: Cognitive therapy (28) C: 1: Relaxation (RELAX) (28) D: Anaerobic exercise (Anaerobic Activity Therapy [ACT]/progressive rehabilitation) (29) Duration of Treatment: 6 months Duration of follow-up: 1 year	Fatigue Severity Scale 9- item (1 to 7), mean (SD) 12 months: 5.77 (1.43) vs. 5.62 (1.06) vs. 5.37 (1.19) vs. 5.87 (1.01); p=NR	Beck Depression Inventory (0 to 21), mean (SD) 12 months: 13.95 (13.08) vs. 11.86 (7.36) vs. 16.94 (11.82) vs. 13.50 (9.97), p<0.001	Overall Function: SF-36 physical function(0 to100), mean (SD): 12 months: 58.64 (30.44) vs. 61.09 (23.74) vs. 61.20 (27.70) vs. 39.72 (27.63) p<0.01 for CBT and COG over time vs. ACT over time % Achieving clinically significant improvement: 18.2 vs. 30.4 vs. 21.7 vs. 11.1; p=0.49
Knoop, 2008 ⁶⁷ Fukuda	A: Self-guided CBT (85) B: Wait list (86) Duration of Treatment: At least 16 weeks Duration of follow-up: At least 16 weeks	Fatigue: Checklist Individual Strength, fatigue severity subscale (8 to 56) mean (SD): Second assessment: 38.9 (12.1) vs. 46.4 (8.7); p<0.001 % With reduction in Checklist Individual Strength, fatigue severity subscale (<35 score 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	Not reported	Overall Function: SF-36 physical function (0 to100), mean (SD) Second assessment: 65.9 (23.2) vs. 60.2 (23.7); p=0.011 Mean (SD) functional impairment Sickness Impact Profile (SIP-8) (0 to 5,799) Second assessment: 1,079 (690) vs. 1,319 (619); p<0.001
Lopez, 2011 ⁶⁸ Fukuda	A: Group cognitive behavioral stress management (44) B: Psycho- educational (half day) (25) Duration of Treatment: 12 weeks Duration of follow-up: 12 weeks	Fatigue: POMS fatigue subscale (0 to 28), mean (SD) After treatment: 17.85 (7.34) vs. 20.09 (6.99); p=0.06	Not reported	Overall Function: Not reported

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)*	Depression Outcomes*	Function Outcomes*
O'Dowd, 2006 ⁶⁹ Fukuda	A: CBT (52) B: Education and support (8 sessions every other week, 2 hours each) (50) C: Usual care (51) Duration of Treatment: 16 weeks Duration of follow-up: 12 months	Chalder Fatigue Scale 11- item (0 to 33), mean (SD) 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 6 and 12 months pooled CBT vs. group 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	HADS- Depression 6 months: 6.84 (3.46) vs. 8.20 (3.81) vs. 7.78 (3.76) 12 months: 6.82 (3.80) vs. 7.74 (4.02) vs. 7.44 (4.42) Mean difference, adjusted for baseline: -0.13 (-1.13 to 0.87) vs. -0.56 (-1.69 to 0.58) vs. - 0.43 (-1.56 to 0.70), p=0.52	SF-36 physical function (0 to 100), mean (SD); 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)
Sharpe, 1996 ⁷⁰ Oxford	A: CBT (30) B: Usual medical care (30) Duration of Treatment: 4 months Duration of follow-up: 12 months	Fatigue severity (0 to 10), mean: 12 months: 4.3 vs. 6.3 Change from baseline, -3.5 vs. -1.6; difference 1.9, 95% CI 0.5 to 3.3	HADS- Depression, mean 12 months: 3.6 vs. 5.8 Change from baseline: -3.1 vs. -1.0; difference 2.0, 95% CI 0.0 to 4.1	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); p<0.001 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); p<0.001
Stubhaug, 2008 ⁷¹ Oxford (90%) or Fukuda (40%)	A: CBT (23) B: Mirtazapine 15 to 45 mg/day (28) C: Placebo (24) Duration of Treatment: 12 weeks (initial therapy) Duration of follow-up: 24 weeks (after crossover)	Chalder Fatigue Scale 11- item (0 to 33) score at 12 weeks: 23.7 (21.0 to 26.5) vs. 22.7 (21.4 to 24.1) vs. 23.7 (21.0 to 26.5), p=0.014 Chalder Fatigue Scale 11- item (0 to 33) score at 24 weeks: 23.3 (20.1 to 26.5) vs. 23.7 (22.4 to 25.0) vs. 24.2 (21.4 to 27.1) vs. 18.7 (15.4 to 22.0); p<0.001	Hamilton Rating Scale for Depression , mean (95% CI) 12 weeks: 12.9 (10.1 to 15.7) vs. 12.6 (11.4 to 13.8) vs. 13.5 (10.9 to 16.1)	Not reported

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)*	Depression Outcomes*	Function Outcomes*
Tummers, 2012 ⁷² Fukuda	A: Self-guided CBT (62) B: Wait list (61) Duration of Treatment: At least 20 weeks Duration of follow-up: At least 20 weeks	Checklist Individual Strength, fatigue severity subscale (8 to 56 scale), mean (SD) Second assessment: 39.6 (14.1) vs. 48.3 (8.1); p<0.01 % With reduction in Checklist Individual Strength, fatigue severity subscale (score <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)	Not reported	SF-36 physical function (0 to 100), mean (SD) Second assessment: 65.4 (24.9) vs. 59.3 (22.9); p=0.08 Subanalysis of baseline group with SF-36 physical function score ≤70 Self-instruction (n=53) vs. wait list (n=50) Mean (SD) SF-36 physical function (0 to 100) Second assessment: 63.0 (25.9) vs. 53.4 (18.7) Change from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05
White, 2011 ³⁶ Oxford	A: Adaptive pacing therapy + specialist medical care (160) B: CBT + specialist medical care (161) C: Graded exercise + specialist medical care (160) D: Specialist medical care (160) Duration of Treatment: 23 weeks (booster at 36 weeks) Duration of follow-up: 12 months	Fatigue: Chalder Fatigue Scale 11-item (0 to 33), mean (SD) 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) at 52 weeks: CBT vs. control: -3.4 (-5.0 to -1.8) p=0.0001 CBT vs. APT: -2.7 (-4.4 to - 1.1) p=0.0027 % 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)	HADS- Depression, mean (SD) 52 weeks: 7.2 (4.5) vs. 6.2 (3.7) vs. 6.1 (4.1) vs. 7.2 (4.7); CBT vs. control: p=0.0003 CBT vs. APT: p=0.382	SF-36 physical function (0 to 100), mean (SD): 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 at 52 weeks: CBT vs. control: 7.1 (2.0 to 12.1) p=0.0068 CBT vs. APT: 10.5 (5.4 to 15.6) p=0.0002 % 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 ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)*	Depression Outcomes*	Function Outcomes*
Wiborg, 2015 ⁷³ Fukuda	A: 1. Group CBT, 8 patients per group B. Group CBT, 4 patients per group C: Wait list Duration of Treatment: 6 months Duration of follow-up: 6 months	A+B vs. C Fatigue severity, mean (SD): 33.5 (13.6) vs. 46.6 (8.5), treatment effect -13.8 (95% CI, -17.2 to -10.3), p<0.001 Improvement in fatigue severity: 49.3% (67/139) vs. 8.8% (6/68), OR 10.0 (95 CI, 4.1 to 24.8), p<0.001 Normal functioning in fatigue severity: 32.4% (44/136) vs. 2.9% (2/68), OR 15.8 (95% CI, 3.7 to 67.4), p<0.001	Not reported	A+B vs. C SF-36 physical function (0 to 100), mean (SD): 747.7 (22.0) vs. 63.3 (21.1), treatment effect 14.1 (95% CI, 9.0 to 19.3), p<0.001

*A vs. B vs. C vs. D, unless otherwise noted

Abbreviations: ACT = anaerobic activity therapy; APT = adaptive pacing therapy; CBT = cognitive behavioral therapy; CI = confidence interval; CFS = chronic fatigue syndrome; COG = cognitive therapy; GET = graded exercise therapy; iCBT = internet-based cognitive-behavioral therapy; KPS = Karnofsky Performance Scale; ME = myalgic encephalomyelitis; NR = not reported; NS = not significant; OR = odds ratio; POMS = profile of mood states; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey; SIP-8 = Sickness Impact Profile 8-item

Cognitive behavioral therapy versus inactive controls

Nine trials (N=1,656) compared CBT versus usual care (2 trials),^{69,70} usual specialist care (1 trial),³⁶ wait list (4 trials),^{66,67,72,73} an attention control (education, 2 trials),^{68,69} or placebo medication (1 trial)⁷¹ (**Tables 7 and 8, Evidence Table Appendix E2**). Three of these trials were added for this review; two of the trials^{66,73} used the Fukuda case definition and one⁷¹ used Fukuda or Oxford. The duration of the CBT intervention ranged from 12 weeks to 6 months. Seven trials evaluated patients at the end of the intervention and three trials^{36,69,70} evaluated patients 6.7 to 8.4 weeks following the end of the intervention. One trial⁶⁸ was rated high risk of bias and the others were rated medium risk of bias.

Fatigue

CBT was associated with decreased fatigue severity versus wait list, usual specialist care, or an attention control at the end of treatment (7 trials, N=1,129, SMD -0.61, 95% CI -0.83 to -0.40, $I^2=64%$;^{36,66-68,71-73} **Figure 30**). Mean differences were -2.53 (95% CI -4.06 to -1.00, $I^2=0%$) in two trials (N=347) that used the 11-item 0 to 33 Chalder scale,^{36,71} -9.20 (95% CI -12.09 to -6.31, $I^2=66%$) in four trials (N=724) that used the 8 to 56 Checklist Individual Strength fatigue severity scale,^{66,67,72,73} and -2.24 (95% CI -6.09 to 1.61, $I^2=98%$) in one trial (N=422) that used the 0 to 28 Profile of Mood States (POMS) fatigue/inertia scale. Estimates consistently favored CBT when trials were stratified by the control type, ME/CFS case definition, and CBT type (**Table 9**). A statistically significant subgroup effect was present for control type (p for subgroup difference=0.05), with the strongest estimate for trials of CBT versus wait list (4 trials, N=724, SMD -0.77, 95% CI -0.99 to -0.55, $I^2=50%$) compared with trials of CBT versus placebo medication, usual specialist care, or an attention control (SMD's ranged from -0.31 to -0.40). For ME/CFS case definition, there was a subgroup effect of borderline statistical significance (Fukuda: 5 trials, N=782, SMD -0.72, 95% CI -0.94 to -0.49, $I^2=53%$; Oxford: 1 trial, N=300,

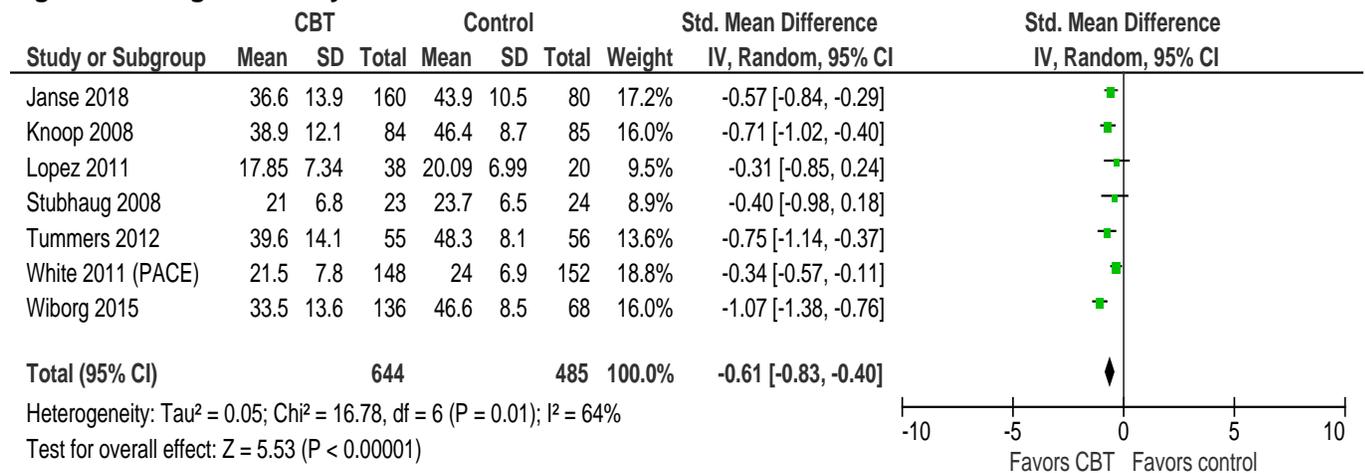
SMD -0.34, 95% CI -0.57 to -0.11; and Oxford or Fukuda: 1 trial: N=47, SMD -0.40, 95% CI -0.98 to 0.18; p for subgroup difference=0.07). There was no subgroup effect for CBT type; the most common CBT type was group/face-to-face (3 trials, N=309, SMD -0.63, 95% CI -1.18 to -0.09, I²=75%).^{68,71,73} Excluding the high risk of bias trial⁶⁸ had little effect on the pooled estimate (6 trials, N=1,071, SMD -0.65, 95% CI -0.88 to -0.41, I²=68%).

CBT was also associated with decreased fatigue severity versus controls at post-intervention follow-up, though the estimate was based on fewer studies (3 trials, N=489, SMD -0.57, 95% CI -0.89 to -0.25, I²=57%; **Figure 31**).^{36,69,70} Statistical heterogeneity was moderate; however, estimates favored CBT in all trials (SMD ranged from -0.36 to -1.06).

CBT was associated with increased likelihood of improvement in fatigue versus wait list or usual specialist care (4 trials, N=784, RR 3.00, 95% CI 0.95 to 9.49, I²=93%; **Figure 32**).^{36,67,72,73} In three trials, improvement in fatigue was defined as a Checklist Individual Strength severity subscale score <35 and reliable change index >1.96.^{67,72,73} The fourth trial (PACE) found CBT associated with increased likelihood of improvement in fatigue versus usual specialist care, based on ≥2 point improvement on the 11-item 0 to 33 Chalder fatigue scale (76% vs. 65%, RR 1.17, 95% CI 1.01 to 1.36; ARD 11%, 95% CI 1% to 21%).³⁶ This differed from the original PACE protocol, which defined improvement in fatigue as a score ≤3 on the 11-item 0 to 11 Chalder fatigue scale or >50% improvement from baseline (26% vs. 13%, RR 1.99, 95% CI 1.23 to 3.20).³⁸ Using the PACE protocol definition for fatigue improvement, the pooled estimate was very similar (4 trials, N=805, RR 3.30, 95% CI 1.96 to 5.55, I²=51%).

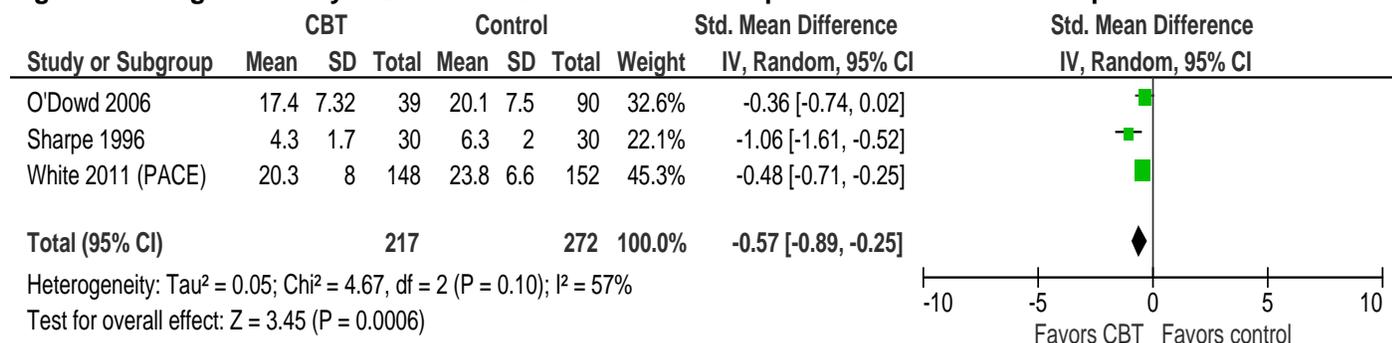
The PACE trial also evaluated longer-term, post-trial outcomes (median duration from randomization 31 months).⁵⁹ Thirty-one percent of patients in the CBT group and 63 percent in the usual specialist care group received non-randomly allocated therapies between the end of the trial at 1 year and long-term follow-up. Fatigue severity on the 11-item 0 to 33 Chalder scale was slightly improved at long-term follow-up compared with end-of-trial scores in both the exercise (mean change -2.2 points, 95% CI -3.7 to -0.6) and usual specialist care groups (-3.9 points, 95% CI -5.3 to -2.6). At long-term post-trial follow-up, there were no differences between CBT vs. specialist medical care in fatigue (mean difference -1.4, 95% CI -3.4 to 0.7), based on mixed model analyses.

Figure 30. Fatigue severity: CBT versus inactive controls at end of treatment



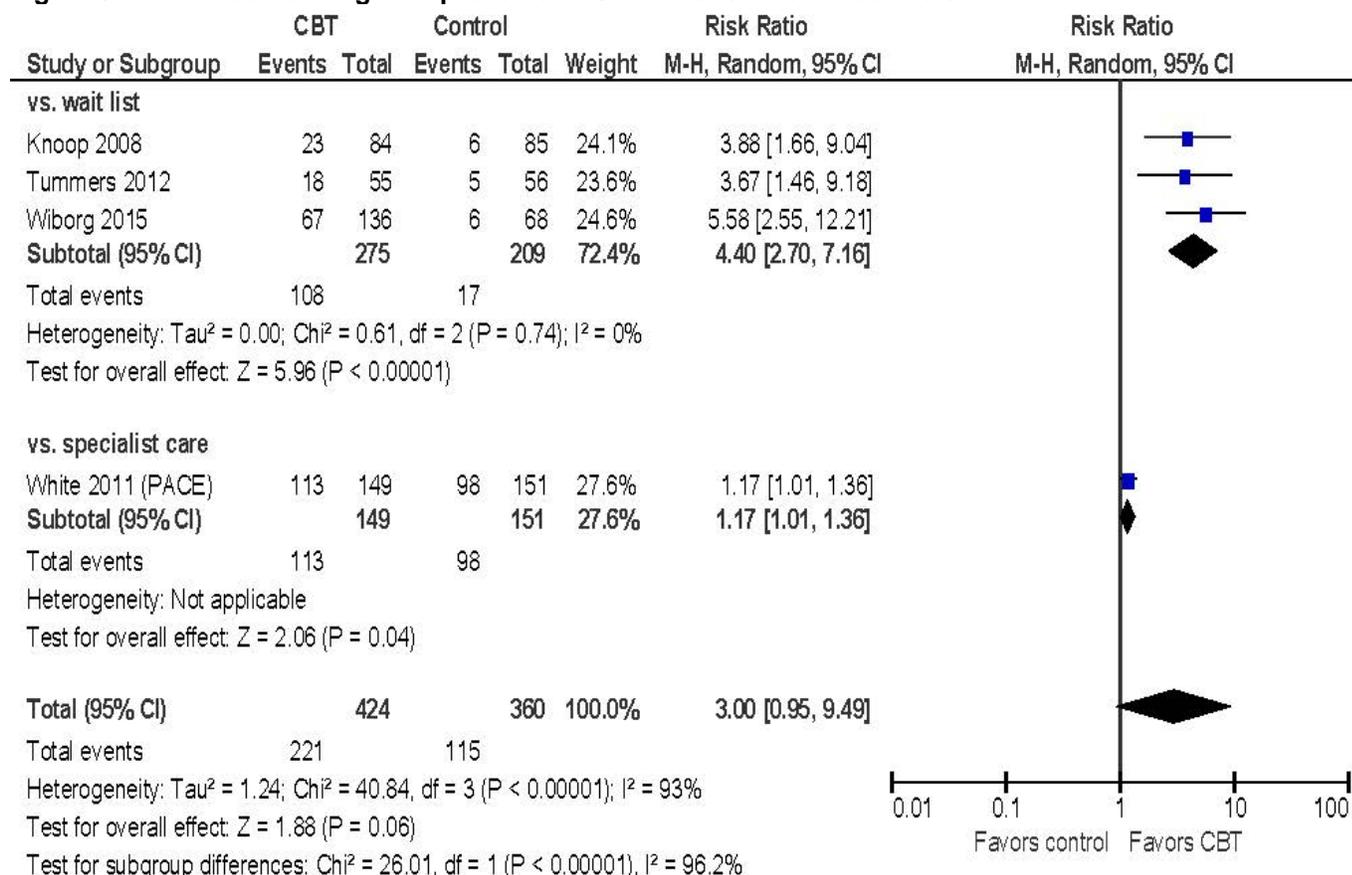
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 31. Fatigue severity: CBT versus inactive controls at post-intervention follow-up



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 32. Likelihood of fatigue improvement: CBT versus inactive controls



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Function

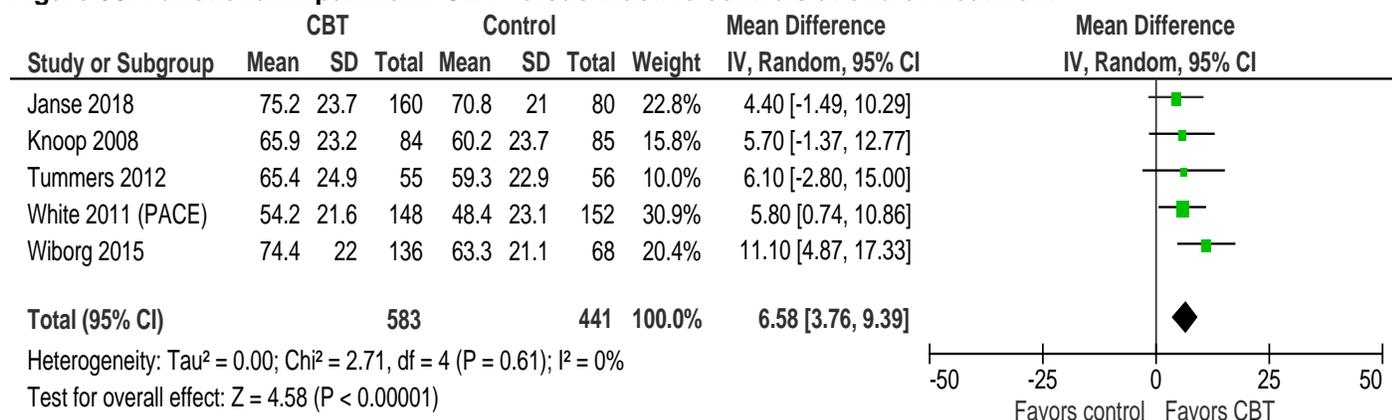
CBT was associated with decreased severity of functional impairment versus wait list or usual specialist care (5 trials, N=1024, mean difference 6.58, 95% CI 3.76 to 9.39, $I^2=0\%$;^{36,66,67,72,73} **Figure 33**). Estimates consistently favored CBT when trials were stratified according to the control type, ME/CFS case definition, or type of CBT, and there were no statistically significant subgroup differences (Table 1). The most commonly ME/CFS case definition was the Fukuda criteria (4 trials, N=724, mean difference 6.92, 95% CI 3.54 to 10.31, $I^2=0\%$).^{66,67,72,73}

CBT was also associated with decreased severity of functional impairment versus controls at post-intervention follow-up (3 trials, N=489, SMD 0.37, 95% CI 0.08 to 0.66, $I^2=50\%$;^{36,69,70} **Figure 34**). Although statistical heterogeneity was present, results from all trials favored CBT. One trial evaluated function with the SF-36 physical function subscale (mean difference 7.40 on a 0 to 100 scale, 95% CI 1.88 to 12.92),³⁶ one trial used the SF-36 physical component summary (mean difference 1.50 on a 0 to 100 scale, 95% CI -1.66 to 4.66),⁶⁹ and one trial reported the percentage interference with activity (mean difference 13.00 on a 0 to 100 scale [reversed so higher score indicates decreased functional impairment], 95% CI 5.04 to 20.96).⁷⁰

Three trials evaluated improvement in function as a dichotomous outcome.^{36,69,70} Functional improvement was defined as SF-36 physical component summary score improved $\geq 15\%$ from baseline,⁶⁹ Karnofsky Performance Scale (KPS) improved ≥ 10 points from baseline,⁷⁰ or SF-36 physical function subscale score improved ≥ 8 points from baseline.³⁶ The latter trial (PACE) used a different definition in the main publication than the study protocol,³⁷ which defined functional improvement as an SF-36 physical function score of ≥ 75 or $\geq 50\%$ improvement from baseline. Using the definition from the main PACE publication, there was no difference between CBT versus attention control, usual care, or specialist care in likelihood of functional improvement (3 trials, N=488, RR 1.06, 95% CI 0.83 to 1.35, $I^2=47\%$; **Figure 35**). Results were similar when using data based on the PACE protocol definition³⁸ (3 trials, N=509, RR 1.03, 95% CI 0.86 to 1.22, $I^2=0\%$).

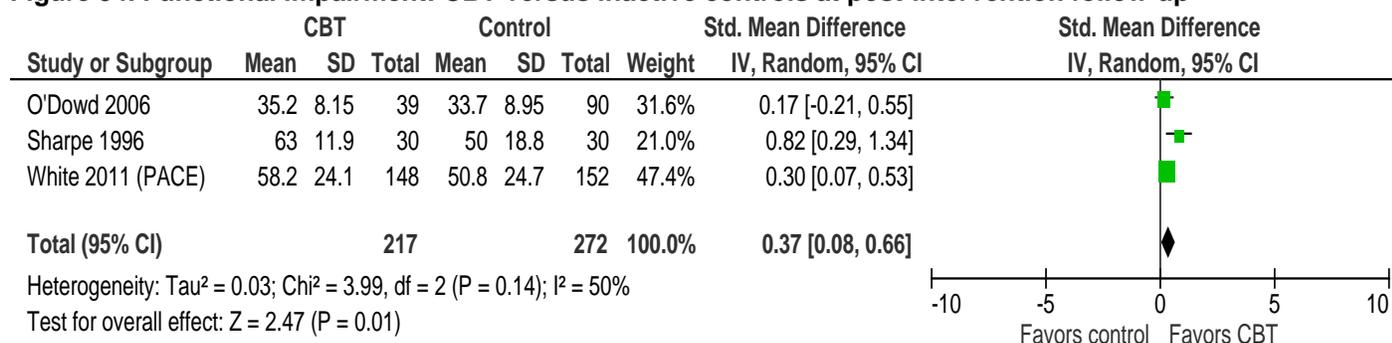
The PACE trial also evaluated longer-term, post-trial outcomes (median duration from randomization 31 months).⁵⁹ For SF-36 physical function, both CBT (mean change 3.3, 95% CI 0.02 to 6.7) and usual specialist care (mean change 7.1, 95% CI 4.0 to 10.3) were associated with improved scores at long-term follow-up compared with the end of the trial. At long-term follow-up, there was no difference between graded exercise vs. usual specialist medical care in SF-36 physical function (mean difference 2.8, 95% CI -3.2 to 8.8), based on mixed model analyses.

Figure 33. Functional impairment: CBT versus inactive controls at end of treatment



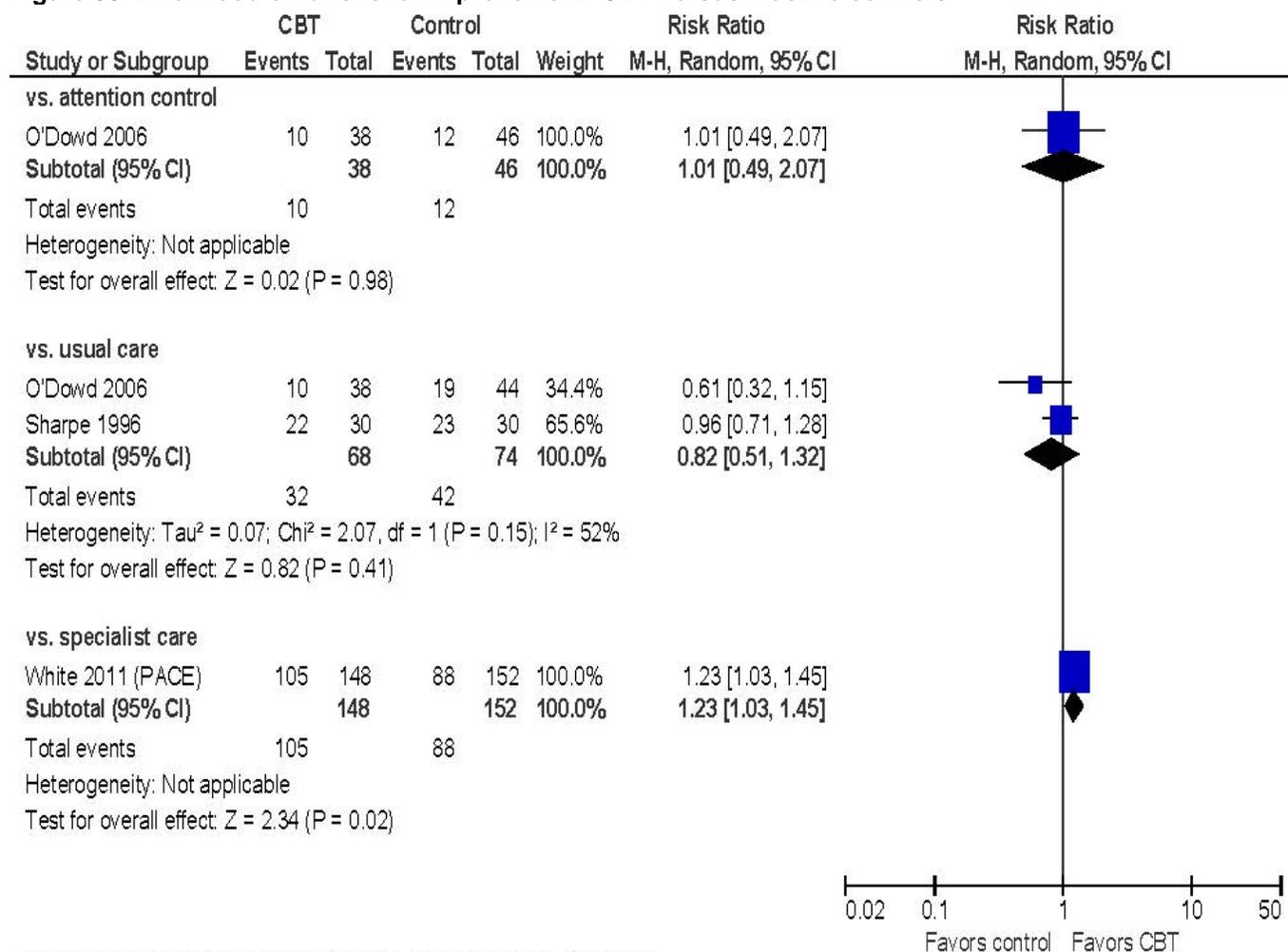
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 34. Functional impairment: CBT versus inactive controls at post-intervention follow-up



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 35. Likelihood of functional improvement: CBT versus inactive controls



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

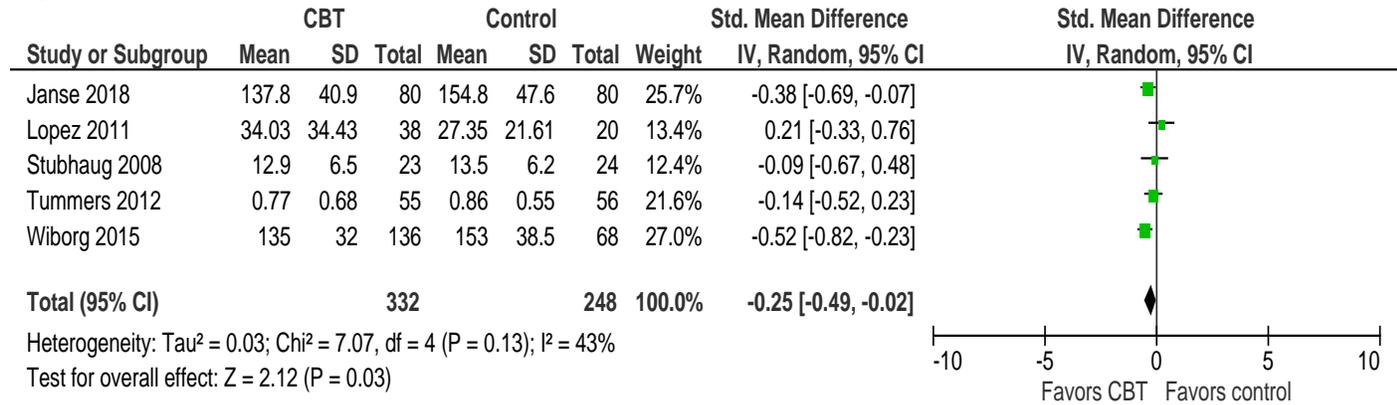
Depression and anxiety

CBT was associated with decreased depression severity versus wait list, placebo medication, or an attention control at the end of the intervention (5 trials, N=660, SMD -0.25, 95% CI -0.49 to -0.02, I²=43%;^{66,68,71-73} **Figure 36**). In two trials (N=444) that used the 90 to 450 Symptom Checklist-90 scale (SCL-90) the mean difference was -17.66 (95% CI -25.66 to -9.65, I²=0%).^{66,73} The other trials each used a different scale for depression severity (**Table 9**). Excluding a high risk of bias trial⁶⁸ had little effect on the pooled estimate (4 trials, N=602, SMD -0.35, 95% CI -0.54 to -0.17, I²=11%). CBT was also associated with decreased depression severity versus usual care, usual specialist care, or an attention control at post-intervention follow-up (3 trials, N=483, mean difference -1.24, 95% CI -2.01 to -0.47 on the 0 to 21 HADS depression scale, I²=12%;^{36,69,70} **Figure 37**).

CBT was associated with decreased anxiety severity versus usual care, usual specialist care, or an attention control at post-intervention follow-up (3 trials, N=481, mean difference -1.22, 95% CI -1.94 to -0.49 on the 0 to 21 HADS anxiety scale, I²=0%;^{36,69,70} **Figure 38**). No trial evaluated anxiety at the end of the intervention.

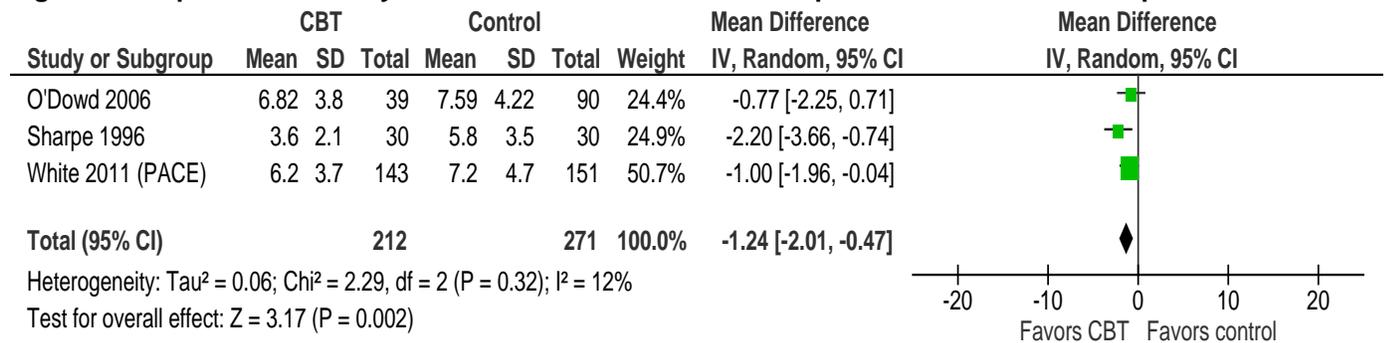
For both depression and anxiety, results were consistent in stratified analyses based on control type, ME/CFS criteria, or CBT type, with no statistically significant subgroup differences (Table 9). However, stratified analyses were based on small numbers of trials.

Figure 36. Depression severity: CBT versus inactive controls at end of treatment



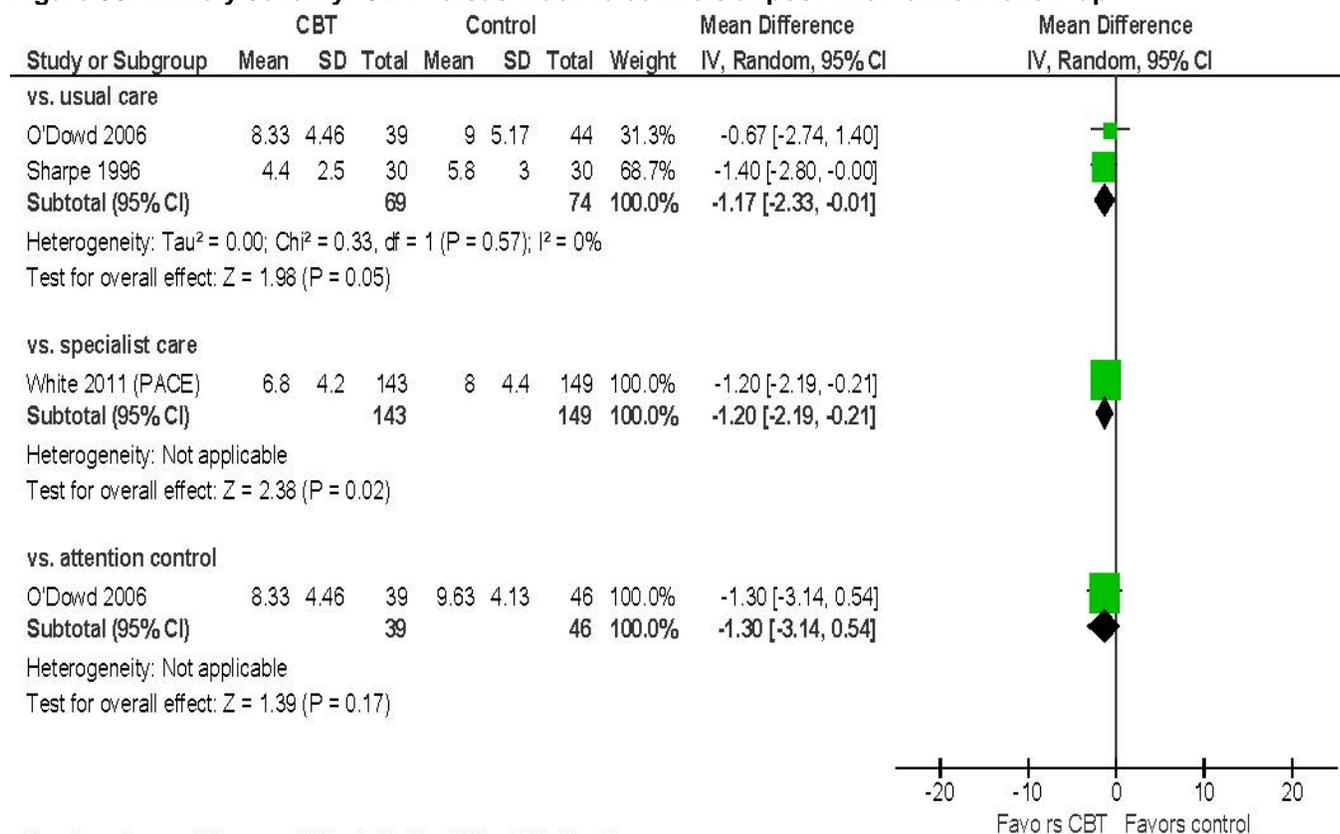
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; IV = instrumental variable; SD = standard deviation; Std = standard

Figure 37. Depression severity: CBT versus inactive controls at post-intervention follow-up



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 38. Anxiety severity: CBT versus inactive controls at post-intervention follow-up



Test for subgroup differences: Chi² = 0.01, df = 2 (P = 0.99), I² = 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Sleep

One trial found CBT associated with improved sleep quality versus usual specialist care at post-intervention follow-up (N=292, mean difference -1.20 on the 0 to 20 Jenkins Sleep Questionnaire, 95% CI -2.19 to -0.21).³⁶ No trial evaluated effects of CBT versus controls on sleep quality at the end of the intervention.

Pain

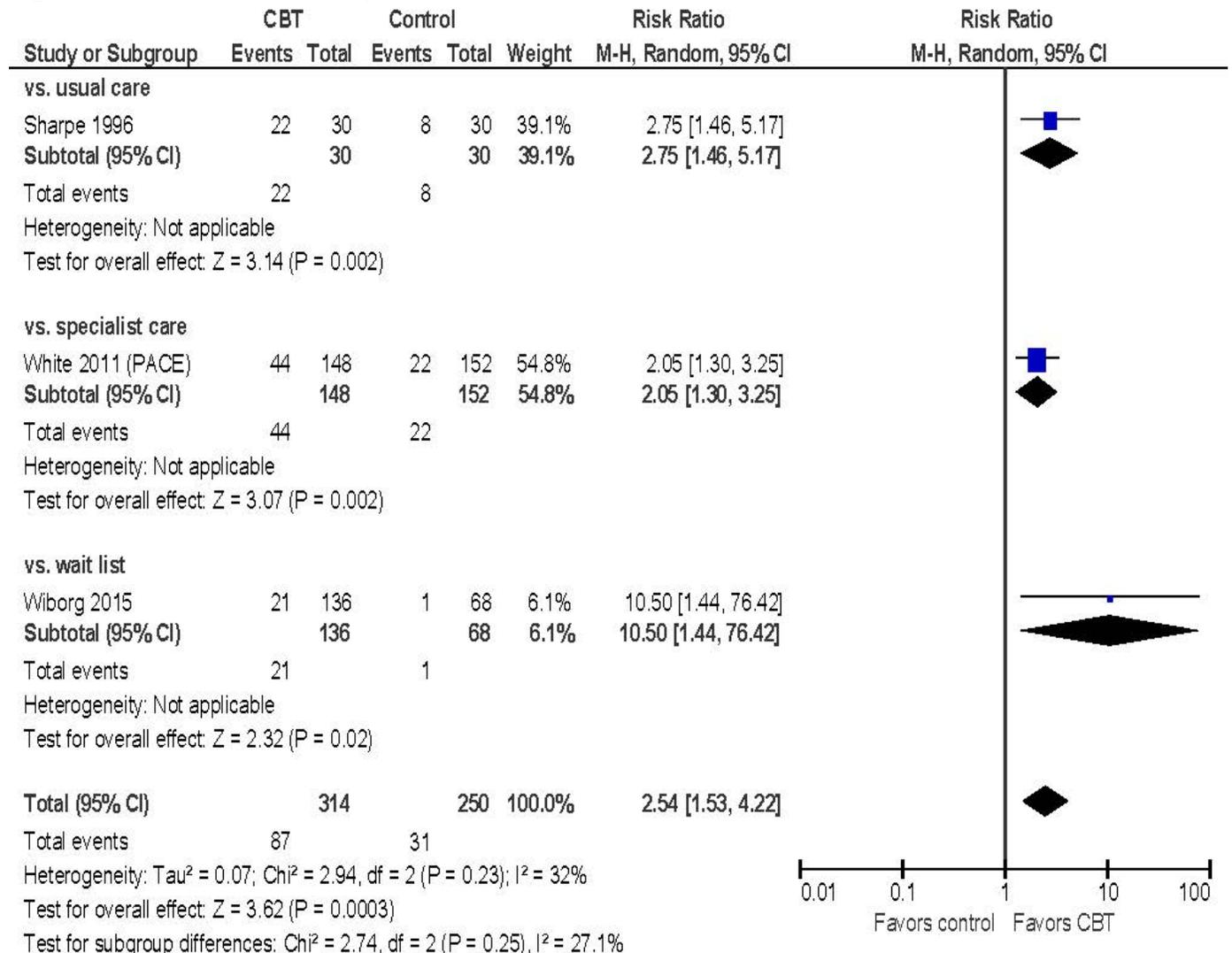
A post-hoc analysis of the PACE trial found CBT associated with decreased severity of muscle pain (mean difference -0.38, 95% CI -0.69 to -0.08 on a 0 to 4 scale).⁶⁰ The effect on joint pain was not statistically significant (mean difference -0.25, 95% CI -0.58 to 0.08).

Recovery

Three trials evaluated effects of CBT versus usual care, usual specialist care, or wait list on likelihood of recovery.^{36,70,73} One trial⁷⁰ defined recovery as a KPS final score of ≥80 and one trial⁷³ defined recovery as a Checklist Individual Strength severity subscale score <27, SF-36 physical function score ≥80, and Sickness Impact Profile total score <203. The third trial, PACE, used a different definition for recovery in the main publication than described in the original protocol (see Results, exercise for details).³⁶ Based on the published results from PACE (proportion of patients meeting definition for recovery 28% vs. 14%), CBT was associated with increased likelihood of recovery versus usual care, usual specialist care, or wait list (3 trials,

N=564, RR 2.54, 95% 1.53 to 4.22, $I^2=32\%$; ARD 21%, 95% CI 8% to 34%;^{36,70,73} **Figure 39**). Replacing the data from PACE with results based on the original protocol definition for recovery (proportion meeting definition 7% vs. 3%)³⁷ resulted in a similar pooled estimate (3 trials, N=585, RR 2.88, 95% CI 1.62 to 5.11, $I^2=9\%$; ARD 17%, 95% CI 2% to 32%).

Figure 39. Likelihood of recovery: CBT versus inactive controls



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Overall improvement

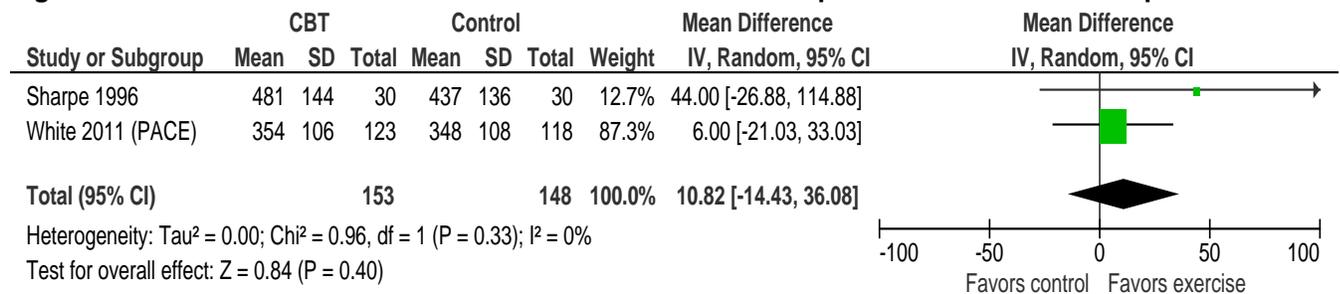
In the PACE trial, a composite outcome for overall improvement, based on an 11-item Chalder fatigue scale (0 to 11) score ≤ 3 or $>50\%$ improvement from baseline and SF-36 physical function score ≥ 75 or $>50\%$ improvement from baseline at 52 weeks, was described as the primary outcome in the study protocol³⁷ but not reported in the main publication. In a subsequent publication, the authors reported that CBT plus usual specialist care was associated with greater likelihood of overall improvement than usual specialist care alone, using the protocol definition³⁸ (20% vs. 10%, RR 1.99, 95% CI 1.14 to 3.48).

One other trial found CBT associated with improved overall efficacy (defined as Checklist Individual Strength fatigue severity subscale score <36 and reliable change index >1.96, SF-36 physical function score ≥65, and Sickness Impact Profile overall impairment score <700) versus wait list (38% vs. 2.9%, RR 13.00, 95% CI 3.26 to 51.78).⁷³

6-minute walk test

Two trials found no difference between CBT versus usual care or usual specialist care in the 6-minute walk test at post-intervention follow-up (2 trials, N=301, mean difference 10.82 meters, 95% CI -14.43 to 36.08, I²=0%,^{36,70} **Figure 40**).

Figure 40. Six-minute walk test: CBT versus inactive controls at post-intervention follow-up



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Harms

Data on harms were limited to the PACE trial (N=321), which found no differences between CBT versus usual specialist care alone in likelihood of serious adverse events (RR 0.99, 95% 0.36 to 2.77) or physical function worsening (RR 0.83, 95% CI 0.26 to 2.66).³⁶ Only one case of withdrawal due to adverse events occurred. In PACE, CBT was associated with decreased likelihood of post-exertional malaise (49% vs. 63%, RR 0.78, 95% CI 0.64 to 0.95).

Table 9. Cognitive behavioral therapy vs. inactive controls

Outcome	Number of studies (N)	Estimate (95% CI)	I ²	p for subgroup difference
<i>Fatigue, end of intervention</i>	7 (1129)	SMD -0.61 (-0.83 to -0.40)	64%	--
By control type: vs. wait list	4 (724)	SMD -0.77 (-0.99 to -0.55)	50%	0.05
vs. usual specialist care	1 (300)	SMD -0.34 (-0.57 to -0.11)	--	--
vs. attention control	1 (58)	SMD -0.31 (-0.85 to 0.24)	--	--
vs. placebo medication	1 (47)	SMD -0.40 (-0.98 to 0.18)	--	--
On original scale: Chalder (11-item, 0 to 33)	2 (347)	MD -2.53 (-4.06 to -1.00)	0%	--
Checklist Individual Strength, fatigue severity (8 to 56)	4 (724)	MD -9.20 (-12.09 to -6.31)	66%	--
Profile of Mood States fatigue/inertia (0 to 28)	1 (58)	MD -2.24 (-6.09 to 1.61)	--	--
By ME/CFS criteria: Oxford	1 (300)	SMD -0.34 (-0.57 to -0.11)	--	0.07
Fukuda	5 (782)	SMD -0.72 (-0.94 to -0.49)	53%	--
Oxford or Fukuda	1 (47)	SMD -0.40 (-0.98 to 0.18)	--	--
By CBT type: Individual, face-to-face	1 (300)	SMD -0.34 (-0.57 to -0.11)	--	0.14
Individual, self-guided	2 (280)	SMD -0.73 (-0.97 to -0.48)	0%	--
Individual, web-based	1 (240)	SMD -0.57 (-0.84 to -0.29)	--	--
Group, face-to-face	3 (309)	SMD -0.63 (-1.18 to -0.09)	75%	--

Outcome	Number of studies (N)	Estimate (95% CI)	I ²	p for subgroup difference
Excluding high risk of bias trial	6 (1071)	SMD -0.65 (-0.88 to -0.41)	68%	--
Using difference in change from baseline	6 (1049)	SMD -0.69 (-0.98 to -0.40)	79%	--
<i>Fatigue, post-intervention</i>	3 (489)	SMD -0.57 (-0.89 to -0.25)	57%	--
By control type: vs. usual care	1 (143)	SMD -0.61 (-1.47 to 0.24)	--	0.95
vs. usual specialist care	1 (300)	SMD -0.48 (-0.71 to -0.25)	--	--
vs. attention control	1 (85)	SMD -0.52 (-0.96 to -0.09)	--	--
On original scale: Chalder (11-item, 0 to 33)	2 (429)	MD -3.29 (-4.71 to -1.86)	0%	--
0 to 10 Likert	1 (60)	MD -2.00 (-2.94 to -1.06)	--	--
By ME/CFS criteria Oxford	2 (360)	SMD -0.72 (-1.28 to -0.15)	74%	0.31
Fukuda	1 (129)	SMD -0.36 (-0.74 to 0.02)	--	--
By CBT type: Individual, face-to-face	2 (360)	SMD -0.72 (-1.28 to -0.15)	74%	0.31
Group, face-to-face	1 (129)	SMD -0.36 (-0.74 to 0.02)	--	--
Using difference in change from baseline	3 (489)	SMD -0.58 (-0.87 to -0.29)	47%	--
<i>Fatigue improvement (dichotomous)</i>	4 (784)	RR 3.00 (0.95 to 9.49)	93%	--
By control type vs. wait list	3 (484)	RR 4.40 (2.70 to 7.16)	0%	<0.00001
vs. usual specialist care	1 (300)	RR 1.17 (1.01 to 1.36)	--	--
By ME/CFS criteria Oxford	1 (300)	RR 1.17 (1.01 to 1.36)	--	--
Fukuda	3 (484)	RR 4.40 (2.70 to 7.16)	0%	--
By CBT type Individual, face-to-face	1 (300)	RR 1.17 (1.01 to 1.36)	--	<0.00001
Individual, self-guided	2 (280)	RR 3.78 (2.03 to 7.04)	0%	--
Group, face-to-face	1 (204)	RR 13.00 (3.26 to 51.78)	--	--
Using original PACE definition	4 (805)	RR 3.30 (1.96 to 5.55)	51%	--
<i>SF-36 physical function (0 to 100), end of intervention</i>	5 (1024)	MD 6.58 (3.76 to 9.39)	0%	--
By control type: vs. wait list	4 (724)	MD 6.92 (3.54 to 10.31)	0%	0.72
vs. usual specialist care	1 (300)	MD 5.80 (0.74 to 10.86)	--	--
By ME/CFS criteria: Oxford	1 (300)	MD 5.80 (0.74 to 10.86)	--	0.72
Fukuda	4 (724)	MD 6.92 (3.54 to 10.31)	0%	--
By CBT type Individual, face-to-face	1 (300)	MD 5.80 (0.74 to 10.86)	--	0.44
Individual, self-guided	2 (280)	MD 5.85 (0.32 to 11.39)	0%	--
Individual, web-based	1 (160)	MD 4.40 (-1.49 to 10.29)	--	--
Group, face-to-face	1 (204)	MD 11.10 (4.87 to 17.33)	--	--
Using difference in change from baseline	5 (1024)	MD 9.24 (4.68 to 13.79)	64%	--
<i>Function, post-intervention</i>	3 (489)	SMD 0.37 (0.08 to 0.66)	50%	--
By control type: vs. usual care	1 (143)	SMD 0.40 (-0.37 to 1.18)	--	0.97
vs. usual specialist care	1 (300)	SMD 0.30 (0.07 to 0.53)	--	--
vs. attention control	1 (85)	SMD 0.33 (-0.10 to 0.76)	--	--
On original scale: SF-36 physical function (0 to 100)	1 (300)	MD 7.40 (1.88 to 12.92)	--	--
SF-36 physical component summary (0 to 100)	1 (129)	MD 1.50 (-1.66 to 4.66)	--	--
Percentage interference with activity (0 to 100, reversed so that higher score indicates better function)	1 (60)	MD 13.00 (5.04 to 20.96)	--	--
By ME/CFS criteria Oxford	2 (360)	SMD 0.50 (0.01 to 0.99)	67%	0.29
Fukuda	1 (129)	SMD 0.17 (-0.21 to 0.55)	--	--
By CBT type Individual, face-to-face	2 (360)	SMD 0.50 (0.01 to 0.99)	67%	0.29

Outcome	Number of studies (N)	Estimate (95% CI)	I ²	p for subgroup difference
Group, face-to-face	1 (129)	SMD 0.17 (-0.21 to 0.55)	--	--
Using difference in change from baseline	3 (489)	SMD 0.37 (-0.07 to 0.81)	77%	--
<i>Functional improvement</i>	3 (488)	RR 1.06 (0.83 to 1.35)	47%	--
By control type: vs. usual care	2 (142)	RR 0.82 (0.51 to 1.32)	52%	0.27
vs. usual specialist care	1 (300)	RR 1.23 (1.03 to 1.45)	--	--
vs. attention control	1 (84)	RR 1.01 (0.49 to 2.07)	--	--
By ME/CFS criteria: Oxford	2 (360)	RR 1.11 (0.88 to 1.41)	52%	0.25
Fukuda	1 (128)	RR 0.76 (0.42 to 1.40)	--	--
By CBT type Individual, face-to-face	2 (360)	RR 1.11 (0.88 to 1.41)	52%	0.25
Group, face-to-face	1 (128)	RR 0.76 (0.42 to 1.40)	--	--
Using original PACE definition	3 (509)	RR 1.03 (0.86 to 1.22)	0%	--
<i>Depression, end of intervention</i>	5 (660)	SMD -0.26 (-0.49 to -0.03)	45%	--
By control type: vs. wait list	3 (555)	SMD -0.38 (-0.58 to -0.18)	18%	0.10

Abbreviations: CFS = chronic fatigue syndrome; CI = confidence interval; CBT = cognitive behavioral therapy; MD = mean difference; ME = myalgic encephalomyelitis; PACE = pacing, graded activity, cognitive behavior therapy; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference

CBT versus active interventions

Four trials (N=876) compared CBT versus active interventions in adults (**Table 7 and 8, Evidence Table Appendix E2**).^{36,51,65,71} The active interventions were exercise (2 trials),^{36,51} relaxation (2 trials),^{51,65} cognitive therapy (1 trial),⁵¹ adaptive pacing (1 trial),³⁶ and mirtazapine (1 trial).⁷¹ All the trials except for one (mirtazapine)⁷¹ were included in the prior AHRQ report. The duration of the CBT intervention ranged from 12 weeks to 6 months. Three trials^{36,65,71} evaluated patients at the end of the intervention and two trials^{36,51} evaluated patients 26 to 29 weeks following the end of the intervention. All of the trials were rated medium risk of bias. Results stratified by the active comparator are summarized in **Table 10** and shown in **Figures 41 to 56**.

CBT versus exercise

See Results for exercise (Table 6; Figures 12, 14, 17, 19, 21, 23).

CBT versus relaxation

Two trials compared CBT versus relaxation in patients who met the Fukuda case definition.⁵¹ or both the Oxford and Fukuda case definitions.⁶⁵ The duration of therapy was 4 to 6 months. One trial⁶⁵ evaluated outcomes at the end of therapy and both trials evaluated outcomes 6 months following the completion of therapy. There was no difference between CBT versus relaxation in fatigue severity at the end of the intervention (1 trial, N=60, mean difference -0.3, 95% CI -2.4 to 1.8 on the 11-item 0 to 11 Chalder scale, **Figure 41**) or at post-intervention follow-up (2 trials, N=117, SMD -0.49, 95% CI -1.03 to 0.04, I²=52%, **Figure 42**). CBT was associated with decreased severity of functional impairment at the end of therapy (1 trial, mean difference 21.6, 95% CI 7.8 to 35.4 on the 0 to 100 SF-36 physical function subscale, **Figure 43**) but the difference was not statistically significant at post-intervention follow-up (2 trials, N=117, mean difference 15.45, 95% CI -19.60 to 50.49, I²=91%, **Figure 44**). Statistical heterogeneity was present at post-intervention follow-up for both fatigue (SMD -0.76, 95% CI -1.29 to -0.24 in one trial⁶⁵ and SMD -0.22, 95% CI -0.74 to 0.30 in the other trial)⁵¹ and function (mean difference

33.2, 95% CI 19.31 to 47.09 on the SF-36 physical function subscale in one trial⁶⁵ and -2.6, 95% CI -17.7 to 12.5 in the other trial).⁵¹

There were no differences between CBT versus relaxation in depression at the end of therapy (1 trial, N=60, mean difference -3.0, 95% CI -6.3 to 0.3 on the 0 to 63 Beck Depression Inventory, **Figure 45**)⁶⁵ or at post-intervention follow-up (2 trials, N=117, mean difference -1.4, 95% CI -4.7 to 1.9 on the Beck Depression Inventory, **Figure 46**).^{51,65} One trial found no differences between CBT versus relaxation in anxiety, pain, sleep quality, the 6-minute walking test, or severity of sore throat, tender lymph nodes, impaired memory, or headache symptoms at post-intervention follow-up.⁵¹

CBT was associated with increased likelihood of functional improvement versus relaxation (2 trials, N=110, RR 1.78, 95% CI 0.41 to 7.86, $I^2=79%$).^{51,65} However, statistical heterogeneity was present (RR 0.80, 95% CI 0.28 to 2.34 in one trial⁶⁵ and RR 3.66, 95% CI 1.60 to 8.35 in the other trial)⁵¹ Functional improvement was defined as SF-36 physical function score improved by ≥ 50 or end score ≥ 83 in one trial and as improvement in SF-36 physical function score greater than the age adjusted reliable change index and within 1 standard deviation of the normative value in the other trial.⁵¹ CBT was also associated with increased likelihood of recovery (2 trials, N=110, RR 4.41, 95% CI 1.79 to 10.83, $I^2=0%$).^{51,65} Recovery was defined as an 11-item Chalder fatigue score < 4 in one trial⁶⁵ and as no longer meeting CFS criteria based on physician diagnosis in the other trial.⁵¹ One trial found CBT associated with increased likelihood of having a global improvement rating of better or much better (70% vs. 31%, RR 2.29, 95% CI 1.22 to 4.28).⁶⁵ One trial found no difference between CBT versus relaxation in severity of post-exertional malaise (mean difference 3.4, 95% CI -14.6 to 21.4 on the 0 to 100 CFS Questionnaire).⁵¹ The trials did not report serious adverse events, withdrawals due to adverse events, or other harms.

One of the trials (N=53) evaluated long-term outcomes at 5 years (4 years after trial completion).⁷⁴ Around 56% of patients in both groups received additional post-trial CFS treatments. CBT was associated with increased likelihood of self-rated global improvement of “much better” or “very much better” (68% vs. 36%, RR 1.90, 95% CI 1.08 to 3.35). There were no differences in likelihood of functional improvement (SF-36 physical function > 83 , 48% vs. 32%, RR 1.49, 95% CI 0.76 to 2.93), fatigue improvement (11-item 0 to 11 Chalder < 4 , 28% vs. 25%, RR 1.12, 95% CI 0.46 to 2.75), and psychological distress (General Health Questionnaire < 4 , 48% vs. 54%, RR 0.90, 95% CI 0.53 to 1.53), though some estimates were imprecise.

CBT versus adaptive pacing

The PACE trial included a comparison of CBT versus adaptive pacing (n=320). Outcomes were reported at the end of therapy at 24 weeks and 28 weeks later.³⁶ CBT was associated with decreased fatigue severity versus adaptive pacing at the end of the intervention (mean difference -2.2, 95% CI -3.9 to -0.5 on the 11-item 0 to 33 Chalder scale) and at post-intervention follow-up (mean difference -2.8, 95% CI -4.5 to -1.1). CBT was also associated with decreased severity of functional impairment at the end of the intervention (mean difference 11.00, 95% CI 6.16 to 15.84 on the SF-36 physical function subscale) and at post-intervention follow-up (mean difference 12.30, 95% CI 6.76 to 17.84), as well as decreased depression severity at post-intervention follow-up (mean difference -1.0, 95% CI -2.0 to -0.05 on the 0 to 21 HADS depression scale). Effects on sleep quality (mean difference -0.7, 95% CI -1.9 to 0.5 on the 0 to 20 Jenkins sleep scale), the 6-minute walk test (mean difference 20 meters, 95% CI -9 to 49) and anxiety (mean difference -0.17, 95% CI -0.4 to 0.06 on the 0 to 21 HADS anxiety scale) favored

CBT at post-intervention follow-up, but differences were small and not statistically significant. In a post-hoc analysis, CBT was associated with decreased severity of muscle pain (mean difference -0.34, 95% CI -0.65 to -0.02) and joint pain (mean difference -0.35, 95% CI -0.68 to -0.02) versus specialist care (each assessed on a 0 to 4 scale).⁶⁰

CBT was associated with increased likelihood of improvement in fatigue (76% vs. 65%, RR 1.16, 95% CI 1.00 to 1.35), improvement in function (71% vs. 49%, RR 1.45, 95% CI 1.19 to 1.75), and recovery (30% vs. 16%, RR 1.82, 95% CI 1.18 to 2.81) versus adaptive pacing, based on the definitions in the main PACE publication. Results were similar using the original protocol definitions³⁷ for improvement in fatigue (26% vs. 14%, RR 1.80, 95% CI 1.14 to 2.85), functional improvement (49% vs. 40%, RR 1.22, 95% CI 0.95 to 1.56), and overall improvement (composite of improvement in fatigue and function, 20% vs. 9%, RR 2.11, 95% CI 1.19 to 3.74),³⁸ though the estimate for functional improvement was attenuated and no longer statistically significant. CBT was also associated with lower likelihood of post-exertional malaise (49% vs. 63%, RR 0.78, 95% CI 0.64 to 0.95).³⁶ There were no differences between CBT versus adaptive pacing in risk of serious adverse events, withdrawal due to adverse events, or worsening of function, but estimates were imprecise (**Table 10**).

The PACE trial also evaluated longer-term, post-trial outcomes (median duration from randomization 31 months).⁵⁹ About 31% of patients in the CBT group and 50% in the adaptive pacing group received non-randomly allocated therapies between the end of the trial at 1 year and long-term follow-up. Fatigue severity was decreased at long-term follow-up compared with end-of-trial scores in the CBT (mean change -2.2, 95% CI -3.7 to -0.6 on the 11-item, 0 to 33 Chalder scale) and adaptive pacing (mean change -3.0, 95% CI -4.4 to -1.6) groups. SF-36 physical function also improved between the end of the trial and long-term follow-up in the CBT (mean change 3.3, 95% CI 0.02 to 6.7 on a 0 to 100 scale) and adaptive pacing groups (mean change 8.5, 95% CI 4.5 to 12.5), though the change was smaller in the CBT group. At long-term follow-up, mixed model analysis showed no difference between CBT versus adaptive pacing in fatigue severity (mean difference -1.6, 95% CI -3.6 to 0.3), but CBT was associated with decreased functional impairment (mean difference 6.4, 95% CI 0.4 to 12.4).

CBT versus cognitive therapy

One trial included a comparison of CBT versus cognitive therapy (N=57).⁵¹ Outcomes were evaluated 6 months following completion of 6 months of treatment. There were no differences between CBT versus cognitive therapy in severity of fatigue, functional impairment, depression, anxiety or pain; sleep quality; or distance on the 6-minute walking test (**Table 10**). CBT was associated with higher severity of sore throat (mean difference 16.4, 95% CI 1.5 to 31.3 on the 0 to 100 CFS Questionnaire) and tender lymph node symptoms (mean difference 15.9, 95% CI 0.3 to 31.5). There were no differences in severity of post-exertional malaise (mean difference 1.5, 95% CI -17.2 to 20.3), impaired memory (mean difference -3.1, 95% CI -17.3 to 11.1), or headache (mean difference 11.6, 95% CI -8.6 to 32.0) symptoms. There was also no difference in likelihood of functional improvement or recovery, but estimates were imprecise.

CBT versus medication (mirtazapine)

One trial (N=48) compared CBT versus mirtazapine (an antidepressant).⁷¹ Outcomes were evaluated at the completion of 12 weeks of treatment. Effects on fatigue severity favored mirtazapine, but the difference was not statistically significant (mean difference -1.7, 95% CI -4.8 to 1.4 on the 11-item, 0 to 33 Chalder scale). There was no difference between CBT versus

mirtazapine in depression severity (mean difference 0.30, 95% CI -2.6 to 3.2 on the 0 to 52 Hamilton Rating Scale for Depression). The trial did not evaluate harms.

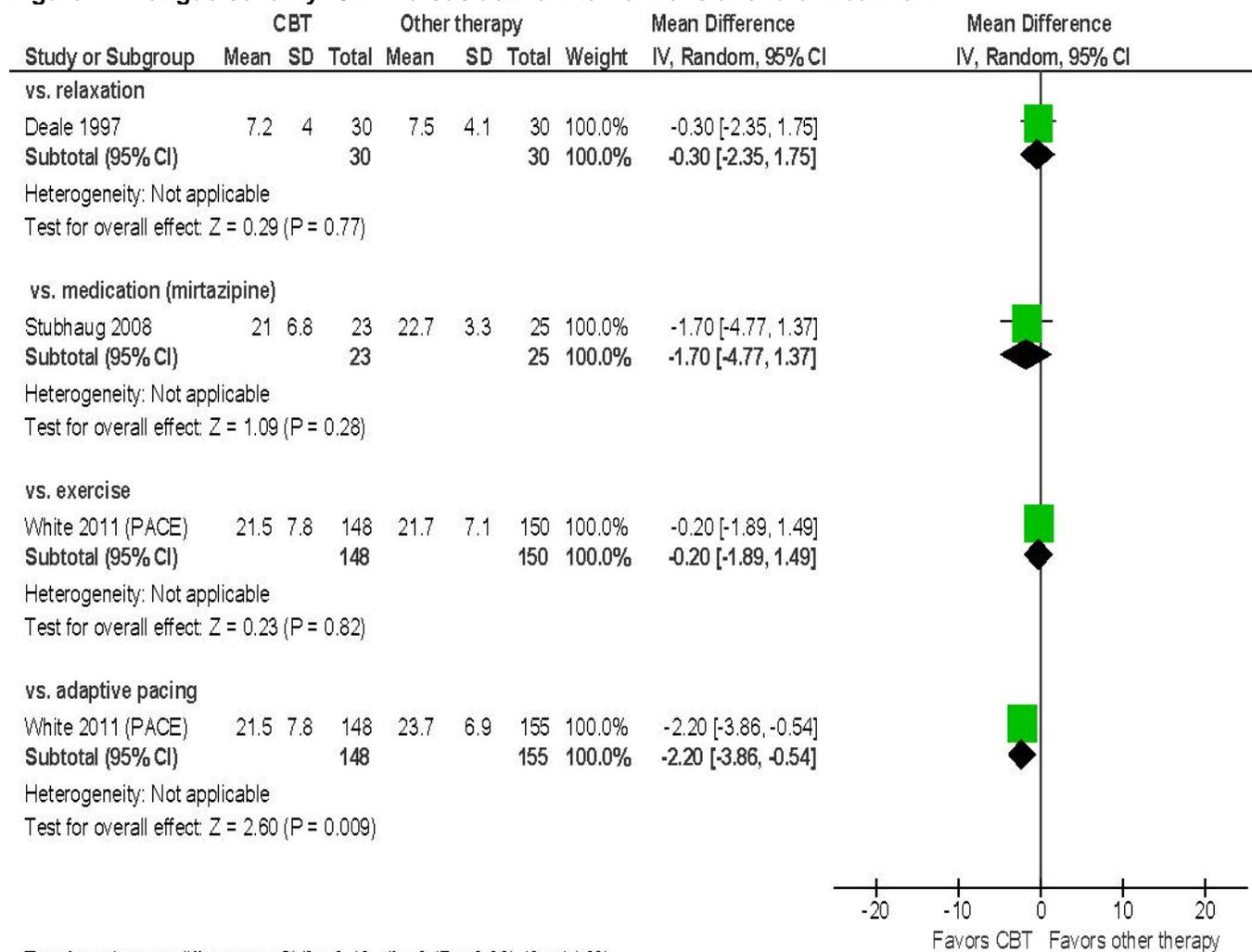
Table 10. CBT versus active interventions: Summary of stratified results

Outcome	Number of studies (N)	Estimate (95% CI)	I ²
<i>Fatigue, end of intervention</i>			
vs. exercise	1 (298)	SMD -0.03 (-0.25 to 0.20)	--
vs. relaxation	1 (60)	SMD -0.07 (-0.58 to 0.43)	--
vs. adaptive pacing	1 (303)	SMD -0.30 (-0.52 to -0.07)	--
vs. mirtazapine	1 (48)	SMD -0.32 (-0.89 to 0.25)	--
<i>Fatigue, post-intervention</i>			
vs. exercise	2 (360)	SMD -0.08 (-0.29 to 0.13)	0%
vs. relaxation	2 (117)	SMD -0.49 (-1.03 to 0.04)	52%
vs. cognitive therapy	1 (57)	SMD -0.45 (-0.97 to 0.08)	--
vs. adaptive pacing	1 (301)	SMD -0.36 (-0.59 to -0.14)	--
<i>SF-36 physical function (0 to 100), end of intervention</i>			
vs. exercise	1 (298)	MD -1.20 (-6.30 to 3.90)	--
vs. relaxation	1 (60)	MD 21.60 (7.80 to 35.40)	-
vs. adaptive pacing	1 (303)	MD 11.00 (6.16 to 15.84)	--
<i>SF-36 physical function (0 to 100), post-intervention</i>			
vs. exercise	2 (360)	MD 8.36 (-9.50 to 26.21)	80%
vs. relaxation	2 (117)	MD 15.45 (-19.60 to 50.49)	91%
vs. cognitive therapy	1 (57)	MD -2.45 (-16.59 to 11.69)	--
vs. adaptive pacing	1 (301)	MD 12.30 (6.76 to 17.84)	--
<i>Depression, end of intervention</i>			
vs. relaxation	1 (60)	SMD -0.45 (-0.96 to 0.06)	--
vs. mirtazapine	1 (48)	SMD 0.06 (-0.51 to 0.63)	--
<i>Depression, post-intervention</i>			
vs. exercise	2 (345)	SMD -0.02 (-0.23 to 0.19)	0%
vs. relaxation	2 (117)	SMD -0.12 (-0.49 to 0.24)	0%
vs. cognitive therapy	1 (57)	SMD 0.19 (-0.33 to 0.71)	--
vs. adaptive pacing	1 (292)	SMD -0.24 (-0.47 to -0.01)	--
<i>Anxiety, post intervention</i>			
vs. exercise	2 (345)	SMD 0.07 (-0.28 to 0.14)	0%
vs. relaxation	1 (57)	SMD 0.00 (-0.52 to 0.52)	--
vs. cognitive therapy	1 (57)	SMD 0.28 (-0.24 to 0.80)	--
vs. adaptive pacing	1 (292)	SMD -0.17 (-0.40 to 0.06)	--
<i>Sleep, post intervention</i>			
vs. exercise	2 (345)	SMD -0.17 (-0.04 to 0.39)	0%
vs. relaxation	1 (57)	SMD 0.30 (-0.22 to 0.82)	--
vs. cognitive therapy	1 (57)	SMD 0.12 (-0.40 to 0.64)	--
vs. adaptive pacing	1 (293)	SMD -0.14 (-0.37 to 0.09)	--
<i>Brief Pain Inventory (0 to 10), post intervention</i>			
vs. exercise	1 (58)	MD 0.35 (-1.32 to 2.02)	--
vs. relaxation	1 (57)	MD -0.34 (-1.94 to 1.26)	--
vs. cognitive therapy	1 (57)	MD 0.74 (-0.85 to 2.33)	--
<i>6-minute walk test (meters), end of intervention</i>			
vs. exercise	2 (291)	MD 4.23 (-67.52 to 75.99)	71%
vs. relaxation	1 (57)	MD 34.55 (-42.91 to 112.01)	--
vs. cognitive therapy	1 (57)	MD 8.88 (-67.88 to 85.63)	--
vs. adaptive pacing	1 (234)	MD 20.00 (-8.72 to 48.72)	--
<i>Recovery</i>			
vs. exercise	2 (360)	RR 1.10 (0.78 to 1.55)	0%
vs. relaxation	2 (110)	RR 4.41 (1.79 to 10.83)	0%
vs. cognitive therapy	1 (58)	RR 2.00 (0.40 to 10.08)	--
vs. adaptive pacing	1 (301)	RR 1.82 (1.18 to 2.81)	--
<i>Fatigue improvement</i>			
vs. exercise	1 (303)	RR 0.95 (0.84 to 1.07)	--

Outcome	Number of studies (N)	Estimate (95% CI)	I²
vs. adaptive pacing	1 (301)	RR 1.16 (1.00 to 1.35)	--
<i>Functional improvement</i>			
vs. exercise	2 (360)	RR 1.02 (0.88 to 1.18)	0%
vs. relaxation	2 (110)	RR 1.78 (0.41 to 7.86)	79%
vs. cognitive therapy	1 (57)	RR 0.54 (0.20 to 1.40)	--
vs. adaptive pacing	1 (301)	RR 1.45 (1.19 to 1.75)	--
<i>Serious adverse events</i>			
vs. exercise	1 (321)	RR 0.54 (0.22 to 1.31)	--
vs. adaptive pacing	1 (320)	RR 0.46 (0.19 to 1.10)	--
<i>Withdrawal due to worsening</i>			
vs. exercise	1 (321)	RR 0.20 (0.01 to 4.11)	--
vs. adaptive pacing	1 (320)	RR 0.14 (0.01 to 2.71)	--
<i>Physical function worsening</i>			
vs. exercise	1 (321)	RR 0.99 (0.29 to 3.37)	--
vs. adaptive pacing	1 (320)	RR 0.71 (0.23 to 2.18)	--
<i>Post-exertional malaise</i>			
vs. exercise	1 (321)	RR 1.10 (0.87 to 1.40)	--
vs. adaptive pacing	1 (319)	RR 0.78 (0.64 to 0.95)	--

Abbreviations: CI = confidence interval; CBT = cognitive behavioral therapy; MD = mean difference; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference

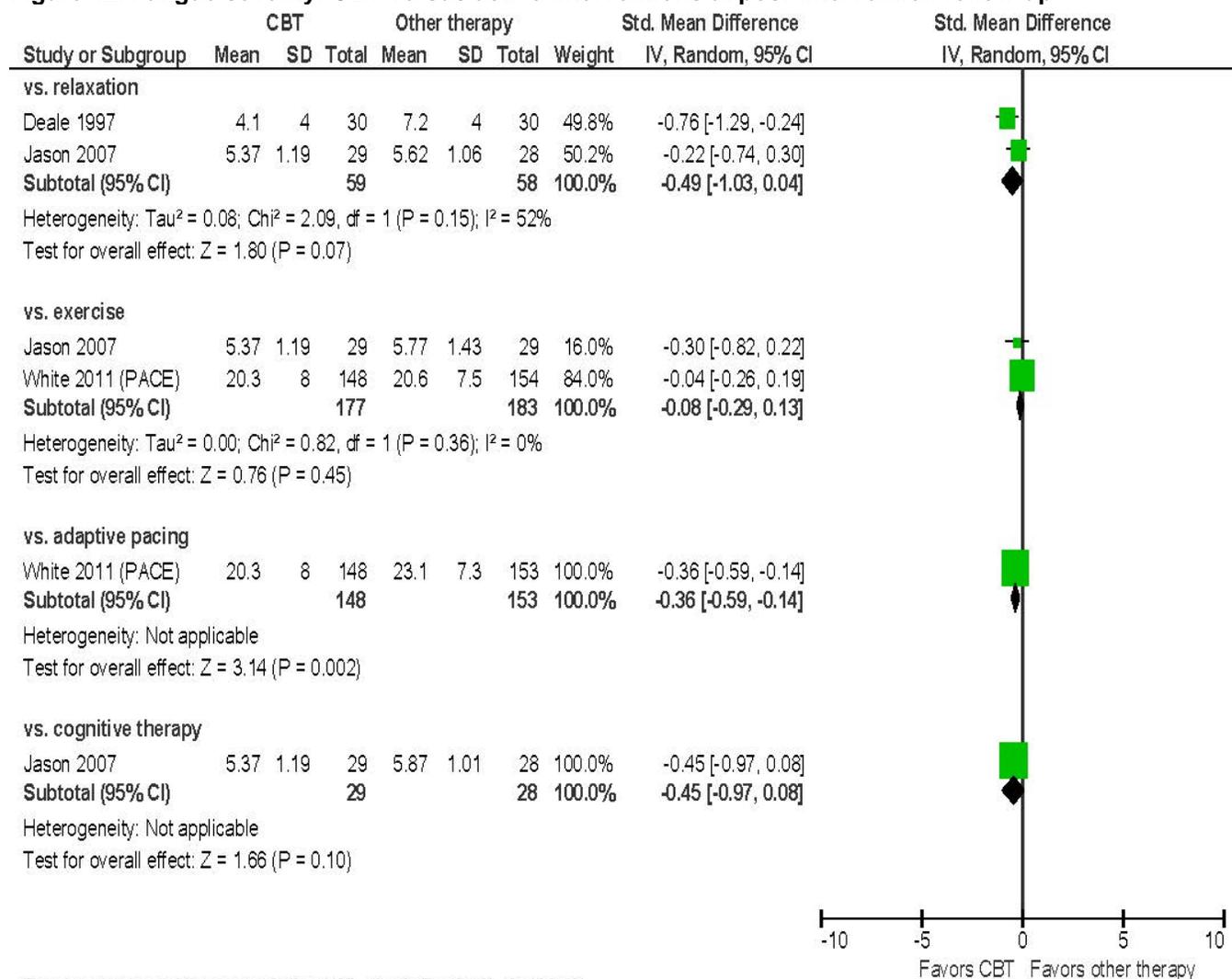
Figure 41. Fatigue severity: CBT versus active interventions at end of treatment



Test for subgroup differences: Chi² = 3.49, df = 3 (P = 0.32), I² = 14.2%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

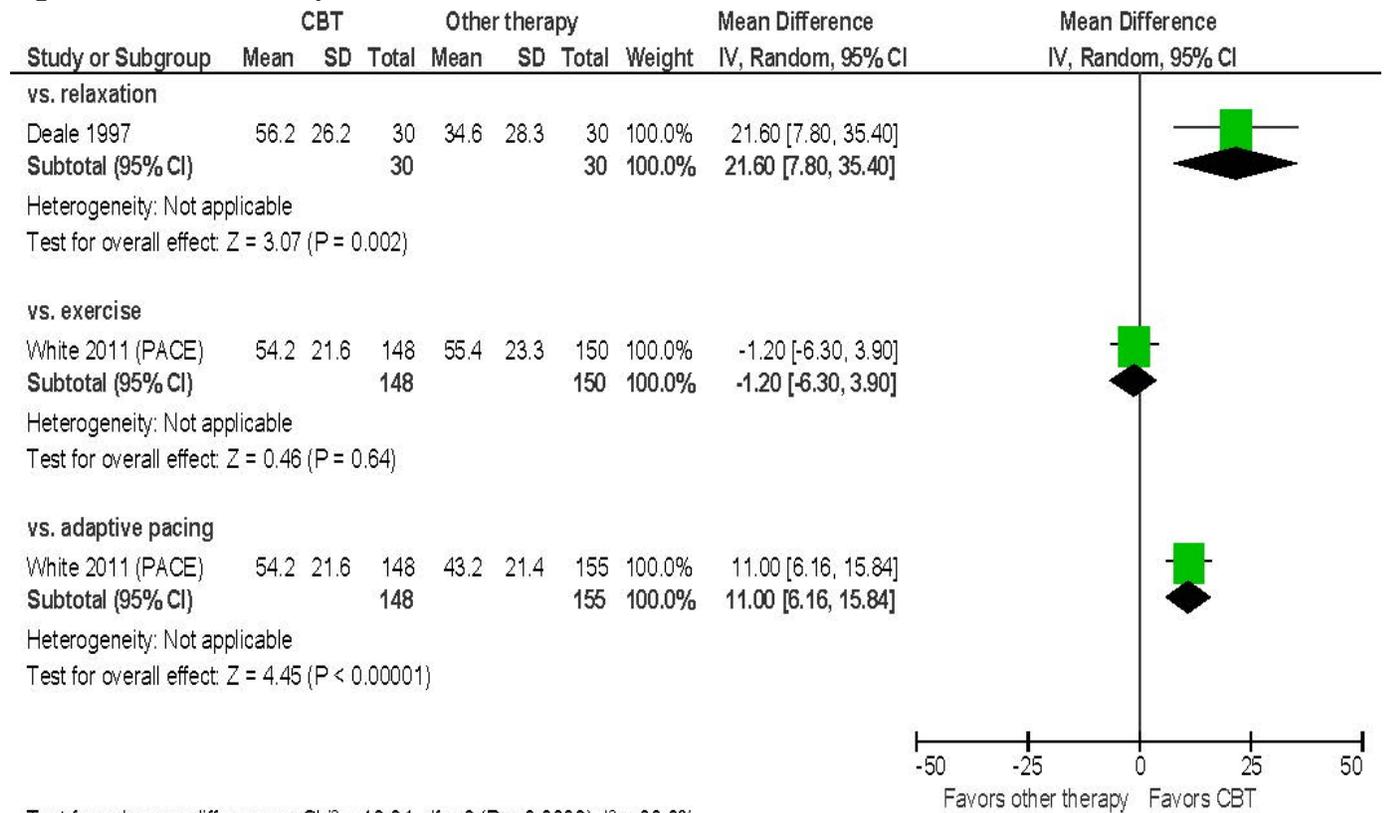
Figure 42. Fatigue severity: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: Chi² = 4.87, df = 3 (P = 0.18), I² = 38.4%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation; Std. = standard

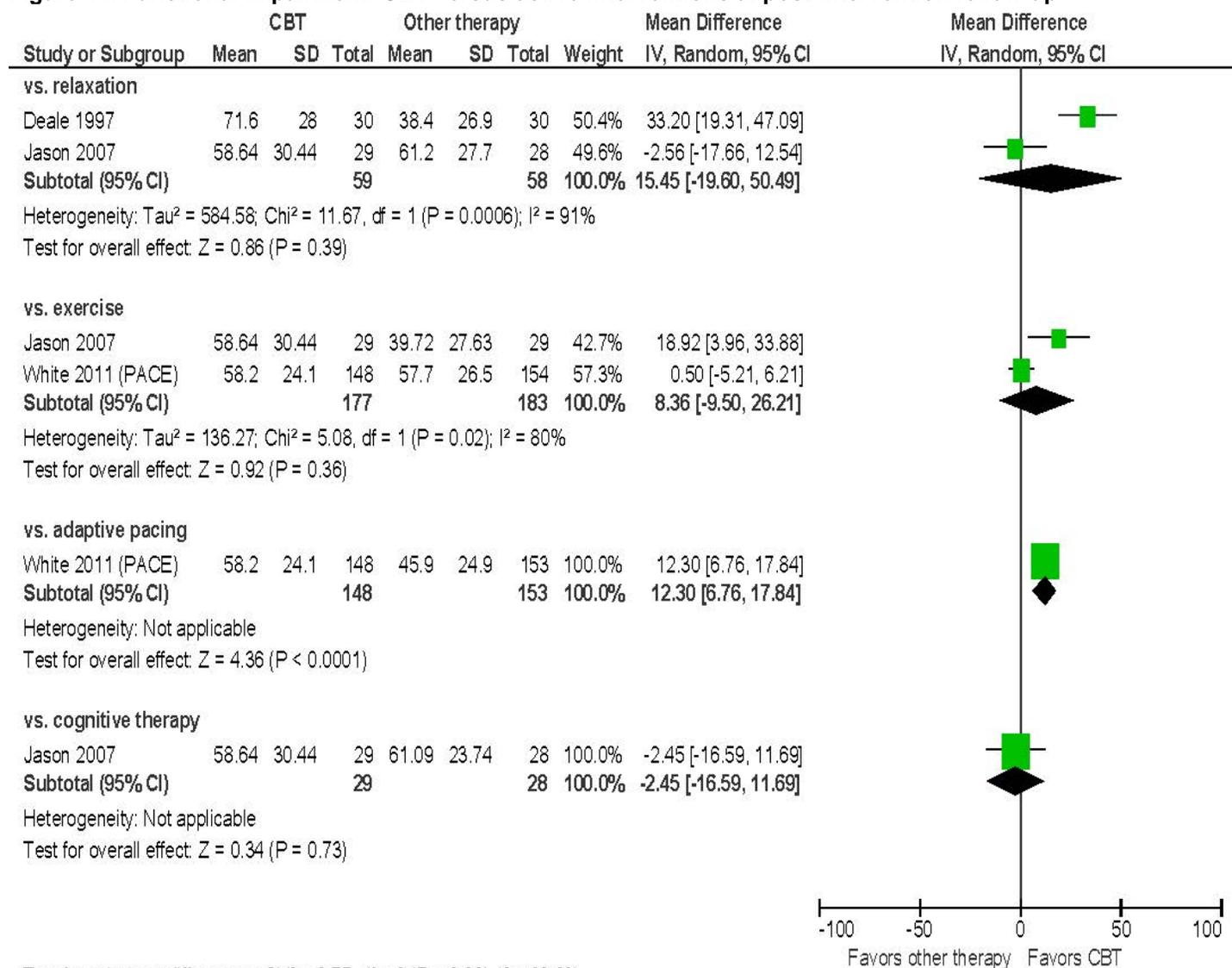
Figure 43. Functional impairment: CBT versus active interventions at end of treatment



Test for subgroup differences: Chi² = 16.64, df = 2 (P = 0.0002), I² = 88.0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

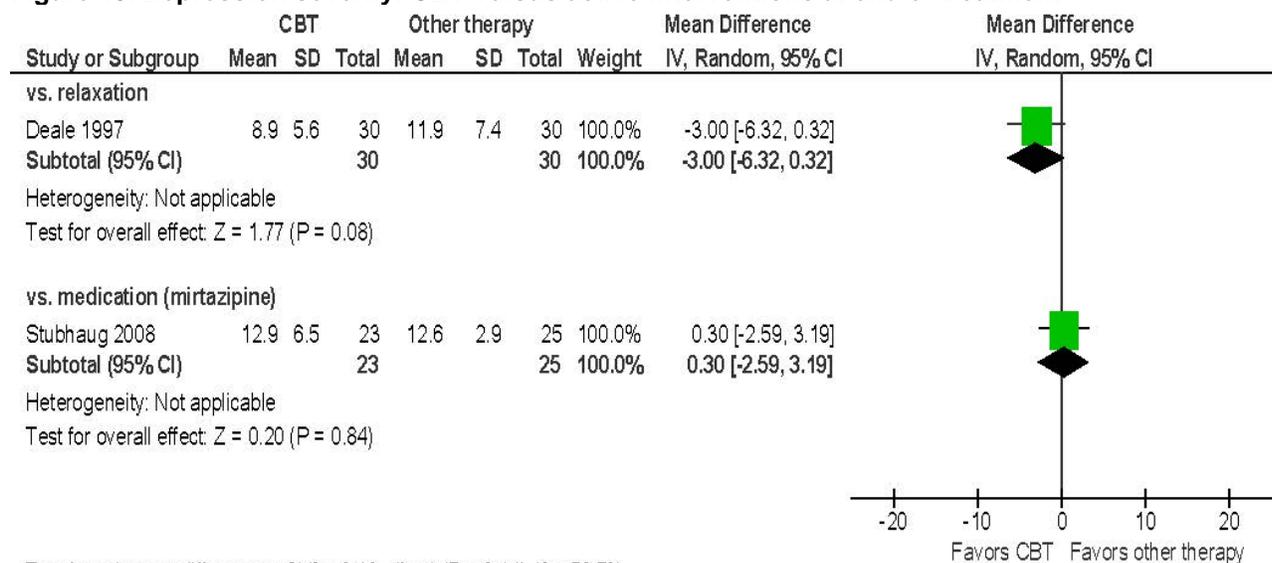
Figure 44. Functional impairment: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: Chi² = 3.75, df = 3 (P = 0.29), I² = 20.0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

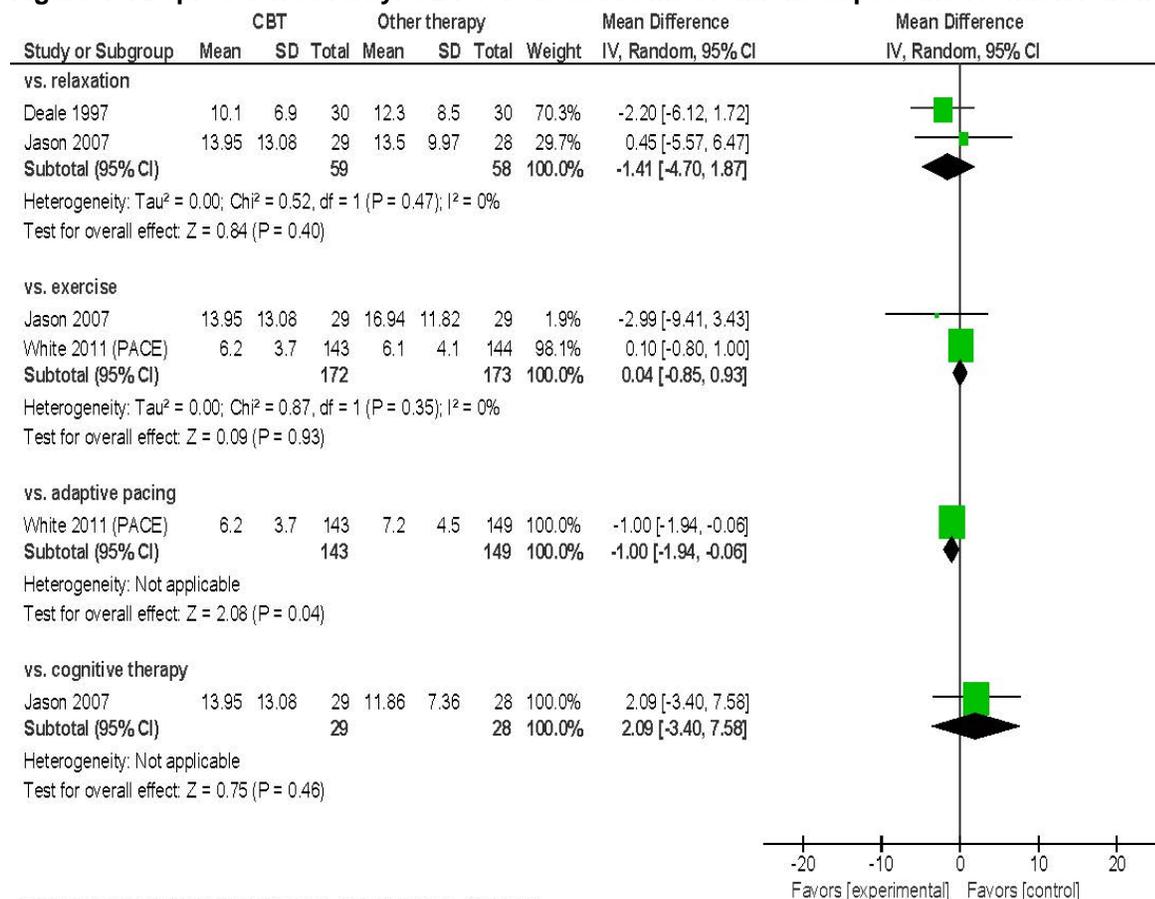
Figure 45. Depression severity: CBT versus active interventions at end of treatment



Test for subgroup differences: $\text{Chi}^2 = 2.16$, $\text{df} = 1$ (P = 0.14), $I^2 = 53.7\%$

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; IV = instrumental variable; SD = standard deviation

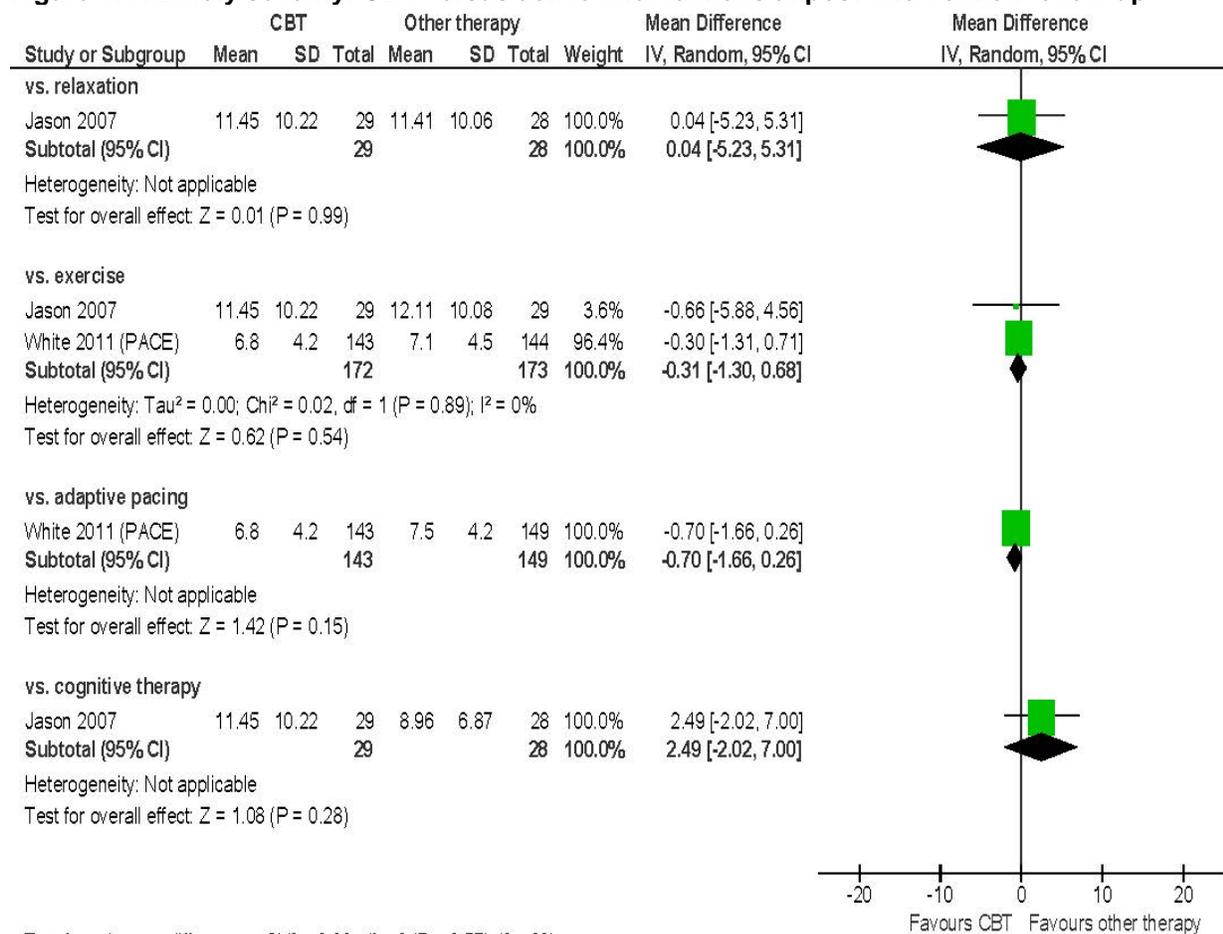
Figure 46. Depression severity: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: $\text{Chi}^2 = 3.61$, $\text{df} = 3$ (P = 0.31), $I^2 = 16.9\%$

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

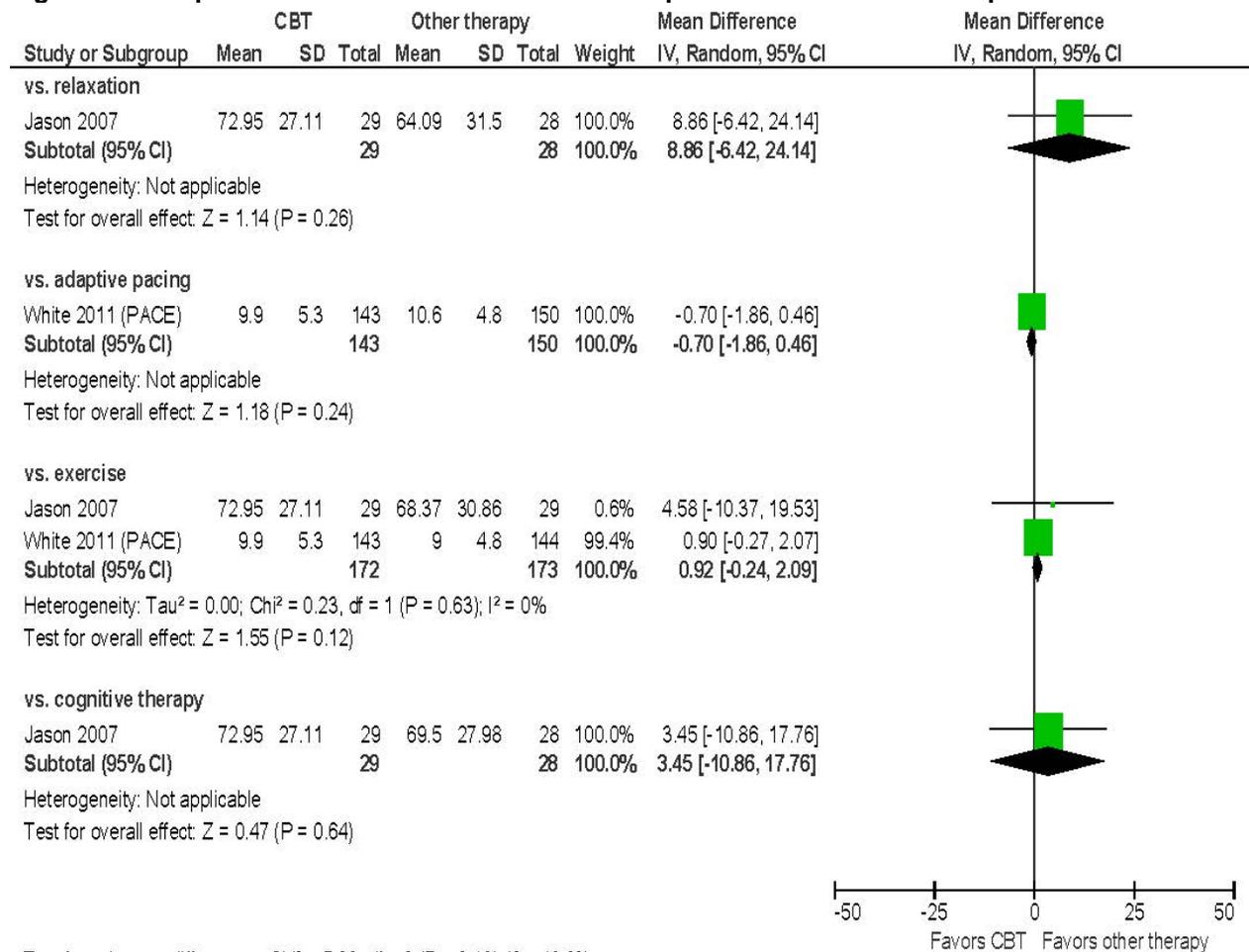
Figure 47. Anxiety severity: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: Chi² = 2.00, df = 3 (P = 0.57), I² = 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

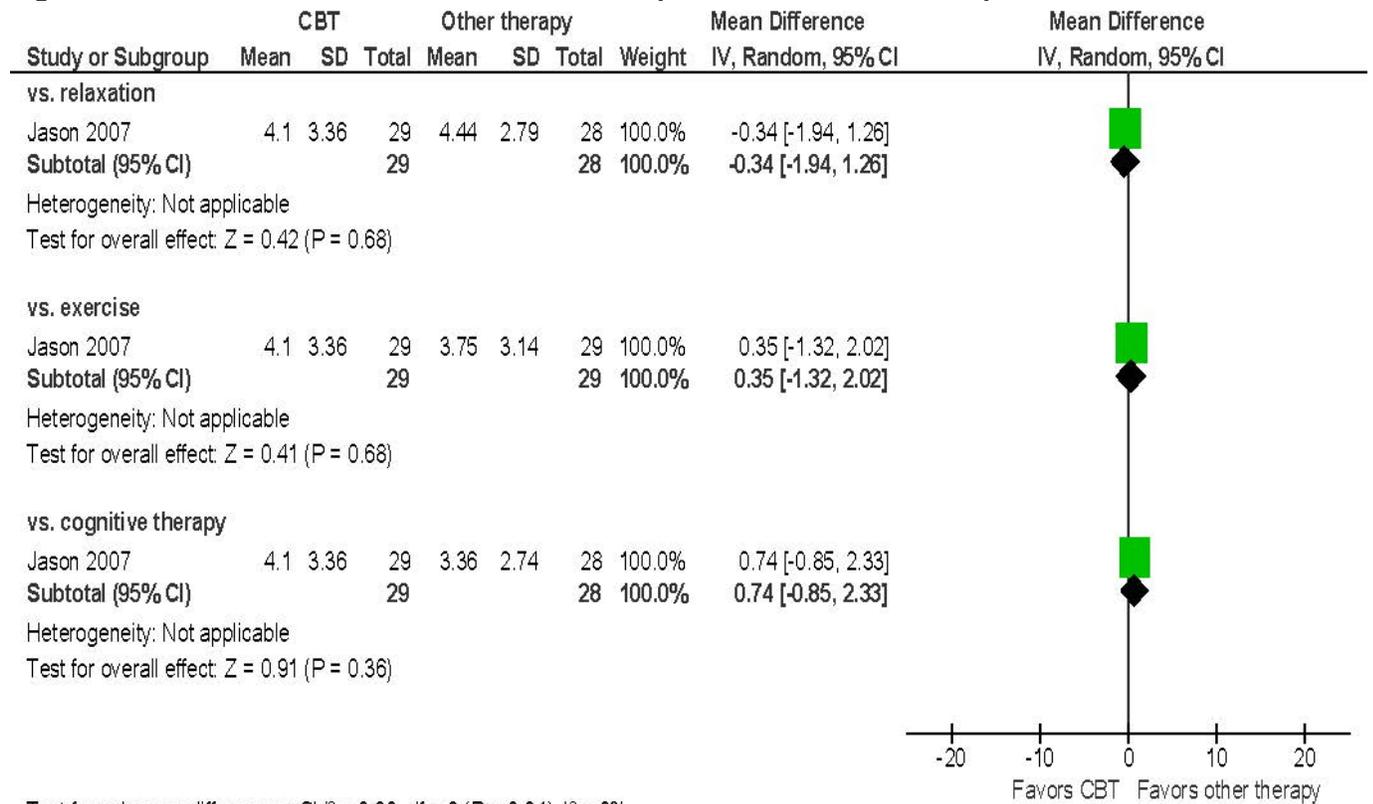
Figure 48. Sleep: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: Chi² = 5.20, df = 3 (P = 0.16), I² = 42.3%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

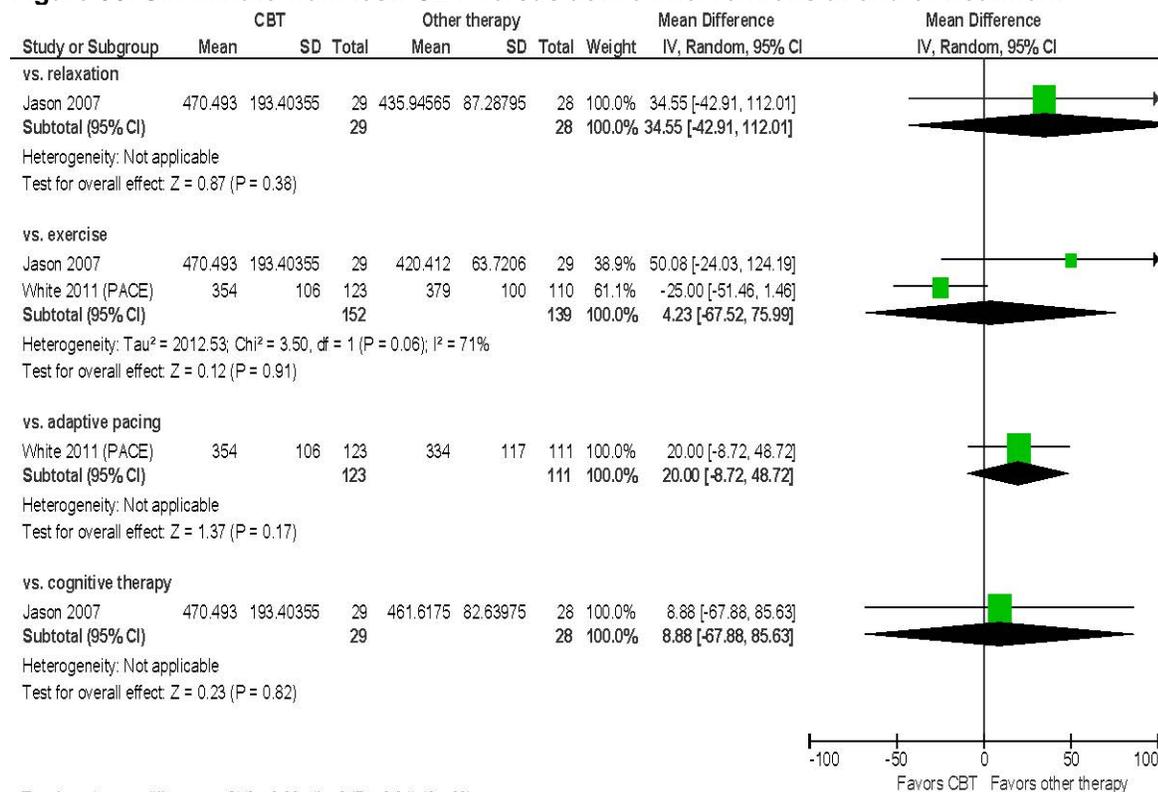
Figure 49. Pain: CBT versus active interventions at post-intervention follow-up



Test for subgroup differences: Chi² = 0.90, df = 2 (P = 0.64), I² = 0%

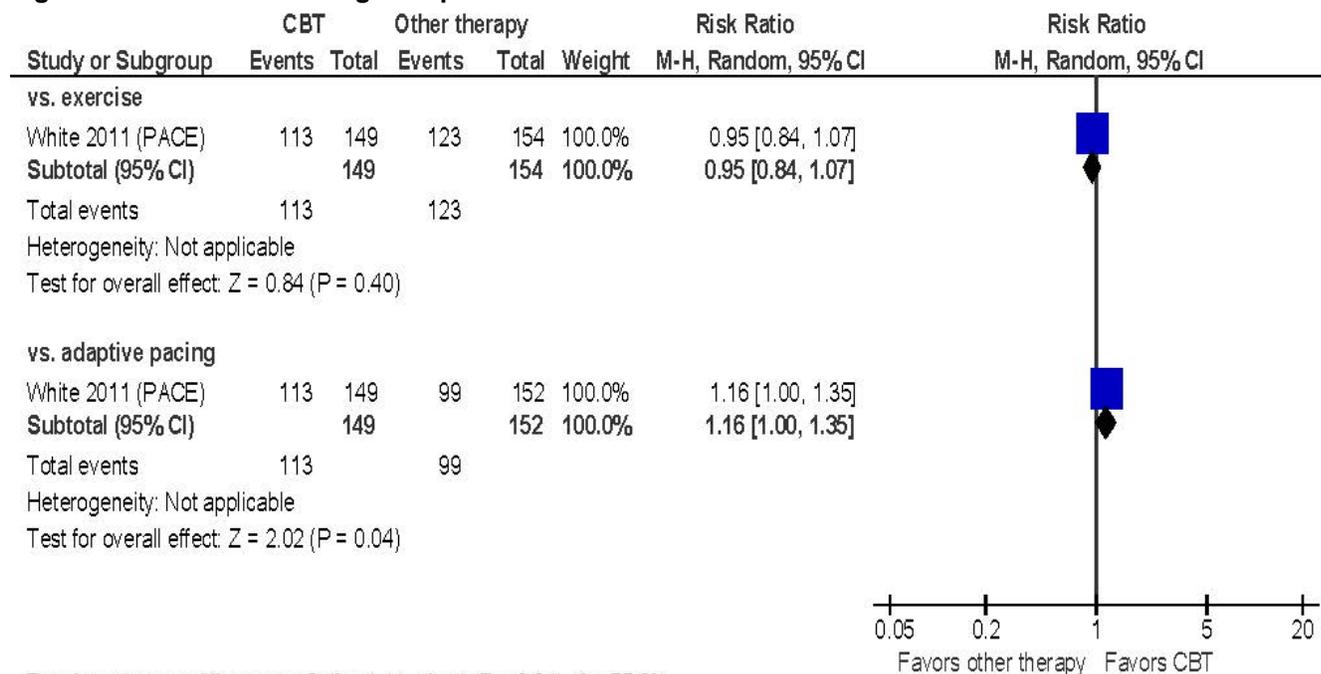
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; IV = instrumental variable; SD = standard deviation

Figure 50. Six-minute walk test: CBT versus active interventions at end of treatment



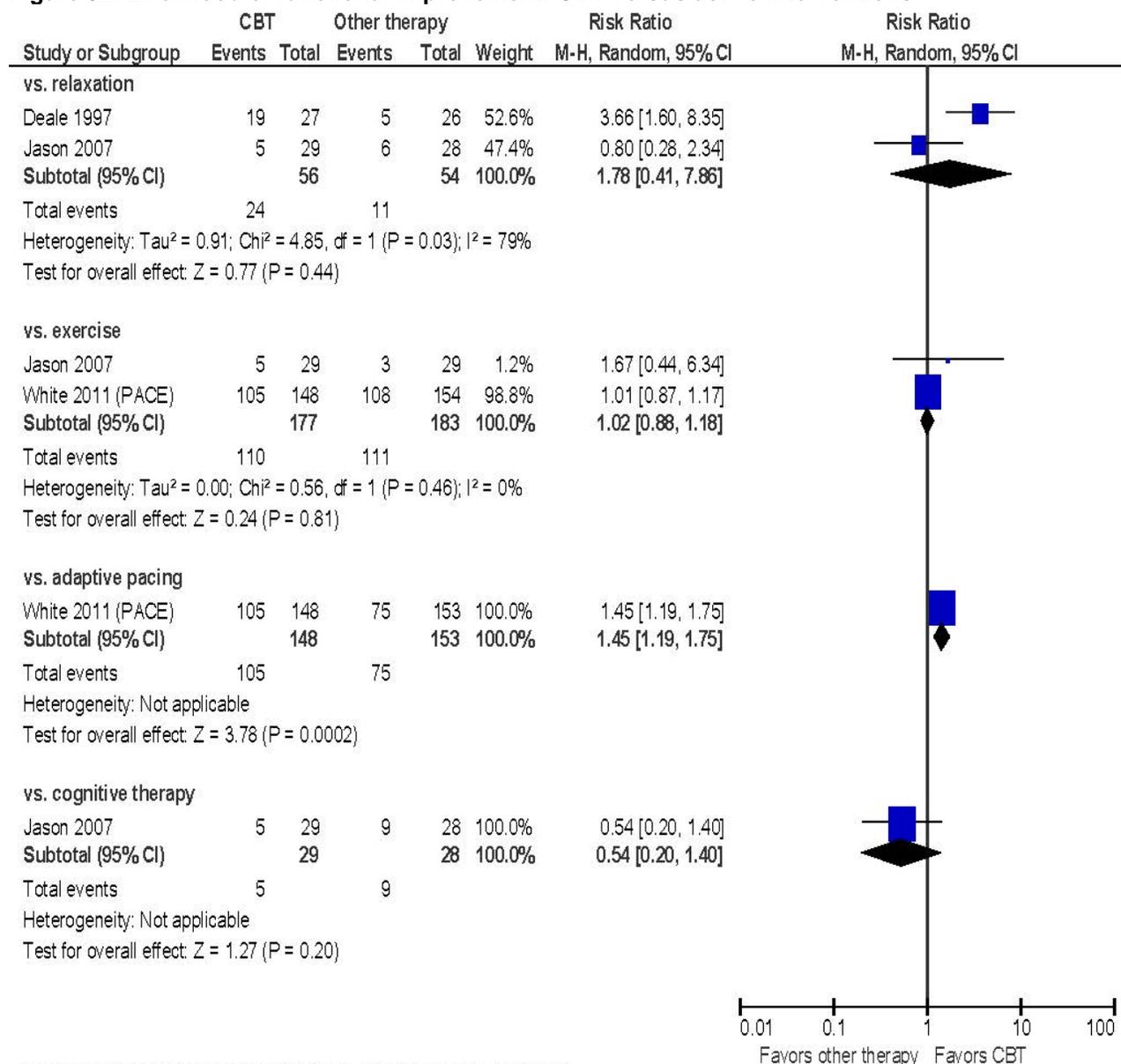
Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; PACE = pacing, graded activity, cognitive behavior therapy; IV = instrumental variable; SD = standard deviation

Figure 51. Likelihood of fatigue improvement: CBT versus active interventions



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

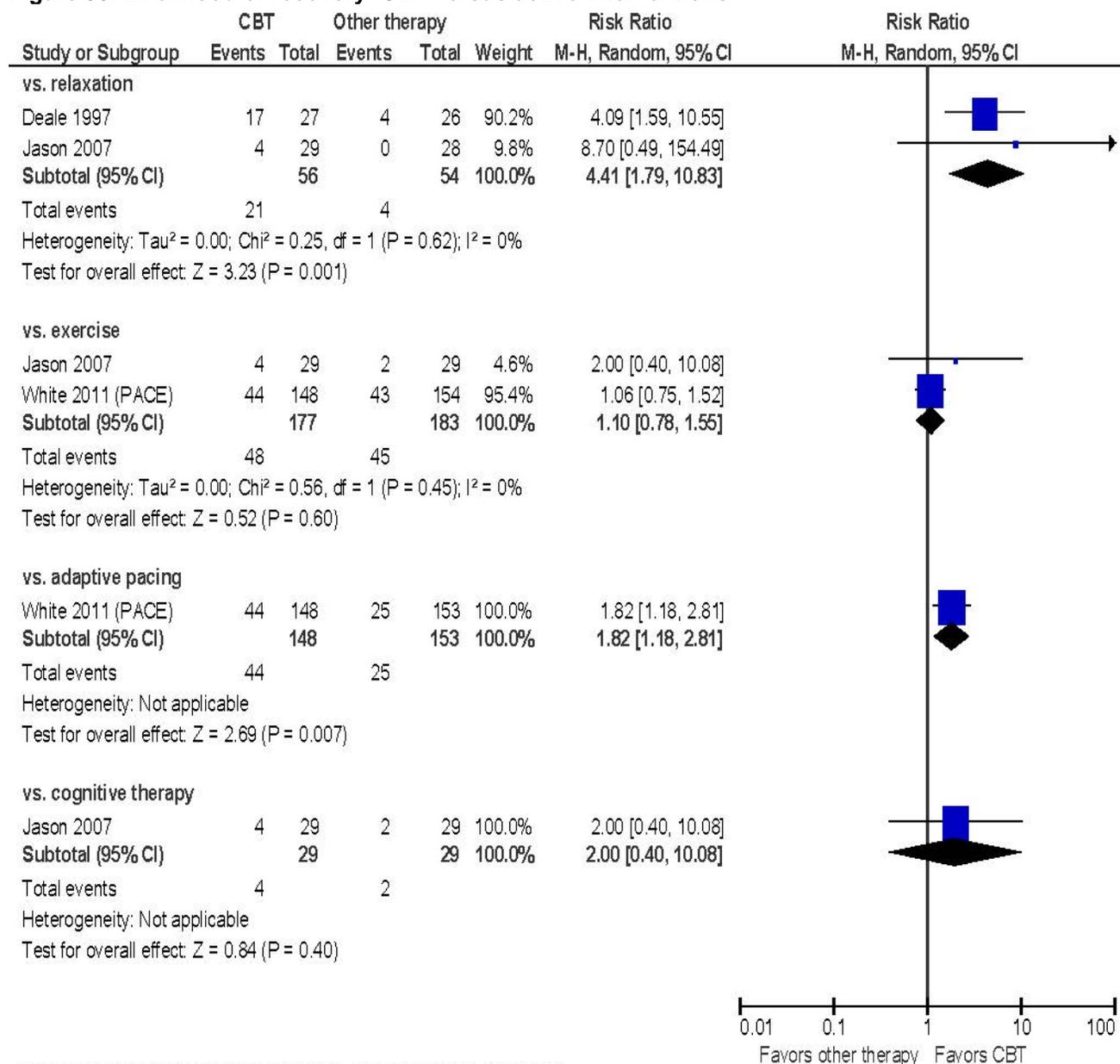
Figure 52. Likelihood of functional improvement: CBT versus active interventions



Test for subgroup differences: Chi² = 11.01, df = 3 (P = 0.01), I² = 72.8%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

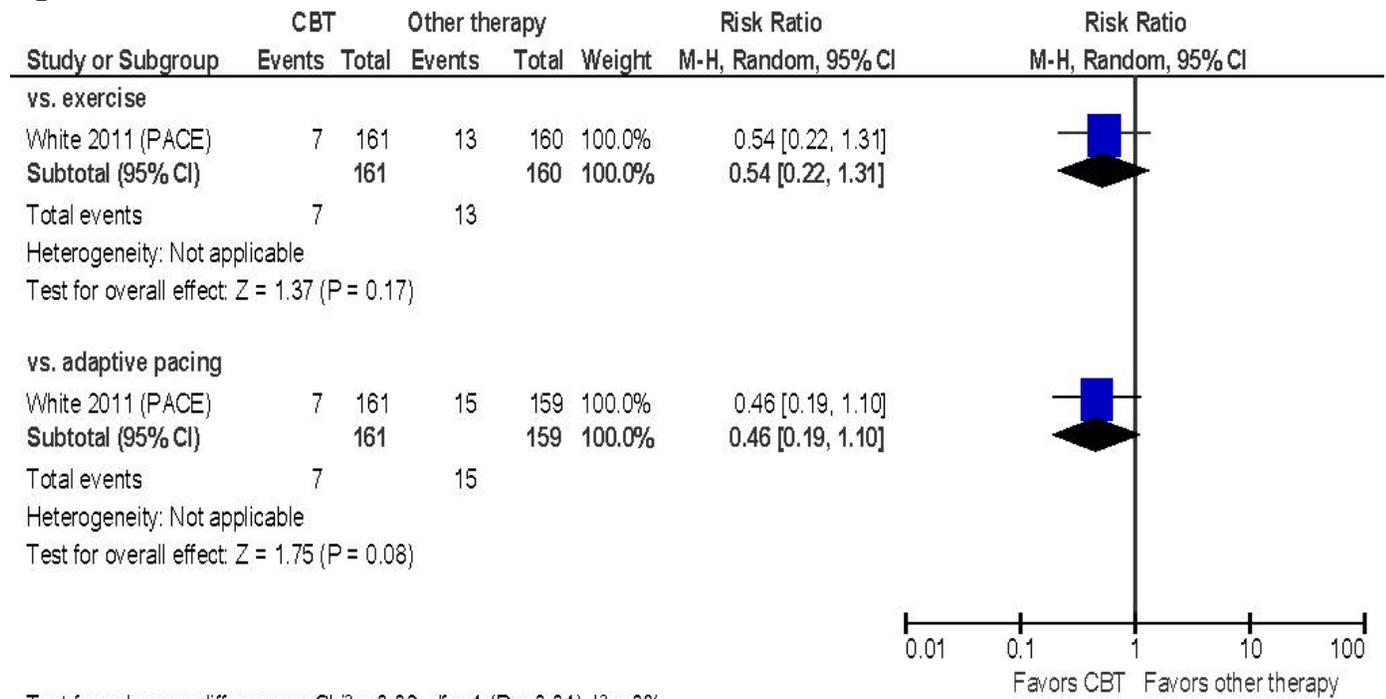
Figure 53. Likelihood of recovery: CBT versus active interventions



Test for subgroup differences: Chi² = 9.54, df = 3 (P = 0.02), I² = 68.5%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

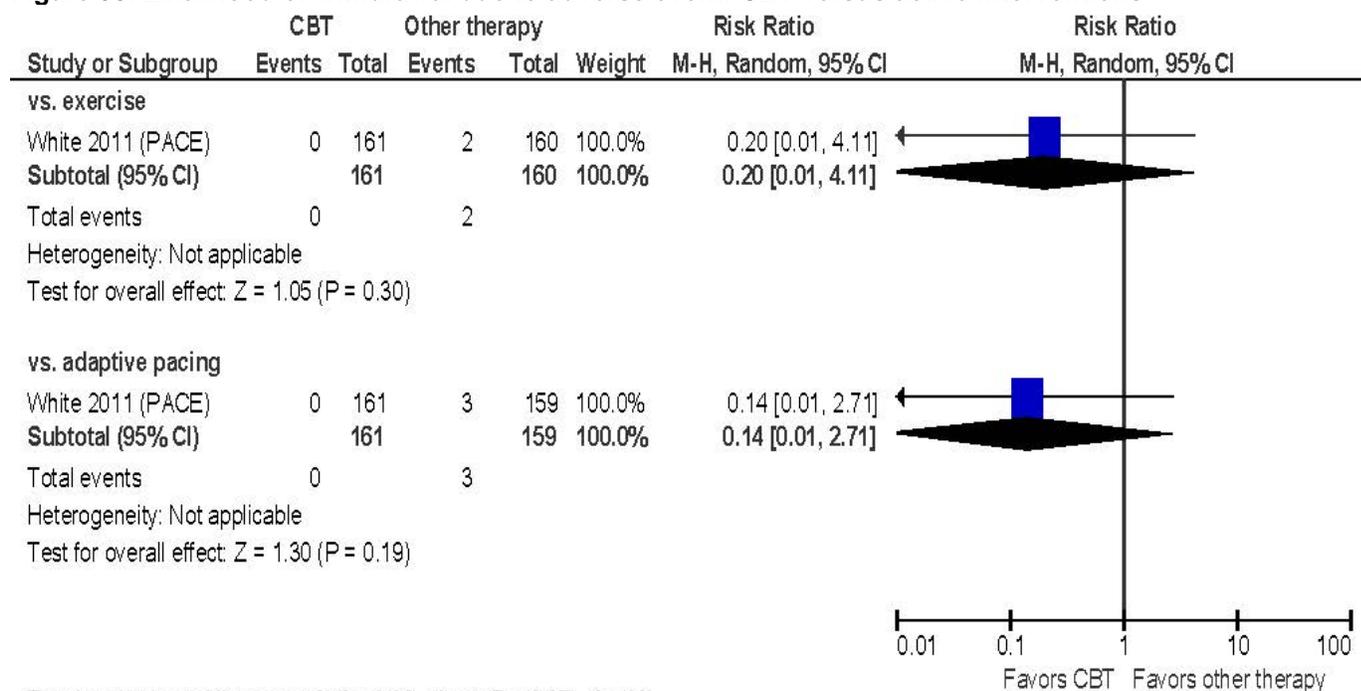
Figure 54. Likelihood of serious adverse event: CBT versus active interventions



Test for subgroup differences: $\text{Chi}^2 = 0.06$, $\text{df} = 1$ ($P = 0.81$), $I^2 = 0\%$

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

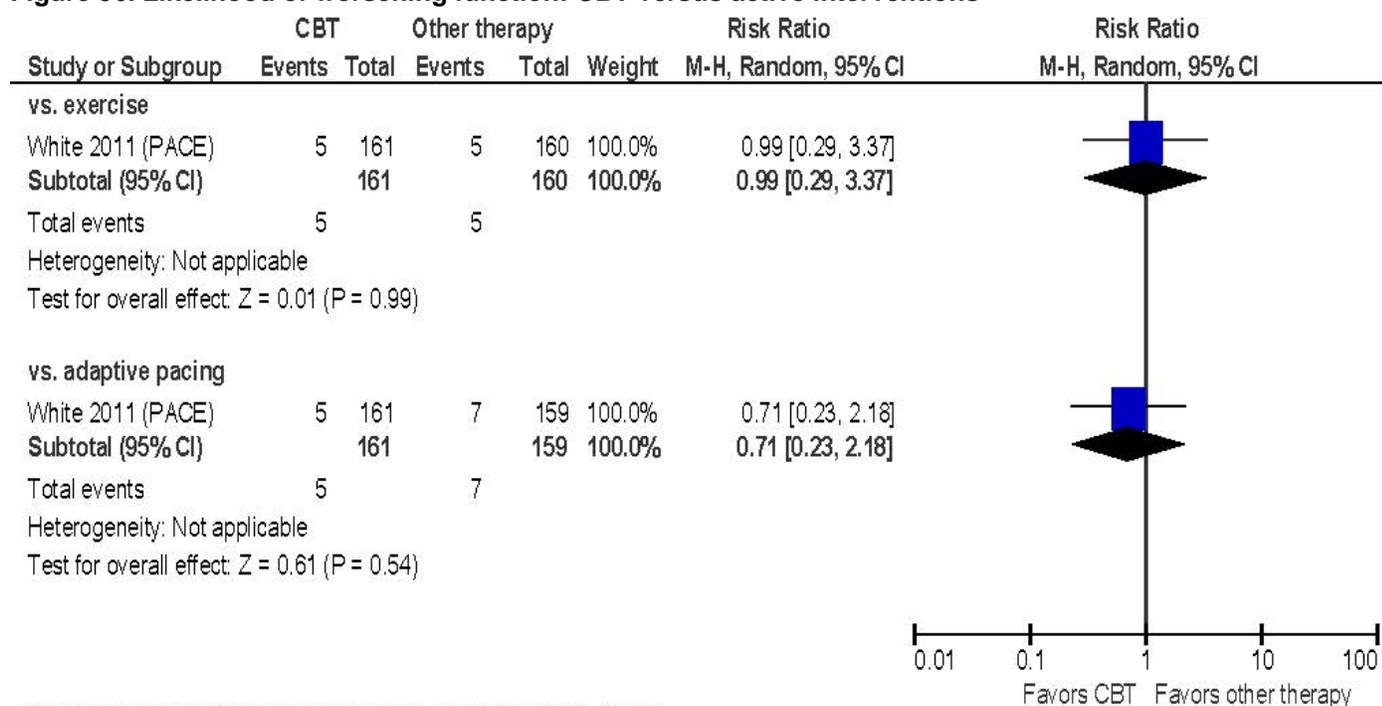
Figure 55. Likelihood of withdrawal due to adverse event: CBT versus active interventions



Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

Figure 56. Likelihood of worsening function: CBT versus active interventions



Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; M-H = Mantel-Haenszel test; PACE = pacing, graded activity, cognitive behavior therapy

One method of CBT delivery versus another

Face to face versus telephone CBT

One trial (N=58) compared face to face versus telephone CBT (with face to face assessment and discharge appointment).⁶⁴ The duration of therapy was 6 months and outcomes were evaluated at the end of the intervention though 12 months following the completion of therapy. The trial was rated medium risk of bias. There were no differences between face to face versus telephone CBT in fatigue or function at the end of the intervention or at post-intervention follow-up or in likelihood of a global improvement rating of much better or very much better.

Other behavioral approaches in adults

Illness management and peer counseling versus wait list

One medium risk of bias trial (N=47) included in the prior report compared an illness management and peer counseling intervention (8 biweekly 2 hour group sessions over 4 months, 1 month break, and 7 months of one-on-one peer counseling) versus wait list in patients who met the Fukuda case definition (**Tables 11 and 12, Evidence Table Appendix E2, Risk of Bias Table Appendix F**).⁷⁵ The intervention involved 8 biweekly 2 hour group sessions over 4 months, followed by a 1 month break, then 7 months of individual peer counseling. At baseline, the mean Chronic Fatigue Syndrome Symptoms Rating Form score was 14.6 on a 0 to 100 scale. At the end of the intervention, there was no difference in severity of symptoms (mean difference -0.9, 95% CI -2.8 to 1.0 on the 0 to 100 Chronic Fatigue Syndrome Symptoms Rating Form), the Quality of Life Index overall quality of life scale (mean difference 1.1, 95% CI -1.2 to 3.4 on a 0 to 30 scale) or the Quality of Life Index health and functioning, social and economic, psychological and spiritual, and family subscales (differences ranged from 0.1 to 0.5, each on a 0 to 30 scale). The trial did not report harms.

Mindfulness-based cognitive therapy versus usual care or wait list

Two small trials (N=18 and 35) evaluated mindfulness-based cognitive therapy versus usual care or wait list in patients who met the Fukuda case definition or either the Fukuda or Oxford case definition^{76,77} (**Tables 11 and 12, Evidence Table Appendix E2, Risk of Bias Table Appendix F**). Neither trial was included in the prior AHRQ report. At baseline, mean scores on the 11-item 0 to 33 Chalder scale were 24.3 and 23.4 and on SF-36 physical function were 41.5 and 58.3. Mindfulness training occurred in weekly group classes for 8 weeks in both trials; in one trial⁷⁶ there was 1 follow-up class at 4 months. Both trials were rated high risk of bias (**Risk of Bias Table Appendix F**).

For outcomes assessed at the end of the intervention, both trials found mindfulness training associated with reduced fatigue severity, though the difference was only statistically significant in one trial (mean differences -1.82, p=0.08 and -3.9, p=0.01 on the 11-item 0 to 33 Chalder scale). There were no statistically significant effects on SF-36 physical function (mean differences 3.50, p=0.58 and 12.2, p=0.12 on a 0 to 100 scale). Both trials found mindfulness-based cognitive therapy associated with decreased depression severity versus wait list or usual care, but the difference was statistically significant in only one trial (mean differences -1.17, p=0.28 and -3.6, p=0.04 on the 0 to 21 HADS depression scale). Although one trial found mindfulness-based cognitive therapy associated with decreased anxiety severity, the difference was small (mean differences -1.6, p=0.17 and -0.41, p=0.01 on the 0 to 21 HADS anxiety scale).

One of the trials also evaluated outcomes 2 months following the completion of therapy.⁷⁶ Effects of mindfulness based cognitive therapy persisted at post-intervention follow-up (mean difference -3.7, $p=0.03$). There were no statistically significant differences between mindfulness-based cognitive therapy versus wait list in function, depression, or anxiety.

One trial reported that there were “no substantive adverse events” and the other trial did not report harms.

Self-management versus usual care

Two trials ($N=124$ and 125) compared self-management interventions versus usual care in patients with ME/CFS^{78,79} (**Tables 11 and 12, Evidence Table Appendix E2**). Neither trial was included in the prior AHRQ report. In one trial,⁷⁸ the self-management intervention was delivered using a booklet and audio compact discs (CDs) and in the other trial⁷⁹ the self-management intervention was conducted by a peer counselor and occupational therapist in group sessions. Both trials were rated medium risk of bias (**Risk of Bias Table Appendix F**).

One trial ($N=124$) compared two self-management interventions versus usual care in patients who met the Fukuda case definition.⁷⁸ At baseline, mean scores were 6.5 on the Fatigue Severity Scale (1 to 7 scale) and 37.9 for SF-36 physical function (0 to 100 scale). Both self-management interventions were delivered using a booklet and audio CDs and differed in the way that fatigue and compliance was monitored (web diaries and actigraphy [activity monitor] versus paper diaries and a step counter). Outcomes were assessed at the end of 3 months of therapy and at 12 months. Effects of the two self-management interventions were similar and we combined the results. Self-management was associated with decreased fatigue severity versus usual care at the end of therapy (mean difference -0.40, 95% CI -0.66 to -0.14) and at post-intervention follow-up (mean difference -0.37, 95% CI -0.66 to -0.08). Self-management was also associated with increased likelihood of improvement in fatigue, defined as Fatigue Severity Scale score at 12 months >2 standard deviations below the baseline sample mean (26% vs. 8.7%, RR 2.98, 95% CI 1.09 to 8.15). There was no difference in function at end of therapy (mean difference 6.24, 95% CI -1.58 to 14.06 on SF-36 physical function) or at post-intervention follow-up (mean difference 2.06, 95% CI -6.62 to 10.74). The self-management interventions were associated with reduced depression severity (differences of 4.7 to 4.9 points on the 0 to 63 Beck Depression Inventory) but no difference in anxiety severity. There was no difference in the likelihood of post-exertional malaise >24 hours (33% vs. 34%, RR 0.96, 95% CI 0.66 to 1.41) or in the 6-minute walk test (data not provided).

The other trial ($N=125$) compared a group self-management intervention (8 biweekly 2.5 hour sessions) versus usual care in patients who met the Fukuda and 2003 Canadian case definitions.⁷⁹ At 6 months follow-up (2 months after completion of therapy) self-management was associated with less improvement in fatigue severity versus usual care (difference in change from baseline 2.5, $p=0.04$), with no differences between groups in SF-36 physical function, the SF-36 physical component summary, or the SF-36 mental component summary. At 12 months, there were no differences in fatigue or SF-36 measures at 12 months follow-up. The trial did not report harms.

Table 11. RCTs of behavioral approaches in adults: Study characteristics

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Friedberg, 2016 ⁷⁸ United States Medium	n: 124 Age: 48.4 % Female: 88	Criteria: Fukuda Duration: 14.5 years	Fatigue Scale: Fatigue Severity Scale 9-item (1 to 7) Baseline: 6.5 (SD 0.48) Post-exertional fatigue: not reported	Major depression: Current or past depression with melancholic or psychotic features excluded Baseline depression: Beck Depression Inventory (0 to 63): 19.2 (SD 10.8) Baseline function: SF-36 physical function (0 to 100): 40.6 (SD 20.8)	A: Self-management with web diaries and actigraphs B: Self-management with paper diaries and step counters C: Usual care Frequency: not described Session length: not described Duration of Treatment: 12 weeks Duration of follow-up: 12 months
Pinxterhuis, 2017 ⁷⁹ Norway Medium	n: 125 Age: 43.9 % Female: 86	Criteria: Fukuda or Canadian Criteria (2003) Duration: Median 3 years	Fatigue Scale: Fatigue Severity Scale (9 to 63) Baseline: 57.3 (SD 5.1) Post-exertional fatigue: Not reported	Major depression: Not reported Baseline depression: Not reported Baseline function: SF-36 physical function (0 to 100): 46.0 (SD 19.2)	A: Group based self-management B: Usual care Frequency: 8 sessions every other week Session length: 2.5 hours Duration of Treatment: 16 weeks Duration of follow-up: 1 year
Rimes, 2013 ⁷⁶ United Kingdom High	n: 35 Age: 43.5 % Female: 83	Criteria: Fukuda or Oxford Duration: Mean 7.2 years	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 24.3 (SD 4.5) Post-exertional fatigue: Not reported	Major depression: Excluded for current major depression (29% on antidepressants at baseline) Baseline depression: HADS depression (0 to 21): 7.3 (SD 4.5) Baseline function: SF-36 physical function (0 to 100): 58.3 (SD 23.2)	A: Mindfulness-based cognitive therapy B: Wait list Frequency: 8 weekly sessions and 1 follow-up class at 4 months Session length: 2.25 hours Duration of Treatment: 2 months Duration of follow-up: 4 months
Surawy, 2005 ⁷⁷ United Kingdom High	n: 17 Age: Not reported (range 18 to 65) % Female: 56	Criteria: Fukuda Duration: Not reported	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 23.4 (SD 7.8) Post-exertional fatigue: Not reported	Major depression: Excluded Baseline depression: HADS depression (0 to 21): 9.7 (SD 4.0) Baseline function: SF-36 physical function (0 to 100): 41.5 (SD 24.8)	A: Group mindfulness training B: Usual care Frequency: 8 sessions over 8 weeks Session length: not described Duration of Treatment: 8 weeks Duration of follow-up: 8 weeks

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Taylor, 2004 ⁷⁵ United States Medium	n: 47 Age: Not reported % Female: 96	Criteria: Fukuda Duration: Not reported	Fatigue Scale: Chronic Fatigue Syndrome Symptom Rating Scale (0 to 100) Baseline: 14.6 (SD 2.9) Post-exertional fatigue: Not reported	Major depression: Not reported Baseline depression: Not reported Baseline function: Not reported	A: Illness management and peer counseling B: Wait list Frequency: Biweekly illness management sessions over 4 months, then 7 months of peer counseling (frequency not reported) Session length: 2 hours for illness management sessions, not described for peer counseling Duration of Treatment: 11 months Duration of follow-up: 11 months

Abbreviations: CFS = chronic fatigue syndrome; HADS = Hospital Anxiety and Depression Scale; ME = myalgic encephalomyelitis; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Table 12. RCTs of behavioral approaches in adults: Study results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow- up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Friedberg, 2016 ⁷⁸ Fukuda	A: Self-management with web diaries and actigraphs (45) B: Self-management with paper diaries and step counters (44) C: Usual care (48) Duration of Treatment: 12 weeks Duration of follow-up: 12 months	Fatigue Severity Scale 9- item (1 to 7), mean (SE): 3 months: 6.12 (0.11) vs. 5.92 (0.11) vs. 6.42 (0.10), FSM:ACT vs. FSM:CTR p<0.05, other comparisons p>0.05 12 months: 6.00 (0.13) vs. 6.10 (0.13) vs. 6.42 (0.12), all comparisons p>0.05	Beck Depression Inventory (0 to 63), mean (SE): 3 months: 14.40 (1.65) vs. 14.98 (1.65) vs. 19.36 (1.55), all comparisons p>0.05 12 months: 13.08 (1.48) vs. 14.42 (1.48) vs. 18.64 (1.39), Usual care vs. both other arms p<0.05, intervention arms vs. each other p>0.05	Overall function: SF-36 physical function (0 to100 scale) mean, (SE): 3 months: 43.25 (3.20) vs. 43.75 (3.32) vs. 37.26 (3.13), all comparisons p>0.05 12 months: 46.50 (3.68) vs. 45.75 (3.68) vs. 44.07 (3.47), all comparisons p>0.05
Pinxterhuis, 2017 ⁷⁹ Fukuda or Canadian Criteria (2003)	A: Group based self- management (73) B: Usual care (73) Duration of Treatment: 16 weeks Duration of follow-up: 1 year	Fatigue Severity Scale (9 to 63), mean (SD): 6 months: 56.0 (6.8) vs. 55.5 (8.2); p=0.039; Mean change from baseline (95% CI): -0.2 (- 1.7, 1.3) vs. -2.7 (-4.7, - 0.7) 12 months: 56.4 (6.9) vs. 57.1 (6.7); p=NS; Mean change from baseline (95% CI): 0.4 (-1.4, 2.2) vs. -1.4 (-3.0, 0.1)	Not reported	SF-36 physical function (0 to 100), mean (SD): 6 months: 47.5 (21.2) vs. 50.5 (23.7); p=NS; Mean change from baseline (95% CI): 0.6 (-2.9, 4.0) vs. 4.3 (-0.4, 8.9) 12 months: 48.9 (17.7) vs. 46.3 (22.3); p=NS; Mean change from baseline (95% CI): 0.8 (- 4.2, 5.7) vs. -0.3 (-5.4, 4.9)
Rimes, 2013 ⁷⁶ Fukuda or Oxford	A: Mindfulness-based cognitive therapy (18) B: Wait list (19) Duration of Treatment: 2 months Duration of follow-up: 4 months	Modified Chalder Fatigue Scale 11-item (0 to 33), mean (SD): 2-month follow up: 21.3 (6.2) vs. 25.0 (6.1)	HADS depression (0 to 21), mean (SD): 2-month follow up: 5.6 (2.9) vs. 7.7 (4.6); p=0.153	PF-10 (0 to 100), mean (SD): 2-month follow up: 65.6 (26.3) vs. 55.9 (23.3) Work and Social Adjustment Scale (0 to 40), mean (SD): 2-month follow up: 20.0 (10.4) vs. 25.8 (6.7)
Surawy, 2005 ⁷⁷ Fukuda	A: Group mindfulness training (9) B: Usual care (9) Duration of Treatment: 8 weeks Duration of follow-up: 8 weeks	Chalder Fatigue Scale 14-item (0 to 42)), mean (SD):18.56 (8.13) vs. 20.38 (8.26), p=0.08	HADS depression (0 to 21) mean (SD): 8.33 (1.66) vs. 9.50 (3.96), p=0.28	SF-36 physical function (0 to 100), mean (SD): 40.00 (16.78) vs. 35.50 (27.00), p=0.58
Taylor, 2004 ⁷⁵ Fukuda	A: Illness management and peer counseling (23) B: Wait list (24) Duration of Treatment: 11 months Duration of follow-up: 11 months	Not reported	Not reported	Not reported

Abbreviations: ACT = anaerobic activity therapy; CI = confidence interval; CFS = chronic fatigue syndrome; FSM:CTR = fatigue self-management with paper diaries and step counters; HADS = Hospital Anxiety and Depression Scale; ME = myalgic encephalomyelitis; NS = not significant; PF = physical function; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SF-36 = 36-item Short Form Health Survey

CBT in adolescents

Five trials evaluated CBT in adolescents with ME/CFS.⁸⁰⁻⁸⁴ Three trials⁸¹⁻⁸³ compared CBT versus inactive controls, one trial compared CBT plus biofeedback versus biofeedback alone,⁸⁰ and one trial⁸⁴ compared CBT versus pacing (**Tables 13 and 14; Evidence Table Appendix E2**). Three trials^{80,82,83} used the , one trial⁸⁴ used the Oxford case definition, and one trial⁸¹ used the Fukuda or Oxford case definitions. The duration of ME/CFS symptoms ranged from a mean or median of 26 weeks to 2 years. Sample sizes ranged from 13 to 127 (total N=438) and the mean age ranged from 12 to 16 years. The duration of treatment ranged from 6 to 18 months. All trials assessed outcomes at the end of treatment and one trial also assessed outcomes 12 months following the end of the intervention. Four trials were rated medium risk of bias and two trials^{80,84} were rated high risk of bias (**Risk of Bias Table Appendix F**).

Table 13. RCTs of CBT and behavioral approaches in adolescents: Study Characteristics

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Al-Haggar, 2016 ⁸⁰ Egypt High	n: 92 Age: 12.6 % Female: 73	Criteria: Fukuda Duration: 26.4 weeks	Fatigue Scale: Fatigue Activity Scale (reported as %) Baseline: 53.5 (SD 3.9) Post-exertional fatigue: not reported	Major depression: Excluded Baseline depression: not reported Baseline function: not reported	A: CBT plus biofeedback B: Biofeedback Frequency: 40 to 60 sessions over 18 months once to twice weekly Session length: not reported Duration of Treatment: 18 months Duration of follow-up: 18 months
Chalder, 2010 ⁸¹ United Kingdom Medium	n: 63 Age: 15 median % Female: 68	Criteria: Oxford or Fukuda Duration: 24 months	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 23.6 (SD 5.4) Post-exertional fatigue: Not reported	Major depression: Excluded Baseline depression: not reported Baseline function: SF-36 physical function (0 to 100): 46.5 (SD 25.6)	A: Family-focused CBT B: Psycho-education (4 sessions over 6 months) Frequency: 13 sessions biweekly Session length: 1 hour Duration of Treatment: 6 months Duration of follow-up: 18 months
Crawley, 2018 ⁸⁵ United Kingdom Medium	n: 81 Age: 14.6 % Female: 76	Criteria: NICE Duration: 12 months	Fatigue Scale: Chalder (11-item, 0 to 33) Baseline: 25.0 (SD 4.2) Post-exertional fatigue: Not reported	Major depression: not reported Baseline depression: HADS depression (0 to 21): 7.8 (SD 3.8) Baseline function: SF-36 physical function (0 to 100): 54.5 (SD 20.2)	A: Osteopathy, life coaching, and neurolinguistic programming intervention (Lightning Process) plus specialist medical care B: Specialist medical care Frequency: 3 four-hour sessions plus 2 follow-up sessions Session length: 4 hours for initial three sessions Duration of Treatment: 3 days Duration of follow-up: 12 months
Nijhof, 2012 ⁸² (FITNET) The Netherlands Medium	n: 127 Age: 15.8 % Female: 82	Criteria: Fukuda Duration: Median 16 vs. 19 months	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 51.4 (SD 4.5) Post-exertional fatigue: not reported	Major depression: Excluded for primary depression Baseline depression: Children's Depression Inventory (0 to 54): 11.3 (SD 5.2) Baseline function: Child Health Questionnaire- CF87 physical functioning (0 to 100): 58.8 (SD 18.0)	A: Web-based CBT B: Usual care Frequency: Weekly then biweekly therapist contact; 21 interactive modules Session length: Not described Duration of Treatment: 6 months Duration of follow-up: 6 months

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Stulemeijer, 2005 ⁸³ The Netherlands Medium	n: 62 Age: 15.6 % Female: 90	Criteria: Fukuda Duration: Median 16 vs. 18 months	Fatigue Scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline: 52.1 (SD 4.0) Post-exertional fatigue: Not reported Pervasively passive: 25% Relatively active: 72%	Major depression: Excluded for psychiatric comorbidity Baseline depression: Depression scale not assessed Baseline function: SF-36 physical function (0 to 100): 43.7 (SD 16.8)	A: CBT based on activity pattern, with parental involvement B: Wait list Frequency: 10 sessions over 5 months Session length: Not described Duration of Treatment: 5 months Duration of follow-up: 5 months
Wright, 2005 ⁸⁴ United Kingdom High	n: 13 Age: Mean not reported, range 8.9 to 16.9 years % Female: Not reported	Criteria: Oxford Duration: Median 12 vs. 14.5 months	Fatigue Scale: Chalder (14-item, 0 to 42) Baseline: 20.4 (SD 7.9) Post-exertional fatigue: Not reported	Major depression: Proportion with depression not reported Baseline depression: Birlson Depression Scale (0 to 36): 15.0 (SD 5.6) Baseline function: Young Persons' Functional Ability Scale (0 to 100): 59.2 (SD 20.8)	A: Cognitive therapy and education (STAIRway to Health) B: Pacing Frequency: Weekly x 1 month, every 2 weeks for 3 months, every 3 weeks for 2 months, and every 4 weeks for 6 months Session length: Not described Duration of Treatment: 12 months Duration of follow-up: 12 months

Abbreviations CBT = cognitive behavioral therapy; CFS = chronic fatigue syndrome; FITNET = fatigue in teenagers on the internet; HADS = Hospital Anxiety and Depression Scale; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; SF-36 = 36-item Short Form Health Survey

Table 14. RCTs of CBT and behavioral approaches in adolescents: Study results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Al-Haggar, 2016 ⁸⁰ Fukuda	A: CBT plus biofeedback (50) B: Biofeedback (46) Duration of Treatment: 18 months Duration of follow-up: 18 months	Fatigue severity, mean (SD) Checklist Individual Strength, fatigue severity subscale (8 to 56): 32.2 (3.8) vs. 46.5 (14.2), p=0.02	Not reported	School attendance, mean (SD) hours per month: 92.8 (18.4) vs. 66.6 (22.8), p=0.004
Chalder, 2010 ⁸¹ Oxford or Fukuda	A: Family-focused CBT (32) B: Psycho-education (4 sessions over 6 months) (27) Duration of Treatment: 6 months Duration of follow-up: 18 months	Chalder fatigue Likert score at 6-month follow-up (11- item, 0 to 33), mean (SD): 13.3 (5.9) vs. 14.2 (8.4), mean difference: 0.24, 95% CI -3.61 to 4.10	Not reported	No significant effects of group x time (6 and 24 months) in fatigue, SF-36 physical function, global functioning, satisfaction, or recovery
Crawley, 2018 ⁸⁵ NICE	A: Osteopathy, life coaching, and neurolinguistic programming intervention (Lightning Process) plus specialist medical care (51) B: Specialist medical care (49) Duration of Treatment: 3 days Duration of follow-up: 12 months	Chalder Fatigue Scale 11- item (0 to 33) 6 months, mean: 14.4 vs. 19.8, adjusted difference in means: -4.7 (95% CI, -7.9 to 1.6), p=0.003 Fatigue, Mean Chalder Fatigue Scale 11-item (0 to 33) 12 months: 12.3 vs. 15.7, adjusted difference in means: -3.2 (95% CI, -6.3 to 0.10), p=0.045	HADS- Depression, mean: 6 months: 4.2 vs. 5.9, p=0.141 12 months: 2.8 vs. 4.6, p=0.033	Overall Function, SF-36 physical function (0 to 100) at 6 months, mean: 81.7 vs. 70.2, adjusted (based on age, gender and baseline outcome) difference in means: 12.5 (95% CI, 4.5 to 20.5), p=0.003
Nijhof, 2012 ⁸² (FITNET) Fukuda	A: Web-based CBT (68) B: Usual care (67) Duration of Treatment: 6 months Duration of follow-up: 6 months	Fatigue severity at 6 months, Checklist Individual Strength, fatigue severity subscale (8 to 56), cutoff score <40: 85% (57/67) vs. 27% (17/64), RR 3.2 (95% CI, 2.1 to 4.9), NNT 1.7, p<0.0001	Not reported	Physical functioning: Child Health Questionnaire-CF87 physical functioning (0 to 100) cutoff score of 85% or more) at 6 months: 78% (52/67) vs. 20% (13/64), RR 3.8 (95% CI, 2.3 to 6.3), NNT 1.8, p<0.0001
Stulemeijer, 2005 ⁸³ Fukuda	A: CBT based on activity pattern, with parental involvement (36) B: Wait list (35) Duration of Treatment: 5 months Duration of follow-up: 5 months	Fatigue severity subscale of the checklist of individual strength at 5 months, mean (SD): 30.2 (16.8) vs. 44.0 (13.4), treatment effect 17.3 (95% CI, 6.2 to 28.4), p=0.003	Not reported	SF-36 physical function (0 to 100) at 5 months, mean (SD): 69.4 (28.0) vs. 55.3 (21.1), treatment effect 14.5 (95% CI, 7.4 to 21.6), p=0.001

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Wright, 2005 ⁸⁴ Oxford	A: Cognitive therapy and education (STAIRway to Health) (7) B: Pacing (6) Duration of Treatment: 12 months Duration of follow-up: 12 months	Fatigue score (Chalder 0 to 42 14 item version): 25.2 (219.8 to 9.49); F= 0.67; p= 0.44	Not reported	Young Person Functional Ability Scale (0 to 100): 17.0 (217.0 to 51.0) F=1.3; p= 0.28

Abbreviations: CBT = cognitive behavioral therapy; CFS = chronic fatigue syndrome; CHQ-CF = child health questionnaire-child form; CI = confidence interval; FITNET = fatigue in teenagers on the internet; ME = myalgic encephalomyelitis; NICE = National Institute for Health and Care Excellence; NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; SE = standard error; SF-36 = 36-item Short Form Health Survey

CBT versus inactive controls in adolescents

Three trials compared individual CBT versus usual care, wait list, or an attention control (psycho-education) in adolescents with ME/CFS.⁸¹⁻⁸³ The mode of administration was face-to-face in two trials and via web in one trial. All three trials noted a family focus or involvement of patients in CBT. The duration of therapy was 5 to 6 months. All trials evaluated outcomes at the end of the intervention and one trial evaluated outcomes 1 year following the completion of therapy. Two of the trials also reported longer-term, post-trial follow-up based on the original randomized groups.^{81,82} All of the trials were rated medium risk of bias (**Risk of Bias Table Appendix F**).

Fatigue

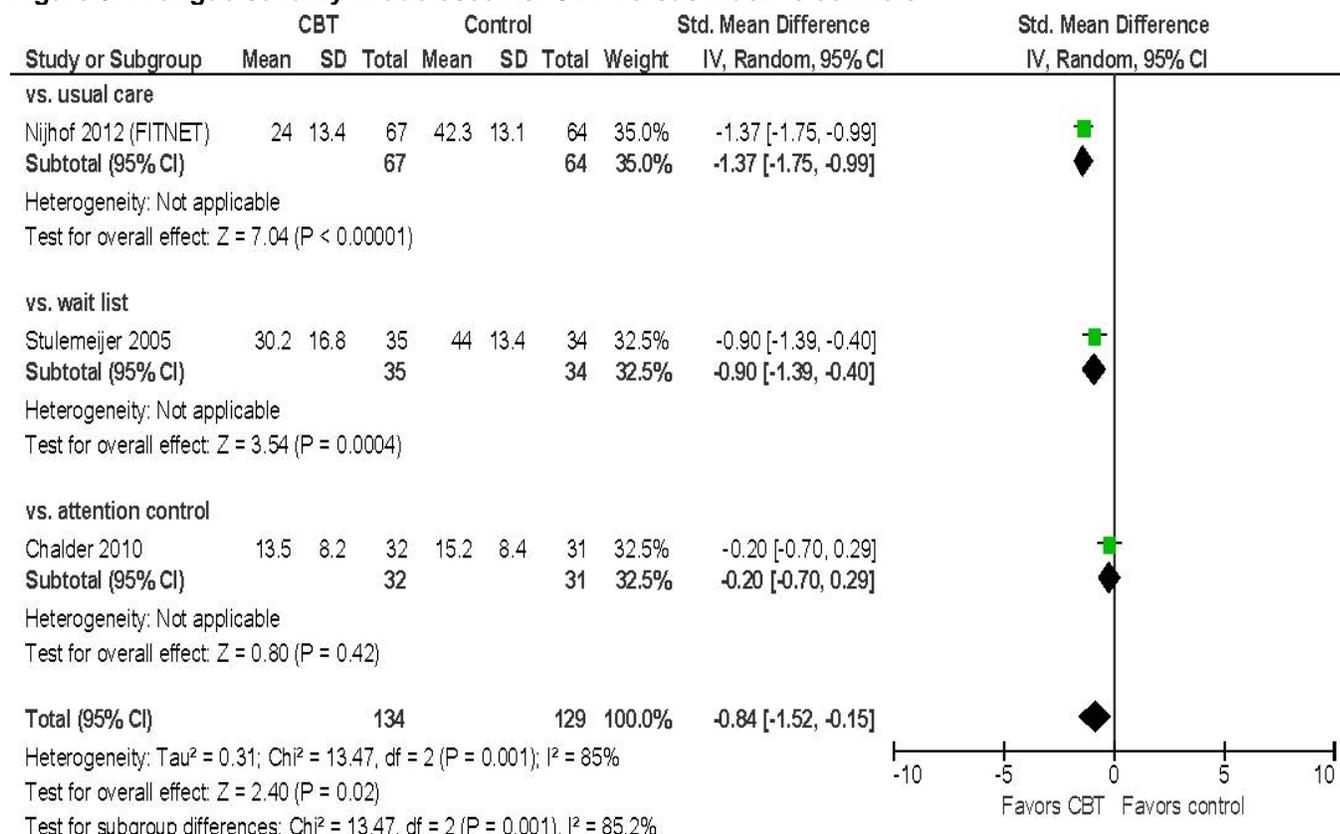
CBT was associated with decreased fatigue severity versus usual care, wait list, or an attention control (3 trials, N=263, SMD -0.84, 95% CI -1.52 to -0.15, $I^2=85%$;⁸¹⁻⁸³ **Table 15, Figure 57**). Although the estimate in all trials favored CBT, statistical heterogeneity was large. One trial of CBT versus an attention control (psychoeducation) reported a small and non-statistically significant effect on fatigue severity (SMD -0.20, 95% CI -0.70 to 0.29).⁸¹ The other two trials, which compared CBT versus usual care or wait list, each reported larger effects, with a statistically significant pooled estimate (2 trials, N=200, mean difference -16.9, 95% CI -21.0 to -12.9 on the 8 to 56 Checklist Individual Strength fatigue severity subscale, $I^2=8%$).^{82,83}

The trial of CBT versus an attention control found no difference in fatigue severity at 1 year post-intervention follow-up (N=63, mean difference -1.9, 95% CI -5.3 to 1.5 on the 0 to 33 11-item Chalder scale).⁸¹

CBT was associated with increased likelihood of improvement in fatigue versus usual care or wait list (2 trials, N=200, RR 3.13, 95% CI 2.18 to 4.49, $I^2=0%$; ARD 51%, 95% CI 32% to 69%).^{82,83} Improvement in fatigue was defined as an improvement in the Checklist Individual Strength fatigue severity subscale score <40 in one trial⁸² and as a score ≤ 35.7 and reliable change index >1.96 in the other trial.⁸³

One study (N=44) that reported long-term, post-trial follow-up at 24 months (12 months after trial completion) found no difference in severity of fatigue (data not provided).⁸⁶

Figure 57. Fatigue severity in adolescents: CBT versus inactive controls



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; FITNET = fatigue in teenagers on the internet; IV = instrumental variable; SD = standard deviation; Std = standard

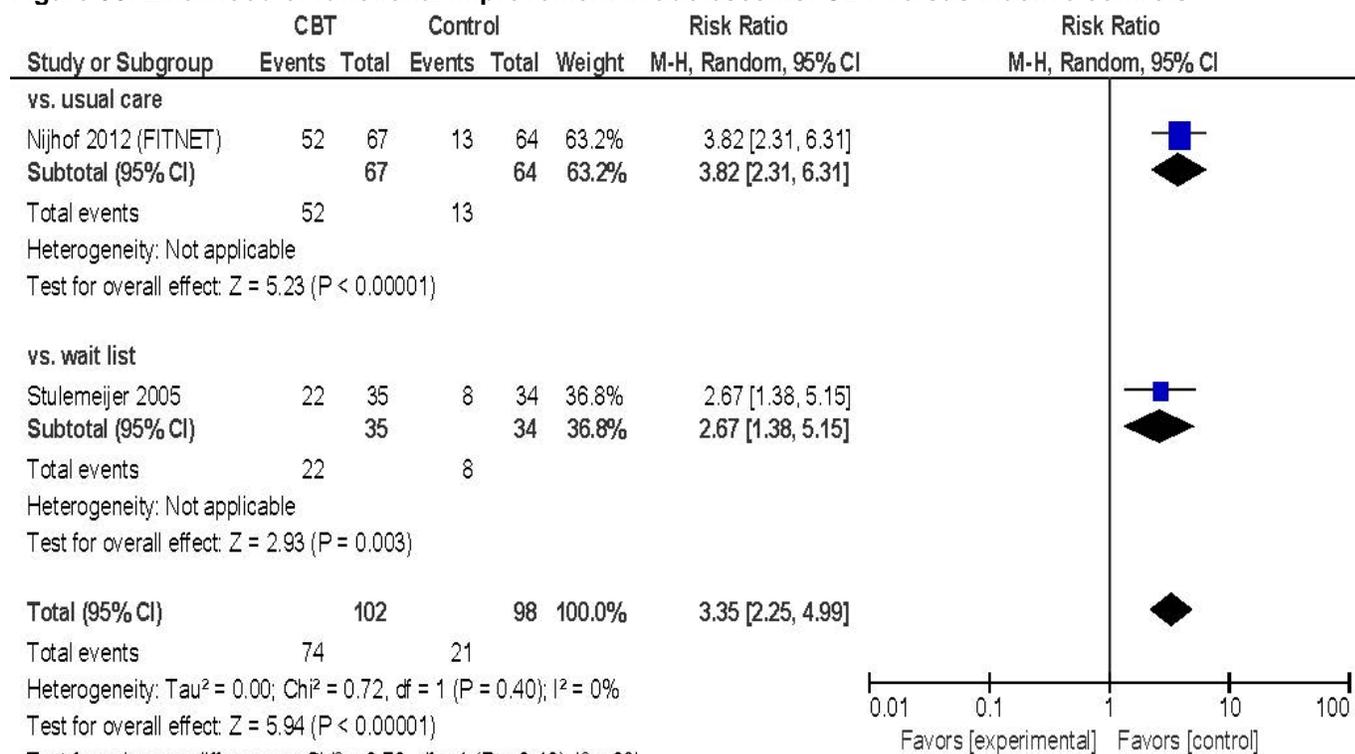
Function

There was no statistically significant difference between CBT versus usual care, wait list, or an attention control in severity of functional impairment, though the estimate favored CBT (3 trials, N=263, SMD 0.49, 95% CI -0.34 to 1.32, I²=90%).⁸¹⁻⁸³ Statistical heterogeneity was large, and the pooled estimate was imprecise. The trial⁸¹ that compared CBT versus an attention control (psychoeducation) did not report a positive effect on severity of functional impairment (SMD -0.28, 95% CI -0.77 to 0.22) while the other two trials^{82,83} found CBT associated with less severe functional impairment versus usual care or wait list (SMD 1.16, 95% CI 0.79 to 1.53 and SMD 0.56, 95% CI 0.08 to 1.04). In these trials, differences were 14 to 18 points on the 0 to 100 SF-36 or Child Health Questionnaire-CF87 physical function subscales.

The trial of CBT versus an attention control also found no difference in severity of functional impairment at 1 year post-intervention follow-up (N=63, mean difference 6.1, 95% CI -9.2 to 21.4 on the 0 to 100 SF36 physical function subscale).⁸¹ There was also no difference in patients originally randomized to this trial at long-term (24 month) post-trial follow-up (mean difference 5.6, 95% CI -12.1 to 23.3).⁸⁶

CBT was associated with increased likelihood of improvement in function versus usual care or wait list (2 trials, N=200, RR 3.35, 95% CI 2.25 to 4.99, I²=0%; ARD 50%, 95% CI 33% to 68%;^{82,83} **Figure 58**). One trial⁸² defined improvement in fatigue as a Child Health Questionnaire-CF87 score ≥ 85 and the other trial⁸³ as an SF-36 physical function score increase ≥ 50 or score ≥ 75 .

Figure 58. Likelihood of functional improvement in adolescents: CBT versus inactive controls

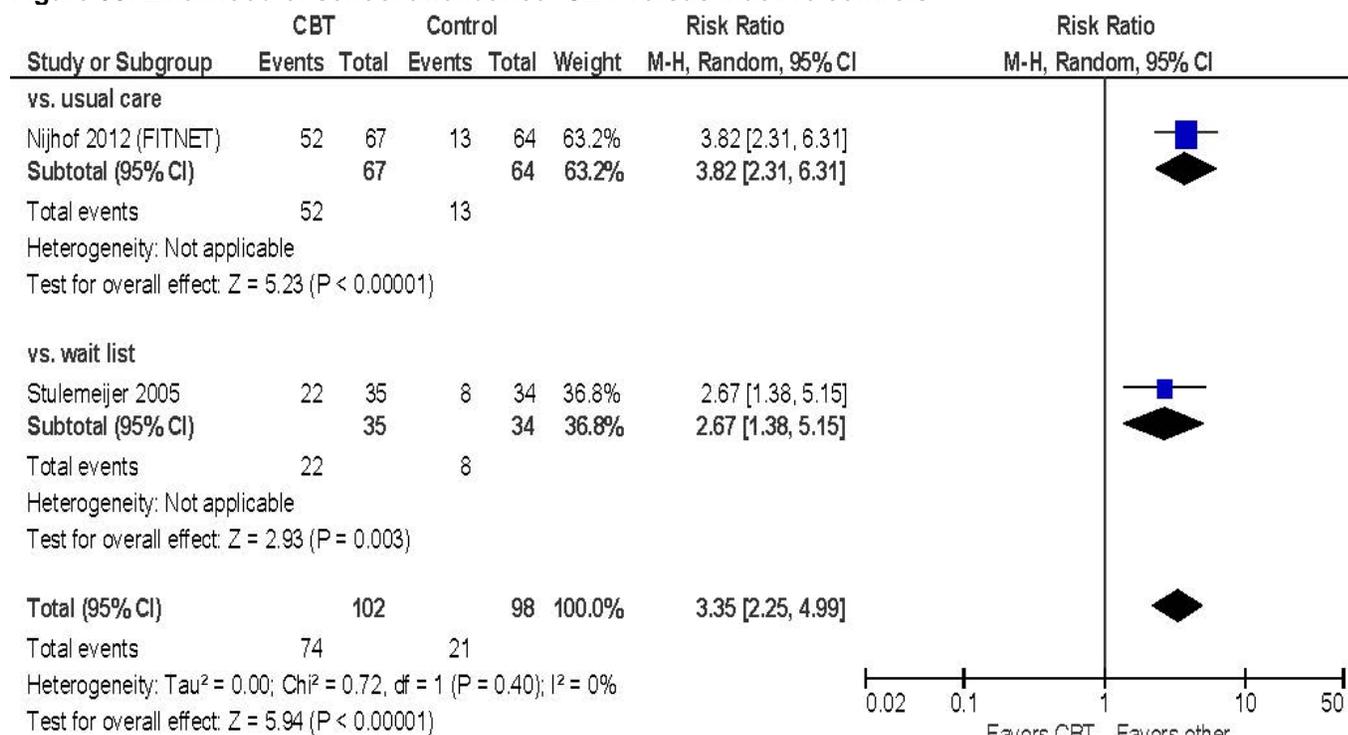


Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; FITNET = fatigue in teenagers on the internet; M-H = Mantel-Haenszel test

School attendance

There was no statistically significant difference between CBT versus usual care, wait list, or an attention control in likelihood of school attendance (3 trials, N=251, RR 1.96, 95% CI 0.57 to 6.79, I²=95%; **Figure 59**).⁸¹⁻⁸³ Although the estimate favored CBT, statistical heterogeneity was large and the estimate was imprecise. The trial of CBT versus an attention control showed no effect on likelihood of school attendance (N=53, RR 0.85, 95% CI 0.61 to 1.17);⁸¹ results were similar at long-term (24 month) post-trial follow-up.⁸⁶ In the other two trials CBT was associated with increased likelihood of school attendance versus usual care of wait list (2 trials, N=198, RR 3.06, 95% CI 1.25 to 7.49; I²=78%; ARD 45%, 95% CI 14% to 75%).

Figure 59. Likelihood of school attendance: CBT versus inactive controls



Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; FITNET = fatigue in teenagers on the internet; M-H = Mantel-Haenszel test

Overall improvement

There was no statistically significant difference between CBT versus usual care, wait list, or an attention control in likelihood of overall improvement (3 trials, N=256, RR 1.66, 95% CI 0.67 to 4.10, I²=95%).⁸¹⁻⁸³ Although the estimate favored CBT, statistical heterogeneity was substantial and the estimate was imprecise. The trial that compared CBT versus an attention control showed no effect on likelihood of overall improvement, defined as a child-reported global improvement “good outcome” (N=56, RR 0.99, 95% CI 0.83 to 1.19).⁸¹ The other two trials each found CBT associated with increased likelihood of overall improvement, defined as self-rating of “I have completely recovered” or “I feel much better but still experience some symptoms” (2 trials, N=200, RR 2.18, 95% CI 1.21 to 3.93, I²=73%).^{82,83}

Recovery

One trial found web-based CBT associated with increased likelihood of recovery versus usual care at the end of treatment (N=131, 78% vs. 20%, RR 3.82, 95% CI 2.31 to 6.31).⁸² Recovery was defined as school absence <10%, Checklist Individual Strength, fatigue severity subscale <40, CHQ-CF87 ≥85, and overall assessment of “I have completely recovered” or “I feel much better but still experience some symptoms.” However, there was no difference in this trial in likelihood of recovery at long-term (2.7 year) post-trial follow-up (64% vs. 53%, RR 1.20, 95% CI 0.81 to 1.78).⁸⁷ Another trial found no differences between CBT versus an attention control in likelihood of recovery (defined as 11-item 0 to 33 Chalder score ≤18 and school attendance ≥70%) at 6-month post-intervention follow-up (68% vs. 69%)⁸¹ or at long-term, 24 month post-trial follow-up (79% vs. 64%, p=0.34).⁸⁶

Additional Fukuda 1994 Fukuda criteria symptoms

One trial (N=69) found CBT associated with improvement in severity of unrefreshing sleep (mean difference -1.2, 95% CI -1.8 to -0.6), muscle pain (mean difference -1.1, 95% CI -1.6 to -0.6), and impaired concentration (mean difference -1.1, 95% CI -1.5 to -0.65) versus wait list (all assessed on a 4 point Likert scale).⁸³ There were no differences in severity of headache, impaired memory, multi-joint pain, or sensitive lymph nodes.

Harms

One serious adverse event was reported in two trials.^{82,83} One trial found CBT associated with decreased tiredness after exercise versus wait list (N=69, mean difference -1.0, 95% CI -1.5 to -0.5 on a 4 point Likert scale).⁸³

Table 15. CBT versus inactive controls in adolescents: Summary of results

Outcome	Number of studies (N)	Estimate (95% CI)	I ²
Fatigue, end of intervention	3 (263)	SMD -0.84 (-1.52 to -0.15)	85%
11-item Chalder fatigue scale (0 to 33), post-intervention	1 (63)	MD -1.9 (-5.3 to 1.5)	--
Fatigue improvement (dichotomous)	2 (200)	RR 3.13 (2.18 to 4.49)	0%
Function, end of intervention	3 (263)	SMD 0.49 (-0.34 to 1.32)	90%
SF-36 physical function (0 to 100), post-intervention	1 (63)	MD 6.1 (-9.2 to 21.4)	--
Functional improvement	2 (200)	RR 3.35 (2.25 to 4.99)	0%
School attendance	3 (251)	RR 1.96 (0.57 to 6.79)	95%
Overall improvement	3 (256)	RR 1.66 (0.67 to 4.10)	95%
Recovery	1 (131)	RR 3.82 (2.31 to 6.31)	--

Abbreviations: CI = confidence interval; CBT = cognitive behavioral therapy; MD = mean difference; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference

Cognitive behavioral therapy plus biofeedback versus biofeedback

One trial (N=92) compared CBT plus biofeedback versus biofeedback alone in adolescents (Tables 13 and 14).⁸⁰ The duration of treatment was 18 months and outcomes were assessed at the end of therapy. The trial was rated high risk of bias; attrition was high (40%) and persons who withdrew were excluded from the analysis. CBT plus biofeedback was associated with less severe fatigue (mean difference 12.2, 95% CI 7.4 to 14.8 on the 0 to 100 Fatigue Activity Scale) and greater school attendance (mean difference 23 hours/month, 95% CI 20.6 to 26.8). CBT plus biofeedback was also associated with less severity of unrefreshing sleep (mean difference -1.20, 95% CI -1.62 to -0.78) and myalgia (mean difference -0.80, 95% CI -1.23 to -0.37), with no difference in joint pains or tender glands (each symptom assessed on a 4-point Likert scale). Harms were not reported.

Cognitive therapy and education versus pacing

One small (N=17) pilot trial compared a cognitive therapy and education program (STAIRway to Health) versus pacing in adolescents. The duration of treatment was 12 months and outcomes were assessed at the end of therapy (Tables 13 and 14).⁸⁴ There were no differences in fatigue, function, anxiety or depression, though estimates were imprecise. Global health ratings favored the cognitive therapy and education program (mean difference -1.8, 95% CI -2.7 to -0.9 on a 1 to 5 scale).

Other behavioral approaches in adolescents

Osteopathy, life coaching and neurolinguistic programming intervention plus usual specialist care versus usual specialist care

One medium risk of bias trial (N=81) compared an osteopathy, life coaching and neurolinguistic programming intervention (“Lightning Process”) plus usual specialist care versus usual specialist care alone in adolescents (mean age 14.6 years) who met the NICE case definition (**Table 13 and 14, Evidence Table Appendix E2, Risk of Bias Table Appendix F**).⁸⁵ The intervention consisted of 3 four-hour sessions plus 2 follow-up sessions and outcomes were assessed through 12 months. At the end of follow-up, the intervention was associated with improved function (adjusted mean difference 12.9, 95% CI 3.6 to 22.1 on the 0 to 100 SF-36 physical function subscale); results were similar at 6-month follow-up. There were no statistically significant effects of the intervention on fatigue, pain, anxiety, depression, or quality of life at 6 or 12 months. There was also no difference between groups in school attendance at 6 months, though the intervention was associated with higher attendance at 12 months (adjusted mean difference 1.0, 95% CI 0.2 to 1.8 for days of attendance in the previous week).

Predictors of treatment response in trials of exercise therapy and CBT

The PACE trial, which enrolled patients who met the Oxford case definition, was the only trial to evaluate how application of different ME/CFS case definitions impacted outcomes.³⁶ It found no interactions between whether patients met the 2003 International CFS criteria definition,²⁰ the 1994 London case definition, or presence of a primary depressive or anxiety disorder and effects of interventions on fatigue or function.

Evidence on the interaction between severity of baseline functional impairment and effects of exercise of CBT was limited and inconsistent. The GETSET trial found an interaction between worse physical function at baseline and larger effects of exercise on function at follow-up, though there was no interaction between baseline physical function and fatigue.⁴⁹ However, two trials found lower baseline function associated with poorer response to exercise or CBT.^{67,88} One other trial found that effects of CBT versus wait list on fatigue and function were slightly greater in the subgroup of patients with baseline SF-36 physical function score ≤ 70 compared to the whole study population, but did not report results in the subgroup with a score >70 or perform statistical testing for a subgroup effect.⁷²

Three trials found no interaction between baseline depression and effects of exercise or CBT.^{49,65,88} One trial also found no interaction between receipt of antidepressant therapy, sleep disturbance, duration of illness, or initial illness beliefs and effects of exercise.⁸⁸

Other therapies

Medications

Nineteen randomized controlled trials (RCTs) evaluated pharmacological treatment of ME/CFS.^{56,71,89-106} The pharmacological therapy was an immune modulating drug (rintatolimod, IgG, rituximab, anakinra, and alfa-interferon) in nine trials,^{89,90,94-96,99-102} an antidepressant in four trials,^{56,71,98,105} and a corticosteroid in two trials;^{91,106} valganciclovir,⁹³ galantamine,¹⁰³ clonidine,⁹⁷ and methylphenidate plus a nutritional supplement aimed at modulating mitochondrial function were each evaluated in one trial (**Tables 16 and 17; Evidence Table Appendix E2, Risk of Bias Table Appendix F**).¹⁰⁴ Eleven of these were not included in the

prior AHRQ report (6 trials of immune modulators, 3 trials of antidepressants, 1 of clonidine, and 1 of methylphenidate). None of the studied medications have been FDA-approved for treating ME/CFS. Intravenous rintatolimod is not FDA approved for any indication, although it was reviewed by the FDA for ME/CFS and failed to receive approval in 2012. All of the studies compared the study drug versus matching placebo; one study of fluoxetine also randomized patients to GET (see exercise Results for comparison of graded exercise versus fluoxetine).⁵⁶ The median duration of study treatment was 12 weeks (range 4 to 42 weeks). The timing of outcome assessment ranged from the end of treatment to 30 weeks after the end of treatment. Eight of the trials were conducted in the United States, six in Europe, and two in Australia. All of the included studies evaluated the effect of the study drug on ME/CFS symptoms; one trial of an antidepressant stratified randomization based on depression status at baseline to measure the impact on depression symptoms (see Question 3a).⁹⁸

Ten RCTs enrolled patients based on the Fukuda case definition,^{89,91-93,97,99,101-106} three used the prior CDC case definition (Holmes, 1988),^{94,95,100} one used a combination of the Fukuda and Holmes criteria,⁹⁶ two used the Oxford case definition,^{56,98} and one used the Canadian Consensus criteria (Carruthers 2003).⁹⁰ Seventeen trials enrolled adults, weighted mean age 37.5 years (range of mean enrolled age 31 to 49),^{56,71,89-96,98-101,103-106} and two trials enrolled only adolescents, both with a mean age of 15 years.^{97,102} The proportion female ranged from 47% to 100% and the sample size ranged from 26 to 423 (N=1,150). Most trials did not report race or ethnicity, but when reported, most participants were white. The mean duration of illness ranged from 18 months to 13 years in 12 trials that provided this information.^{56,91-102,106} Methods for measuring severity of baseline fatigue and functional status varied and some trials did not report baseline values (Table 16). The most common methods for measuring baseline fatigue were the Chalder 14-item 0 to 42 scale (two trials, mean score at baseline 32 in one trial and not reported in the other)^{56,103} or 11-item 0 to 33 scale (1 trial, mean 19.2)⁹⁷ and the POMS, fatigue subscale in two trials (mean 18.8 and 18.7 out of 24).^{91,99} The most common methods for measuring baseline functional status were the SF-36 physical function subscale (2 trials, mean 53.9 and 59.5 on a 0 to 100 scale),^{100,105} and the KPS (3 trials, mean ranged from 51 to 70.3 on a 0 to 100 scale);^{95,96,99} the other trials used different methods to evaluate function,^{101,103} or did not report baseline functional status. One antidepressant trial excluded patients with major depression at baseline¹⁰⁵ and in another antidepressant trial 50% of patients had major depression at baseline.⁹⁸ Three non-antidepressant medication trials reported that 3% to 24% had major depression at baseline;^{56,91,95} the other trials did not describe depression status.

Three trials (anakinra,¹⁰¹ clonidine,⁹⁷ and rituximab⁹⁰) were rated low risk of bias and one trial (alfa-2a interferon)⁹⁴ was rated high risk of bias, primarily due to poor reporting of methods or attrition⁹⁴ (**Evidence Table Appendix E2**). The other trials were rated moderate risk of bias. Eight of the trials reported funding and/or drug and matching placebo provided by pharmaceutical companies, five trials without industry support reported funding from foundations or other sources, and three trials did not report sources of support (**Risk of Bias Table Appendix F**).

Table 16. Medication RCTs: Study Characteristics

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency Duration of treatment Duration of follow up
Arnold, 2015 ¹⁰⁵ United States Medium	n=57 Age: 44 % Female: 87	Criteria: Fukuda Duration: >6 months	Fatigue Scale: CDC Symptom Inventory Baseline: 40.0 (SD 133)	Major depression: Excluded Baseline depression: HADS depression (0-21): 9.27 (SD 3.9 Function: SF-36 physical function (0 to 100): 59.5 (SD 19.8)	A: Duloxetine 120 mg/d B: Placebo Duration of treatment: 12 weeks (4 weeks at maximum dose) Duration of follow up: 12 weeks
Blacker, 2004 ¹⁰³ United Kingdom Medium	n=423 Age: 38 % Female: 68	Criteria: Fukuda Duration: <7 years	Fatigue Scale: Chalder Baseline: NR	Major Depression: NR Baseline Depression: NR Function: FIQ 13.47 (SD NR)	A: Galantamine 2.5 mg B: Galantamine 5 mg C: Galantamine 7.5 mg D: Galantamine 10 mg E: Placebo Duration of treatment: 4 months (16 weeks, 8 weeks at full dose) Duration of follow up: 4 weeks
Blockmans, 2003 ¹⁰⁶ Belgium Medium	n=80 Age: 38 % Female: 91	Criteria: Fukuda Duration: mean 30 months	Fatigue Scale: # criteria for CFS Baseline: 6 (SD 2)	Major Depression: NR Baseline Depression: HADS depression (0 to 21): 9.6 (SD 3.5) Function: SF-36 Physical Function (0 to 100): 27.3 (SD 12.3)	A: Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day B: Placebo Duration of treatment: 3- month treatment; 3- month placebo crossover Duration of follow up: end of 3-month crossover
Fluge, 2011 ⁸⁹ Norway Medium	N=30 Age: 34.4 % Female: 70	Criteria: Fukuda Duration: mean 6.6 years	Fatigue Scale: VAS (0 to 10) Baseline: 8	Major Depression: NR Baseline Depression: NR Function: SF-36 physical function (%, lower score denotes increasing symptoms): 34.5 (SD 6.5)	A. Rituximab 500 mg/m ² , maximum 1,000 mg B. Placebo Duration of treatment: 2 weeks Duration of follow-up: 12 months
Fluge, 2019 ⁹⁰ Norway Low	N=152 Age: 36.7 % Female: 82	Criteria: Canadian consensus (Carruthers, 2003) Duration: mean 8 years	Fatigue Scale: Scale not named (0 to 6) Baseline: 3.0	Major Depression: NR Baseline Depression: 8.5% Function: SF-36 Physical Function (%, lower score denotes increasing symptoms): 33.8	A. Rituximab 500 mg/m ² , maximum 1,000 mg B. Placebo Duration of treatment: 12 months Duration of follow-up: 24 months

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency Duration of treatment Duration of follow up
McKenzie, 1998 ⁹¹ United States Medium	N=70 Age: 38 % Female: 80	Criteria: Fukuda and Holmes Duration: 54 months	Fatigue Scale: POMS fatigue subscale (0 to 28) Baseline: 18.7 (SD 5.2)	Major Depression: 3% Baseline Depression: HADS depression (0 to 21): 9.6 (SD 3.5) Function: NR	A. Hydrocortisone 20- 30 mg every morning, 5 mg every evening B: Placebo Duration of treatment: 12 weeks Duration of follow up: 12 weeks
Montoya, 2018 ¹⁰⁴ United States Medium	N=128 Age: 49 % Female: 63	Criteria: Fukuda Duration: 13.1 years	Fatigue Scale: MFI-20 (20 to 100) Baseline: 78.6 (SD NR)	Major Depression: NR Baseline Depression: NR Function: NR	A: Methylphenidate 20mg/day + Mitochondrial nutritional supplement: 4 tablets twice daily. B: Placebo Duration of treatment: 12 weeks (10 weeks at full dose) Duration of follow up: 12 weeks
Montoya, 2013 ⁹³ United States Medium	N=30 Age: 43 % Female: 72	Criteria: Fukuda Duration: 53% <10 years, 47% >10 years	Fatigue Scale: MFI-20 (20 to 100) Baseline: 79.5 (SD 13.40)	Major Depression: NR Baseline Depression: NR Function: NR	A: Valganciclovir 900 mg BID for 21 days, then 900 mg/day B: Placebo Duration of treatment: 6 months Duration of follow up: 12 months
Peterson, 1990 ¹⁰⁰ United States Medium	N=28 Age: 38 % Female: 73	Criteria: Holmes Duration: 3.8 years	Fatigue Scale: # of CFS criteria Baseline: 8.8 (SD NR)	Major Depression: NR Baseline Depression: NR Function: SF-36 physical function (0 to 100): 53.9 (SD 22.7)	A: IgG 1 g/kg IV every 30 days B: Placebo Duration of treatment: 6 months Duration of follow up: 6 months
Roenik 2017 ¹⁰¹ The Netherlands Low	n=50 Age: 31 % Female:	Criteria: Fukuda Duration: 41 months	Fatigue Scale: Mean fatigue severity CIS- fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue) Baseline: 51.5	Major Depression: NR Baseline Depression: MR Function: Sickness Impact Profile (SIP-8) (0 to 5,799): 1647 vs. 1706	A: Anakinra 100 mg SQ daily B: Placebo Duration of treatment: 4 weeks Duration of follow up: 20 weeks after treatment

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency Duration of treatment Duration of follow up
Rowe, 1997 ¹⁰² Australia Medium	n=70 Age: 15 % Female: 100	Criteria: Fukuda Duration: 41 months	Fatigue Scale: CIS-fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue) Baseline: 52 (SD NR)	Major Depression: NR Baseline Depression: NR Function: Mean functional impairment Sickness Impact Profile (SIP-8) (0 to 5,799): 1677 (SD NR)	A: IgG 1 gm/kg IV every 30 days B: Placebo Duration of treatment: 12 weeks Duration of follow up: 25 weeks follow-up
See, 1996 ⁹⁴ United States High	n=26 Age: 37 % Female: 80	Criteria: Holmes Duration: 4.6 years	Fatigue Scale: NR Baseline: NR	Major Depression: NR Baseline Depression: NR Function: NR	A: Alfa-2a Interferon 3 mu SQ 3 times per week B: Placebo Duration of treatment: 12 weeks Duration of follow up: 12 weeks
Strayer, 1994 ⁹⁵ United States Medium	n=84 Age: NR % Female: 75	Criteria: Holmes and Fukuda, 1994) Duration: 5.25 years	Fatigue Scale: NR Baseline: NR	Major Depression: 24% Baseline Depression: NR Function: KPS (0 to 100): 51 (SD NR)	A: Rintatolimod 200 mg IV twice weekly 4 times, then 400 mg twice weekly B: Placebo Duration of treatment: 6 months Duration of follow up: 6 months
Strayer, 2012 ⁹⁶ United States Medium	n=240 Age: 44 % Female: 71	Criteria: Holmes and Fukuda Duration: 9.7 years	Fatigue Scale: NR Baseline: NR	Major Depression: NR Baseline Depression: NR Function: NR	A: Rintatolimod 400 mg IV twice weekly B: Placebo Duration of treatment: 40 weeks Duration of follow up: 40 weeks
Sulheim, 2014 ⁹⁷ Norway Low	n=96 Age: 15 % Female: 72	Criteria: Fukuda Duration: 18 months	Chalder Fatigue Scale 11-item (0 to 33): Baseline: 19.2 (SD NR)	Major Depression: NR Baseline Depression: NR Function: NR	A: Clonidine 25-50 mcg based on weight. B: Placebo Duration of treatment: 9 weeks treatment Duration of follow up: 30 weeks follow-up

Author, year Country Risk of Bias	Study N (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency Duration of treatment Duration of follow up
Vercoulen, 1996 ⁹⁸ The Netherlands Medium	n=96 Age: 39 % Female: 47%	Criteria: Oxford Duration: 6 years	Fatigue Scale: Subjective fatigue, daily observed fatigue score, measured 4 times a day on a 4-point scale, and combined, with higher scores indicating worse fatigue: Baseline: 9.4 (SD NR)	Major Depression: 50% Baseline Depression: Beck Inventory (0 to 63): 22.5 in depressed group; 7,5 in non- depressed Function: NR	A: Fluoxetine 20 mg/day B: Placebo Duration of treatment: 8 weeks treatment Duration of follow up: 10 weeks follow-up
Vollmer-Conna, 1997 ⁹⁹ Australia Medium	n=99 Age: 40 % Female: 76	Criteria: Fukuda Duration: 6.25	Fatigue Scale: POMS fatigue subscale (0 to 28): Baseline: 18.8 (SD 6.3)	Major Depression: NR Baseline Depression: POMS Depression (0 to 60): 15.7 (SD 12.1) Function: KPS (0 to 100): 70.3 (SD 10)	A: IgG 0.5 gm/kg B: IgG 1.0 mg/kg C: IgG 2.0 mg/kg D: Placebo IV every 30 days Duration of treatment: 12 weeks Duration of follow up: 12 weeks
Wearden, 1998 ⁵⁶ United Kingdom Medium	n=68 Age: 39 % Female: 71	Criteria: Oxford Duration: 28 months	Fatigue Scale: Chalder Fatigue Scale 14-item (0 to 42) Baseline: 34 (SD NR)	Major Depression: 10% Baseline Depression: HADS depression score (0 to 21): 8.8 (SD 3.5) Function: NR	A: Fluoxetine 20 mg/day B: Placebo Duration of treatment: 26 weeks Duration of follow up: 26 weeks

Abbreviations: BDI = Beck Depression Inventory; BID = twice daily; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; FIQ = Fibromyalgia Impact Questionnaire; HADS-D = Hospital Anxiety and Depression Scale-depression; IgG = immunoglobulin G; IV = intravenous; KPS = Karnofsky Performance Scale; ME = myalgic encephalomyelitis; MFI-20 = Multidimensional Fatigue Inventory 20-item; NR = not reported; POMS = profile of mood states; q = every; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey; SIP-8 = Sickness Impact Profile; SQ = subcutaneous

Table 17. Medication RCTs: Study results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Arnold, 2015 ¹⁰⁵ Fukuda	A. Duloxetine 120 mg/d (30) B. Placebo (30) Duration of treatment: 12 weeks Duration of follow up: 12 weeks	MFI-20 general fatigue subscale (4 to 20), observed mean change (SD): -3.3 (4.2) vs. -1.8 (2.8), model-based difference between groups: -1.0 (95% CI, -2.8 to 0.7), p=0.23	SF-36 physical function (0 to 100): 14.3 (22.6) vs. 7.5 (27.4); difference: 6.8, 95% CI -8.5 to 22.0, p=0.38	HADS-Depression, change from baseline: -1.6 (2.9) vs. -1.9 (3.0), p=0.67 HADS-Anxiety: -3.2 (2.2) vs. 2.0 (3.2), p=0.24 Brief pain inventory (0 to 10): Average pain severity, mean (SD): -1.6 (1.5) vs. -0.8 (2.3): 0.73 (95% CI, 0.54 to 1.00), p=0.05 Average pain interference, mean (SD): -1.9 (1.3) vs. -1.1 (2.8): 0.70 (95% CI, 0.51 to 0.96), p=0.03 CDC Symptom Inventory, CFS Questions: mean change (SD): -9.7 (13.1) vs. -8.2 (14.6), between-group difference at endpoint: -1.5 (95% CI, -9.9 to 6.9), p=0.72
Blacker, 2004 ¹⁰³ Fukuda	A: Galantamine 7.5 mg (89) B: Galantamine 15 mg (86) C: Galantamine 22.5 mg (91) D: Galantamine 30 mg (86) E: Placebo (82) Duration of treatment: 4 months Duration of follow up: 4 weeks	Chalder Fatigue Scale (mean change from baseline) Physical: 9.25 vs. 8.77 vs. 11.02 vs. 9.99 vs. 9.86, no significant differences Mental: 6.46 vs. 5.89 vs. 7.74 vs. 6.60 vs. 6.80, no significant differences	Not reported	Pittsburgh Sleep Quality Index Total score (0-21, higher score indicates worse sleep): -1.60 vs. -2.28 vs. -1.43 vs. -1.73 vs. -2.02, no significant differences
Blockmans, 2003 ¹⁰⁶ Fukuda	A. Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day (50) B. Placebo Duration of treatment: 3 months + 3 months crossover (50) Duration of follow up: end of 3-month crossover	VAS(0 to 10), mean (SD): 6.6 (2.0) vs. 6.7 (2.1), p=0.76 Short fatigue questionnaire score: 8 (5) vs. 7 (5), p=0.69	SF-36 physical function (0 to 100): 31.7 (18.2) vs. 30.4 (18.1), p=0.34	Depression: HADS depression (0 to 21): 8 (5) vs. 9 (4), p=0.04, but not significant after Bonferroni correction Anxiety: HADS anxiety (0 to 21): 9 (4) vs. 10 (4), p=0.28

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Fluge, 2011 ⁸⁹ Fukuda	A: Rituximab 500 mg/m ² , maximum 1,000 mg (15) B: Placebo (15) Duration of treatment: 2 weeks Duration of follow-up: 12 months	Fatigue: Major clinical responses: 9 (60%) vs. 7 (7%), p=0.002 Moderate clinical responses: 1 (7%) vs. 1 (7%) Overall, 95% CI: 10 (67%) (95% CI, 41% to 85%) vs. 2 (13%) (95% CI, 4% to 38%), p=0.003 Response duration: weeks, mean (range): 25 (8 to >44), n=10 vs. 41 (34 to >48), n=2 Difference between groups in self-reported fatigue score at 40 to 52 weeks: 0.63 (95% CI, -0.09 to 1.34), adjusted p value: 0.25 Difference in physician-assessed fatigue score at 12 months after intervention: 0.62 (95% CI, -0.09 to 1.34), adjusted p-value: 0.17	SF-36 physical function, (percent, lower score denotes increasing symptoms), max change %, mean (SD): 39 (33) vs. 11 (22)	NR
Fluge, 2019 ⁹⁰ Canadian consensus (Carruthers, 2003)	A: Rituximab 500 mg/m ² , maximum 1,000 mg (77) B: Placebo (75) Duration of treatment: 12 months Duration of follow-up: 24 months	Fatigue: Fatigue score (0 to 6), at 16 to 20 months: 3.12 vs. 3.18, mean difference: -0.06 (95% CI, -0.51 to 0.39), p=0.79 Fatigue Severity Scale (9 to 63), mean at 18 months: 55.98 vs. 56.05, mean difference: -0.07 (95% CI, -3.21 to 3.08), p=0.68	Overall Function: SF-36 physical function(0 to 100) at 18 months: 45.67 vs. 45.23, mean difference: 0.42 (95% CI, -8.12 to 8.96), p=0.52 Function level, % at 16 to 20 months: 25.25 vs. 25.93, mean difference: -0.68 (95% CI, -5.90 to 4.54), p=0.31	Mean steps per 24 hours, 17 to 21 months: 3,777 vs. 3,904, mean difference: -127 (95% CI, -1004 to 749), p=0.58
McKenzie, 1998 ⁹¹ Fukuda and Holmes	A. Hydrocortisone 20-30 mg every morning, 5 mg every evening (35) B. Placebo (35) Duration of treatment: 12 weeks Duration of follow up: 12 weeks	POMS, mean change: fatigue subscale: -3.6 (5.3) vs. -1.8 (4.5); p=0.21 POMS vigor subscale: 1.2 (3.3) vs. 0.7 (3.3); p=0.45	Activity Scale, mean change: 0.3 (1.1) vs. 0.7 (1.4); p=0.32	Beck Depression Inventory (0-63, higher most severe) change: -2.1 (5.1) vs. -0.4 (4.1); p=0.17

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Montoya, 2018 ¹⁰⁴ Fukuda	A. Methylphenidate 20mg/d + Mitochondrial nutritional supplement: 4 tablets twice daily. (67) B. Placebo (68) Duration of treatment: 12 weeks Duration of follow up: 12 weeks	CIS total score (20 to 140): 95.3 vs 98.6, mean change from baseline: -16.9 (±23.52) vs. -13.8 (±22.15), (95% CI, -11.1 to 4.0), p=0.359 VAS fatigue change from baseline: -18.2 mm (±25.05) vs. -11.1 mm (±22.08), (95% CI, -11.5 to 2.3), p=0.189	NR	NR
Montoya, 2013 ⁹³ Fukuda	A. Valganciclovir 900 mg BID for 21 days, then 900 mg/day (20) B. Placebo (10) Duration of treatment: 6 months Duration of follow up: 12 months	Fatigue Severity Scale 9-item (1 to 7) (change in score, negative indicates better health): -0.06 vs. 0.02; p=0.006 MFI-20 (20 to 100), change in score: -6.15 vs. -1.10; p=0.224	Self-reported physical function: 1.02 vs. 0.46; p=0.217 CDC Symptom Inventory: NS	NR
Peterson, 1990 ¹⁰⁰ Holmes	A. IgG 1 g/kg IV every 30 days (15) B. Placebo (15) Duration of treatment: 6 months Duration of follow up: 6 months	NR	MOS-SF social function higher in placebo group: 5.2 (5.5) vs. 9.4 (7.9); p<0.05 MOS-SF physical function (0 to 100): 56.0 (23.2) vs. 51.8 (22.2); p=NS	NR
Roerink, 2017 ¹⁰¹ Fukuda	A. Anakinra 100 mg SQ daily (25) B. Placebo (25) Duration of treatment: 4 weeks Duration of follow up: 20 weeks after treatment	CIS-fatigue score: 4 weeks: 46.7 vs. 45.1, p=0.59 24 weeks:45.3 vs. 44.0, p=0.69	SF-36 physical function (0 to 100): 4 weeks: 58.2 vs. 61.2, p=0.53 24 weeks: 60.8 vs. 64.8, p=0.47 Sickness Impact Profile (SIP-8) (0 to 5,799): 4 weeks: 1472.2 vs. 1353.7, p=0.47 24 weeks: 1351.5 vs. 1260.4, p=0.62	Psychological symptoms: SCL-90 (90 to 450): 4 weeks: 144.4 (136.6 to 152.2) vs. 139.9 (132.1 to 147.7), p=0.42 24 weeks: 143.5 (135.3 to 151.7) vs. 140.5 (132.3 to 148.7), p=0.63 Pain (VAS): 4 weeks: 7.4 (6.5 to 8.3) vs. 6.3 (5.4 to 7.2), p=0.104 24 weeks: 6.9 (5.9 to 7.9) vs. 6.6 (5.6 to 7.6), p=0.63

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Rowe, 1997 ¹⁰² Fukuda	A. IgG 1 gm/kg IV every 30 days (36) B. Placebo (35) Duration of treatment: 12 weeks Duration of follow up: 25 weeks follow-up	NR	Investigator scale; % of normal 3 months: Not improved (<25% improvement)/ Improved (>25% improvement) %: NS 6 months: Not improved (<25% improvement).%: 27.8 (10/36) vs. 55.9 (19/34); p=0.02 (RR 0.50, 95% CI 0.21 to 0.91) Improved (>25% improvement) %: 72.2 (26/36) vs. 44.1 (15/34) p=0.02 (RR 1.64, 95% CI 1.07 to 2.51) Returned to full function (not defined) at 6 months, %: 25 (9/36) vs. 11 (4/34), p<0.04	Depression and Anxiety: SCL-90-R (90 to 450): NS
See, 1996 ⁹⁴ Holmes	A. Alfa-2a Interferon 3 mu SQ 3 times per week (15) B. Placebo (15) Duration of treatment: 12 weeks Duration of follow up: 12 weeks	NR	NR	NR
Strayer, 1994 ⁹⁵ Fukuda and Holmes	A. Rintatolimod 200 mg IV twice weekly 4 times, then 400 mg twice weekly (45) B. Placebo (47) Duration of treatment: 6 months Duration of follow up: 6 months	NR	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	NR

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Strayer, 2012 ⁹⁶ Fukuda and Holmes	A. Rintatolimod 400 mg IV twice weekly (117) B. Placebo (117) Duration of treatment: 40 weeks Duration of follow up: 40 weeks	NR	Cardiopulmonary exercise tolerance % change from baseline: 36.5% vs. 15.2%; p=0.047	NR
Sulheim, 2014 ⁹⁷ Fukuda	A. Clonidine 25 - 50 mcg based on weight. (60) B. Placebo (60) Duration of treatment: 9 weeks Duration of follow up: 30 weeks	Chalder Fatigue Scale 11-item (0 to 33) at 30 weeks: 11.1 vs. 13.5, difference 0.5, 95% CI: - 14.7 to 15.7, p=0.95	Mean Functional Disability Inventory (0 to 60) at 30 weeks: 17.5 vs. 16.8, difference 0.2, 95% CI: -13.3 to 13.6, p=0.98	Pain Brief pain inventory (0 to 10): 8 weeks: 4.1 vs. 3.4, p=0.14 30 weeks: 3.8 vs. 3.3, p=0.32 Sleep (KSQ Insomnia Score): 8 weeks: 3.7 vs. 3.8, p=0.54 30 weeks: 3.6 vs. 3.6, p=0.74
Vercoulen, 1996 ⁹⁸ Oxford	A. Fluoxetine 20 mg/d (54) B. Placebo (53) Duration of treatment: 8 weeks Duration of follow up: 10 weeks	Daily observed fatigue score: NS	Self-reported change: NS	Depression: Beck Depression Inventory (0 to 63, mean difference): - 0.186 (95% CI, 0.35 to 0.02), p=NS
Vollmer-Conna, 1997 ⁹⁹ Fukuda	A: IgG 0.5 gm/kg (22) B: IgG 1.0 mg.kg (28) C: IgG 2.0 mg/kg (23) D. Placebo (26) IV every 30 days Duration of treatment: 12 weeks Duration of follow up: 12 weeks	POMS energy score: No significant difference between groups, data NR	KPS (0 to 100): median (1st to 3rd IQR): 80.0 (80 to 70) vs. 80.0 (80 to 70) vs. 75.0 (80 to 70) vs. 77.5 (80 to 70), difference in change between groups: p>0.13	NR

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Function Outcomes	Other Outcomes (depression, sleep, pain, etc.)
Wearden, 1998 ⁵⁶ Oxford	A. Fluoxetine 20 mg/day (35) B. Placebo (34) Duration of treatment: 26 weeks Duration of follow up: 26 weeks	Chalder Fatigue Scale 14-item (0 to 42) (mean change from baseline): 12 weeks: -1.6 (-4.4 to 1.2) vs. -2.0 (-4.1 to 0.1) 26 weeks: -3.0 (-5.9 to - 0.2) vs. -2.7 (-5.4 to 0.01) Chalder Fatigue Scale (cases of non-fatigue): 12 weeks: 1 (3/35) vs. 6 (2/34) 26 weeks: 6 (2/ 35) vs. 6 (2/34) Exercise improved Chalder Fatigue Scale scores, mean change: 12 weeks: 2.1 (95% CI - 0.6 to 4.8), p=0.13 26 weeks: 2.9 (95% CI - 0.2 to 6.1), p=0.07	Functional work capacity (mean change): 12 weeks: 0.4 (-1.2 to 2.0) vs. 0.4 (-0.9 to 1.7) 26 weeks: 1.0 (-0.9 to 3.0) vs. -0.1 (-1.7 to 1.6)	Depression: HADS depression (0 to 21): Week 12: -1.1 (95% CI - 0.03 to -2.2; P=0.04) Week 26: -1.7 (-3.0 to - 0.5) vs. -1.3 (-2.3 to -0.3)

Abbreviations: ADL = activities of daily living; BDI = Beck Depression Inventory; BID = twice daily; BPI = Brief Pain Inventory; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; CI = Confidence Interval; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale-Anxiety; HADS-D = Hospital Anxiety and Depression Scale-depression; IgG = immunoglobulin G; IV = intravenous; KPS = Karnofsky Performance Scale; KSQ = Karloinska Sleep Questionnaire; MDD = major depressive disorder; ME = myalgic encephalomyelitis; MFI-20 = Multidimensional Fatigue Inventory 20-item; MOS-SF = Medical Outcome Study-short form; NR = not reported; NS = not significant; POMS = profile of mood states; q = every; RCT = randomized controlled trial; RR = relative risk; SCL-90 = symptom checklist 90; SCL-90-R = symptom checklist 90-revised; SD = standard deviation; SF-36 = 36-item Short Form Health Survey; SIP-8 = Sickness Impact Profile; SQ = subcutaneous; VAS = visual analogue scale; TID = three times daily

Immune Modulators

Rintatolimod versus placebo. Two moderate risk of bias trials (N=332) evaluated rintatolimod, a synthetic derivative of inosinic acid with antiretroviral and immunomodulatory activities, in adults who met the Holmes case definition or both the Holmes and Fukuda case definitions.^{95,96} Both studies evaluated exercise-related outcomes as the primary outcome; the prevalence of post-exertional fatigue at baseline was not reported. Effects on fatigue severity were not directly measured in either trial.

In the first trial (N=92), patients with a mean baseline KPS score of 51 (scale of 0-100, range 20 to 60) were randomized to intravenous rintatolimod (200 mg twice weekly for 4 weeks, then 400 mg twice weekly for a total of 24 weeks) versus placebo.⁹⁵ Rintatolimod was associated with greater improvement from baseline to week 24 in exercise duration (10.3 minutes vs. 2.1 minutes; p=0.007), exercise work (11.8 Kcal vs. 5.8 Kcal; p=0.011), activities of daily living (ADL) (23.1 vs. 14.1; p=0.034), and KPS (20 vs. 0; p=0.023). In subgroup analysis, there was no difference based on presence of markers of human herpes virus-6 (HHV-6) virus reactivation at baseline (based on mononuclear cell evaluation). There were no serious adverse events or

withdrawals due to adverse events. Insomnia was reported more frequently in the placebo group, and dry skin in the rintatolimod group ($p < 0.05$ for both outcomes, data otherwise not reported).

A second trial ($N=240$) randomized patients with KPS scores of 40 to 60 (mean not reported) to rintatolimod 400 mg twice weekly for 40 weeks versus placebo.⁹⁶ Rintatolimod was associated with greater mean percentage change in exercise tolerance (based on treadmill testing duration) at week 40 versus placebo (37% vs. 15%; $p=0.047$). Although other function outcomes were measured, they were not compared between groups (and reported data were not adequate to evaluate differences). In the rintatolimod and placebo groups, the mean values at endpoint were: KPS: 55 versus 50 (0 to 100 scale), ADL: 72.4 versus 69.4 (higher values better, but scale range unclear), SF-36 vitality subscale: 10 versus 10, and SF-36 general health perception subscale: 20 versus 25 (both 0 to 100 scales). More participants in the treatment group reported decreased use of medications for relief of CFS symptoms (68% vs. 55%; $p=0.048$) Adverse events occurred more frequently with rintatolimod than placebo with infusion-related headache the most common adverse event (64% vs. 20%, $P < 0.01$). Other adverse events reported more often with rintatolimod were flu-like syndrome, chills, vasodilatation, and dyspnea ($p < 0.05$). Serious adverse events and withdrawals due to adverse events were not reported.

Immunoglobulin G versus placebo. Three moderate risk of bias trials ($N=197$) evaluated intravenous IgG (administered as a monthly infusion) versus placebo in patients with ME/CFS.^{99,100,102} Two trials enrolled adults (one using the Holmes case definition¹⁰⁰ and the other using the Fukuda case definition,⁹⁹ mean age 38 and 40 years, mean duration of ME/CFS 3.8 and 6.3 years) and one trial adolescents (Fukuda case definition, mean age 15 years, mean duration of ME/CFS 18 months).¹⁰² The duration of treatment ranged from 12 to 24 weeks and the specific product was Gammimune N® or Gammagard®. All three trials used a 1 gm/kg dose, with one study also evaluating a 0.5 gm/kg and a 2gm/kg dose. The timing of outcome assessment ranged from the end of treatment to 6 months following completion of therapy. Baseline fatigue was 18.8 on the POMS fatigue subscale (0 to 28) in the one trial;⁹⁹ fatigue was not a reported outcome and baseline fatigue not reported in the other trials.^{100,102} Regarding baseline function, one trial of adults reported mean SF-36 physical function score of 54 (0 to 100 scale),¹⁰⁰ and the other trial of adults reported a mean KPS score of 70 (0 to 100 scale).⁹⁹ The trial of adolescents used a non-validated measure of function, with a mean baseline score of 25%.¹⁰²

In the two trials of adults, there were no statistically significant differences between IgG (any dose) versus placebo in severity of functional impairment at any follow-up timepoint.^{99,100} One trial also found no effects on severity of fatigue or quality of life outcomes.⁹⁹

In the trial of adolescents, using an unvalidated 0 to 100% scale, there was no difference between groups in mean function at end of treatment (3 months; 49.9% vs. 44.6%, RR 1.1, 95% CI 0.84 to 1.45) or at three months after end of treatment (64.1% vs. 52.1%, mean difference -12.0, 95% CI -26.1 to 2.12).¹⁰² A subgroup analysis found no difference in effects based on the duration of ME/CFS symptoms. The proportion of patients with at least 25% improvement in function was not different between groups at end of treatment (3 months, 52% vs. 31%, RR 1.67, 95% CI 0.94 to 3.0), but was significantly greater with IgG at 3 months after end of treatment (72% vs. 44%, RR 1.64, 95% CI 1.07 to 2.5).

In adolescents, IgG infusion was associated with increased likelihood of severe headache versus placebo following first infusion (64% vs. 20% RR 3.14 95% CI 2.09 to 4.73) following first infusion; withdrawals due to adverse events or serious adverse events were not reported.¹⁰² In adults, the study of 1 gm/kg infusions found IgG associated with increased risk of severe

infusion-related headache (93% vs. 60%, RR 1.56, 95% CI 1.0 to 2.4).¹⁰⁰ Withdrawals due to adverse events (13% vs. 13%, RR 1.00, 95% CI 0.16 to 6.2) and serious adverse events (13% vs. 20%, RR 0.67, 95% CI 0.13 to 3.4) were not different between groups. The dose-ranging study of IgG in adults found similar incidence of “constitutional symptoms” including headache, fatigue, malaise, and concentration problems across IgG doses and placebo, with 71% versus 88% in the 1 gm/kg vs placebo groups (RR 0.81, 95% CI 0.62 to 1.06).⁹⁹ More withdrawals due to adverse events occurred in the IgG groups than placebo, but the estimate was very imprecise and not statistically significant (5.7% vs. 0%, RR 10.1, 95% CI 0.57 to 178.5).

Rituximab versus placebo. Two trials (N=181) evaluated the anti-CD20 monoclonal antibody rituximab, which results in depletion of B-lymphocytes, versus placebo infusions in adults who met the Fukuda case definition.⁸⁹ or the Canadian consensus criteria⁹⁰ The dosing in the earlier, medium risk of bias, pilot study was two infusions of 500 mg/m² or saline given two weeks apart with 12 months of follow-up,⁸⁹ while in the second, low risk of bias trial the same initial dosing was used, followed by fixed-dose infusions of 500 mg at 3, 6, 9, and 12 months.⁹⁰ Mean baseline fatigue was 8.0 on a self-rated 1 to 10 severity scale in the pilot study (based on scoring of fatigue, post-exertional exhaustion, need for rest, and daily functioning) and 59.6 on the Fatigue Severity Scale (range 9 to 63) in the subsequent study. Mean function at baseline in the second trial was 19 on a 0 to 100% scale, and 34 on the SF-36 Physical Function scale (range 0 to 100).⁹⁰ The pilot study reported on chronic fatigue symptoms at baseline, with a mean of 8.1 on a 1 to 10 self-assessed scale.⁸⁹

In the pilot study (N=30), the primary endpoint of CFS symptoms (Fatigue scores) at 3 months was not significantly different between groups when assessed by the patients (mean difference 0.00, 95% CI -0.31 to 0.31) or by a physician (mean difference 0.13, 95% CI -0.35 to 0.61);⁸⁹ however, a significant interaction was found for symptom scores based on an analysis of intervention and time (p=0.018). Overall response was defined as a fatigue score of ≥ 4.5 for at least six consecutive weeks, further categorized as major or moderate. A major response required some fatigue symptoms rated as having major improvement by the patient (6 points on a 0 to 6 scale). Rituximab was associated with increased likelihood of experiencing an overall response (67% vs. 13%, RR 5.0, 95% CI 1.31 to 19.1). Most of the patients with response met criteria for a major response (60% vs. 7%, RR 9.00, 95% CI 1.30 to 62.51). The mean response duration was 25 weeks (range 8 to >44) with rituximab and 41 weeks (range 34 to >48) with placebo. Function, as assessed by the SF-36 Physical health summary score was significantly improved in the rituximab group compared with the placebo group (mean maximum change 54% vs. 26%, mean difference 28%, 95% CI 1.8% to 54%). The SF-36 mental health component score was not significantly different between groups (mean maximum change 9% vs. 5%, mean difference 4%, 95% CI -38% to 29%). This study reported no withdrawals due to adverse events, or serious adverse events. Overall, there were similar numbers of patients reporting infusion-related adverse events (33% vs. 27%, RR 1.25, 95% CI 0.42 to 3.77).

The second, larger (N=151) RCT of rituximab, which added additional infusions every three months after the initial set of two infusions, did not find rituximab associated with increased likelihood of a response using a similar definition as the pilot study, but requiring 8 rather than 6 consecutive weeks of improvement (35% vs. 26%, mean difference 9.2%, 95% CI -5.5 to 23.3).⁹⁰ There was also no difference in mean fatigue scores over 24 months (mean difference 0.02, 95% CI -0.27 to 0.31) and no effect on secondary measures, including the SF-36 Physical Function score (mean difference -0.41, 95% CI -7.73 to 6.92), function level (0 to 100% scale, mean difference -0.21%, 95% CI -4.18% to 3.76%), the Fatigue Severity Scale (mean difference,

-0.25, 95% CI -2.44 to 1.95) or the number of steps per 24 hours (mean difference -177, 95% CI -1004 to 749). No patients withdrew due to adverse events, and 26% in the rituximab group versus 19% in the placebo group had serious adverse events (RR 1.37, 95% CI 0.75 to 2.5). Infusion-related adverse events were reported in 10% of rituximab patients and zero placebo patients (RR 26, 95% CI 1.57 to 429).

Anakinra versus placebo. One low risk of bias trial (N=50) compared anakinra, an interleukin-1 receptor antagonist (100 mg subcutaneously for 28 days) versus placebo in adults who met the Fukuda case definition.¹⁰¹ Baseline fatigue was 51 on the CIS fatigue subscale (range 8 to 56), and mean baseline functional impairment based on the Sickness Impact Profile was 1677 (0 to 5799 scale). There were no differences between anakinra versus placebo in SF-36 physical function, SIP functional impairment, and the CIS fatigue subscale at the end of treatment or at 24 weeks. There were also no differences between groups in psychological symptoms measured using the SCL-90 or pain measured on a visual analog scale.

Anakinra was associated with increased risk of any adverse event versus placebo (95% vs. 56%, RR 1.71 95% CI 1.20 to 2.45), with one patient discontinuing treatment in the anakinra group (4% vs. 0%, RR 3.00, 95% CI 0.13 to 70.30). There were no serious adverse events. Anakinra was also associated with increased likelihood of injection site reactions (68% vs 4%, RR 17.00 95% CI 2.44 to 118.20) and infections (24% vs. 16%, RR 1.50, 95% CI 0.48 to 4.78).

Alfa-2a Interferon versus placebo. One small (N=26), high risk of bias, crossover trial compared alfa-2a interferon (3 million units subcutaneously three times per week for 12 weeks) versus placebo in adults who met the Holmes case definition.⁹⁴ Quality of life was assessed using a 10-item clinical well-being scale addressing many symptoms found in ME/CFS patients (fatigue, fevers, sore throat, lymphadenopathy, muscle aches, headaches, joint pains, depression, concentration, and insomnia, range 0 to 60, with lower score representing greater well-being). The mean score at baseline was 35.7. After 12 weeks there was no significant difference between groups (31.4 vs. 28.4, mean difference 3.0, 95% CI -5.6 to 11). This study reported the results for interferon from both the initial and crossover phase (n=26), but only reported results from the initial phase for placebo (n=13). No other clinical outcomes were reported. A subgroup analysis found that patients with NK cell dysfunction (N=11) at baseline experienced improvement in quality of life with interferon (mean difference 23.4, 95% CI -35.3 to -11.5). However, this was a very small subgroup, with only 7 interferon patients and 3 placebo patients.

Although no serious adverse events were reported, 27% of interferon patients withdrew due to adverse events, compared with none in the placebo group (RR 9.00 95% CI 0.53 to 151.95). Adverse events in the interferon group included flu-like syndrome (27% vs. 0%, RR 9.00 95% CI 0.53 to 151.95) and diarrhea (13% vs. 0%, RR 5.00 95% CI 0.26 to 95.02).

Antidepressants

Four moderate risk of bias RCTs (N=285) evaluated antidepressants.^{56,71,98,105} Two trials evaluated the SSRI antidepressant 20 mg per day of fluoxetine,^{56,98} one evaluated the serotonin-norepinephrine reuptake inhibitor duloxetine at 120 mg per day,¹⁰⁵ and one evaluated the noradrenergic and specific serotonergic mirtazapine at 15 mg to 45 mg per day.⁷¹

Fluoxetine versus placebo. Two fluoxetine trials enrolled adults meeting the Oxford case definition for ME/CFS, but were too heterogeneous to combine.^{56,98} In one trial, 10% of patients had major depressive disorder (MDD) at baseline, with a mean HADS-depression scale score of 8.8 (0 to 21 scale) and mean fatigue severity score of 34 (14-item 0 to 42 Chalder scale).⁵⁶ After six months of treatment, there was no statistically significant difference between groups in

Chalder fatigue scores (-0.30, 95% CI -4.3 to 3.7) or functional work capacity (-1.1, 95% CI -3.7 to 1.5). There was also no difference between groups in depression severity (mean difference 0.40, 95% CI -1.23 to 2.03) on the 0 to 21 HADS-depression scale. In the second trial, randomization to eight weeks of fluoxetine or placebo was stratified by presence/absence of MDD, and mean baseline fatigue was 9.4 on the Subjective Daily Observed Fatigue Scale (0 to 16 scale).⁹⁸ Baseline function was not reported in either trial. Although randomization was stratified by presence of depression, main results were not stratified by depression status. However, graphical presentation of results stratified by depression status showed very similar findings. The difference between groups at eight weeks was not significant for fatigue (mean difference -0.16, 95% CI -0.64 to 0.31). While the effect on depression severity was statistically significant (mean difference -0.19, 95% CI -0.35 to -0.0 on the 0 to 63 Beck Depression Inventory), the difference was very small (less than 0.25 points).⁹⁸ More patients in the fluoxetine groups reported deterioration in CFS symptoms, but the differences were not statistically significant (patients with major depression 38% vs. 26%, RR 1.46, 95% CI 0.6 to 3.5 and patients without major depression 35% vs. 14%, RR 2.43, 95% CI 0.84 to 7.07).

In both trials, fluoxetine was associated with increased risk of withdrawal due to adverse events (13% vs. 4%, RR 3.93, 95% CI 0.87 to 17.64⁹⁸ and 15% vs. 3%, RR 4.37, 95% CI 1.02 to 18.78⁵⁶). One trial found fluoxetine associated with increased risk of tremor (67% vs. 40%, RR 1.57 95% CI 0.87 to 2.83), perspiration (40% vs. 26%, RR 1.70 95% CI 1.14 to 2.53), discontinuations due to skin reactions (6% vs. 2%, RR 2.94 95% CI 0.32 to 27.42), and headache (2% vs. 4%, RR 1.96 95% CI 0.18 to 21.01).⁹⁸ The other trial did not report specific adverse events.⁵⁶ Serious adverse events were not reported in either trial.

Duloxetine versus placebo. One trial (N=57) compared 12 weeks of duloxetine versus placebo in patients who met the Fukuda case definition.¹⁰⁵ Patients with major depression were excluded (mean HADS depression score 9.27 on a 0 to 21 scale). At baseline, the mean CDC Fukuda CFS case definition symptom score was 40 (0 to 152 scale) and mean SF-36 physical function score was 59.5 (0 to 100 scale). At 12 weeks, there was no difference in function based on the SF-36 physical function subscale score (mean difference -2.7, 95% CI -15.5 to 10.1) or other SF-36 subscales. Fatigue was also not significantly different between groups, based on the MFI general fatigue scale or subscales on physical fatigue, reduced activity, or reduced motivation subscales. The mental fatigue subscale showed more change in the duloxetine group, but the difference was very small (-0.1, 95% CI, -0.3 to 0.0 on a 4 to 20 scale). There was no significant difference in improvement in the CDC Symptom Inventory overall or for CFS symptoms (mean difference -1.5, 95% CI -9.9 to 6.9). There were also no significant differences between groups in depression or anxiety (mean difference -0.9, 95% CI -2.4 to 0.6 on the HADS anxiety scale and 0.94, 95% CI 0.72 to 1.23 on the HADS depression scale). Patient assessments of improvement in disease severity were greater with duloxetine (-1.1 vs. -0.4, p=0.06, 1 to 7 scale). Duloxetine was associated with decreased pain severity (mean difference -0.73, 95% CI -1.00 to -0.54 on the 0 to 10 BPI pain intensity scale) and pain interference (mean difference -0.70, 95% CI -0.96 to -0.51 on the 0 to 10 BPI pain interference scale).

Duloxetine was also associated with increased risk of withdrawal due to adverse events versus placebo (10% vs. 0%, RR 7.00 95% CI 0.38 to 129.93).¹⁰⁵ One patient assigned to duloxetine had suicidal ideation; no other serious adverse events were reported. Duloxetine was associated with increased likelihood of dry mouth (21% vs. 3.3%, RR 6.21, 95% CI 0.80 to 48.4).

Mirtazapine versus placebo. One trial (N=49) compared mirtazapine versus placebo in patients who met the Oxford or Fukuda case definitions (results for CBT arm reported in the CBT section). It did not report the proportion of patients with major depression; the mean HADS depression score at baseline was 14.51 (0 to 21 scale).⁷¹ At baseline, the mean Fatigue score was 24.97 on a 0 to 100 scale, and a mean score of 28.94 on the SF-36 Physical Function scale (0 to 100). After 12 weeks, there were no differences between mirtazapine and placebo in fatigue severity (mean difference 1.00, 95% CI -2.10 to 4.1) or depression severity (mean difference 1.2, 95% CI -2.7 to 5.1). Effects on function were not reported.

Mirtazapine was associated with increased risk of any adverse event versus placebo (100% vs. 45%, RR 2.18, 95% CI 1.41 to 3.37). Sedation was the most common adverse event in patients randomized to mirtazapine (proportion not reported in placebo group). Withdrawal due to adverse events and serious adverse events were not reported.

Corticosteroids versus placebo. Two moderate risk of bias trials evaluated corticosteroids versus placebo in adults meeting the Fukuda case definition.^{91,106} One parallel group trial (N=70) compared oral hydrocortisone (20-30 mg am and 5 mg pm for 12 weeks) versus placebo⁹¹ and one crossover trial (N=100) compared hydrocortisone (5 mg/day) plus 9-alpha fludrocortisone (50 µg/day) for 12 weeks versus placebo.¹⁰⁶ Neither trial reported statistically significant differences between corticosteroids versus placebo in fatigue or function. In the hydrocortisone (only) trial, the mean difference between groups in change in score on a 10-point activity scale was -0.4 (p=0.32), and -1.9 on the POMS Fatigue subscale (range 0 to 28, p=0.21).⁹¹ The trial of hydrocortisone/fludrocortisone also did not find a significant difference in fatigue (mean difference on a 0 to 100 visual analogue scale [VAS] 0.1, 95% CI -0.3 to 0.6 and Abbreviated Fatigue Questionnaire -1, 95% CI -2 to 1, 7-point scale) or on the SF-36 Physical Component Summary scale (mean difference -1.3, 95% CI -4.7 to 2.1, 0 to 100 scale).¹⁰⁶ There was no correlation between cortisol levels at baseline or during treatment or follow-up and the primary outcome of Global Wellness.⁹¹

In the hydrocortisone/fludrocortisone trial, one patient withdrew from the steroid arm due to acne and weight gain.¹⁰⁶ Stimulated cortisol was significantly suppressed with treatment compared with placebo (mean difference 127 nmol/L, 95% CI 81 to 171). Adverse events were not otherwise reported. In the hydrocortisone trial, the steroid group had increased incidence of suppression of adrenal glucocorticoid responsiveness (34% vs. 0%, RR 1.00, 95% CI 1.54 to 406.5); increased appetite (49% vs. 23%, RR 2.12, 95% CI 1.06 to 4.27), weight gain (54% vs. 23%, RR 2.38, 95% CI 1.21 to 4.69); and difficulty sleeping (49% vs. 23%; RR 2.12, 95% CI 1.06 to 4.27).⁹¹

Other Drugs

Valganciclovir versus placebo. One moderate risk of bias trial (N=30) evaluated the antiviral medication valganciclovir in patients with suspected viral onset of ME/CFS, based on history and presence of elevated HHV-6 or Epstein-Barr Virus antibody titers.⁹³ Patients met the Fukuda case definition for ME/CFS. Patients were randomized to oral valganciclovir (900 mg twice daily for 21 days, then 900 mg once daily for a total of 6 months) versus placebo, with final outcomes measured at 9 months. Baseline fatigue was 78.6 on the Multidimensional Fatigue Inventory 20-item (MFI-20, 20 to 100 scale). Function was not reported. Valganciclovir was associated with decreased fatigue severity versus placebo based on the Fatigue Severity Scale (mean difference -0.06 vs. 0.02, p=0.006 for interaction of time and study arm); however, the difference was small (<0.1 point on a 9 to 63 scale). No statistically significant differences were found between

valganciclovir and placebo on the MFI-20 total score (-0.88 vs. 0.29, $p=0.11$), MFI-20 mental fatigue subscale (-0.27 vs. -0.05, $p=0.05$), the CDC Symptom Inventory total scores (-2.63 vs. -2.69 on a 0 to 304 scale, range 0 to 304, $p=0.96$), the sleep assessment questionnaire (-0.17 vs. -0.14 on a 0 to 68 scale, $p=0.86$), and HADS depression (typical: 0.01 versus -0.14, $p=0.66$ and atypical: 0.07 vs. 0.04, $p=0.54$). Valganciclovir was associated with greater improvement in self-reported cognitive functioning (1.72 vs. 0.59, $p=0.02$), but not self-reported physical functioning (1.02 vs. 0.46, range 1% to 100%, $p=0.22$). The study evaluated the effects of treatment on monocyte counts but did not evaluate whether there was a subgroup effect according to baseline levels.

Valganciclovir was not discontinued due to hematologic or hepatic adverse events. There were two serious adverse events (cancer diagnosis) in the valganciclovir group that were deemed unrelated to the medication..

Galantamine versus placebo. One moderate risk of bias trial ($N=423$) evaluated galantamine (an acetyl-cholinesterase inhibitor) at various doses (7.5, 15, 22.5, or 30 mg/day for 16 weeks) versus placebo in patients who met the Fukuda case definition.¹⁰³ It was the largest of the medication trials. Baseline function was 13.5 on the Fibromyalgia Impact Questionnaire-Physical scale (0 to 10 scale); baseline fatigue was not reported. The primary outcome was response, defined as a score of zero or one (very much or much improved) on the Clinical Global Impression scale, with a clinically important difference defined as at least a 25% improvement. There were no differences between galantamine versus placebo in likelihood of a response (35% to 45% for galantamine at various doses, vs. 30% for placebo, $p>0.05$ for each galantamine dose vs. placebo). The study also reported no statistically significant differences between groups on other outcomes. The change from baseline on the Chalder fatigue 14-item scale physical subscale ranged from 8.77 to 11.02 with galantamine and was 9.86 with placebo; for the mental subscale the change from baseline ranged from 5.80 to 7.74 with galantamine and was 6.80 for placebo. There were also no differences in quality of life measured by the Nottingham Health profile or sleep quality based on the Pittsburgh Sleep Quality Index.

The likelihood of withdrawal due to adverse events was similar between the lowest dose galantamine (7.5 mg/d) and placebo (14% vs. 15%), but higher in the other doses of galantamine (23%, 24%, 26%). Serious adverse events were reported in 8 of 352 (2.3%) patients assigned to galantamine (any dose), with none in the placebo group. The most common adverse events were nausea, headache, and symptoms of depression in both galantamine and placebo groups. One patient committed suicide (galantamine 10 mg/day), and three others had suicidal ideation (1 each in the galantamine 7.5 mg, 22.5 mg and placebo groups).

Clonidine versus placebo. One low risk of bias trial ($N=120$) evaluated clonidine (25 or 50 mcg based on body weight) versus placebo in adolescents (mean age 15 years) who met the Fukuda case definition.⁹⁷ Baseline fatigue was 19.2 on the 11-item 0 to 33 Chalder scale, and baseline function was 24 on the Functional Disability Inventory scale (0 to 60 scale). There were no significant differences between clonidine versus placebo in fatigue, function, CFS hypersensitivity symptoms, insomnia or pain after 8 weeks of treatment or at 30 weeks of follow-up. The mean differences at these time points on the Chalder fatigue 11-item scale (0 to 44) were 1.7, 95% CI -2.3 to 5.6 and 0.5, 95% CI -14.7 to 15.7. The mean differences on the Functional Disability Inventory (0 to 60) scale were 0.2, 95% CI -10.3 to 10.8 and 0.2, 95% CI -13.3 to 13.6. The mean differences on the CFS symptom inventory hypersensitivity subscale score (0 to 10) were 0.1, 95% CI -0.2 to 0.5 and -0.03, 95% CI -0.4 to 0.3. The mean differences on the Karolinska Sleep Questionnaire insomnia subscale (range 1 to 6) were 0.1, 95% CI -0.4 to 0.2

and 0.1, 95% CI -0.3 to 0.4. The mean differences on the BPI (range 0 to 10) were 0.5, 95% CI -0.16 to 1.16 and 0.4, 95% CI -0.4 to 1.1. There was also no significant difference in the primary outcome of change in number of steps per day (51 vs. -560, mean difference at 8 weeks (-637, 95% CI -1328 to 53) and (119, 95% CI -796 to 1035) at 30 weeks of follow-up.

The trial did not report withdrawal due to adverse event or serious adverse events. There was no statistically significant difference in risk of any adverse event (75% vs. 65%, RR 1.30, 95% CI 0.99 to 1.72). Clonidine was associated with increased likelihood of dizziness (28% vs. 10%, RR 3.2, 95% CI 1.25 to 8.18).

Methylphenidate versus placebo. One moderate risk of bias trial (N=128) evaluated the stimulant methylphenidate (20 mg/day) given with a nutritional supplement designed to improve mitochondrial function (consisting of amino acids, vitamins, and other supplements) versus placebo.¹⁰⁴ Baseline fatigue severity was 112 on the 20 to 140 CIS total scorescale; baseline function was not reported. At 12 weeks, there was no significant difference between methylphenidate versus placebo in fatigue severity. Pre-planned subgroup analyses evaluated patients with more severe ME/CFS symptoms and those taking analgesics at baseline. While both subgroups showed larger effects than the overall group, there were no statistically significant subgroup effects. Methylphenidate plus nutritional supplement was associated with increased likelihood of withdrawal due to adverse events (13% vs. 5%, RR 2.83, 95% CI 0.79 to 10.21) and dizziness (7% vs. <2%, RR 4.18, 95% CI 0.48 to 36.47).

Subgroup effects

The ability to evaluate how effects of medications vary in subgroups was limited. The trials did not report subgroup analyses based on factors such as age, sex, race/ethnicity, and ME/CFS severity or type of onset. Most trials used the Fukuda or Holmes CDC case definitions for ME/CFS and there were too few trials of each medication to perform reliable cross-trial comparisons. A trial of alfa-interferon (rated high risk of bias) evaluated the subgroup effects related to baseline NK cell dysfunction, but the trial and subgroups had very small samples and no statistical test for subgroup effects was performed.⁹⁴ A trial of rintatolimod found no subgroup effect based on presence of markers of HHV-6 reactivation at baseline.⁹⁵ Among trials of IgG,^{99,100,102} one trial of adolescents found an effect on function,¹⁰² but two trials in adults did not. The small number of trials and heterogeneity (e.g., dosing and duration, type of IgG used eligibility criteria and outcome measures) precludes meaningful conclusions about differences in effects based on age. The trial in adolescents performed a stratified analysis based on the duration of ME/CFS symptoms and found no subgroup effect.¹⁰² One trial of corticosteroids found no correlation between cortisol levels at baseline and the primary outcome of Global Wellness.⁹¹

Complementary and alternative therapies

Dietary interventions, herbal supplements, or homeopathy

Nine trials evaluated dietary interventions, herbal supplements or homeopathy in adult patients with ME/CFS (**Tables 18 and 19, Evidence Table Appendix E2**). Sample sizes ranged from 14 to 268 (total N=739). Five trials evaluated various dietary changes or supplements. Three¹⁰⁷⁻¹⁰⁹ trials compared dietary supplements versus placebo, and two trials compared one dietary supplement versus another (one of the trials also evaluated the combination of supplements). Four trials evaluated homeopathy or herbal supplements. One trial¹¹⁰ compared

melatonin supplements versus phototherapy, one trial¹¹¹ compared pollen versus placebo, one compared dengzhanshengmai herbal supplement versus placebo when used with an SSRI, and one compared¹¹² homeopathy versus placebo. Six trials were included in the prior report.¹⁰⁹⁻¹¹⁴ No trials were conducted in the United States, eight trials in Europe, and one trial in China. The mean age of participants ranged from 35 to 50 years in all but one trial of older patients (mean age 76.2 years) and the proportion female ranged from 49 percent to 100 percent. The case definition for ME/CFS was the Oxford criteria in two trials and the Fukuda criteria in 6 trials, and the Fukuda criteria or Holmes⁸ criteria in one trial. The duration of ME/CFS ranged from 14.5 months to 6 years in four trials that reported this information. Baseline fatigue was measured using a variety of scales (**Table 18**). Details regarding the presence of post-exertional fatigue and activity patterns were lacking.

No trial was rated low risk of bias, four trials were rated medium risk of bias^{107,109,112,114} and five trials^{108,110,111,113,115} were rated high risk of bias (**Risk of Bias Table Appendix F**). Methodological limitations included failure to report attrition, inadequate description of randomization or allocation concealment methods, and failure to blind or unclear blinding status of outcomes assessors and data analysts.

Table 18. RCTs of dietary interventions, herbal supplements, or homeopathy: Study Characteristics

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Hobday, 2008 ¹¹³ United Kingdom High	n: 39 Age: 44 vs. 42 % Female: 88 vs. 78	Criteria: Fukuda Duration: Not reported	Fatigue scale: Chalder Fatigue Scale 14-item (0 to 56) Baseline fatigue: 23.0 vs. 22.0	Baseline depression: HADS depression (0 to 21): 8.1 vs. 7.0 Baseline function: SF-36 physical function (0 to100): 34.6 vs. 38.7	A: Low sugar/low yeast B: Healthy eating Frequency: Daily Duration of treatment: 24 weeks Duration of follow-up: End of treatment
Li, 2015 ¹¹⁵ China High	n: 268 (unclear if 45 dropouts included in analyses) Age: 35.1 vs. 36.8 % Female: 59	Criteria: Fukuda Duration, months: 15.7 vs. 14.5	Fatigue scale: MFI- 20 general fatigue subscale (4 to 20) Baseline fatigue: 10.7 vs. 10.2	Baseline depression: not reported Baseline function: not reported	A: Dengzhanshengmai herbal supplement 1.08g + SSRI, Seroxat 10 to 30 mg or Zoloft 25 to 100mg B: SSRI, Seroxat 10 to 30 mg or Zoloft 25 to 100mg Frequency: Daily Duration of treatment: 12 weeks Duration of follow-up: End of treatment
Malaguarnera, 2008 ¹⁰⁷ Italy Medium	n: 96 Age: 76.2 vs. 78.4 % Female: 49	Criteria: Fukuda or Holmes (CDC, 1998) Duration: Not reported	Fatigue scale: Fatigue Severity Scale 9 to 63) and Wessely and Powell Scales (8- item physical, 5- item mental, maximum score 26) Baseline fatigue: Fatigue Severity Scale (9 to 63), mean: 50.4 vs. 50.1 Wessely and Powell Scales: 13.4 vs. 13.1	Baseline depression: not reported Baseline function: PF-10 (0 to 100): 69.8 vs. 70.2	A: Acetyl L-carnitine 2 g B: Placebo Frequency: twice daily Duration of treatment: 180 days Duration of follow-up: End of treatment

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Ockerman, 2000 ¹¹¹ Sweden High	n: 43 Age: 50 % Female: 86	Criteria: Fukuda Duration: Not reported	Fatigue scale: Unclear which scale was used, higher score indicates worse outcome Baseline fatigue: 7.95 vs. 7.32 (this includes participants at the start of each 3- month phase)	Baseline depression: unclear scale: 5.9 vs. 6.7 Baseline function: not reported	A: Pollen extract (Polbax), 7 tablets B: Placebo Frequency: Daily for 3 months, then crossover to other arm Crossover design: Pollen/Placebo, n=5 Placebo/Pollen, n=5 Pollen/Pollen, n=6 Placebo/Placebo, n=6 Duration of treatment: 3 months Duration of follow-up: End of treatment
Ostojic, 2016 ¹⁰⁸ Serbia High	n: 14 Age: 39.3 % Female: 100	Criteria: Fukuda Duration: not reported	Fatigue scale: MFI- 20 general fatigue subscale (4 to 20) Baseline mean: 12.1	Baseline depression: not reported Baseline function: not reported	A: Guanidinoacetic acid supplement, 2.4 grams B: Placebo, cellulose Frequency: Daily Duration of treatment: 3 months, Duration of follow-up: End of first treatment period; 3 months after randomization
The, 2007 ¹⁰⁹ The Netherlands Medium	n: 57 Age: 40.9 vs. 43.4 % Female: 77 vs. 59	Criteria: Fukuda Duration: not reported	Fatigue scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) Baseline fatigue: 46.5 (7.4) vs. 46.2 (7.9)	Baseline depression: not reported Baseline function: Sickness Impact Profile (SIP-8) (0 to 5,799): 1484 vs. 1317	A: Aclydine supplement, declining dose from 1000mg/day to 250mg/2 days + amino acid supplement B: Placebo aclydine + placebo amino acid supplement Frequency: Daily decreasing to every other day Duration of treatment: 14 weeks Duration of follow-up: End of treatment
Vermeulen, 2004 ¹¹⁴ The Netherlands Medium	n: 89 Age: 42 vs. 37 vs. 38 % Female: 76	Criteria: Fukuda Duration, years: 6.0 vs. 5.5 vs. 3.0	Fatigue Scale: MFI-20 general fatigue subscale (4 to 20) Baseline: 19.0 vs. 17.6 vs. 18.0	Baseline depression: not reported Baseline function: not reported	A: Acetyl-L-carnitine 2g + Propionyl-L-carnitine 2g B: Acetyl-L-carnitine 2g C: Propionyl-L-carnitine 2g Frequency: Daily Duration of treatment: 24 weeks Duration of follow-up: 2 weeks after end of treatment

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Weatherley-Jones, 2004 ¹¹² United Kingdom Medium	n: 103 Age: 38.9 vs. 38.8 % Female: 57 vs. 62	Criteria: Oxford Duration, years: 4.8 vs. 3.7	Fatigue scale: MFI-20 (20 to 100) Baseline fatigue: MFI-20 general fatigue subscale (4 to 20): 18.4 vs. 18.1	Baseline depression: not reported Baseline function: Functional Limitations Profile physical dimension: 20.4 vs. 22.1 Functional Limitations Profile psychosocial dimension: 35.1 vs. 36.3	A: Homeopathy B: Placebo Frequency: Monthly visits to homeopath, treatments varied Duration of treatment: 6 months Duration of follow-up: 1 month after end of treatment; 7 months after randomization
Williams, 2002 ¹¹⁰ United Kingdom Medium	n: 30 Age: 44.5 % Female: 57	Criteria: Oxford Duration, years: 3.6	VAS (0 to 10): 7.1 vs. 6.6 Mental Fatigue Inventory (0 to 36): 25 vs. 24	Baseline depression: HADS depression (0 to 21): 11 vs. 9 Baseline function: SF-36 physical function (0 to 100): 25 vs. 42.2	A: Melatonin 5mg B: Phototherapy with 2500 Lux Lightbox for 30 minutes in the morning Frequency: Daily Duration of treatment: 60 weeks: 12 weeks placebo, 12 weeks treatment, 12-week washout or placebo, then 12-week crossover and 12-week washout or placebo Duration of follow-up: End of treatment

Abbreviations: CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; HADS-D = Hospital Anxiety and Depression Scale-depression; ME = myalgic encephalomyelitis; MFI-20 = Multidimensional Fatigue Inventory 20-item; RCT = randomized controlled trial; SF-36 = 36-item Short Form Health Survey; SIP-8 = Sickness Impact Profile; SSRI = selective serotonin reuptake inhibitor; VAS = visual analogue scale

Table 19. RCTs of dietary interventions, herbal supplements, or homeopathy: Study Results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Hobday, 2008 ¹¹³ Fukuda	A: Low sugar/low yeast (19) B: Healthy eating (20) Duration of treatment: 24 weeks Duration of follow-up: End of treatment	Chalder Fatigue Scale 14-item (0 to 56)mean (SD): 16.0 (8.2) vs. 17.7 (10.0); p=0.6	HADS depression (0 to 21), mean (SD): 6.5 (3.6) vs. 5.4 (3.7); p=0.33	SF-36 physical function (0 to 100), mean: 42.3 (29.2) vs. 52.2 (24.1); p=0.25 SF-36 social functioning subscale, mean: 42.0 (29.3) vs. 50.6 (29.4), p=0.35
Li, 2015 ¹¹⁵ Fukuda	A: Dengzhanshengmai herbal supplement + SSRI (134) B: SSRI alone (134) Duration of treatment: 12 weeks Duration of follow-up: End of treatment	MFI-20 general fatigue subscale (4 to 20), mean improvement: Improvement from week 2 to end of treatment General Fatigue: 1.3 (0.7) vs. 0.8 (0.6), p<0.01 Physical Fatigue: 1.0 (0.4) vs. 0.6 (0.3), p<0.01 Reduced Activity: 1.3 (0.6) vs. 1.0 (0.5), p<0.01 Improvement from week 8 to end of treatment Reduced Motivation: 2.4 (1.0) vs. 2.1 (0.8), p<0.01 No improvement Mental Fatigue: data not shown, p>0.05	No significant differences, data not shown	Not reported
Malaguarnera, 2008 ¹⁰⁷ Fukuda or Holmes	A: Acetyl L-carnitine 2 g (48) B: Placebo (48) Duration of treatment: 180 days Duration of follow-up: End of treatment	Fatigue Severity Scale 9-item (1 to 7), mean (SD): 27.9 (9.7) vs. 48.9 (6.9), p=0.000 Physical Fatigue: Wessely and Powell Scales(8-item physical, 5-item mental, maximum score 26): 6.4 (2.2) vs. 12.6 (2.4), p=0.000	Not reported	Physical function: PF-10 (0 to 100), mean (SD): 86.9 (17.40 vs. 70.8 (19.1), p=0.000
Ockerman, 2000 ¹¹¹ Fukuda	A: Pollen extract (Polbax) (21) B: Placebo (22) Duration of treatment: 3 months Duration of follow-up: End of treatment	Fatigue, Mean score (Likert scale 0=no problem to 10=extremely serious symptom) 7.52 vs. 7.14; p=NR	Mean depression score (Likert scale 0=no problem to 10=extremely serious symptom) 5.16 vs. 6.60; p=NR	Not reported

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Ostojic, 2016 ¹⁰⁸ Fukuda	A: Guanidinoacetic acid supplement (not reported) B: Placebo, cellulose (not reported) Duration of treatment: 3 months, Duration of follow-up: End of first treatment period; 3 months after randomization	Fatigue scale: MFI-20 (20 to 100) General fatigue subscale (4 to 20): 11.6 (1.3) vs. 11.8 (1.5), p=0.44 Physical fatigue subscale (4 to 20): 11.7 (1.2) vs. 11.6 (1.4), p=0.99 Reduced activity subscale (4 to 20): 13.9 (1.2) vs. 11.7 (1.8), p=0.00 Reduced motivation subscale (4 to 20): 13.1 (1.9) vs. 15.0 (1.8), p=0.03 Mental fatigue subscale (4 to 20): 12.2 (1.7) vs. 14.0 (0.9), p=0.01	Not reported	Not reported
The, 2007 ¹⁰⁹ Fukuda	A: Acelydine + amino acid supplements (30) B: Placebo (27) Duration of treatment: 14 weeks Duration of follow-up: End of treatment	Fatigue scale: Checklist Individual Strength, fatigue severity subscale (8 to 56) 14 weeks: 42.4 (11.6) vs. 43.0 (12.6); p=0.70	Not reported	14 weeks: 1,228.1 (619.7) vs. 1,120.2 (543.0); p=0.65
Vermeulen, 2004 ¹¹⁴ Fukuda	A: Acetyl-L-carnitine + Propionyl-L-carnitine (30) B: Acetyl-L-carnitine (29) C: Propionyl-L-carnitine (30) Duration of treatment: 24 weeks Duration of follow-up: 2 weeks after end of treatment	General fatigue at 24 weeks; MFI-20 general fatigue subscale (4 to 20): 17.3 (3.3) vs. 15.9 (4.2) vs. 16.5 (3.1); p=0.004 for propionyl-L-carnitine change from baseline; p=0.000 for combination change from baseline Physical fatigue subscale (4 to 20) at 24 weeks: 16.5 (3.4) vs. 15.7 (4.4) vs. 16.4 (3.2), not significant Mental fatigue subscale (4 to 20) at 24 weeks: 14.6 (4.0) vs. 15.1 (3.6) vs. 13.9 (3.5); p=0.015 for acetyl-L-carnitine change from baseline	Not reported	Not reported

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Weatherley-Jones, 2004 ¹¹² Oxford	A: Homeopathy (50) B: Placebo (53) Duration of treatment: 6 months Duration of follow-up: 1 month after end of treatment; 7 months after randomization	MFI-20 (20 to 100) : General fatigue subscale (4 to 20), mean change (SD): 2.70 (3.93) vs. 1.35 (2.66), p=0.04 Physical fatigue subscale (4 to 20), mean change (SD): 2.13 (4.00) vs. 1.28 (2.74), p=0.21 Mental fatigue subscale (4 to 20), mean change (SD): 2.70 (4.01) vs. 2.05 (86), p= Reduced activity subscale (4 to 20), mean change (SD): 2.72 (4.47) vs. 1.81 (2.82), p=0.16 Reduced motivation subscale (4 to 20), mean change (SD): 1.35 (4.15) vs. 1.65 (3.02), p=0.82 Fatigue Impact Scale, mean change (SD): 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	Not reported	Functional Limitations Profile, mean change (SD): 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, 2002 ¹¹⁰ Oxford	A: Melatonin 5mg (42) B: Phototherapy with 2500 Lux Lightbox for 30 minutes in the morning (42) All 30 patients received both treatments, in two possible orders. Duration of treatment: 60 weeks: 12 weeks placebo, 12 weeks treatment, 12-week washout or placebo, then 12-week crossover and 12-week washout or placebo Duration of follow-up: End of treatment	Median (IQR) VAS score for How fatigued are you? (1 to 10 scale, lower score indicates better health) After treatment: 6.1 (4.8 to 8.0) vs. 7.2 (5.5 to 8.3); p=NS Median (IQR) Mental Fatigue Inventory (0 to 36) After treatment: 23 (15.0 to 27.0) vs. 24 (21.0 to 29.0); p=NS	HADS depression (0 to 21): 10 (7.7 to 11.2) vs. 10 (6.0 to 14.0), p= NS	Overall Function: Median (IQR) SF-36 physical function (0 to100) After treatment: 42.5 (16.3 to 53.8) vs. 45 (22.5 to 60.0); p=NS

Abbreviations: CFS = chronic fatigue syndrome; HADS = Hospital Anxiety and Depression Scale; HADS-D = Hospital Anxiety and Depression Scale-depression; IQR = interquartile range; ME = myalgic encephalomyelitis; MFI-20 = Multidimensional

Dietary Supplements versus Placebo

One medium risk of bias trial¹⁰⁷ (N=96) compared acetyl L-carnitine (2 grams twice per day) versus placebo in older (age >70 years) patients with CFS. Carnitines are amino acid compounds that have a role in metabolism and have been promoted for cognitive benefits. All patients met either the Fukuda or Holmes⁸ criteria; in addition, all patients were positive on the Fukuda minor criterion of prolonged post-exercise fatigue. Patients were evaluated at the end of six months of therapy. Acetyl L-carnitine was associated with decreased fatigue severity (mean difference -21.00, 95% CI -24.41 to 17.59 on the 9 to 63 Fatigue Severity Scale), decreased functional limitations (mean difference 16.10, 95% CI 8.70 to 23.50 on the 0 to 100 Physical Function functional limitations scale), and improved cognitive status (mean difference 2.70, 95% CI 1.48 to 3.92 on the 0 to 30 Mini-Mental Status Examination). There was no difference between acetyl L-carnitine versus placebo in severity of disability (mean difference -0.60, 95% CI -8.36 to 7.16 on the 0 to 100 Physical Function disability scale). On individual CFS case definition criteria, acetyl L-carnitine was associated with decreased likelihood of prolonged post-exercise fatigue (48% vs. 96%, RR 0.50, 95% CI 0.37 to 0.68), activity reduction >50% (56% vs. 75%, RR 0.75, 95% CI 0.56 to 1.01), muscle pain (67% vs. 90%, RR 0.74, 95% CI 0.60 to 0.93), and sleep disorder (62% vs. 84%, RR 0.75, 95% CI 0.58 to 0.97), with no statistically significant differences in likelihood of painful throat, painful lymph nodes, neuropsychiatric complaints, spreading arthralgias, or headaches. The trial reported no adverse events or laboratory abnormalities in either group.

One small (N=14)¹⁰⁸ high risk of bias crossover trial evaluated guanidinoacetic acid (GAA, 2.4 g/day) versus placebo in women meeting the Fukuda case definition for CFS. GAA naturally occurs in the body as an immediate precursor of creatine. At the end of three months of therapy, GAA was associated with improved scores on the reduced activity (mean difference -2.2, $p<0.005$), reduced motivation (mean difference -1.9, $p=0.03$), and mental fatigue (mean difference -1.8, $p=0.01$) subscales of the MFI-20 (each on a 4 to 20 scale), but no difference on the general fatigue (mean difference -0.2, $p=0.44$) or physical fatigue (mean difference 0.1, $p=0.99$) subscales. There were no differences in musculoskeletal soreness at rest (mean difference -0.2 on a 0 to 10 VAS, $p=0.31$) or during activity (mean difference -0.6 on a 0 to 10 VAS, $p=0.18$). GAA was also associated with better scores on the SF-36 physical (mean difference 2.4, $p=0.04$) and mental (mean difference 5.3, $p<0.005$) component summary scores (both on a 0 to 100 scale, higher scores indicating higher quality of life). The trial reported no harms in either group.

One medium risk of bias trial¹⁰⁹ (N=57) comparing the dietary supplement aclydine plus amino acids versus placebo in patients meeting the Fukuda case definition. Aclydine has been claimed to increase insulin-like growth factor 1 concentrations by stimulating growth hormone releasing hormone. At the end of 14 weeks of treatment, there were no differences between aclydine plus amino acids versus placebo in fatigue severity (mean difference in change from baseline 1.1, 95% CI -4.4 to 6.5 on the 8 to 56 Checklist Individual Strength fatigue subscale, $p=0.70$), functional impairment (mean difference in change from baseline 59.1, 95% CI -201.7 to 319.8 on the 0 to 5,799 Sickness Impact Profile-8 scale) or activity level (mean difference in change from baseline 4.1, 95% CI -5.9 to 14.0 measured with an actometer). No “important” (not defined) side effects were reported in either group.

Head-to-head comparisons of dietary interventions

One medium risk of bias, open-label trial¹¹⁴ (N=89) compared dietary supplementation with acetyl L-carnitine (2 grams/day) versus propionyl L-carnitine (2 grams/day) versus both in patients meeting the Fukuda case definition. Acetyl L-carnitine and propionyl L-carnitine are supplements believed to promote mitochondrial energy and decrease oxidative stress. At the end of 24 weeks of treatment, the acetyl L-carnitine and propionyl L-carnitine groups were both associated with higher likelihood of improvement (based on Global Impression of Change score ≥ 2 on a -3 to +3 scale) than the combination (59% vs. 63% vs. 37%). However, at 2-week post-intervention follow-up, no patient met criteria for improvement in any group. There were no differences between groups in severity general, physical, or mental fatigue assessed with the MFI-20. Harms were not reported.

One small (N=39), high risk of bias, trial¹¹³ randomized patients meeting the Fukuda case definition to either a low sugar low yeast diet or a healthy eating diet for 24 weeks. Full compliance occurred in only 24% of patients assigned to the low sugar low yeast diet and 67% of those assigned to healthy diet. At the end of the intervention, there were no differences between dietary interventions in fatigue severity (mean difference -1.7, 95% CI -7.5 to 4.1 on the 14-item, 0 to 42 Chalder scale), depression severity (mean difference 1.1, 95% CI -1.2 to 3.5 on the 0 to 21 HADS depression scale), or anxiety severity (mean difference 1.2, 95% CI -1.8 to 4.2 on the 0 to 21 HADS anxiety scale). Differences in the 8 SF-36 subscales ranged from -15.1 (body pain) to 2.9 (mental health); however, none of the differences were statistically significant. The trial did not report harms.

Homeopathy or herbal supplements versus placebo

One medium risk of bias trial¹¹² (n=103) compared homeopathy for 6 months versus placebo in patients meeting the Oxford criteria for CFS. Homeopathic remedies were individualized by the pharmacy for each patient. Fatigue was measured using the MFI-20 (score on each subscale 4 to 20). Homeopathy was associated with greater improvement from baseline versus placebo on the general fatigue subscale (-2.70 vs. -1.35, $p=0.04$), but differences in the physical fatigue, mental fatigue, activity, and motivation subscales were not statistically significant (differences ranged from -0.91 [reduced activity subscale] to 0.30 [reduced motivation subscale]). There were also no differences between homeopathy versus placebo in the likelihood of ≥ 3 -point improvement in any MFI-20 subscale or the likelihood of ≥ 3 -point improvement in all MFI-20 subscales. The trial did not report harms.

A small (N=43), high risk of bias¹¹¹ crossover trial compared of pollen extract (Polbax) versus placebo in adults meeting the Fukuda case definition. The pollen extract is believed to have an antioxidative effect. At the end of 3 months of treatment, there were no differences between pollen extract versus placebo in total well-being, fatigue, fatigability, sleep problems, depression, or intestinal problems. The trial reported no clear side effects except for slight gastrointestinal complaints in 1 or 2 patients.

Other comparisons involving herbal supplements

One high risk of bias, open label trial¹¹⁵ (N=268) compared the Chinese herbal supplement Dengzhanshengmai (1.08 grams/day) plus an SSRI (paroxetine 10 to 30 mg/day or sertraline 25 to 100 mg/day) versus an SSRI alone for 12 weeks in patients meeting the Fukuda case definition. Results were reported poorly in this trial. At 12 weeks, Dengzhanshengmai plus SSRI was associated with greater change from baseline in the MFI-20 general fatigue, reduced

activity, physical fatigue, and reduced motivation subscales versus SSRI alone ($p < 0.05$ for general fatigue and $p < 0.01$ for the other subscales), but the effects were small (~0.5 on each subscale, each on a 4 to 20 scale). There was no difference in the MRI mental fatigue subscale. There were no differences between Dengzhanshengmai plus SSRI versus an SSRI alone in severity of depression or anxiety (measured using the HADS scales). Rates of any adverse event (41.0% vs. 41.8%) and specific adverse events were similar between groups, with the exception of an increased likelihood of hypertension with the combination (5.8% vs. 1.5%, $p = 0.05$).

A small ($N = 30$),¹¹⁰ high risk of bias crossover trial evaluated melatonin (5 mg/day) versus phototherapy (2500 Lux lightbox for 1 hour each morning) for 12 weeks in patients who met the Oxford case definition. The purpose of the therapies was to alleviate circadian rhythm disturbances which are often present in CFS. Neither melatonin nor phototherapy were associated with significant improvements (based on assessments using a 0 to 10 VAS) in fatigue, depression, anxiety, waking refreshed, low energy, poor concentration, or muscle pain during treatment with melatonin or phototherapy. Although phototherapy, but not melatonin, was associated with a statistically significant improvement from baseline in severity of sleep disturbance (mean change 1.5 points, $p = 0.03$), the scores at the end of treatment were similar in the melatonin and phototherapy groups (5.5 vs. 5.1). Neither melatonin nor phototherapy were associated with improvements from baseline in any SF-36 subscale or HADS depression or anxiety. Harms were not reported, but the study stated that both treatments were well tolerated and not considered responsible for study withdrawals.

Qigong, yoga, or abdominal tuina

Four trials evaluated qigong (two studies),¹¹⁶⁻¹¹⁸ yoga (one study),¹¹⁹ or abdominal tuina (one study)¹²⁰ in adult patients with ME/CFS (**Tables 20 and 21, Evidence Tables Appendix E2**). One trial was included in the prior report.^{116,118} Sample sizes ranged from 28 to 137 (total $N = 272$). One trial was conducted in Europe, one trial in Hong Kong, one trial in China, and one trial in Japan. The mean age of participants ranged from 38 to 44 years and the proportion female ranged from 77 percent to 88 percent. The case definition for ME/CFS was the Fukuda criteria in all four trials. The duration of ME/CFS ranged from 10.4 months to 11.9 years in seven trials that reported this information. Baseline fatigue was measured using a variety of scales (**Table 20**). Details regarding the presence of post-exertional fatigue and activity patterns were lacking.

All four trials were rated medium risk of bias (**Risk of Bias Table Appendix F**). Methodological limitations included inadequate description of randomization or allocation concealment methods, and failure to blind or unclear blinding status of outcomes assessors and data analysts.

Qigong versus wait list or no treatment

Two trials ($N = 137$ and 28)¹¹⁶⁻¹¹⁸ investigated Qigong versus wait list or no treatment. The larger trial ($N = 137$)¹¹⁶ compared Qigong versus wait list. The Qigong intervention consisted of training twice weekly in 2-hour sessions for 5 weeks, followed by 12 weeks of home exercise (participants asked to practice at least 30 minutes daily). After 4 months of treatment, Qigong was associated with decreased fatigue severity versus wait list (mean change from baseline -13.1 vs. -6.6 on the 14-item 0 to 42 Chalder scale total fatigue score, $p < 0.0005$). Qigong was also associated with decreased depression severity (mean change from baseline -1.3 vs. 0.4 on the 0 to 21 HADS depression scale, $p = 0.002$), though there was no difference in anxiety severity

(mean change from baseline -1.1 vs. -0.6 on the 0 to 21 HADS anxiety scale, $p=0.58$). The trial did not report harms.

A second ($N=28$) trial¹¹⁷ compared Qigong versus no Qigong. Qigong training consisted of 15 weekly, 2-hour sessions of gradually more complex exercises. At completion of therapy, Qigong was associated with greater improvement in fatigue severity (mean difference in change from baseline -0.5, 95% CI -0.9 to -0.02 on the 1 to 7 Fatigue Severity Scale). However, the Fatigue Severity Scale was ≥ 5 in all patients at the end of the trial, indicating significant fatigue remained present. There were no differences between Qigong versus no Qigong in any SF-36 subscale, including physical function and bodily pain. However, Qigong was associated with greater reduction in pain intensity that was borderline statistical significance (mean change from baseline 1.4 vs. “similar” [data not provided], $p=0.05$). There were no effects on depression severity (HADS). The trial did not report harms.

Abdominal tuina versus acupuncture

One medium risk of bias¹²⁰ trial ($N=77$) compared abdominal tuina versus acupuncture 5 days per week for 4 weeks in patients who met the Fukuda case definition. Abdominal tuina is a massage technique that uses traditional Chinese medicine principles. At 3 months following the completion of therapy, tuina was associated with decreased fatigue severity versus acupuncture (mean 6.6 vs. 7.6, mean difference 1.0, 95% CI 0.11 to 1.88 on the 0 to 14 Fatigue-Scale 14, $p=0.015$). Tuina was also associated with decreased depression severity (6.3 vs. 7.0, mean difference 0.70, 95% CI 0.13 to 1.27 on the 0 to 52 Hamilton Depression Rating scale, $p=0.044$), and borderline associated with anxiety severity (47.0 vs. 49.0, mean difference 2.0, 95% CI -0.05 to 4.05 on the 20 to 80 Zung Self-Rating Anxiety Scale). No serious harms were reported, and there was no significant difference in the likelihood of adverse events.

Yoga versus plus conventional pharmacotherapy versus pharmacotherapy alone

One small ($N=30$),¹¹⁹ medium risk of bias compared yoga plus conventional pharmacotherapy (medications not described) versus pharmacotherapy alone in patients who met the Fukuda case definition. Yoga sessions occurred every 2 to 3 weeks for two months (mean number of visits: 5.6), with follow-up 2 months after completion of therapy. Yoga was associated with decreased fatigue severity versus pharmacotherapy alone (mean 19.2 vs. 25.8, difference 6.6, 95% CI 1.55 to 11.65 on the 14-item 0 to 42 Chalder fatigue scale total score). Reported harms were minor and primarily involved occasional dizziness when practicing yoga. No patient reported post-exertional malaise after yoga sessions.

Distant healing versus no treatment

A low risk of bias trial¹²¹ ($N=409$) compared distant healing (prayer, or imagining transmission of healing energy, light or healing power) versus wait list in patients that met the Oxford case definition. This study was included in the prior report. Patients had a mean age of 50 years, were 74% female, and had a mean duration of ME/CFS of 11.9 years. Patients were randomized to blinded or unblinded distant healing and wait list (4 arms total). After 6 months of treatment, there were no differences between distant healing versus wait list in SF-36 mental ($p=0.18$) or physical ($p=0.32$) component summary scores. There was no interaction between blinding status and effects of distant healing. The trial did not report effects on fatigue. Harms were not reported.

Table 20. RCTs of Qigong, yoga, abdominal tuina, or distant healing: Study Characteristics

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Chan, 2013 ¹¹⁶ Hong Kong Medium	n: 137 Age: 42.4 % Female: 77	Criteria: Fukuda Duration: not reported	Fatigue Scale: Chalder Baseline (14-item, 0 to 56): 39.8 (SD 6.5) Post-exertional fatigue: not reported	Major depression: Excluded Baseline depression: HADS depression (0 to 21): 9.2 (SD 2.1) Baseline function: not reported	A: Qigong B: Wait list Frequency: Twice weekly Session length: 2 hours Exercise intensity: Qigong ≥30 minutes daily Duration of Treatment: 4 months (5 weeks Qigong training and 12 additional weeks home exercise) Duration of follow-up: 4 months
Dybwad, 2007 ¹¹⁷ Norway Medium	n: 28 Age: 36 % Female: 84	Criteria: Fukuda Duration: 8.1 years	Fatigue scale: Fatigue Severity Scale 9-item (1 to 7) Baseline fatigue, mean: 6.5	Baseline depression: HADS depression (0 to 21): 4.9 Baseline function: SF-36 physical function (0-100 scale, lower score indicates better health): 48	A: Qigong B: No Qigong Frequency: Once weekly Session length: 2 hours Exercise intensity: not reported, but gradually progressed in complexity Duration of treatment: 15 weeks Duration of follow-up: end of treatment
Huanan, 2017 ¹²⁰ China Medium	n: 77 Age: 41.8 vs 42.63 % Female: 44 vs. 37	Criteria: Fukuda Duration, months: 10.4 vs. 10.6	Fatigue scale: Fatigue Scale- 14 (0 to 14, higher score indicates greater severity of fatigue) Baseline fatigue, mean: 8.9 vs. 9.3	Baseline depression: Hamilton Rating Scale for Depression (0 to 52): 11.0 vs. 10.9 Baseline function: Not reported	A: Abdominal tuina B: Acupuncture Frequency: 5 days per week with 2 days off between weeks Duration of treatment: 4 weeks Duration of follow-up: 3 months after treatment
Oka, 2014 ¹¹⁹ Japan Medium	n: 30 Age: 38 % Female: 80	Criteria: Fukuda Duration: Not reported	Fatigue scale: Chalder Fatigue Scale 14-item (0 to 56) Baseline fatigue, mean: 30.8	Baseline depression: not reported Baseline function: not reported	A: Yoga + pharmacotherapy B: Pharmacotherapy alone Frequency: Every 2-3 weeks Duration of treatment: 2 months, mean 5.6 visits Duration of follow-up: 2 months after yoga ended

Author, year Country Risk of Bias	Study n (analyzed) Age, mean years % Female	ME/CFS criterion ME/CFS duration	Fatigue Scale Baseline fatigue	Baseline Depression Baseline Function	Intervention Frequency, duration, and intensity Duration of treatment Duration of follow-up
Walach, 2008 ^{1,21} Germany and Austria Low	n: 409 Age: 47.5, 48.1, 46.2, 50.4 % Female: 74.3, 76.5, 76.6, 75	Criteria: Fukuda or Oxford severe idiopathic CFS Duration, years: 11.3, 9.6, 9.6, 11.9	Fatigue scale: Fatigue Severity Scale 9-item (1 to 7) Baseline fatigue: 6.2, 6.1, 6.1, 6.0	Baseline depression: not reported Baseline function: SF-36 mental health (0 to 100): 36.67, 34.88, 37.28, 35.16 SF-36 physical function (0 to100): 31.02, 31.75, 31.78, 32.71	A: Distant Healing (blinded) B: Distant Healing (unblinded) C: Deferred treatment (blinded) D: Deferred treatment (unblinded) Frequency: Duration of treatment: 6 months Duration of follow-up: 6 months

Abbreviations: CFS = chronic fatigue syndrome; HADS = Hospital Anxiety and Depression Scale; HADS-D = Hospital Anxiety and Depression Scale-depression; HAM-D = Hamilton Depression Rating Scale; ME = myalgic encephalomyelitis; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Table 21. RCTs of Qigong, yoga, abdominal tuina, or distant healing: Study Results

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Chan, 2013 ¹¹⁶ Fukuda	A: Qigong (72) B: Wait list (65) Duration of Treatment: 4 months Duration of follow-up: 4 months	Fatigue score change at 12-weeks, mean (SD): Chalder Fatigue Scale 14-item (0 to 56) total fatigue scores: -13.1 (11.7) vs. -6.6 (8.3), p=0.000 Chalder Fatigue Scale physical fatigue scores: -8.8 (7.3) vs. -3.8 (5.0), p=0.000 Chalder Fatigue Scale mental fatigue scores: -4.3 (5.3) vs. -2.7 (3.9), p=0.50	Depression score HADS depression (0 to 21) change, mean (SD): -1.3 (2.7) vs. 0.4 (3.7), p=0.002	Not reported
Dybwad, 2007 ¹¹⁷ Fukuda	A: Qigong (14) B: No Qigong (14) Duration of treatment: 15 weeks Duration of follow-up: end of treatment	Fatigue Severity Scale 9- item (1 to 7), mean change (SD): -0.44 (0.60) vs. 0 (0.6), p=0.04, adjusted for baseline values All participants in both groups still clinically fatigued	No significant changes observed after intervention within or between groups, data not shown	SF-36, physical functioning, mean change (SD): 4.7 (13) vs. 1.3 (16), p=0.34 adjusted for baseline value.
Huanan, 2017 ¹²⁰ Fukuda	A: Abdominal tuina (39) B: Acupuncture therapy (38) Duration of treatment: 4 weeks Duration of follow-up: 3 months after treatment	Fatigue Scale-14 (0 to 14, higher score indicates greater severity of fatigue): 7.1 (1.7) vs. 8.2 (2.0), p=0.015	Hamilton Rating Scale for Depression (0 to 52): 6.3 (1.2) vs. 7.0 (1.5), p=0.044	Not reported
Oka, 2014 ¹¹⁹ Fukuda	A: Yoga + pharmacotherapy (15) B: Pharmacotherapy alone (15) Duration of treatment: 2 months, mean 5.6 visits Duration of follow-up: 2 months after yoga ended	Fatigue, mean (SD), time x group interaction Chalder Fatigue Scale physical fatigue (14-item, 0 to 56): 12.3 (3.8) vs. 16.1 (3.6), p=0.009 Chalder Fatigue Scale mental fatigue: 6.9 (4.4) vs. 9.7 (3.1), p=0.007 Chalder Fatigue Scale total fatigue: 19.2 (7.5) vs. 25.8 (5.9), p=0.003	Not reported	Not reported

Author, year ME/CFS criterion	Intervention A: intervention (n) B: control (n) Duration of treatment Duration of follow-up	Fatigue Outcomes (fatigue and post- exertional fatigue)	Depression Outcomes	Function Outcomes
Walach, 2008 ¹²¹ Fukuda or Oxford	A: Distant Healing, blinded (105) B: Distant Healing, unblinded (102) C: Deferred treatment, blinded (94) D: Deferred treatment, unblinded (108) Duration of treatment: 6 months Duration of follow-up: 6 months	Not reported	Not reported	Change from baseline: SF-36 Physical Function (0-100 scale, lower score indicates better health): 3.66 (6.83) vs. 3.04 (7.38) vs. 3.29 (7.28) vs. 0.75 (7.85); p=not significant, data not shown SF-36 mental health (0 to 100): -0.29 (9.54) vs. 1.74 (10.25) vs. 1.16 (11.07) vs. 0.81 (10.45); p=not significant, data not shown

Abbreviations: CFS = chronic fatigue syndrome; HAM-D = Hamilton Depression Rating Scale; ME = myalgic encephalomyelitis; RCT = randomized controlled trial; SD = standard deviation; SF-36 = 36-item Short Form Health Survey

Discussion

This review synthesizes evidence on the evaluation and management of ME/CFS. Specifically, it addresses the prevalence of non-ME/CFS conditions in persons presenting with fatigue and the benefits and harms of treatments for ME/CFS. Although we also sought to synthesize evidence on the benefits and harms of receiving an ME/CFS diagnosis versus no diagnosis, no study met inclusion criteria. The key findings of this review are summarized in the summary of evidence table (**Table 22**).

The bulk of the evidence in this report addressed the effectiveness of treatments for ME/CFS. The prior AHRQ report found GET and CBT were associated with improved fatigue and function versus inactive controls, but the applicability of findings to more disabled populations with ME/CFS and those diagnosed using more current ME/CFS criteria was uncertain.¹ The prior report also found that rintalolimod was associated with improved exercise performance in some patients, but the strength of evidence was low. There was insufficient evidence to determine effects of other treatments and harms of therapy. The findings of this report regarding treatments for ME/CFS expands upon the prior AHRQ report by including new studies, adding children as a population of interest, and evaluating outcomes in addition to fatigue and function (e.g., depression, anxiety, sleep, and pain). We also sought to determine how effects of treatment differed in subgroups based on ME/CFS disease severity, duration of symptoms, ME/CFS case definition used, demographic factors, comorbidities, and intervention characteristics (e.g., type of exercise, method of delivering CBT).

As in the prior AHRQ report, exercise and CBT remained the most frequently studied interventions in adults with ME/CFS, with 33 new trials of these interventions added for this update. Like the prior report, we found some evidence that graded exercise and CBT are associated with improved fatigue and function versus inactive controls (wait list, usual care, usual specialist care, attention control, or placebo) at the end of the intervention, with more limited data indicating sustained benefits at post-intervention follow-up 2 to 12 months following completion of therapy. However, these findings must be interpreted with caution. In a number of pooled analyses, statistical heterogeneity was large and not fully explained in subgroup analyses based on the type of control, the scale used to measure fatigue or function, or the method for delivering CBT. Although an outlier trial⁵³ of exercise that reported unusually strong results was identified, it was unclear why results of this trial differed from the others and statistical heterogeneity remained present when it was excluded. In addition, the magnitude of effects was relatively modest. For fatigue and function, pooled SMD's ranged from -0.55 to -0.76, or within the "moderate" range (0.50 to 0.80).³³ However, mean differences based on the original scales were 2 to 3 points in trials that used the 11-item 0 to 33 Chalder fatigue scale, 3 to 4 points in trials that used the 11-item 0 to 11 Chalder fatigue scale, and 5 to 6 points on the 0 to 100 SF-36 physical function subscale. These effects ranged from below to slightly above proposed thresholds for minimum clinically important differences (2.3 points on the 11-item 0 to 11 Chalder scale and 10 points on the SF-36 physical function subscale). For exercise, effects on fatigue and function were attenuated and below the "moderate" threshold when the outlier trial described above was excluded (SMD's 0.32 to 0.35). The applicability of results to patients with more severe ME/CFS symptoms also remains unclear. At baseline, mean scores on the SF-36 physical function subscale ranged from ~30 to ~60, with most trials reporting scores in the 40 to 50 range. Whether similar effects would occur in patients with more severe functional limitations and symptoms due to ME/CFS is unknown. The applicability of findings to patients with severe post-exertional fatigue is also uncertain. Only one exercise trial required patients to have post-

exertional fatigue at baseline;⁴⁹ the others did not report the prevalence or severity of post-exertional fatigue. Similarly, the applicability of findings to patients diagnosed using more recent, specific ME/CFS case definitions is uncertain. Although we found similar results for exercise and CBT regardless of the ME/CFS case definition used, subgroup analyses were limited by small numbers of trials. In addition, the most commonly used case definition in the exercise trials was the Oxford case definition, resulting in a substantially higher prevalence of ME/CFS than more specific case definitions. This could have resulted in potential misclassification (overdiagnosis) of patients with non-ME/CFS fatiguing conditions. There were also methodological limitations in the trials. It was not possible to blind patients and care providers to the exercise and CBT interventions, potentially resulting in bias related to delivery of interventions, expectations of treatment, provider enthusiasm for different treatments, and assessment of outcomes.¹²² The inability to blind is of particular concern for subjective outcomes such as fatigue and function. Most trials also had other methodological limitations, including unclear randomization or allocation concealment methods and high attrition. Because of these issues, the strength of evidence for exercise therapy and CBT versus inactive therapies was rated low, even though these represented the most robust bodies of evidence on treatments for ME/CFS.

There were other challenges in interpreting our findings. Exercise and CBT were also associated with increased likelihood of improvement in fatigue, function, and recovery, based on differences in the proportion of patients meeting a defined threshold. Such dichotomous outcomes can be more informative than continuous outcomes based on average improvements, because they indicate the proportion of patients who experience clinically meaningful benefits. However, few trials reported dichotomous outcomes, the thresholds used to define dichotomous outcomes varied, and findings were largely driven by the largest trial, PACE. The PACE trial has been criticized because of protocol modifications involving the definitions used for dichotomous outcomes, including the primary outcome of overall efficacy (a composite of fatigue and function), recovery, and improvement in fatigue and function.⁶² These changes resulted in less stringent thresholds that were met by higher proportions of patients. The modified definition for recovery was of particular concern because it encompassed patients with significant symptoms; furthermore, some patients meeting the criteria for recovery at the time of study entry, contradicting the concept of recovery. However, findings were similar in sensitivity analyses that utilized data based on the original PACE protocol definitions for these outcomes.³⁸

Exercise and CBT were also associated with small beneficial effects on depression and anxiety versus inactive therapies (differences 1.2 to 2.4 points on the 0 to 21 HADS depression or anxiety scales; proposed minimum clinically important difference 1.7) and sleep. Data on effects on the 6-minute walk test were limited but indicated small but statistically significant for exercise versus inactive controls (mean difference 31 minutes), but not CBT. Data on harms were very limited, mostly reported from the PACE and GETSET trials. There was no increase in risk of serious adverse events, withdrawal due to worsening, or physical function worsening, but some estimates were imprecise. In the PACE trial, exercise and CBT were associated with decreased likelihood of post-exertional malaise versus usual specialist care.³⁶

Evidence on the comparative effectiveness of exercise or CBT versus other active therapies for ME/CFS was limited. There were no differences between exercise versus CBT in fatigue, function, or other outcomes, though findings were based on one or two trials (including PACE), with imprecise estimates. Data were also too limited for reliable comparisons of exercise or CBT versus other active therapies (relaxation, cognitive therapy, adaptive therapy, medications),

though the PACE trial³⁶ generally found that adaptive pacing generally performed worse than either exercise or CBT.

For adolescents with ME/CFS, evidence on the effectiveness of treatments mostly focused on CBT. Evidence found CBT with a family focus or parental involvements associated with decreased fatigue severity versus inactive controls, though there was heterogeneity in the magnitude of effects, which ranged from small to large. Although estimates also favored CBT for severity of functional impairment and school attendance, the differences were not statistically significant. All estimates were based on a small number of trials (three) and statistical heterogeneity was very high. No trial evaluated the effectiveness of exercise in adolescents. One new trial found an osteopathy, life coaching, and neurolinguistic programming intervention (“Lightning Process”) associated with improved function versus usual specialist care, with no statistically significant effects on fatigue, anxiety, depression, or quality of life.⁸⁵ This trial involves an intensive but brief intervention with limited follow-up sessions; additional research is needed to reproduce and verify these findings.

Regarding medications for ME/CFS, a new placebo-controlled trial of rituximab, a monoclonal antibody against the CD20 protein with immunomodulatory effects, failed to confirm positive results of an earlier pilot trial, showing no statistically significant effects on fatigue, function, or other clinical outcomes.^{89,90} Small, more recent trials of anakinra,¹⁰¹ duloxetine,¹⁰⁵ mirtazapine,⁷¹ clonidine, and methylphenidate¹⁰⁴ in patients with ME/CFS also found no beneficial effects on fatigue, function or other clinical outcomes. The only trial of a medication in adolescents with ME/CFS found IgG associated with improvement in function after 3 months versus placebo, but not at other measurement time points.¹⁰² Two trials of adults found no differences between IgG versus placebo in fatigue, function, or other clinical outcomes.^{99,100} There was no new evidence on rintatolimod, which is not approved by the FDA for any indication. Rintatolimod was reviewed by the FDA in 2012 and failed to receive approval. Two trials included in the prior report found some evidence of improved exercise tolerance with rintatolimod versus placebo, but improvements in overall function seen in an initial, smaller trial were not replicated in a subsequent, larger trial.^{95,96} Rintatolimod was associated with infusion-related headaches and flu-like symptoms in one trial. No new trial of rintatolimod has been published since 2012. A small trial of patients with suspected viral onset of ME/CFS found no statistically significant differences between valganciclovir versus placebo in the MFI-20 total fatigue, CDC symptom inventory scores, sleep quality, or depression, though valganciclovir was associated with improved self-reported cognitive functioning and severity of mental fatigue.⁹³ Antidepressants did not significantly improve depressive symptoms in those without MDD at baseline, and improvements did not meet clinically important differences in one study that enrolled patients with MDD. The evidence on other medications for ME/CFS was sparse and did not indicate benefits.

Evidence on the effectiveness of other therapies was limited. Limited evidence indicated that Qigong was associated with beneficial effects on fatigue and function; evidence on other complementary and alternative approaches, dietary supplements, and dietary interventions was limited but did not indicate beneficial effects. One trial of home orthostatic training found orthostatic training associated with a decrease in blood pressure drop with standing versus sham training, but did not measure effects on orthostatic symptoms.¹²³

Our findings are generally consistent with a recent systematic review on exercise therapy for ME/CFS that concluded that exercise probably has a positive effect on fatigue in adults compared to usual care or passive therapies, but noted uncertain applicability to patients

diagnosed with case definitions other than the Oxford and Fukuda criteria.¹²⁴ This review also found that there was limited evidence on exercise versus other active therapies, limiting its ability to determine comparative effectiveness. With regard to the use of medications for ME/CFS, our findings are consistent with a recent systematic review that found limited evidence on medications for ME/CFS, which was insufficient to draw conclusions.¹²⁵ An older systematic review found CBT associated with small improvement versus usual care, but was conducted in 2008, prior to the publication of PACE and other trials of CBT.¹²⁶

Evidence to determine the degree to which patient characteristics predict treatment effects was limited. The PACE trial, which enrolled patients using the Oxford case definition, found no interaction between whether patients met alternative case definitions (2003 Reeves, 1994 London)²⁰ or presented with a primary depressive or anxiety disorder and estimates of effectiveness. Evidence on the interaction between severity of baseline functional impairment and effects of exercise or CBT was limited and inconsistent, with some trials finding worse baseline function associated with greater response to therapy and others finding worse baseline function associated with worse response. Three trials found no interaction between baseline depression and effects of exercise or CBT.

The prevalence of non-ME/CFS conditions in patients presenting with fatigue is high, though estimates appeared to vary depending on the setting. In a systematic review of patients who sought care for fatigue or tiredness in primary care settings, the most common non-ME/CFS conditions were depression (18.5%), anemia (2.8%), malignancy (0.6%), and serious somatic diseases (including diabetes, anemia, hypothyroidism, and malignancy, 4.3%).⁴³ In specialty settings of patients referred for evaluation of possible ME/CFS, the most common non-ME/CFS conditions were psychological (15% to 51%) and sleep disorders (6% to 30%). A variety of other non-ME/CFS conditions were reported in both primary care and specialty settings, highlighting the importance of the clinical and diagnostic evaluation of patients with fatigue.

Table 22. Summary of Evidence

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
Exercise vs. inactive therapies (adults)	Fatigue, end of intervention	6 (1034)	Direct	Precise	Moderate	Inconsistent	SMD -0.55 (-0.91 to -0.19); SMD -0.32 (-0.52 to -0.12) without outlier trial	Low
	Fatigue, post-intervention	3 (625)	Direct	Precise	Moderate	Inconsistent	SMD -0.76 (-1.48 to -0.05); SMD -0.35 (-0.58 to -0.12) without outlier trial	Low
	Fatigue improvement	1 (305)	Direct	Precise	Moderate	Unable to assess	RR 1.23 (1.07 to 1.42)	Low
	SF-36 physical function (0 to 100), end of intervention	5 (965)	Direct	Precise	Moderate	Inconsistent	MD 11.73 (2.33 to 21.14); MD 5.89 (2.52 to 9.25) without outlier trial	Low
	SF-36 physical function (0 to 100), post-intervention	3 (711)	Direct	Precise	Moderate	Inconsistent	MD 17.07 (-2.02 to 36.16); MD 6.37 (1.89 to 10.85) without outlier trial	Low
	Functional improvement	3 (618)	Direct	Imprecise	Moderate	Inconsistent	RR 2.48 (0.77 to 7.97); RR 1.41 (1.15 to 1.74) without outlier trial	Low
	HADS depression (0 to 21), end of intervention	4 (688)	Direct	Precise	Moderate	Inconsistent	MD -1.83 (-3.65 to -0.01); MD -0.97 (-1.71 to -0.23) without outlier trial	Low
	HADS depression (0 to 21), post-intervention	3 (699)	Direct	Imprecise	Moderate	Inconsistent	MD -2.36 (-4.98 to 0.27)	Low
	HADS anxiety (0 to 21), end of intervention	3 (620)	Direct	Precise	Moderate	Consistent	MD -1.59 (-2.41 to -0.77); MD -1.31 (-2.12 to -0.51) without outlier trial	Low
	HADS anxiety (0 to 21), post-intervention	3 (697)	Direct	Precise	Moderate	Inconsistent	MD -1.07 (-2.64 to 0.49); MD -0.38 (-1.52 to 0.76) without outlier trial	Low
	Sleep, end of intervention	2 (420)	Direct	Precise	Moderate	Consistent	SMD -0.35 (-0.56 to -0.13); SMD -0.31 (-0.57 to -0.05) without outlier trial	Low
	Sleep, post-intervention	3 (700)	Direct	Precise	Moderate	Inconsistent	SMD -0.39 (-0.71 to -0.07); SMD -0.26 (-0.56 to 0.03) without outlier trial	Low
	Recovery	3 (536)	Direct	Precise	Moderate	Consistent	RR 2.01 (1.35 to 3.01)	Low
Serious adverse events	2 (518)	Direct	Imprecise	Moderate	Consistent	RR 1.59 (0.69 to 3.66)	Low	

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
	Withdrawal due to worsening	1 (320)	Direct	Imprecise	Moderate	Unable to assess	RR 2.00 (0.18 to 21.84)	Low
	Physical function worsening	2 (518)	Direct	Imprecise	Moderate	Consistent	RR 0.83 (0.52 to 1.34)	Low
	Post-exertional malaise	1 (320)	Direct	Precise	Moderate	Unable to assess	RR 0.70 (0.57 to 0.87)	Low
CBT vs. inactive therapies (adults)	Fatigue, end of intervention	7 (1129)	Direct	Precise	Moderate	Inconsistent	SMD -0.61 (-0.83 to -0.40)	Low
	Fatigue, post-intervention	3 (489)	Direct	Precise	Moderate	Inconsistent	SMD -0.57 (-0.89 to -0.25)	Low
	Fatigue improvement	4 (784)	Direct	Precise	Moderate	Inconsistent	RR 3.00 (0.95 to 9.49)	Low
	SF-36 physical function (0 to 100), end of intervention	5 (1024)	Direct	Precise	Moderate	Consistent	MD 6.58 (3.76 to 9.39)	Low
	Function, post-intervention	3 (489)	Direct	Precise	Moderate	Inconsistent	SMD 0.37 (0.08 to 0.66)	Low
	Functional improvement	3 (488)	Direct	Imprecise	Moderate	Inconsistent	RR 1.06 (0.83 to 1.35)	Low
	Depression, end of intervention	5 (660)	Direct	Precise	Moderate	Inconsistent	SMD -0.26 (-0.49 to -0.03)	Low
	HADS depression (0 to 21), post-intervention	3 (483)	Direct	Precise	Moderate	Consistent	MD -1.24 (-2.01 to -0.47)	Low
	HADS anxiety (0 to 21), post-intervention	3 (481)	Direct	Precise	Moderate	Consistent	MD -1.22 (-1.94 to -0.49)	Low
	Jenkins Sleep Questionnaire (0 to 20), post-intervention	1 (292)	Direct	Precise	Moderate	Unable to assess	MD -1.20 (-2.19 to -0.21)	Low
	Recovery	3 (564)	Direct	Precise	Moderate	Consistent	RR 2.54 (1.53 to 4.22)	Low
	Serious adverse events	1 (321)	Direct	Imprecise	Moderate	Unable to assess	RR 0.99 (0.36 to 2.77)	Low
	Withdrawal due to worsening	1 (321)	Direct	Imprecise	Moderate	Unable to assess	RR 0.33 (0.01 to 8.07)	Low
	Physical function worsening	1 (321)	Direct	Imprecise	Moderate	Unable to assess	RR 0.83 (0.26 to 2.66)	Low
	Post-exertional malaise	1 (321)	Direct	Precise	Moderate	Unable to assess	RR 0.78 (0.64 to 0.95)	Low

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
CBT vs. inactive therapies (adolescents)	Fatigue, end of intervention	3 (263)	Direct	Precise	Moderate	Inconsistent	SMD -0.84 (-1.52 to -0.15)	Low
	11-item Chalder fatigue scale (0 to 33), post-intervention	1 (63)	Direct	Imprecise	Moderate	Unable to assess	MD -1.9 (-5.3 to 1.5)	Low
	Fatigue improvement (dichotomous)	2 (200)	Direct	Imprecise	Moderate	Consistent	RR 3.13 (2.18 to 4.49)	Low
	Function, end of intervention	3 (263)	Direct	Imprecise	Moderate	Inconsistent	SMD 0.49 (-0.34 to 1.32)	Low
	SF-36 physical function (0 to 100), post-intervention	1 (63)	Direct	Imprecise	Moderate	Unable to assess	MD 6.1 (-9.2 to 21.4)	Low
	Functional improvement	2 (200)	Direct	Imprecise	Moderate	Consistent	RR 3.35 (2.25 to 4.99)	Low
	School attendance	3 (251)	Direct	Imprecise	Moderate	Inconsistent	RR 1.96 (0.57 to 6.79)	Low
	Overall improvement	3 (256)	Direct	Imprecise	Moderate	Inconsistent	RR 1.66 (0.67 to 4.10)	Low
	Recovery	1 (131)	Direct	Precise	Moderate	Unable to assess	RR 3.82 (2.31 to 6.31)	Low
Exercise vs. CBT (adult)	Fatigue, function, depression, anxiety, sleep, pain, recovery, fatigue improvement, functional improvement, serious adverse events, withdrawal due to worsening, physical function worsening, post-exertional malaise	1 to 2 (58 to 360)	Direct	Imprecise for most outcomes	Moderate	Varies	Overall no differences between exercise vs. CBT in various outcomes	Low

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
Exercise vs. other active therapies (relaxation, adaptive pacing, biofeedback, fluoxetine) (adults)	Fatigue, function, depression, anxiety, sleep, pain, recovery, fatigue improvement, functional improvement, serious adverse events, withdrawal due to worsening, physical function worsening, post-exertional malaise	1 to 2 (24 to 305)	Direct	Imprecise for most outcomes	Moderate	Varies	Overall no differences between exercise vs. active therapies; 1 trial found exercise associated with better outcomes versus adaptive pacing	Low (adaptive pacing, relaxation) to insufficient (biofeedback, fluoxetine)
CBT vs. other active therapies (relaxation, cognitive therapy, adaptive pacing, mirtazapine)	Fatigue, function, depression, anxiety, sleep, pain, recovery, fatigue improvement, functional improvement, serious adverse events, withdrawal due to worsening, physical function worsening, post-exertional malaise	1 to 2 (57 to 320)	Direct	Imprecise for most outcomes	Moderate	Varies	Overall no differences between CBT vs. other active therapies; 1 trial found CBT associated with better outcomes versus adaptive pacing	Low (adaptive pacing, relaxation) to insufficient (cognitive therapy, mirtazapine)
Illness management and peer counseling vs. wait list (adults)	Fatigue, quality of life, function	1 (47)	Direct	Imprecise	Moderate	Unable to assess	Overall no differences in outcomes	Low
Mindfulness-based cognitive therapy vs. usual care or wait list (adults)	Fatigue, function, depression, anxiety	2 (53)	Direct	Imprecise	High	Consistent	Overall no statistically significant differences	Insufficient
Self-management versus usual care (adults)	Fatigue, function, depression, anxiety	2 (249)	Direct	Imprecise for most outcomes	Moderate	Inconsistent	Inconsistent effects in two trials	Insufficient

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
Osteopathy, life coaching, and neurolinguistic programming versus usual specialist care	Fatigue, function, pain, anxiety, depression, quality of life, school attendance	1 (81)	Direct	Imprecise for most outcomes	Moderate	Unable to assess	Intervention associated with improved function, but no differences in fatigue, pain, anxiety, depression, or quality of life. School attendance improved at 12 months but not at 6 months.	Low
Home orthostatic training vs. sham training	Fatigue, blood pressure drop on standing	1 (27)	Direct	Imprecise for fatigue	Moderate	Unable to assess	No difference in fatigue; orthostatic training associated with reduction in blood pressure drop with standing	Low
Aclydine vs. placebo	Function, fatigue, physical activity (actometer)	1 (57)	Direct	Imprecise	High	Unable to assess	No effect	Insufficient
Anakinra vs. placebo	Fatigue, function	1 (50)	Direct	Imprecise	Low	Unable to assess	No difference in fatigue or function	Insufficient
Alfa-2a interferon vs. placebo	Quality of life	1 (26)	Direct	Imprecise	High	Unable to assess	No difference in quality of life	Insufficient
Clonidine vs. placebo	Fatigue, function	1 (120)	Direct	Imprecise	Moderate	Unable to assess	No difference in fatigue or function	Low
Duloxetine vs. placebo	Fatigue, function	1 (57)	Direct	Imprecise	Moderate	Unable to assess	No difference in fatigue or function	Insufficient
Fluoxetine vs. placebo	Fatigue, function	2 (166)	Direct	Imprecise	Medium	Consistent	No difference in fatigue or function	Low
Galantamine vs. placebo	Fatigue	1 (423)	Direct	Imprecise	Medium	Unable to assess	No difference in fatigue or quality of life	Insufficient
Hydrocortisone vs. placebo	Fatigue, function	1 (80)	Direct	Imprecise	Medium	Unable to assess	No difference in fatigue or function	Insufficient
Immunoglobulin G vs. placebo in Adults	Function, quality of life	2 (127)	Direct	Imprecise	Medium	Consistent	No difference in function or quality of life	Low
Immunoglobulin G vs. placebo in adolescents	Function	1 (70)	Direct	Imprecise	Moderate	Unable to assess	No difference in function at end of treatment, but IgG associated with improved function at 3-month post-intervention follow-up	Insufficient
Methylphenidate vs. placebo	Function	1 (128)	Direct	Imprecise	Moderate	Unable to assess	No difference in function	Low

Intervention	Outcomes	Number of RCTs (number of subjects)	Directness	Precision	Study limitations	Consistency	Findings (95% CI)	Strength of Evidence
Mirtazapine vs. placebo	Fatigue	1 (49)	Direct	Imprecise	Medium	Unable to assess	No difference in fatigue	Insufficient
Rintatolimod vs. placebo	Function, exercise work capacity	2 (316)	Direct	Imprecise	Medium	Consistent	Rintatolimod associated with improved function and measures of exercise capacity	Low
Rituximab vs. placebo	Fatigue	2 (181)	Direct	Imprecise	Medium	Consistent (fatigue); inconsistent (function)	No difference in fatigue; inconsistent effects on function, with no effect in larger trial	Low
Valganciclovir vs. placebo	Fatigue, function	1 (30)	Direct	Imprecise	Medium	Unable to assess	No difference in function, fatigue improved	Insufficient
Dietary interventions, herbal supplements, homeopathy vs. placebo, usual diet, or another dietary/herbal intervention	Fatigue, function, depression, anxiety, sleep, pain, recovery, fatigue improvement, functional improvement	9 (each evaluated a different intervention, n ranged from 14 to 268)	Direct	Imprecise	High	Inconsistent	Evidence insufficient due to imprecision and study limitations, with results based on a single study for specific interventions	Insufficient
Qigong vs. wait list or usual care	Fatigue, depression, function	2 (165)	Direct	Precise	Medium	Consistent (fatigue); inconsistent (depression); unable to assess (function)	Qigong associated with decreased fatigue severity (2 studies); inconsistent effects on depression (1 study); no difference in function (1 study)	Low for fatigue; insufficient for depression and function
Abdominal tuina vs. acupuncture, yoga + pharmacotherapy vs. pharmacotherapy, distant healing vs. no treatment	Fatigue, function, depression, anxiety, sleep, pain, recovery, fatigue improvement, functional improvement	3 RCTs (each evaluated a different intervention, n ranged from 28 to 409)	Direct	Imprecise	High	Inconsistent	Evidence insufficient due to imprecision and study limitations, with results based on a single study for each intervention	Insufficient

Abbreviations: CBT = cognitive behavioral therapy; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; MD = mean difference; RCT = randomized controlled trial; RR = relative risk; SF-36 = 36-item Short Form Health Survey; SMD = standardized mean difference; SOE = strength of evidence

Limitations

The evidence based in this review had important limitations. First, as previously noted, most trials had methodological limitations. It is not possible to blind patients or care providers to nonpharmacological interventions such as exercise or CBT, potentially resulting in performance bias or differences in effects based on patient expectations of benefits. Although outcome assessors can generally be blinded even when patients and care providers cannot, most trials did not report blinded outcomes assessment, which could have resulted in bias in measurement or analysis of outcomes. Trials had other limitations, including failure to describe randomization or allocation concealment methods and high attrition. Most studies were small and many were underpowered to detect significant differences. The largest trial, PACE, incorporated a number of protocol modifications in measurement and definitions of outcomes. Second, studies varied with regard to the methods used to measure outcomes. This limited our ability to compare results across studies except in meta-analyses, where SMD's (a unitless measures) were calculated. However, interpretation of SMD's can be a challenge because the numerator is based on the difference between groups on an outcome measure and the denominator is based on the precision of the estimates, using the pooled standard deviation. This means that trials that report same average difference in fatigue or function but are more precise (e.g., due to larger sample sizes) will have larger SMD's. Therefore, we also calculated pooled estimates based on the original scales used to calculate pooled SMD's. In some cases, the magnitude of the differences on the original scales were below proposed minimum clinically important difference thresholds when the SMD was within the "moderate" range. Third, there was variability in the ME/CFS case definitions used. Many trials used the earlier Oxford case definition, which includes patients with 6 months of unexplained fatigue with physical and mental impairment, but does not require other specific features commonly present in ME/CFS. Using this case definition classifies more patients with ME/CFS compared with more current case definitions, potentially resulting in misclassification and misleading results. Fourth, most interventions and comparisons were evaluated in small numbers of trials and estimates were frequently imprecise. Due to the small number of trials, meta-analysis was restricted to exercise and CBT, the most frequently evaluated interventions. Fifth, the trials often failed to report important patient characteristics (such as prevalence of post-exertional malaise) and few trials evaluated the effects of important patient characteristics on outcomes. Sixth, harms were reported poorly in most trials. Seventh, there were few trials of ME/CFS treatment in adolescents; most of the available trials in this age group addressed CBT.

There were also limitations in the methods used to conduct this review. First, a number of analyses were characterized by high statistical heterogeneity. To address anticipated heterogeneity, we utilized random effects models and conducted sensitivity and stratified analyses. Second, for meta-analyses of exercise or CBT versus other active therapies, we did not pool results across active comparators, given differences in mechanisms of action and potential therapeutic effects. Findings for each of these comparisons were based on small numbers (one or two) trials. Third, we pooled analyses across different "inactive" therapies (placebo, wait list, usual care, attention control). Because the type of inactive therapy could potentially impact treatment estimates, we stratified analyses by the control type; findings were generally consistent and similar across these controls. Fourth, we restricted inclusion to English language articles. Fifth, we did not perform graphical or statistical tests for small sample effects, a potential marker for publication bias, due to the small numbers of trials.

Future Research

Research is needed to clarify, further quantify, and understand the effectiveness of exercise, CBT, and other treatments for ME/CFS in patients diagnosed using more specific ME/CFS case definitions that are universally accepted and used in clinical settings. Future research should address the limitations identified above, with improvements in methodological design and conduct that will reduce the risk of bias and improve the strength of the evidence.

Study populations should be more well defined and reported, specifically characteristics that are important in understanding the effects of treatments for ME/CFS. Trials should be designed and adequately powered to evaluate subgroup effects based on the severity of symptoms, duration of symptoms, type of onset, demographic factors, biomarkers, and presence of post-exertional malaise and other key symptoms. Studies of adolescents are needed, and additional studies are needed to corroborate the findings for interventions with potential for benefit.

The development of standardized, clinically relevant criteria to define recovery, improvement in fatigue, improvement in function, and other dichotomous outcomes is needed, and such outcomes should be measured in future trials. Measurement of more objective measures of function (e.g., activity trackers or the 6-minute walk test) could help interpret effects based on scales of fatigue or function. Outcomes should be both measured and reported more consistently across studies. Trials should be designed to rigorously assess harms including worsening in function and post-exertional malaise. Research is needed to determine effects of treatments on specific symptoms and conditions associated with ME/CFS, such as cognitive difficulties, autonomic dysfunction, gastrointestinal disturbance, pain, orthostatic intolerance, and multiple chemical sensitivity.

For interventions which cannot be blinded, expertise-based trial designs may help reduce bias related to provider preferences and enthusiasm regarding the treatment evaluated.¹²⁷ In this design, instead of having the same providers deliver all of the interventions in a trial, patients are randomized to clinicians with expertise in intervention A or clinicians with expertise in intervention B. However, the expertise-based design does not address potential biases related to patient expectations and preferences regarding treatment.

Future trials should assess patient expectations and preferences regarding treatments and determine effects on treatment outcomes. Research is also needed to understand benefits and harms of ME/CFS diagnosis versus non-diagnosis, optimal sequencing and combinations of treatments.

Conclusions

Evidence on effective treatments for ME/CFS remains limited. Although graded exercise and CBT were more effective than inactive controls in improving fatigue, function, and other outcomes, the magnitude of effects was small to moderate and methodological and other limitations (imprecision, inconsistency, uncertain generalizability) precluded strong conclusions. Other therapies were not shown to be effective or require additional evidence to verify effectiveness. Non-ME/CFS conditions were common in patients presenting with fatigue.

References

1. Smith MEB, Nelson HD, Haney E, et al. Diagnosis and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Evid Rep Technol Assess.* 2014 (219):1-433. doi: 10.23970/ahrqepcerta219. PMID: 30313001.
2. Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J Chronic Fatigue Syndr.* 2003;11(1):7-115. doi: 10.1300/J092v11n01_02.
3. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med.* 2011;270(4):327-38. doi: 10.1111/j.1365-2796.2011.02428.x. PMID: 21777306.
4. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121(12):953-9. PMID: 7978722.
5. Institute of Medicine. *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness.* Washington, DC: National Academies Press; US; 2015.
6. Hooper M. Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research. *J Clin Pathol.* 2007;60(5):466-71. PMID: 16935967.
7. 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. doi: 10.1177/0163278711424281. PMID: 22158691.
8. Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med.* 1988;108(3):387-9. PMID: 2829679.
9. Ramsay AM. Postviral fatigue syndrome: the saga of Royal Free disease: Gower Medical for the Myalgic Encephalomyelitis Association; 1986.
10. A new clinical entity? *Lancet.* 1956;270(6926):789-90. PMID: 13320887.
11. Brurberg KG, Fonhus MS, Larun L, et al. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. *BMJ Open.* 2014;4(2):e003973. doi: 10.1136/bmjopen-2013-003973. PMID: 24508851.
12. Afari N, Buchwald D. Chronic fatigue syndrome: a review. *Am J Psychiatry.* 2003;160(2):221-36. PMID: 12562565.
13. Rangel L, Garralda ME, Levin M, et al. The course of severe chronic fatigue syndrome in childhood. *J R Soc Med.* 2000;93(3):129-34. PMID: 10741312.
14. Crawley EM, Emond AM, Sterne JA. Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *BMJ Open.* 2011;1(2):e000252. doi: 10.1136/bmjopen-2011-000252. PMID: 22155938.
15. Centers for Disease Control and Prevention. *Symptoms and Diagnosis of ME/CFS in Children.* 2018. <https://www.cdc.gov/me-cfs/me-cfs-children/children-symptoms-diagnosis.html>. Accessed January 1, 2020.
16. 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.
17. Center for Drug Evaluation and Research. *The Voice of the Patient: A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative: Chronic Fatigue Syndrome and Myalgic Encephalomyelitis.* U.S. Food and Drug Administration; 2013 <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf>. Accessed April 22, 2019.

18. Sharpe MC, Archard LC, Banatvala JE, et al. A report-chronic fatigue syndrome: guidelines for research. *J R Soc Med.* 1991;84(2):118-21. PMID: 1999813.
19. Dowsett E, Goudsmit E, Macintyre A, et al. Report from the national task force on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME). Westcare. 1994.
20. Reeves WC, Lloyd A, Vernon SD, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. *BMC Health Serv Res.* 2003;3(1):25. PMID: 14702202.
21. Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome-a clinically empirical approach to its definition and study. *BMC Med.* 2005;3:19. PMID: 16356178.
22. National Institute for Health Clinical Excellence. Chronic Fatigue Syndrome/myalgic Encephalomyelitis (or Encephalopathy). Diagnosis and Management of CFS/ME in Adults and Children. Quick Reference Guide. NICE Clinical Guideline 53. NICE; 2007.
23. Jason LA, Bell DS, Rowe K, et al. A pediatric case definition for myalgic encephalomyelitis and chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome.* 2006;13(2-3):1-44. doi: 10.1300/J092v13n02_01.
24. Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. *Am J Biochem Biotechnol.* 2010;6(2):120-35.
25. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. <https://effectivehealthcare.ahrq.gov/topics/ce-r-methods-guide/overview>. Accessed April 18, 2019.
26. Chou R, McDonagh M, Griffin J, et al. Diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic evidence review. PROSPERO: National Institute fo Health Research; 2019. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=142805. Accessed January 1, 2020.
27. Nisenbaum R, Jones JF, Unger ER, et al. A population-based study of the clinical course of chronic fatigue syndrome. *Health Qual Life Outcomes.* 2003;1:49. PMID: 14613572.
28. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20(3 Suppl):21-35. doi: 10.1016/s0749-3797(01)00261-6. PMID: 11306229.
29. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol.* 2011;64(11):1198-207. doi: 10.1016/j.jclinepi.2010.11.021. PMID: 21463926.
30. Goligher EC, Pouchot J, Brant R, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. *J Rheumatol.* 2008;35(4):635-42. PMID: 18322987.
31. Wyrwich KW, Tierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res.* 2005;40(2):577-91. doi: 10.1111/j.1475-6773.2005.00373.x. PMID: 15762908.
32. Lemay KR, Tulloch HE, Pipe AL, et al. Establishing the minimal clinically important difference for the hospital anxiety and depression scale in patients with cardiovascular disease. *J Cardiopulm Rehabil Prev.* 2019;39(6):E6-e11. doi: 10.1097/hcr.0000000000000379. PMID: 30489438.
33. Cohen J. Statistical power analysis for the behavioural sciences. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.

34. Sutton AJ, Abrams KR, Jones DR, et al. *Methods for meta-analysis in medical research*: Wiley Chichester; 2000.
35. Fu R, Holmer HK. Change score or follow-up score? Choice of mean difference estimates could impact meta-analysis conclusions. *J Clin Epidemiol.* 2016;76:108-17. doi: 10.1016/j.jclinepi.2016.01.034. PMID: 26931293.
36. 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. doi: 10.1016/S0140-6736(11)60096-2. PMID: 21334061.
37. White PD, Sharpe MC, Chalder T, et al. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/ myalgic encephalomyelitis or encephalopathy. *BMC Neuro.* 2007;7(6) PMID: 17397525.
38. Goldsmith K, White P, Chalder T, et al. The PACE trial: Analysis of primary outcomes using composite measures of improvement. *Wolfson Institute of Preventive Medicine, London, UK.* 2016.
39. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-58. doi: 10.1002/sim.1186. PMID: 12111919.
40. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557. PMID: 12958120.
41. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ.* 2011;343:d4002. doi: 10.1136/bmj.d4002. PMID: 21784880.
42. *AHRQ Methods for Effective Health Care.* In: Chang SM, Matchar DB, Smetana GW, Umscheid CA, eds. *Methods Guide for Medical Test Reviews.* Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
43. Stadje R, Dornieden K, Baum E, et al. The differential diagnosis of tiredness: a systematic review. *BMC Fam Pract.* 2016;17(1):147. PMID: 27765009.
44. 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. doi: 10.1186/1756-0500-6-309. PMID: 23915640.
45. Devasahayam A, Lawn T, Murphy M, et al. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: service evaluation survey. *JRSM Short Rep.* 2012;3(1):4. doi: 10.1258/shorts.2011.011127. PMID: 22299071.
46. Mariman A, Delesie L, Tobback E, et al. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. *J Psychosom Res.* 2013;75(5):491-6. doi: 10.1016/j.jpsychores.2013.07.010. PMID: 24182640.
47. 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. doi: 10.4997/JRCPE.2010.404. PMID: 21132135.
48. Nijrolder I, van der Windt D, de Vries H, et al. Diagnoses during follow-up of patients presenting with fatigue in primary care. *CMAJ.* 2009;181(10):683-7. doi: 10.1503/cmaj.090647. PMID: 19858240.
49. Clark LV, Pesola F, Thomas JM, et al. Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. *Lancet.* 2017;390(10092):363-73. doi: 10.1016/S0140-6736(16)32589-2. PMID: 28648402.

50. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*. 1997;314(7095):1647-52. doi: 10.1136/bmj.314.7095.1647. PMID: 9180065.
51. 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.
52. 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.
53. Powell P, Bentall RP, Nye FJ, et al. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ*. 2001;322(7283):387-90. PMID: 11179154.
54. Wallman KE, Morton AR, Goodman C, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust*. 2004;180(9):444-8. PMID: 15115421.
55. 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. doi: 10.1136/bmj.c1777. PMID: 20418251.
56. Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry*. 1998;172:485-90. PMID: 9828987.
57. Windthorst P, Mazurak N, Kuske M, et al. Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: an exploratory pilot study. *J Psychosom Res*. 2017;93:6-13. doi: 10.1016/j.jpsychores.2016.11.014. PMID: 28107894.
58. Powell P, Bentall RP, Nye FJ, et al. Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. *Br J Psychiatry*. 2004;184:142-6. PMID: 14754826.
59. Sharpe M, Goldsmith KA, Johnson AL, et al. Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. *Lancet Psychiatry*. 2015;2(12):1067-74. doi: 10.1016/S2215-0366(15)00317-X. PMID: 26521770.
60. Bourke JH, Johnson AL, Sharpe M, et al. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. *Psychol Med*. 2014;44(7):1545-52. doi: 10.1017/S0033291713002201. PMID: 23967878.
61. Wilshire C, Kindlon T, Matthees A, et al. Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial. *Fatigue*. 2017;5(1):43-56. doi: 10.1080/21641846.2017.1259724.
62. Wilshire CE, Kindlon T, Courtney R, et al. Rethinking the treatment of chronic fatigue syndrome-a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. *BMC Psychol*. 2018;6(1):6. doi: 10.1186/s40359-018-0218-3. PMID: 29562932.
63. 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. doi: 10.1111/j.1365-2362.2009.02225.x. PMID: 19912315.
64. 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. doi: 10.1017/S1352465811000543. PMID: 21929831.
65. Deale A, Chalder T, Marks I, et al. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry*. 1997;154(3):408-14. PMID: 9054791.
66. Janse A, Worm-Smeitink M, Bleijenberg G, et al. Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. *Br J Psychiatry*. 2018;212(2):112-8. doi: 10.1192/bjp.2017.22. PMID: 29436329.

67. 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. doi: 10.1192/bjp.bp.108.051292. PMID: 18827302.
68. Lopez C, Antoni M, Penedo F, et al. A pilot study of cognitive behavioral stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. *J Psychosom Res*. 2011;70(4):328-34. doi: 10.1016/j.jpsychores.2010.11.010. PMID: 21414452.
69. 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.
70. 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.
71. Stubhaug B, Lie SA, Ursin H, et al. Cognitive-behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial. *Br J Psychiatry*. 2008;192(3):217-23. doi: 10.1192/bjp.bp.106.031815. PMID: 18310583.
72. Tummers M, Knoop H, van Dam A, et al. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. *Psychol Med*. 2012;42(10):2205-15. doi: 10.1017/S0033291712000232. PMID: 22354999.
73. Wiborg JF, van Bussel J, van Dijk A, et al. Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. *Psychother Psychosom*. 2015;84(6):368-76. doi: 10.1159/000438867. PMID: 26402868.
74. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry*. 2001;158(12):2038-42. PMID: 11729022.
75. 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.
76. Rimes KA, Wingrove J. Mindfulness-based cognitive therapy for people with chronic fatigue syndrome still experiencing excessive fatigue after cognitive behaviour therapy: a pilot randomized study. *Clin Psychol Psychother*. 2013;20(2):107-17. doi: 10.1002/cpp.793. PMID: 21983916.
77. Surawy C, Roberts J, Silver A. The effect of mindfulness training on mood and measures of fatigue, activity, and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: a series of exploratory studies. *Behav Cogn Psychother*. 2005;33(1):103-9. doi: 10.1017/S135246580400181X.
78. Friedberg F, Adamowicz J, Caikauskaite I, et al. Efficacy of two delivery modes of behavioral self-management in severe chronic fatigue syndrome. *Fatigue*. 2016;4(3):158-74. doi: 10.1080/21641846.2016.1205876.
79. Pinxsterhuis I, Sandvik L, Strand EB, et al. Effectiveness of a group-based self-management program for people with chronic fatigue syndrome: a randomized controlled trial. *Clin Rehabil*. 2017;31(1):93-103. doi: 10.1177/0269215515621362. PMID: 26672998.
80. Al-Haggar MS, Al-Naggar ZA, Abdel-Salam MA. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. *J Pediatr Neurol*. 2006;4(3):161-9. doi: 10.1055/s-0035-1557320.
81. Chalder T, Deary V, Husain K, et al. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychol Med*. 2010;40(8):1269-79. doi: 10.1017/S003329170999153X. PMID: 19891804.

82. Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012;379(9824):1412-8. doi: 10.1016/S0140-6736(12)60025-7. PMID: 22385683.
83. Stulemeijer M, de Jong LW, Fiselier TJ, et al. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ*. 2005;330(7481):14. PMID: 15585538.
84. Wright B, Ashby B, Beverley D, et al. A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents. *Arch Dis Child*. 2005;90(4):369-72. PMID: 15781925.
85. Crawley EM, Gaunt DM, Garfield K, et al. Clinical and cost-effectiveness of the lightning process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child*. 2018;103(2):155-64. doi: 10.1136/archdischild-2017-313375. PMID: 28931531.
86. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. *Behav Res Ther*. 2012;50(11):719-25. doi: 10.1016/j.brat.2012.08.005. PMID: 22985998.
87. Nijhof SL, Priesterbach LP, Uiterwaal CS, et al. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. *Pediatrics*. 2013;131(6):e1788-95. doi: 10.1542/peds.2012-2007. PMID: 23669515.
88. Bentall RP, Powell P, Nye FJ, et al. Predictors of response to treatment for chronic fatigue syndrome. *Br J Psychiatry*. 2002;181:248-52. PMID: 12204931.
89. Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PLoS ONE*. 2011;6(10):e26358. doi: 10.1371/journal.pone.0026358. PMID: 22039471.
90. Fluge O, Rekeland IG, Lien K, et al. B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med*. 2019;170(9):585-93. doi: 10.7326/m18-1451. PMID: 30934066.
91. 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.
92. McKenzie R, Reynolds JC, O'Fallon A, et al. Decreased bone mineral density during low dose glucocorticoid administration in a randomized, placebo controlled trial. *J Rheumatol*. 2000;27(9):2222-6. PMID: 10990237.
93. 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. doi: 10.1002/jmv.23713. PMID: 23959519.
94. See DM, Tilles JG. Alpha-interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest*. 1996;25(1-2):153-64. PMID: 8675231.
95. 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.
96. 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. doi: 10.1371/journal.pone.0031334. PMID: 22431963.
97. Sulheim D, Fagermoen E, Winger A, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatrics*. 2014;168(4):351-60. doi: 10.1001/jamapediatrics.2013.4647. PMID: 24493300.

98. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet*. 1996;347(9005):858-61. PMID: 8622391.
99. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med*. 1997;103(1):38-43. PMID: 9236484.
100. 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.
101. Roerink ME, Bredie SJH, Heijnen M, et al. Cytokine inhibition in patients with chronic fatigue syndrome: a randomized trial. *Ann Intern Med*. 2017;166(8):557-64. doi: 10.7326/M16-2391. PMID: 28265678.
102. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res*. 1997;31(1):133-47. PMID: 9201655.
103. 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.
104. Montoya JG, Anderson JN, Adolphs DL, et al. KPAX002 as a treatment for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a prospective, randomized trial. *Int J Clin Exp Med*. 2018;11(3):2890-900.
105. Arnold LM, Blom TJ, Welge JA, et al. A randomized, placebo-controlled, double-blinded trial of duloxetine in the treatment of general fatigue in patients with chronic fatigue syndrome. *Psychosomatics*. 2015;56(3):242-53. doi: 10.1016/j.psych.2014.12.003. PMID: 25660434.
106. 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.
107. Malaguarnera M, Gargante MP, Cristaldi E, et al. Acetyl L-Carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr*. 2008;46(2):181-90. PMID: 17658628.
108. Ostojic SM, Stojanovic M, Drid P, et al. Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. *Nutrients*. 2016;8(2):72. doi: 10.3390/nu8020072. PMID: 26840330.
109. The GKH, Bleijenberg G, van der Meer JWM. The effect of acelydine in chronic fatigue syndrome: a randomized controlled trial. *PLoS Clin Trials*. 2007;2(5):e19. PMID: 17525791.
110. 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.
111. Öckerman PA. Antioxidant treatment of chronic fatigue syndrome. *Clin Pract Alternat Med*. 2000;1(2):88-91.
112. 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.
113. Hobday RA, Thomas S, O'Donovan A, et al. Dietary intervention in chronic fatigue syndrome. *J Hum Nutr Diet*. 2008;21(2):141-9. doi: 10.1111/j.1365-277X.2008.00857.x. PMID: 18339054.
114. 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.
115. Li DQ, Li ZC, Dai ZY. Selective serotonin reuptake inhibitor combined with dengzhanshengmai capsule improves the fatigue symptoms: a 12-week open-label pilot study. *Int J Clin Exp Med*. 2015;8(7):11811-7. PMID: 26380022.

116. 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. *Evid Based Complement Alternat Med*. 2013 doi: 10.1155/2013/485341. PMID: 23983785.
117. Dybwad M, Frøslie K, Stanghelle J. Work capacity, fatigue and health related quality of life in patients with myalgic encephalopathy or chronic fatigue syndrome, before and after qigong therapy, a randomized controlled study. *Nesoddtangen, Norway: Sunnaas Rehabilitation Hospital*. 2007.
118. 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. doi: 10.1007/s12160-012-9381-6. PMID: 22736201.
119. Oka T, Tanahashi T, Chijiwa T, et al. Isometric yoga improves the fatigue and pain of patients with chronic fatigue syndrome who are resistant to conventional therapy: a randomized, controlled trial. *Biopsychosoc Med*. 2014;14(27):1-9. doi: 10.1186/s13030-014-0027-8. PMID: 25525457.
120. Huanan L, Wang J, Zhang W, et al. Chronic fatigue syndrome treated by the traditional Chinese procedure abdominal tuina: a randomized controlled clinical trial. *J Tradit Chin Med*. 2017;37(6):819-26. doi: 10.1016/S0254-6272(18)30046-3.
121. 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. doi: 10.1159/000116609. PMID: 18277062.
122. Day SJ, Altman DG. Statistics notes: blinding in clinical trials and other studies. *BMJ*. 2000;321(7259):504. doi: 10.1136/bmj.321.7259.504. PMID: 10948038.
123. Whitehead L, Champion P. Can general practitioners manage chronic fatigue syndrome? A controlled trial. *J Chronic Fatigue Syndr*. 2002;10(1):55-64. doi: 10.1300/J092v10n01_05.
124. Larun L, Brurberg KG, Odgaard-Jensen J, et al. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2019;10:Cd003200. doi: 10.1002/14651858.CD003200.pub8. PMID: 31577366.
125. Collatz A, Johnston SC, Staines DR, et al. A systematic review of drug therapies for chronic fatigue syndrome/myalgic encephalomyelitis. *Clin Ther*. 2016;38(6):1263-71.e9. doi: 10.1016/j.clinthera.2016.04.038. PMID: 27229907.
126. Price JR, Mitchell E, Tidy E, et al. Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev*. 2009 (2).
127. Devereaux PJ, Bhandari M, Clarke M, et al. Need for expertise based randomised controlled trials. *BMJ*. 2005;330(7482):88. doi: 10.1136/bmj.330.7482.88. PMID: 15637373.

Abbreviations and Acronyms

Abbreviation	Definition
ACT	anaerobic activity therapy
ADL	activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AMD	adjusted mean difference
ANOVA	analysis of variance
AP	anteroposterior
APT	adaptive pacing therapy
ARD	adjusted risk difference
BDI	Beck Depression Inventory
BMI	body mass index
BPI	Brief Pain Inventory
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CDs	compact discs
CFS	chronic fatigue syndrome
CGI	Clinical Global Impression of Change
CGS-S	Clinical Global Impression Severity Score
CHQ-CF	child health questionnaire-child form
CI	confidence interval
CIBEROBN	Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion
CNS	central nervous system
COG	cognitive therapy
COPD	Chronic Obstructive Pulmonary Disease
Ctr	Counter
DF	degrees of freedom
DSM-III-R	Diagnostic Statistical Manual third edition revised
DSM-IV	Diagnostic Statistical Manual IV
EPC	Evidence-based Practice Center
ESS	Epworth Sleepiness Scale
FDA	U.S. Food and Drug Administration
FINE	Fatigue Intervention by Nurses Evaluation
FIQ	Fibromyalgia Impact Questionnaire
FITNET	fatigue in teenagers on the internet
FSM	fatigue self-management
FSM:ACT	fatigue self-management with web diaries and actigraphs
FSM:CTR	fatigue self-management with paper diaries and step counters
GAA	guadidinoacetic acid
GES	guided graded exercise self-help
GET	graded exercise therapy
GETSET	guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome
GHQ	general health questionnaire
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-anxiety
HADS-D	Hospital Anxiety and Depression Scale-depression
HAM-D	Hamilton Depression Rating Scale
HHV-6	human herpes virus-6
HRSD	Hamilton Rating Scale
HTA	Health Technology Assessment

iCBT	internet-based cognitive-behavioral therapy
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10th revision
IGF1	insulin-like growth factor-1
IGFBP3	insulin like growth factor binding protein 3
IgG	immunoglobulin G
IOM	Institute of Medicine
IQR	interquartile range
ITT	intention to treat
IV	Instrumental variable
IV	intravenous
KFSS	Krupp Fatigue Severity Scale
KPS	Karnofsky Performance Scale
KSQ	Karolinska Sleep Questionnaire
MBCT	mindfulness-based cognitive therapy
MCT	multi convergent therapy
MD	mean difference
MDD	major depressive disorder
ME	myalgic encephalomyelitis
MFI-20	Multidimensional Fatigue Inventory 20-item
M-H	Mantel-Haenszel test
MOS	Medical Outcome Study
MOS-SF	Medical Outcome Study – Short Form
MRI	magnetic resonance imaging
NAFKAM	Norway's National Research Center in Complementary and Alternative Medicine
NH&MRC	National Health and Medical Research Council
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	number needed to treat
NR	not reported
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PACE	pacing, graded activity, cognitive behavior therapy
PF	physical function
PHQ	patient health questionnaire
PICOTS	populations, interventions, comparators, outcomes, timing, and setting/study design
POMS	profile of mood states
QLI	quality of life index
QLS	quality of life score
QOL	Quality of Life
QOLI	quality of life inventory
QOL-SF	quality of life short form
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SCL-90	symptom checklist 90
SCL-90-R	symptom checklist 90-revised
SD	standard deviation
SE	standard error

SEID	systemic exertion intolerance disease
SEM	standard error of the mean
SES	standardized effect sizes
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SGR	support the activities of research groups
SIP-8	Sickness Impact Profile 8-item
SMC	specialist medical care
SMD	standardized mean difference
SOE	strength of evidence
SSRI	selective serotonin reuptake inhibitor
Std	standard
VAS	visual analogue scale
WMD	weighted mean difference
ZonMW	ZorgOnderzoek Nederland and Medische wetenschappen

Key Informants

Key Informants representing clinical, research, or patient perspectives in ME/CFS participated in calls with the EPC and CDC during the development of the key questions. 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. Key Informants were not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants were asked to disclose any financial conflicts of interest greater than \$5,000 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 list of Key Informants who participated in developing this report will be included in the final report.

Appendix A. Search Strategies

KQ 1-2

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to January 09, 2019

- 1 Fatigue Syndrome, Chronic/
- 2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
- 3 exp Diagnosis/
- 4 di.fs.
- 5 diagnos*.ti,ab,kf.
- 6 (1 or 2) and (3 or 4 or 5)
- 7 limit 6 to (english language and humans)
- 8 letter.pt.
- 9 7 not 8
- 10 limit 9 to yr="1988 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials December 2018

- 1 Fatigue Syndrome, Chronic/
- 2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
- 3 exp Diagnosis/
- 4 di.fs.
- 5 diagnos*.ti,ab,kf.
- 6 (1 or 2) and (3 or 4 or 5)
- 7 limit 6 to english language

Database: PsycINFO 1806 to January Week 1 2019

- 1 chronic fatigue syndrome/
- 2 exp Encephalomyelitis/
- 3 2 and myalgic.ti,ab,id.
- 4 ("chronic fatigue syndrome" or "myalgic encephalomyelitis").ti,ab,id.
- 5 exp diagnosis/
- 6 diagnos*.ti,ab,id.
- 7 1 or (2 and 3) or 4
- 8 (5 or 6) and 7
- 9 limit 8 to (human and english language)
- 10 limit 9 to yr="1988 -Current"

Database: Elsevier Embase® January 11, 2019

('chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab,kw OR 'myalgic encephalomyelitis':ti,ab,kw) AND ('diagnosis'/exp OR 'diagnosis':ti,ab,kw OR 'diagnostic':ti,ab,kw) AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'evidence based medicine'/de OR 'human'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de) AND ('article'/it OR 'article in press'/it OR 'review'/it) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

KQ 3

Database: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 10, 2019

- 1 Fatigue Syndrome, Chronic/
- 2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf. (
- 3 (dh or dt or pc or th).fs.
- 4 exp treatment outcome/
- 5 exp Complementary Therapies/
- 6 exp Counseling/
- 7 exp Psychotherapy/
- 8 exp Exercise Therapy/
- 9 exp Drug Therapy/
- 10 (treatment or therap* or intervention*).ti,ab,kw.
- 11 (1 or 2) and (or/3-10)
- 12 limit 11 to (english language and humans)
- 13 letter.pt.
- 14 12 not 13
- 15 limit 14 to yr="1988 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials December 2018

- 1 Fatigue Syndrome, Chronic/
- 2 ("chronic fatigue syndrome*" or "myalgic encephalomyelitis").ti,ab,kf.
- 3 (dh or dt or pc or th).fs.
- 4 exp treatment outcome/
- 5 exp Complementary Therapies/
- 6 exp Counseling/
- 7 exp Psychotherapy/
- 8 exp Exercise Therapy/
- 9 exp Drug Therapy/
- 10 (treatment or therap* or intervention*).ti,ab,kw.
- 11 (1 or 2) and (or/3-10)
- 12 limit 11 to english language

Database: PsycINFO 1806 to January Week 1 2019

- 1 chronic fatigue syndrome/
- 2 exp Encephalomyelitis/
- 3 2 and myalgic.ti,ab,id.
- 4 ("chronic fatigue syndrome" or "myalgic encephalomyelitis").ti,ab,id.
- 5 2 and 3
- 6 1 or 4 or 5
- 7 exp treatment outcomes/
- 8 exp treatment/
- 9 exp physical treatment methods/
- 10 (treatment or therap* or intervention*).ti,ab,id.

11 or/7-10
12 6 and 11
13 limit 12 to (human and english language)
14 limit 13 to yr="1988 -Current"

Database: Elsevier Embase® January 11, 2019

('chronic fatigue syndrome'/exp OR 'chronic fatigue syndrome':ti,ab,kw OR 'myalgic encephalomyelitis':ti,ab,kw) AND ('treatment outcome'/exp OR 'therapy'/exp OR 'treatment':ti,ab,kw OR 'therapy':ti,ab,kw OR 'intervention':ti,ab,kw) AND [english]/lim AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'double blind procedure'/de OR 'evidence based medicine'/de OR 'human'/de OR 'major clinical study'/de OR 'outcomes research'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) AND ('article'/it OR 'review'/it) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

All KQs

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 9, 2019

1 chronic fatigue syndrome.ti,ab.
2 myalgic encephalomyelitis.ti,ab.
3 1 or 2

Appendix B. ME/CFS PICOTS

	Include	Exclude
Population	<p><u>KQ 1, 2:</u> Persons presenting for possible ME/CFS</p> <p><u>KQ 3:</u> Persons diagnosed with ME, CFS, or both using standard criteria</p>	
Interventions	<p><u>KQ 1:</u> Conditions identified on bases of history, physical examination, or laboratory testing</p> <p><u>KQ 2:</u> Various diagnostic criteria</p> <p><u>KQ 3:</u> Forms of counseling and behavior therapy, graded exercise programs, complementary and alternative medicine (acupuncture, relaxation, massage, nutritional supplements, others), pathogenesis-based medications (e.g., immune modulators), and symptom-based medications (beta blockers, antidepressants, anxiolytics, stimulants, mineralcorticoids, ivabradine, others)</p>	<u>KQ 3:</u> Taxiod vaccines
Comparators	<p><u>KQ 1:</u> N/A</p> <p><u>KQ 2:</u> Diagnostic accuracy studies and diagnostic concordance studies</p> <p><u>KQ 3:</u> Placebo, no treatment, usual care, other active interventions (including combination therapies and head-to-head trials)</p>	<u>KQ 2, 3:</u> No comparator
Outcomes	<p><u>KQ 1:</u> Proportion of patients with diagnosis of other, Non-ME/CFS condition</p> <p><u>KQ 2:</u> Any potential benefit or harm from diagnosis (such as access to treatment, psychological harms, labeling, risk from diagnostic test, misdiagnosis, other)</p> <p><u>KQ 3:</u> 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), outcomes related to associated symptoms (psychiatric, gastrointestinal, autonomic dysfunction, orthostatic intolerance, urinary symptoms, multiple chemical sensitivity, and others), adverse effects of interventions, withdrawals and withdrawals due to adverse events, rates of adverse events due to interventions</p>	<u>KQ 1, 2, 3:</u> Not listed as an included outcome
Settings	All KQs: Clinical settings	
Timing	<p><u>KQ 1, 2:</u> Any duration</p> <p><u>KQ 3:</u> ≥12 weeks of follow-up</p>	<p><u>KQ 1:</u> None</p> <p><u>KQ 3:</u> <12 weeks of follow-up</p>

	Include	Exclude
Study types and designs	<p><u>All KQ:</u> Studies published in 1988 or after</p> <p><u>KQ 1, 2, 3:</u> Systematic reviews or meta-analyses of randomized or controlled clinical trials; primary reports of randomized or controlled clinical trials; and large prospective cohort studies for KQ 1, KQ 2, and evaluation of harms, if data are not available from randomized clinical trials</p>	<p><u>All KQ:</u> 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</p>

Appendix C. List of Included Studies

Al-Haggar MS, Al-Naggar ZA, Abdel-Salam MA. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. *J Pediatr Neurol.* 2006;4(3):161-9. doi: 10.1055/s-0035-1557320.

Arnold LM, Blom TJ, Welge JA, et al. A randomized, placebo-controlled, double-blinded trial of duloxetine in the treatment of general fatigue in patients with chronic fatigue syndrome. *Psychosomatics.* 2015;56(3):242-53. doi: 10.1016/j.psych.2014.12.003. PMID: 25660434.

Bentall RP, Powell P, Nye FJ, et al. Predictors of response to treatment for chronic fatigue syndrome. *Br J Psychiatry.* 2002;181:248-52. PMID: 12204931.

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.

Bourke JH, Johnson AL, Sharpe M, et al. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. *Psychol Med.* 2014;44(7):1545-52. doi: 10.1017/S0033291713002201. PMID: 23967878.

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. doi: 10.1186/1756-0500-6-309. PMID: 23915640.

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. doi: 10.1017/S1352465811000543. PMID: 21929831.

Chalder T, Deary V, Husain K, et al. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychol Med.* 2010;40(8):1269-79. doi: 10.1017/S003329170999153X. PMID: 19891804.

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. *Evid Based Complement Alternat Med.* 2013 doi: 10.1155/2013/485341. PMID: 23983785.

Clark LV, Pesola F, Thomas JM, et al. Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. *Lancet.* 2017;390(10092):363-73. doi: 10.1016/S0140-6736(16)32589-2. PMID: 28648402.

Crawley EM. Internet-based cognitive behavioural therapy (FITNET) is an effective treatment for adolescents with chronic fatigue syndrome. *Arch Dis Child Educ Pract Ed.* 2012;97(6):238. PMID: 22952037.

Crawley EM, Gaunt DM, Garfield K, et al. Clinical and cost-effectiveness of the lightning process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child.* 2018;103(2):155-64. doi: 10.1136/archdischild-2017-313375.

Deale A, Chalder T, Marks I, et al. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry.* 1997;154(3):408-14. PMID: 9054791.

- Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry*. 2001;158(12):2038-42. PMID: 11729022.
- Devasahayam A, Lawn T, Murphy M, et al. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: service evaluation survey. *JRSM Short Rep*. 2012;3(1):4. doi: 10.1258/shorts.2011.011127. PMID: 22299071.
- 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. doi: 10.1016/j.jpsychores.2014.04.002. PMID: 24913337.
- Dybwad M, Frøslie K, Stanghelle J. Work capacity, fatigue and health related quality of life in patients with myalgic encephalopathy or chronic fatigue syndrome, before and after qigong therapy, a randomized controlled study. Nesoddtangen, Norway: Sunnaas Rehabilitation Hospital. 2007.
- Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PLoS ONE*. 2011;6(10):e26358. doi: 10.1371/journal.pone.0026358. PMID: 22039471.
- Fluge O, Rekeland IG, Lien K, et al. B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med*. 2019;170(9):585-93. doi: 10.7326/m18-1451. PMID: 30934066.
- Friedberg F, Adamowicz J, Caikauskaite I, et al. Efficacy of two delivery modes of behavioral self-management in severe chronic fatigue syndrome. *Fatigue*. 2016;4(3):158-74. doi: 10.1080/21641846.2016.1205876.
- Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*. 1997;314(7095):1647-52. doi: 10.1136/bmj.314.7095.1647. PMID: 9180065.
- Goldsmith K, White P, Chalder T, et al. The PACE trial: Analysis of primary outcomes using composite measures of improvement. Wolfson Institute of Preventive Medicine, London, UK. 2016.
- Hlavaty LE, Brown MM, Jason LA. The effect of homework compliance on treatment outcomes for participants with myalgic encephalomyelitis/chronic fatigue syndrome. *Rehabil Psychol*. 2011;56(3):212-8. doi: 10.1037/a0024118. PMID: 21767035.
- 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. doi: 10.1007/s12160-012-9381-6. 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. doi: 10.1111/j.1365-277X.2008.00857.x. PMID: 18339054.
- Huanan L, Wang J, Zhang W, et al. Chronic fatigue syndrome treated by the traditional Chinese procedure abdominal tuina: a randomized controlled clinical trial. *J Tradit Chin Med*. 2017;37(6):819-26. doi: 10.1016/S0254-6272(18)30046-3.
- Janse A, Worm-Smeitink M, Bleijenberg G, et al. Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. *Br J Psychiatry*. 2018;212(2):112-8. doi: 10.1192/bjp.2017.22. PMID: 29436329.
- 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. doi: 10.1016/j.pec.2009.02.015. PMID: 19356884.
- 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.

- 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. doi: 10.1192/bjp.bp.108.051292. PMID: 18827302.
- Li DQ, Li ZC, Dai ZY. Selective serotonin reuptake inhibitor combined with dengzhanshengmai capsule improves the fatigue symptoms: a 12-week open-label pilot study. *Int J Clin Exp Med*. 2015;8(7):11811-7. PMID: 26380022.
- Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. *Behav Res Ther*. 2012;50(11):719-25. doi: 10.1016/j.brat.2012.08.005. PMID: 22985998.
- Lopez C, Antoni M, Penedo F, et al. A pilot study of cognitive behavioral stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. *J Psychosom Res*. 2011;70(4):328-34. doi: 10.1016/j.jpsychores.2010.11.010. PMID: 21414452.
- Malaguarnera M, Gargante MP, Cristaldi E, et al. Acetyl L-Carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr*. 2008;46(2):181-90. PMID: 17658628.
- Mariman A, Delesie L, Tobback E, et al. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. *J Psychosom Res*. 2013;75(5):491-6. doi: 10.1016/j.jpsychores.2013.07.010. PMID: 24182640.
- 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.
- McKenzie R, Reynolds JC, O'Fallon A, et al. Decreased bone mineral density during low dose glucocorticoid administration in a randomized, placebo controlled trial. *J Rheumatol*. 2000;27(9):2222-6. PMID: 10990237.
- Montoya JG, Anderson JN, Adolphs DL, et al. KPAX002 as a treatment for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a prospective, randomized trial. *Int J Clin Exp Med*. 2018;11(3):2890-900.
- 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. doi: 10.1002/jmv.23713. 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. doi: 10.4997/JRCPE.2010.404. PMID: 21132135.
- Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012;379(9824):1412-8. doi: 10.1016/S0140-6736(12)60025-7. PMID: 22385683.
- Nijhof SL, Priesterbach LP, Uiterwaal CS, et al. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. *Pediatrics*. 2013;131(6):e1788-95. doi: 10.1542/peds.2012-2007. PMID: 23669515.
- Nijrolder I, van der Windt D, de Vries H, et al. Diagnoses during follow-up of patients presenting with fatigue in primary care. *CMAJ*. 2009;181(10):683-7. doi: 10.1503/cmaj.090647. PMID: 19858240.

- 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.
- Oka T, Tanahashi T, Chijiwa T, et al. Isometric yoga improves the fatigue and pain of patients with chronic fatigue syndrome who are resistant to conventional therapy: a randomized, controlled trial. *Biopsychosoc Med*. 2014;8doi: 10.1186/s13030-014-0027-8. PMID: 25525457.
- Ostojic SM, Stojanovic M, Drid P, et al. Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. *Nutrients*. 2016;8(2):72. doi: 10.3390/nu8020072. PMID: 26840330.
- 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.
- Pinxsterhuis I, Sandvik L, Strand EB, et al. Effectiveness of a group-based self-management program for people with chronic fatigue syndrome: a randomized controlled trial. *Clin Rehabil*. 2017;31(1):93-103. doi: 10.1177/0269215515621362. PMID: 26672998.
- Powell P, Bentall RP, Nye FJ, et al. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ*. 2001;322(7283):387-90. PMID: 11179154.
- Powell P, Bentall RP, Nye FJ, et al. Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. *Br J Psychiatry*. 2004;184:142-6. PMID: 14754826.
- Rimes KA, Wingrove J. Mindfulness-based cognitive therapy for people with chronic fatigue syndrome still experiencing excessive fatigue after cognitive behaviour therapy: a pilot randomized study. *Clin Psychol Psychother*. 2013;20(2):107-17. doi: 10.1002/cpp.793. PMID: 21983916.
- Roerink ME, Bredie SJH, Heijnen M, et al. Cytokine inhibition in patients with chronic fatigue syndrome: a randomized trial. *Ann Intern Med*. 2017;166(8):557-64. doi: 10.7326/M16-2391. PMID: 28265678.
- Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res*. 1997;31(1):133-47. PMID: 9201655.
- See DM, Tilles JG. Alpha-interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest*. 1996;25(1-2):153-64. PMID: 8675231.
- Sharpe M, Goldsmith KA, Johnson AL, et al. Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. *Lancet Psychiatry*. 2015;2(12):1067-74. doi: 10.1016/S2215-0366(15)00317-X. PMID: 26521770.
- 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.
- Stadje R, Dornieden K, Baum E, et al. The differential diagnosis of tiredness: a systematic review. *BMC Fam Pract*. 2016;17(1):147. PMID: 27765009.
- 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. doi: 10.1371/journal.pone.0031334. PMID: 22431963.

Stubhaug B, Lie SA, Ursin H, et al. Cognitive-behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial. *Br J Psychiatry*. 2008;192(3):217-23. doi: 10.1192/bjp.bp.106.031815. PMID: 18310583.

Stulemeijer M, de Jong LW, Fiselier TJ, et al. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ*. 2005;330(7481):14. PMID: 15585538.

Sulheim D, Fagermoen E, Winger A, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatrics*. 2014;168(4):351-60. doi: 10.1001/jamapediatrics.2013.4647. PMID: 24493300.

Surawy C, Roberts J, Silver A. The effect of mindfulness training on mood and measures of fatigue, activity, and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: a series of exploratory studies. *Behav Cogn Psychother*. 2005;33(1):103-9. doi: 10.1017/S135246580400181X.

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. doi: 10.1111/j.1365-2362.2009.02225.x. 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 acetyldine in chronic fatigue syndrome: a randomized controlled trial. *PLoS Clin Trials*. 2007;2(5):e19. PMID: 17525791.

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. doi: 10.1037/a0020052. PMID: 20873907.

Tummers M, Knoop H, van Dam A, et al. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. *Psychol Med*. 2012;42(10):2205-15. doi: 10.1017/S0033291712000232. PMID: 22354999.

Tummers M, Knoop H, van Dam A, et al. Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. *J Psychosom Res*. 2013;74(5):373-7. doi: 10.1016/j.jpsychores.2013.01.007. PMID: 23597323.

Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet*. 1996;347(9005):858-61. PMID: 8622391.

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.

Vink M, Vink-Niese A. Graded exercise therapy for myalgic encephalomyelitis/chronic fatigue syndrome is not effective and unsafe. Re-analysis of a Cochrane review. *Health Psychol Open*. 2018;5(2):2055102918805187. doi: 10.1177/2055102918805187. PMID: 30305916.

Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med*. 1997;103(1):38-43. PMID: 9236484.

- 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. doi: 10.1159/000116609. PMID: 18277062.
- Wallman KE, Morton AR, Goodman C, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust.* 2004;180(9):444-8. PMID: 15115421.
- 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. doi: 10.1136/bmj.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. doi: 10.1192/bjp.bp.111.107474. 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. doi: 10.1037/a0033561. 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. *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. doi: 10.1017/S0033291713000020. 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. doi: 10.1016/S0140-6736(11)60096-2. PMID: 21334061.
- Wiborg JF, van Bussel J, van Dijk A, et al. Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. *Psychother Psychosom.* 2015;84(6):368-76. doi: 10.1159/000438867. PMID: 26402868.
- 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.
- Wilshire C, Kindlon T, Matthees A, et al. Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial. *Fatigue.* 2017;5(1):43-56. doi: 10.1080/21641846.2017.1259724.
- Wilshire CE, Kindlon T, Courtney R, et al. Rethinking the treatment of chronic fatigue syndrome-a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. *BMC Psychol.* 2018;6(1):6. doi: 10.1186/s40359-018-0218-3. PMID: 29562932.
- Windthorst P, Mazurak N, Kuske M, et al. Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: an exploratory pilot study. *J Psychosom Res.* 2017;93:6-13. doi: 10.1016/j.jpsychores.2016.11.014. PMID: 28107894.
- Wright B, Ashby B, Beverley D, et al. A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents. *Arch Dis Child.* 2005;90(4):369-72. PMID: 15781925.

Appendix D. List of Excluded Studies

Aaron LA, Buchwald D. Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. *Best Pract Res Clin Rheumatol*. 2003;17(4):563-74. PMID: 12849712. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

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. Excluded: excluded population.

Adamowicz JL, Caikauskaite I, Friedberg F. Defining recovery in chronic fatigue syndrome: a critical review. *Qual Life Res*. 2014;23(9):2407-16. doi: 10.1007/s11136-014-0705-9. PMID: 24791749. Excluded: excluded outcome.

Adamowicz JL, Caikauskaite I, Friedberg F, et al. Patient change attributions in self-management of severe chronic fatigue syndrome. *Fatigue*. 2017;5(1):21-32. doi: 10.1080/21641846.2017.1278634. Excluded: excluded study design for Key Question.

Adams D, Wu T, Tai S, et al. Traditional Chinese medicinal herbs for idiopathic chronic fatigue and chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2007 (1)doi: 10.1002/14651858.CD006348. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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*. 2018 (10) PMID: 30321452. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Adolphe AB. Chronic fatigue syndrome: possible effective treatment with nifedipine. *Am J Med*. 1988;85(6):892. PMID: 2848418. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Allen J, Murray A, Di Maria C, et al. Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis-a new potential diagnostic biomarker. *Physiol Meas*. 2012;33(2):231-41. doi: 10.1088/0967-3334/33/2/231. PMID: 22273713. Excluded: excluded outcome.

Alraek T, Lee MS, Choi TY, et al. Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. *BMC Altern Med*. 2011;11:87. doi: 10.1186/1472-6882-11-87. PMID: 21982120. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Ambrogetti A, Olson LG. Consideration of narcolepsy in the differential diagnosis of chronic fatigue syndrome. *Med J Aust*. 1994;160(7):426-9. PMID: 8007866. Excluded: excluded study design for Key Question.

Amihaesei IC, Cojocaru E. Main neuroendocrine features, diagnosis and therapeutic possibilities in the chronic fatigue syndrome, an underdiagnosed entity. *Rev Med Chir Soc Med Nat Iasi*. 2014;118(3):688-91. PMID: 25341286. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

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. Excluded: excluded study design for Key Question.

Anand AC, Kumar R, Rao MK, et al. Low grade pyrexia: is it chronic fatigue syndrome? *J Assoc Physicians India*. 1994;42(8):606-8. PMID: 7868552. Excluded: excluded population.

Anbu AT, Cleary AG. Chronic fatigue syndrome/myalgic encephalopathy in children. *Paediatr Child Health*. 2009;19(2):84-9. doi: 10.1016/j.paed.2008.11.001. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

- 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. Excluded: excluded outcome.
- Anderson VR, Jason LA, Hlavaty LE. A qualitative natural history study of ME/CFS in the community. *Health Care Women Int.* 2014;35(1):3-26. doi: 10.1080/07399332.2012.684816. PMID: 23445264. Excluded: excluded outcome.
- Andersson G, Rozental A, Shafran R, et al. Long-term effects of internet-supported cognitive behaviour therapy. *Expert Rev Neurother.* 2018;18(1):21-8. doi: 10.1080/14737175.2018.1400381. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Andersson M, Bagby JR, Dyrehag LE, et al. Effects of staphylococcus toxoid vaccine on pain and fatigue in patients with fibromyalgia/chronic fatigue syndrome. *Eur J Pain.* 1998;2(2):133-42. PMID: 10700309. Excluded: excluded intervention.
- Antoni MH, Brickman A, Lutgendorf S, et al. Psychosocial correlates of illness burden in chronic fatigue syndrome. *Clin Infect Dis.* 1994;18 Suppl 1:S73-8. PMID: 8148457. Excluded: excluded outcome.
- Arpino C, Carrieri MP, Valesini G, et al. Idiopathic chronic fatigue and chronic fatigue syndrome: a comparison of two case-definitions. *Ann Ist Super Sanita.* 1999;35(3):435-41. PMID: 10721210. Excluded: excluded outcome.
- Arroll MA, Attree EA, Marshall CL, et al. Pilot study investigating the utility of a specialized online symptom management program for individuals with myalgic encephalomyelitis/chronic fatigue syndrome as compared to an online meditation program. *Psychol Res Behav Manag.* 2014;7 PMID: 25214803. Excluded: inadequate duration.
- Arroll MA, Howard A. A preliminary prospective study of nutritional, psychological and combined therapies for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in a private care setting. *BMJ Open.* 2012;2(6)doi: 10.1136/bmjopen-2012-001079. Excluded: excluded study design for Key Question.
- 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. Excluded: excluded population.
- Ash-Bernal R, Wall C, 3rd, Komaroff AL, et al. Vestibular function test anomalies in patients with chronic fatigue syndrome. *Acta Otolaryngol.* 1995;115(1):9-17. PMID: 7762393. Excluded: excluded outcome.
- Ashby B, Wright B, Jordan J. Chronic fatigue syndrome: an evaluation of a community based management programme for adolescents and their families. *Child Adol Ment H.* 2006;11(1):13-8. doi: 10.1111/j.1475-3588.2005.00383.x. Excluded: excluded study design for Key Question.
- 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. Excluded: excluded outcome.
- Asprusten TT, Fagermoen E, Sulheim D, et al. Study findings challenge the content validity of the Canadian consensus criteria for adolescent chronic fatigue syndrome. *Acta Paediatr.* 2015;104(5):498-503. doi: 10.1111/apa.12950. PMID: 25640602. Excluded: excluded outcome.
- 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. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

Awdry R. Homeopathy may help ME. *Int J Alternat Complement Med.* 1996;14(3):12-6. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Ax S, Gregg VH, Jones D. Chronic fatigue syndrome: sufferers' evaluation of medical support. *J R Soc Med.* 1997;90(5):250-4. PMID: 9204018. Excluded: excluded outcome.

Axe EK, Satz P, Rasgon NL, et al. Major depressive disorder in chronic fatigue syndrome: a CDC surveillance study. *J Chronic Fatigue Syndr.* 2004;12(3):7-23. doi: 10.1300/J092v12n03_02. Excluded: excluded population.

Bakken IJ, Tveito K, Aaberg KM, et al. Comorbidities treated in primary care in children with chronic fatigue syndrome / myalgic encephalomyelitis: a nationwide registry linkage study from Norway. *BMC Fam Pract.* 2016;17(1):128. doi: 10.1186/s12875-016-0527-7. PMID: 27590471. Excluded: excluded study design for Key Question.

Bakken IJ, Tveito K, Gunnes N, et al. Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008-2012. *BMC Med.* 2014;12:167. doi: 10.1186/s12916-014-0167-5. PMID: 25274261. Excluded: excluded outcome.

Bakker RJ, van de Putte EM, Kuis W, et al. Effects of an educational video film in fatigued children and adolescents: a randomised controlled trial. *Arch Dis Child.* 2011;96(5):457-60. doi: 10.1136/adc.2009.172072. PMID: 20861404. Excluded: excluded population.

Banerjee A, Hendrick P, Bhattacharjee P, et al. A systematic review of outcome measures utilised to assess self-management in clinical trials in patients with chronic pain. *Patient Educ Couns.* 2018;101(5):767-78. doi: 10.1016/j.pec.2017.12.002. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Baos S, Brigden A, Anderson E, et al. Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to activity management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial. *Trials.* 2018;19(1)doi: 10.1186/s13063-018-2500-3. PMID: 29471861. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Baraniuk JN. Chronic fatigue syndrome prevalence is grossly overestimated using Oxford criteria compared to Centers for Disease Control (Fukuda) criteria in a U.S. population study. *Fatigue.* 2017;5(4):215-30. doi: 10.1080/21641846.2017.1353578. Excluded: excluded outcome.

Baraniuk JN, Clauw DJ, Gaumont E. Rhinitis symptoms in chronic fatigue syndrome. *Ann Allergy Asthma Immunol.* 1998;81(4):359-65. PMID: 9809501. Excluded: excluded outcome.

Barlow JH, Ellard DR. Psycho-educational interventions for children with chronic disease, parents and siblings: an overview of the research evidence base. *Child Care Health Dev.* 2004;30(6):637-45. PMID: 15527474. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Barth A, Schlögelhofer M, Itzlinger U, et al. Diagnostic management of patients suffering from chronic fatigue. *Arbeitsmedizin Sozialmedizin Umweltmedizin.* 2004;39(3):130-2. Excluded: not English but possibly relevant.

Bateman L, Darakjy S, Klimas N, et al. Chronic fatigue syndrome and co-morbid and consequent conditions: evidence from a multi-site clinical epidemiology study. *Fatigue.* 2015;3(1):1-15. doi: 10.1080/21641846.2014.978109. Excluded: excluded population.

Bates DW, Buchwald D, Lee J, et al. A comparison of case definitions of chronic fatigue syndrome. *Clin Infect Dis.* 1994;18 Suppl 1:S11-5. PMID: 8148436. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

- Baumer JH. Management of chronic fatigue syndrome/myalgic encephalopathy (CFS/ME). *Arch Dis Child*. 2005;90(2):ep46-ep50. doi: 10.1136/adc.2005.080085. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- 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. Excluded: excluded study design for Key Question.
- Belcaro G, Cornelli U, Luzzi R, et al. Robuvit (quercus robur extract) supplementation in subjects with chronic fatigue syndrome and increased oxidative stress. A pilot registry study. *J Neurosurg Sci*. 2015;59(2):105-17. PMID: 25394351. Excluded: inadequate duration.
- Belgamwar RB, Jorsh MS, Knisely-Marpole A, et al. Multidisciplinary group treatment for chronic fatigue syndrome. *Prog Neurol Psychiatry*. 2009;13(1):27-9. doi: 10.1002/pnp.109. Excluded: excluded study design for Key Question.
- Bell DS. Illness onset characteristics in children with chronic fatigue syndrome and idiopathic chronic fatigue. *J Chronic Fatigue Syndr*. 1997;3(2):43-51. doi: 10.1300/J092v03n02_05. Excluded: excluded outcome.
- Bell IR, Patarca R, Baldwin CM, et al. Serum neopterin and somatization in women with chemical intolerance, depressives, and normals. *Neuropsychobiology*. 1998;38(1):13-8. PMID: 9701717. Excluded: excluded population.
- Bentler SE, Hartz AJ, Kuhn EM. Prospective observational study of treatments for unexplained chronic fatigue. *J Clin Psychiatry*. 2005;66(5):625-32. PMID: 15889950. Excluded: excluded population.
- Bethune CA, Wright LJ, Stoker SRG, et al. An audit of the investigation of patients with suspected chronic fatigue syndrome. *CPD Bulletin Immunology and Allergy*. 2003;3(2):51-3. Excluded: excluded outcome.
- Blazquez A, Guillamo E, Javierre C. Preliminary experience with dance movement therapy in patients with chronic fatigue syndrome. *Arts Psychother*. 2010;37(4):285-92. doi: 10.1016/j.aip.2010.05.003. Excluded: excluded study design for Key Question.
- Blockmans D, Persoons P, Van Houdenhove B, et al. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *Am J Med*. 2006;119(2):167.e23-30. PMID: 16443425. Excluded: inadequate duration.
- Bonvanie IJ, Kallesoe KH, Janssens KAM, et al. Psychological interventions for children with functional somatic symptoms: a systematic review and meta-analysis. *J Pediatr*. 2017;187:272-81.e17. doi: 10.1016/j.jpeds.2017.03.017. PMID: 28416243. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Bowman MA, Kirk JK, Michielutte R, et al. Use of amantadine for chronic fatigue syndrome. *Arch Intern Med*. 1997;157(11):1264-5. PMID: 9183239. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Bozzini S, Albergati A, Capelli E, et al. Cardiovascular characteristics of chronic fatigue syndrome. *Biomed Rep*. 2018;8(1):26-30. doi: 10.3892/br.2017.1024. Excluded: excluded outcome.
- Bralley JA, Lord RS. Treatment of chronic fatigue syndrome with specific amino acid supplementation. *Journal of Applied Nutrition*. 1994;46(3):74-8. Excluded: excluded study design for Key Question.
- Brigden A, Beasant L, Hollingworth W, et al. Managed activity graded exercise in teenagers and pre-adolescents (MAGENTA) feasibility randomised controlled trial: study protocol. *BMJ Open*. 2016;6(7):e011255. doi: 10.1136/bmjopen-2016-011255. PMID: 27377634. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

- Broadbent S, Coutts R. Graded versus intermittent exercise effects on lymphocytes in chronic fatigue syndrome. *Med Sci Sports Exerc.* 2016;48(9):1655-63. doi: 10.1249/MSS.0000000000000957. PMID: 27116645. Excluded: excluded outcome.
- Broadbent S, Coutts R. Intermittent and graded exercise effects on NK cell degranulation markers LAMP-1/LAMP-2 and CD8+CD38+ in chronic fatigue syndrome/myalgic encephalomyelitis. *Physiol Rep.* 2017;5(5)doi: 10.14814/phy2.13091. PMID: 28275109. Excluded: excluded outcome.
- Brook MG, Bannister BA, Weir WR. Interferon-alpha therapy for patients with chronic fatigue syndrome. *J Infect Dis.* 1993;168(3):791-2. doi: 10.1093/infdis/168.3.791. PMID: 8354926. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- 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. Excluded: excluded outcome.
- Bruce BK, Harrison TE, Bee SM, et al. Improvement in functioning and psychological distress in adolescents with postural orthostatic tachycardia syndrome following interdisciplinary treatment. *Clin Pediatr.* 2016;55(14):1300-4. doi: 10.1177/0009922816638663. PMID: 26983448. Excluded: excluded population.
- Buchwald D, Pascualy R, Bombardier C, et al. Sleep disorders in patients with chronic fatigue. *Clin Infect Dis.* 1994;18 Suppl 1:S68-72. PMID: 8148456. Excluded: excluded population.
- Buchwald D, Pearlman T, Kith P, et al. Screening for psychiatric disorders in chronic fatigue and chronic fatigue syndrome. *J Psychosom Res.* 1997;42(1):87-94. PMID: 9055216. Excluded: excluded population.
- Burgess M, Chalder T. Telephone cognitive behaviour therapy for chronic fatigue syndrome in secondary care: a case series. *Behav Cogn Psychother.* 2001;29(4):447-55. doi: 10.1017/S1352465801004052. Excluded: excluded study design for Key Question.
- Calvo N, Saez-Francas N, Valero S, et al. Comorbid personality disorders in chronic fatigue syndrome patients: a marker of psychopathological severity. *Actas Esp Psiquiatr.* 2015;43(2):58-65. PMID: 25812543. Excluded: excluded outcome.
- Campagnolo N, Johnston S, Collatz A, et al. Dietary and nutrition interventions for the therapeutic treatment of chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Hum Nutr Diet.* 2017;30(3):247-59. doi: 10.1111/jhn.12435. PMID: 28111818. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Carlo-Stella N, Cuccia M. Demographic and clinical aspects of an Italian patient population with chronic fatigue syndrome. *Reumatismo.* 2009;61(4):285-9. PMID: 20143004. Excluded: excluded outcome.
- Carruthers BM, Jain AK, de Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J Chronic Fatigue Syndr.* 2003;11(1):7-115. doi: 10.1300/J092v11n01_02. Excluded: excluded outcome.
- Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. *J Intern Med.* 2011;270(4):327-38. doi: 10.1111/j.1365-2796.2011.02428.x. PMID: 21777306. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Carter BD, Kronenberger WG, Edwards JF, et al. Differential diagnosis of chronic fatigue in children: behavioral and emotional dimensions. *J Dev Behav Pediatr.* 1996;17(1):16-21. PMID: 8675709. Excluded: excluded outcome.
- Carville SF, Arendt-Nielsen L, Bliddal H, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis.* 2008;67(4):536-41. PMID: 17644548. Excluded: excluded population.

Appendix D. List of Excluded Studies

Castro-Marrero J, Faro M, Aliste L, et al. Comorbidity in chronic fatigue syndrome/myalgic encephalomyelitis: a nationwide population-based cohort study. *Psychosomatics*. 2017;58(5):533-43. doi: 10.1016/j.psych.2017.04.010. PMID: 28596045. Excluded: excluded population.

Chalder T. Family focused cognitive behavioural therapy for adolescents with chronic fatigue syndrome. National research register. 2003. Excluded: unable to obtain.

Chalder T, Godfrey E, Ridsdale L, et al. Predictors of outcome in a fatigued population in primary care following a randomized controlled trial. *Psychol Med*. 2003;33(2):283-7. PMID: 12622306. Excluded: excluded population.

Chalder T, Goldsmith KA, White PD, et al. Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial. *Lancet Psychiatry*. 2015;2(2):141-52. doi: 10.1016/S2215-0366(14)00069-8. PMID: 26359750. Excluded: excluded intervention.

Chalder T, Goldsmith KA, White PD, et al. "Methods and outcome reporting in the PACE trial": author's reply. *Lancet Psychiatry*. 2015;2(4):e10-e11. doi: 10.1016/S2215-0366%2815%2900114-5. PMID: 26360091. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chalder T, Wallace P, Wessely S. Self-help treatment of chronic fatigue in the community: a randomized controlled trial. *Br J Health Psychol*. 1997;2(3):189-97. Excluded: excluded population.

Chan JS, Li A, Ng SM, et al. Adiponectin potentially contributes to the antidepressive effects of baduanjin qigong exercise in women with chronic fatigue syndrome-like illness. *Cell Transplant*. 2017;26(3):493-501. doi: 10.3727/096368916X694238. PMID: 27938498. Excluded: excluded population.

Chan JSM, Ho RTH, Chung KF, et al. Qigong exercise alleviates fatigue, anxiety, and depressive symptoms, improves sleep quality, and shortens sleep latency in persons with chronic fatigue syndrome-like illness. *Evid Based Complement Alternat Med*. 2014 doi: 10.1155/2014/106048. PMID: 25610473
Exclusion: 2/

Chen CW. Mechanism and clinical observation on acupuncture in chronic fatigue syndrome. Guangzhou University of Chinese Medicine Doctor's Thesis; 2010. Excluded: not English but possibly relevant.

Chen M, Chen L. Treatment of 60 cases with chronic fatigue syndrome by combination of acupuncture, massage and psychotherapy. *Shanghai J Acupunct Mox*. 2005:26-7. Excluded: not English but possibly relevant.

Chen XL, Xu K, Zhou J, et al. Clinical observation of moxibustion on Guanyuan and Qihai in treatment of chronic fatigue syndrome. *J New Chin Med*. 2011;43:109-10. Excluded: not English but possibly relevant.

Chen XL, Xu K, Zhou J, et al. Clinical observation on chronic fatigue syndrome treated by moxibustion at Guanyuan and Qihai. *J New Chin Med*. 2011:109-10. Excluded: not English but possibly relevant.

Chen XS, Zhang DZ. Acupuncture treatment of 45 cases of chronic fatigue syndrome. *Chin Acupunct Mox*. 2004:111. Excluded: not English but possibly relevant.

Chia JK, Chia AY. Ribavirin and interferon- α for the treatment of patients with chronic fatigue syndrome associated with persistent coxsackievirus B infection: a preliminary observation. *J Appl Res*. 2004;4(2):286-92. Excluded: excluded study design for Key Question.

Cho JH, Cho CK, Shin JW, et al. Myelophil, an extract mix of astragali radix and salviae radix, ameliorates chronic fatigue: a randomised, double-blind, controlled pilot study. *Complement Ther Med*. 2009;17(3):141-6. doi: 10.1016/j.ctim.2008.11.003. PMID: 19398067. Excluded: excluded population.

Appendix D. List of Excluded Studies

Christensen SS, Frostholm L, Ornbol E, et al. Changes in illness perceptions mediated the effect of cognitive behavioural therapy in severe functional somatic syndromes. *J Psychosom Res.* 2015;78(4):363-70. doi: 10.1016/j.jpsychores.2014.12.005. PMID: 25541119. Excluded: excluded population.

Christie D, Wilson C. CBT in paediatric and adolescent health settings: a review of practice-based evidence. *Pediatr Rehabil.* 2005;8(4):241-7. PMID: 16192099. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Chu L, Norris JL, Valencia IJ, et al. Patients diagnosed with Myalgic encephalomyelitis/chronic fatigue syndrome also fit systemic exertion intolerance disease criteria. *Fatigue.* 2017;5(2):114-28. doi: 10.1080/21641846.2017.1299079. Excluded: excluded population.

Ciccone DS, Natelson BH. Comorbid illness in women with chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosom Med.* 2003;65(2):268-75. PMID: 12651994. Excluded: excluded study design for Key Question.

Clapp LL, Richardson MT, Smith JF, et al. Acute effects of thirty minutes of light-intensity, intermittent exercise on patients with chronic fatigue syndrome. *Phys Ther.* 1999;79(8):749-56. PMID: 10440661. Excluded: excluded study design for Key Question.

Clar C, Tsertsvadze A, Court R, et al. Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: systematic review and update of UK evidence report. *Chiropr Man Therap.* 2014;22(1)doi: 10.1186/2045-709X-22-12. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Clauw DJ. Guided graded exercise self-help as a treatment of fatigue in chronic fatigue syndrome. *Lancet.* 2017;390(10092):335-6. doi: 10.1016/S0140-6736(17)30577-9. PMID: 28648401. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Cleare AJ, Heap E, Malhi GS, et al. Low-dose hydrocortisone in chronic fatigue syndrome: a randomised crossover trial. *Lancet.* 1999;353(9151):455-8. PMID: 9989716. Excluded: inadequate duration.

Clements A, Sharpe M, Simkin S, et al. Chronic fatigue syndrome: a qualitative investigation of patients' beliefs about the illness. *J Psychosom Res.* 1997;42(6):615-24. PMID: 9226609. Excluded: excluded outcome.

Cochran JW. Effect of modafinil on fatigue associated with neurological illnesses. *J Chronic Fatigue Syndr.* 2001;8(2):65-70. doi: 10.1300/J092v08n02_06. Excluded: excluded study design for Key Question.

Collatz A, Johnston SC, Staines DR, et al. A systematic review of drug therapies for chronic fatigue syndrome/myalgic encephalomyelitis. *Clin Ther.* 2016;38(6):1263-71.e9. doi: 10.1016/j.clinthera.2016.04.038. PMID: 27229907. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Collin SM, Heron J, Nikolaus S, et al. Chronic fatigue syndrome (CFS/ME) symptom-based phenotypes and 1-year treatment outcomes in two clinical cohorts of adult patients in the UK and the Netherlands. *J Psychosom Res.* 2018;104:29-34. doi: 10.1016/j.jpsychores.2017.11.007. PMID: 29275782. Excluded: excluded outcome.

Collinge W, Yarnold PR, Raskin E. Use of mind/body selfhealing practice predicts positive health transition in chronic fatigue syndrome: a controlled study. *Subtle Energies & Energy Medicine Journal Archives.* 1998;9(3):171-90. Excluded: excluded outcome.

Comiskey C, Larkan F. A national cross-sectional survey of diagnosed sufferers of myalgic encephalomyelitis/chronic fatigue syndrome: pathways to diagnosis, changes in quality of life and service priorities. *Ir J Med Sci.* 2010;179(4):501-5. doi: 10.1007/s11845-010-0585-0. PMID: 20872086. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

- Courtois I, Cools F, Calsius J. Effectiveness of body awareness interventions in fibromyalgia and chronic fatigue syndrome: a systematic review and meta-analysis. *J Bodywork Mov Ther.* 2015;19(1):35-56. doi: 10.1016/j.jbmt.2014.04.003. PMID: 25603742. Excluded: excluded population.
- Cox DL. Chronic fatigue syndrome: an evaluation of an occupational therapy inpatient intervention. *Br J Occup Ther.* 2002;65(10):461-8. Excluded: excluded study design for Key Question.
- Cox DL, Findley LJ. Severe and very severe patients with chronic fatigue syndrome: perceived outcome following an inpatient programme. *J Chronic Fatigue Syndr.* 2000;7(3):33-47. Excluded: excluded study design for Key Question.
- Craske NJM, Turner W, Zammit-Maempe J, et al. Qigong ameliorates symptoms of chronic fatigue: a pilot uncontrolled study. *Evid Based Complement Alternat Med.* 2009;6(2):265-70. doi: 10.1093/ecam/nem088. Excluded: excluded study design for Key Question.
- Crawley E, Hunt L, Stallard P. Anxiety in children with CFS/ME. *Eur Child Adolesc Psychiatry.* 2009;18(11):683-9. doi: 10.1007/s00787-009-0029-4. PMID: 19452195. Excluded: excluded population.
- Crawley E, Mills N, Beasant L, et al. The feasibility and acceptability of conducting a trial of specialist medical care and the lightning process in children with chronic fatigue syndrome: feasibility randomized controlled trial (SMILE study). *Trials.* 2013;14:415. doi: 10.1186/1745-6215-14-415. PMID: 24304689. Excluded: excluded outcome.
- Crawley E, Mills N, Hollingworth W, et al. Comparing specialist medical care with specialist medical care plus the lightning process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial). *Trials.* 2013;14:444. doi: 10.1186/1745-6215-14-444. PMID: 24370208. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Dahan H, Shir Y, Nicolau B, et al. Self-reported migraine and chronic fatigue syndrome are more prevalent in people with myofascial vs nonmyofascial temporomandibular disorders. *J Oral Facial Pain Headache.* 2016;30(1):7-13. doi: 10.11607/ofph.1550. PMID: 26817027. Excluded: excluded population.
- Dai QM, Chen HB. Treatment of 26 cases of chronic fatigue syndrome with Yiqiwenya and acupuncture. *Nei Mongol J Tradit Chin Med.* 2013. Excluded: not English but possibly relevant.
- Daniels J, Brigden A, Kacorova A. Anxiety and depression in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): examining the incidence of health anxiety in CFS/ME. *Psychol Psychother.* 2017;90(3):502-9. doi: 10.1111/papt.12118. PMID: 28244209. Excluded: excluded study design for Key Question.
- Dansie EJ, Furberg H, Afari N, et al. Conditions comorbid with chronic fatigue in a population-based sample. *Psychosomatics.* 2012;53(1):44-50. doi: 10.1016/j.psym.2011.04.001. PMID: 22221720. Excluded: excluded population.
- Darbishire L, Ridsdale L, Seed PT. Distinguishing patients with chronic fatigue from those with chronic fatigue syndrome: a diagnostic study in UK primary care. *Br J Gen Pract.* 2003;53(491):441-5. PMID: 12939888. Excluded: excluded outcome.
- 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. doi: 10.3109/09638288.2011.582925. PMID: 21682669. Excluded: excluded intervention.
- Davenport TE, Stevens SR, Baroni K, et al. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. *Disabil Rehabil.* 2011;33(19-20):1768-75. doi: 10.3109/09638288.2010.546936. PMID: 21208154. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

- Davies S, Crawley E. Chronic fatigue syndrome in children aged 11 years old and younger. *Arch Dis Child*. 2008;93(5):419-21. doi: 10.1136/adc.2007.126649. PMID: 18192312. Excluded: excluded outcome.
- De Becker P, Nijs J, Van H, et al. A double-blind, placebo-controlled study of acetylcysteine in combination with amino acids in patients with chronic fatigue syndrome. *AHMF Proceedings "Myalgic Encephalopathy/Chronic Fatigue Syndrome The Medical Practitioners' Challenge in 2001"*. 2001. Excluded: unable to obtain.
- Deale A, Wessely S. Diagnosis of psychiatric disorder in clinical evaluation of chronic fatigue syndrome. *J R Soc Med*. 2000;93(6):310-2. PMID: 10911826. Excluded: excluded outcome.
- Deale A, Wessely S. Patients' perceptions of medical care in chronic fatigue syndrome. *Soc Sci Med*. 2001;52(12):1859-64. PMID: 11352411. Excluded: excluded intervention.
- Denborough P, Kinsella S, Stevens J, et al. Evaluation of a multidisciplinary inpatient rehabilitation programme for adolescents with chronic fatigue syndrome. *Australas Psychiatry*. 2003;11(3):319-24. doi: 10.1046/j.1440-1665.2003.00559.x. Excluded: excluded study design for Key Question.
- Dennison L, Stanbrook R, Moss-Morris R, et al. Cognitive behavioural therapy and psycho-education for chronic fatigue syndrome in young people: reflections from the families' perspective. *Br J Health Psychol*. 2010;15(Pt 1):167-83. doi: 10.1348/135910709X440034. PMID: 19422732. Excluded: excluded outcome.
- 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. Excluded: excluded intervention.
- Dickson A, Knussen C, Flowers P. Stigma and the delegitimation experience: an interpretative phenomenological analysis of people living with chronic fatigue syndrome. *Psychology & Health*. 2007;22(7):851-67. doi: 10.1080/14768320600976224. Excluded: excluded study design for Key Question.
- Ding WY. Acupuncture at back-shu points of the yang organs in treatment of chronic fatigue syndrome: a randomized single-blinded controlled pilot research; 2011. Excluded: not English but possibly relevant.
- Dowsett E, Goudsmit E, Macintyre A, et al. Report from the national task force on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS), myalgic encephalomyelitis (ME). *Westcare*. 1994. Excluded: unable to obtain.
- Du J. Clinical study on treatment of chronic fatigue syndrome of stagnation of the liver-qi and spleen deficiency with acupuncture and moxibustion. *Changchun University of Chinese Medicine Master's Thesis*. 2010. Excluded: not English but possibly relevant.
- Du Y, Zhu Y. Acupuncture treatment of 42 cases of middle-aged women with chronic fatigue syndrome. *Guangxi J Tradit Chin Med*. 2006;29(5):39-40. Excluded: not English but possibly relevant.
- E JS, Wen BL. Effectiveness observation on treatment of chronic fatigue syndrome by combination of acupuncture and cupping. *Chin Arch Tradit Chin Med*. 2005;23(2):349-64. Excluded: not English but possibly relevant.
- Earl KE, Sakellariou GK, Sinclair M, et al. Vitamin D status in chronic fatigue syndrome/myalgic encephalomyelitis: a cohort study from the North-West of England. *BMJ Open*. 2017;7(11)doi: 10.1136/bmjopen-2016-015296. Excluded: excluded population.
- Edmonds M, McGuire H, Price J. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2004 (3):CD003200. PMID: 15266475. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Appendix D. List of Excluded Studies

Elnicki DM, Shockcor WT, Brick JE, et al. Evaluating the complaint of fatigue in primary care: diagnoses and outcomes. *Am J Med.* 1992;93(3):303-6. doi: 10.1016/0002-9343(92)90237-6. PMID: 1524082. Excluded: excluded outcome.

Engel CC. Tailored cognitive-behavioral therapy plus exercise training improved clinical and functional outcomes in fibromyalgia. *Ann Intern Med.* 2011;154(8):JC4-8. doi: 10.7326/0003-4819-154-8-201104190-02008. PMID: 21502646. Excluded: excluded population.

Ernst E. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. *J Psychosom Res.* 2004;57(5):503; author reply 4. PMID: 15581656. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Fagermoen E, Sulheim D, Winger A, et al. Effects of low-dose clonidine on cardiovascular and autonomic variables in adolescents with chronic fatigue: a randomized controlled trial. *BMC Pediatr.* 2015;15:117. doi: 10.1186/s12887-015-0428-2. PMID: 26357864. Excluded: inadequate duration.

Fagermoen E, Sulheim D, Winger A, et al. Clonidine in the treatment of adolescent chronic fatigue syndrome: a pilot study for the NorCAPITAL trial. *BMC Res Notes.* 2012;5:418. doi: 10.1186/1756-0500-5-418. PMID: 22871021. Excluded: excluded study design for Key Question.

Fan C, He RA, Zhou LJ, et al. Therapeutic effect of acupoint application of Chinese herbal medicine for chronic fatigue syndrome. *J Guangzhou Univ Tradit Chin Med.* 2011;28:484-5. Excluded: not English but possibly relevant.

Fang B, Wang JZ, Zhang HF. Clinical observation of Xiaopiling particles in treatment of chronic fatigue syndrome. *Mod J Integr Tradit Chin West Med.* 2007;16:1622-3. Excluded: not English but possibly relevant.

Fang YQ, Ren YL, Wang GT. Clinical observation of Fu Fang Shen Qi ointment in treatment of chronic fatigue syndrome. *Northwest Pharm J.* 2008;23:389-90. Excluded: not English but possibly relevant.

Field TM, Sunshine W, Hernandez-Reif M, et al. Massage therapy effects on depression and somatic symptoms in chronic fatigue syndrome. *J Chronic Fatigue Syndr.* 1997;3(3):43-51. Excluded: inadequate duration.

Fischler B, Le Bon O, Hoffmann G, et al. Sleep anomalies in the chronic fatigue syndrome. A comorbidity study. *Neuropsychobiology.* 1997;35(3):115-22. PMID: 9170115. Excluded: excluded outcome.

Fjorback LO, Arendt M, Ornbol E, et al. Mindfulness therapy for somatization disorder and functional somatic syndromes: randomized trial with one-year follow-up. *J Psychosom Res.* 2013;74(1):31-40. doi: 10.1016/j.jpsychores.2012.09.006. PMID: 23272986. Excluded: excluded population.

Fluge O, Risa K, Lunde S, et al. B-lymphocyte depletion in myalgic encephalopathy/chronic fatigue syndrome: an open-label phase II study with rituximab maintenance treatment. *PLoS ONE.* 2015;10(7):e0129898. doi: 10.1371/journal.pone.0129898. PMID: 26132314. Excluded: excluded study design for Key Question.

Forsyth LM, Preuss HG, MacDowell AL, et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol.* 1999;82(2):185-91. PMID: 10071523. Excluded: excluded outcome.

Friedberg F, Krupp LB. A comparison of cognitive behavioral treatment for chronic fatigue syndrome and primary depression. *Clin Infect Dis.* 1994;18 Suppl 1:S105-10. PMID: 8148435. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

Friedberg F, Napoli A, Coronel J, et al. Chronic fatigue self-management in primary care: a randomized trial. *Psychosom Med*. 2013;75(7):650-7. doi: 10.1097/PSY.0b013e31829dbed4. PMID: 23922399. Excluded: excluded population.

Friedberg F, Ngan MC, Chang J. Feasibility of a home-based self-management program for chronic fatigue. *Fatigue*. 2014;2(2):110-8. doi: 10.1080/21641846.2014.904066. Excluded: excluded population.

Fuhrer R. [Epidemiology of fatigue in general practice]. *Encephale*. 1994;20 Spec No 3:603-9. PMID: 7843057. Excluded: not English but possibly relevant.

Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med*. 1994;121(12):953-9. PMID: 7978722. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Fukuda S, Takashima S, Iwase M, et al. Development and validation of a new fatigue scale for fatigued subjects with and without chronic fatigue syndrome. *Fatigue Science for Human Health*. New York, NY: Springer Science + Business Media; US; 2008:89-102. Excluded: excluded comparator.

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. Excluded: excluded intervention.

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. Excluded: excluded population.

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. Excluded: excluded intervention.

Galeoto G, Sansoni J, Valenti D, et al. The effect of physiotherapy on fatigue and physical functioning in chronic fatigue syndrome patients: a systematic review. *Clin Ter*. 2018;169(4):e184-e8. doi: 10.7417/T.2018.2076. PMID: 30151552. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Gao J. Acupuncture and moxibustion treatment of 21 cases of chronic fatigue syndrome. *Liaoning J Tradit Chin Med*. 1998;25(5):224. Excluded: not English but possibly relevant.

Geraghty K, Jason L, Sunnquist M, et al. The cognitive behavioural model of chronic fatigue syndrome: critique of a flawed model. *Health Psychol Open*. 2019;6(1):2055102919838907. doi: 10.1177/2055102919838907. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Gialamas A, Beilby JJ, Pratt NL, et al. Investigating tiredness in Australian general practice. Do pathology tests help in diagnosis? *Aust Fam Physician*. 2003;32(8):663-6. PMID: 12973880. Excluded: excluded outcome.

Glady G, Tini-Kuhn P, Kähler D. Oligosol® Cu-Au-Ag for acute and chronic asthenia. An open study in outpatient practice. *Schweizerische Zeitschrift für GanzheitsMedizin*. 2002;14(5):290-5. Excluded: not English but possibly relevant.

Glazachev OS, Dudnik EN, Zagaynaya EE. Pharmacological treatment of patients with chronic fatigue syndrome. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2017;117(4):40-4. doi: 10.17116/jnevro20171174140-44. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

- Godfrey E, Chalder T, Ridsdale L, et al. Investigating the active ingredients of cognitive behaviour therapy and counselling for patients with chronic fatigue in primary care: developing a new process measure to assess treatment fidelity and predict outcome. *Br J Clin Psychol.* 2007;46(Pt 3):253-72. PMID: 17697477. Excluded: excluded outcome.
- Goldenberg DL, Simms RW, Geiger A, et al. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. *Arthritis Rheum.* 1990;33(3):381-7. PMID: 2317224. Excluded: excluded study design for Key Question.
- Goldsmith LP, Dunn G, Bentall RP, et al. Therapist effects and the impact of early therapeutic alliance on symptomatic outcome in chronic fatigue syndrome. *PLoS ONE.* 2015;10(12):e0144623. doi: 10.1371/journal.pone.0144623. PMID: 26657793. Excluded: excluded outcome.
- Gomborone JE, Gorard DA, Dewsnap PA, et al. Prevalence of irritable bowel syndrome in chronic fatigue. *J R Coll Physicians Lond.* 1996;30(6):512-3. PMID: 8961203. Excluded: excluded population.
- Goodnick PJ, Sandoval R. Psychotropic treatment of chronic fatigue syndrome and related disorders. *J Clin Psychiatry.* 1993;54(1):13-20. PMID: 8428892. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Goodnick PJ, Sandoval R, Brickman A, et al. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol Psychiatry.* 1992;32(9):834-8. PMID: 1450297. Excluded: excluded study design for Key Question.
- Gordon BA, Knapman LM, Lubitz L. Graduated exercise training and progressive resistance training in adolescents with chronic fatigue syndrome: a randomized controlled pilot study. *Clin Rehabil.* 2010;24(12):1072-9. doi: 10.1177/0269215510371429. PMID: 20605858. Excluded: inadequate duration.
- Gotts Z, Deary V, Newton JL, et al. Treatment of insomnia reduces fatigue in chronic fatigue syndrome in those able to comply with the intervention. *Fatigue.* 2016;4(4):208-16. doi: 10.1080/21641846.2016.1222699. Excluded: excluded study design for Key Question.
- Gotts ZM, Ellis JG, Newton JL, et al. The role of sleep in chronic fatigue syndrome: a narrative review. *Fatigue.* 2014;2(3):163-84. doi: 10.1080/21641846.2014.935607. Excluded: excluded population.
- Gou C, Tian F, Li N. Clinical research on treatment of chronic fatigue syndrome with moxibustion along the running course of meridians. *J Sichuan J Tradit Chin Med.* 2004;22(3):87-8. Excluded: not English but possibly relevant.
- Gou CY, Tian FW, Li N. Clinical study of moxibustion following channels in the treatment of chronic fatigue syndrome. *Sichuan J Tradit Chin Med.* 2004;22(3):87-8. Excluded: not English but possibly relevant.
- Goudsmit EM, Ho-Yen DO, Dancy 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. doi: 10.1016/j.pec.2009.05.015. PMID: 19576714. Excluded: excluded study design for Key Question.
- Gow JW, Hagan S, Herzyk P, et al. A gene signature for post-infectious chronic fatigue syndrome. *BMC Med Genomics.* 2009;2doi: 10.1186/1755-8794-2-38. Excluded: excluded intervention.
- Gracious B, Wisner KL. Nortriptyline in chronic fatigue syndrome: a double blind, placebo-controlled single case study. *Biol Psychiatry.* 1991;30(4):405-8. PMID: 1912132. Excluded: excluded study design for Key Question.
- Green J, Romei J, Natelson BH. Stigma and chronic fatigue syndrome. *J Chronic Fatigue Syndr.* 1999;5(2):63-95. doi: 10.1300/J092v05n02_04. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

- Gregorowski A, Simpson J, Segal TY. Child and adolescent chronic fatigue syndrome/myalgic encephalomyelitis: where are we now? *Curr Opin Pediatr*. 2019 doi: 10.1097/mop.0000000000000777. PMID: 31045885. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Griffith JP, Zarrouf FA. A systematic review of chronic fatigue syndrome: don't assume it's depression. *Prim Care Companion J Clin Psychiatry*. 2008;10(2):120-8. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Guillamo E, Barbany JR, Blazquez A, et al. Physical effects of a reconditioning program me in a group of chronic fatigue syndrome patients. *J Sports Med Phys Fitness*. 2016;56(5):579-86. PMID: 27285346. Excluded: excluded outcome.
- 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. doi: 10.1177/1359105309350515. PMID: 20348363. Excluded: excluded study design for Key Question.
- Guo AS, Gu YH, Jin HZ. Clinical comparative study moxibustion on chronic fatigue syndrome. *J Liaoning Univ Tradit Chin Med*. 2007;29-30. Excluded: not English but possibly relevant.
- Guo AS, Gu YX, Jin HZ. Effect comparison study of moxibustion in treatment of chronic fatigue syndrome. *J Liaoning Univ Tradit Chin Med*. 2007;9:31-9. Excluded: not English but possibly relevant.
- Guo F, Xu LJSZZ. Preliminary study on treatment of chronic fatigue syndrome by herbal cake-separated moxibustion on five-zang back-shu points. 2006;25(10):11-2. Excluded: not English but possibly relevant.
- Guo J. Treatment of 310 cases with chronic fatigue syndrome by combination of acupuncture moxibustion and psychotherapy. *J Sichuan Tradit Chin Med*. 2005;23(3):93-4. Excluded: not English but possibly relevant.
- Guo J. Chronic fatigue syndrome treated by acupuncture and moxibustion in combination with psychological approaches in 310 cases. *J Tradit Chin Med*. 2007;27(2):92-5. PMID: 17710799. Excluded: excluded outcome.
- Guo YQ. The clinical study of combined therapy of body and auricular acupuncture in the treatment of chronic fatigue syndrome. *Guangzhou University of Chinese Medicine Doctor's Thesis*. 2009. Excluded: not English but possibly relevant.
- Gupta A, Vij G, Sharma S, et al. Curcumin, a polyphenolic antioxidant, attenuates chronic fatigue syndrome in murine water immersion stress model. *Immunobiology*. 2009;214(1):33-9. doi: 10.1016/j.imbio.2008.04.003. PMID: 19159825. Excluded: excluded population.
- 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. Excluded: excluded outcome.
- Haig-Ferguson A, Loades M, Whittle C, et al. "It's not one size fits all"; the use of videoconferencing for delivering therapy in a Specialist Paediatric Chronic Fatigue Service. *Internet Interv*. 2019;15:43-51. doi: 10.1016/j.invent.2018.12.003. Excluded: excluded study design for Key Question.
- Hall DG, Sanders SD, Replogle WH. Fatigue: a new approach to an old problem. *J Miss State Med Assoc*. 1994;35(6):155-60. PMID: 8064846. Excluded: excluded study design for Key Question.
- Hall DL, Lattie EG, Milrad SF, et al. Telephone-administered versus live group cognitive behavioral stress management for adults with CFS. *J Psychosom Res*. 2017;93:41-7. doi: 10.1016/j.jpsychores.2016.12.004. PMID: 28107891. Excluded: inadequate duration.

Appendix D. List of Excluded Studies

- Hall KT, Kossowsky J, Oberlander TF, et al. Genetic variation in catechol-o-ethyltransferase modifies effects of clonidine treatment in chronic fatigue syndrome. *Pharmacogenomics*. 2016;16(5):454-60. doi: 10.1038/tpj.2016.53. PMID: 27457818. Excluded: inadequate duration.
- Hannes B, Mowinckel P, Kjekken I, et al. Effects of a one week multidisciplinary inpatient self-management programme for patients with fibromyalgia: a randomised controlled trial. *BMC Musculoskelet Disord*. 2012;13:189. doi: 10.1186/1471-2474-13-189. PMID: 23013162. Excluded: excluded outcome.
- Hard K, Rickards HE, Haque MS, et al. Pharmacological treatments for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev*. 2014 (2). Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Hareide L, Finset A, Wyller VB. Chronic fatigue syndrome: a qualitative investigation of young patient's beliefs and coping strategies. *Disabil Rehabil*. 2011;33(23-24):2255-63. doi: 10.3109/09638288.2011.568663. PMID: 21473686. Excluded: excluded study design for Key Question.
- Harrison S, Smith A, Sykes R. Residential rehabilitation courses in the self-directed management of chronic fatigue syndrome: a preliminary evaluation. *J Chronic Fatigue Syndr*. 2002;10(2):59-65. doi: 10.1300/J092v10n02_05. Excluded: excluded study design for Key Question.
- Hartz AJ, Bentler S, Noyes R, et al. Randomized controlled trial of Siberian ginseng for chronic fatigue. *Psychol Med*. 2004;34(1):51-61. PMID: 14971626. Excluded: inadequate duration.
- Hartz AJ, Bentler SE, Brake KA, et al. The effectiveness of citalopram for idiopathic chronic fatigue. *J Clin Psychiatry*. 2003;64(8):927-35. PMID: 12927008. Excluded: inadequate duration.
- Hawk C, Jason LA, Pena J. Variables that differentiate chronic fatigue syndrome from depression. *J Hum Behav Soc Environ*. 2007;16(3):1-13. doi: 10.1300/10911350802107652. Excluded: excluded outcome.
- Hawk C, Jason LA, Torres-Harding S. Differential diagnosis of chronic fatigue syndrome and major depressive disorder. *Int J Behav Med*. 2006;13(3):244-51. PMID: 17078775. Excluded: excluded population.
- Hawkes N. Online CBT is trialled for children with chronic fatigue syndrome. *BMJ*. 2016;355:i5860. doi: 10.1136/bmj.i5860. PMID: 27803017. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Heins MJ, Knoop H, Bleijenberg G. The role of the therapeutic relationship in cognitive behaviour therapy for chronic fatigue syndrome. *Behav Res Ther*. 2013;51(7):368-76. doi: 10.1016/j.brat.2013.02.001. PMID: 23639303. Excluded: excluded study design for Key Question.
- Heins MJ, Knoop H, Prins JB, et al. Possible detrimental effects of cognitive behaviour therapy for chronic fatigue syndrome. *Psychother Psychosom*. 2010;79(4):249-56. doi: 10.1159/000315130. PMID: 20502065. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Hickie I, Lloyd A, Wakefield D. Immunological and psychological dysfunction in patients receiving immunotherapy for chronic fatigue syndrome. *Aust N Z J Psychiatry*. 1992;26(2):249-56. PMID: 1642616. Excluded: excluded population.
- Hickie IB, Wilson AJ, Wright JM, et al. A randomized, double-blind placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. *J Clin Psychiatry*. 2000;61(9):643-8. PMID: 11030484. Excluded: inadequate duration.
- Himmel PB, Seligman TM. A pilot study employing dehydroepiandrosterone (DHEA) in the treatment of chronic fatigue syndrome. *J Clin Rheumatol*. 1999;5(2):56-9. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

- Hoad A, Spickett G, Elliott J, et al. Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. *QJM*. 2008;101(12):961-5. doi: 10.1093/qjmed/hcn123. PMID: 18805903. Excluded: excluded population.
- Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition. *Ann Intern Med*. 1988;108(3):387-9. PMID: 2829679. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Houlton A, Christie MM, Smith B, et al. Long-term follow-up of multi-disciplinary outpatient treatment for chronic fatigue syndrome/myalgic encephalopathy. *Fatigue*. 2015;3(1):47-58. doi: 10.1080/21641846.2014.993873. Excluded: excluded study design for Key Question.
- Hui LJCA, Moxibustion. Observation on therapeutic effect of pricking blood therapy in 32 cases of chronic fatigue syndrome. 2004;2. Excluded: not English but possibly relevant.
- Huibers MJ, Beurskens AJ, Van Schayck CP, et al. Efficacy of cognitive-behavioural therapy by general practitioners for unexplained fatigue among employees: randomised controlled trial. *Br J Psychiatry*. 2004;184:240-6. PMID: 14990522. Excluded: excluded population.
- Huibers MJ, Bleijenberg G, van Amelsvoort LG, et al. Predictors of outcome in fatigued employees on sick leave: results from a randomised trial. *J Psychosom Res*. 2004;57(5):443-9. PMID: 15581647. Excluded: excluded population.
- Jackson ML, Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. *J Clin Sleep Med*. 2012;8(6):719-28. doi: 10.5664/jcsm.2276. PMID: 23243408. Excluded: excluded population.
- Jackson ML, Butt H, Ball M, et al. Sleep quality and the treatment of intestinal micro biota imbalance in chronic fatigue syndrome: a pilot study. *Sleep Science*. 2015;8(3):124-33. doi: 10.1016/j.slsi.2015.10.001. Excluded: excluded study design for Key Question.
- Jain V, Arunkumar A, Kingdon C, et al. Prevalence of and risk factors for severe cognitive and sleep symptoms in ME/CFS and MS. *BMC Neuro*. 2017;17(1):117. doi: 10.1186/s12883-017-0896-0. PMID: 28633629. Excluded: excluded population.
- Janse A, Wiborg JF, Bleijenberg G, et al. The efficacy of guided self-instruction for patients with idiopathic chronic fatigue: a randomized controlled trial. *J Consult Clin Psychol*. 2016;84(5):377-88. doi: 10.1037/ccp0000085. PMID: 26950098. Excluded: excluded population.
- Janse A, Worm-Smeitink M, Bussel-Lagarde J, et al. Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial. *BMC Neuro*. 2015;15:137. doi: 10.1186/s12883-015-0392-3. PMID: 26264735. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Jason L, Brown M, Evans M, et al. Measuring substantial reductions in functioning in patients with chronic fatigue syndrome. *Disabil Rehabil*. 2011;33(7):589-98. doi: 10.3109/09638288.2010.503256. PMID: 20617920. Excluded: excluded population.
- 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. doi: 10.1002/jclp.20648. PMID: 19902489. Excluded: excluded intervention.
- Jason L, Evans M, Porter N, et al. The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. *Am J Biochem Biotechnol*. 2010;6(2):120-35. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

- Jason L, Torres-Harding S, Carrico A, et al. Symptom occurrence in persons with chronic fatigue syndrome. *Biol Psychol.* 2002;59(1):15-27. doi: 10.1016/S0301-0511%2801%2900120-X. PMID: 11790441. Excluded: excluded outcome.
- 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. doi: 10.1177/0163278711424281. PMID: 22158691. Excluded: excluded population.
- Jason LA, Brown A, Evans M, et al. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. *Fatigue.* 2013;1(3):168-86. PMID: 23914329. Excluded: excluded study design for Key Question.
- Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med.* 1999;159(18):2129-37. PMID: 10527290. Excluded: excluded outcome.
- 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. doi: 10.4236/psych.2010.11002. PMID: 23685416. Excluded: excluded outcome.
- Jason LA, Sunnquist M, Brown A, et al. Are myalgic encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis. *J Health Psychol.* 2014 doi: 10.1177/1359105313520335. PMID: 24510231. Excluded: excluded population.
- Jason LA, Sunnquist M, Kot B, et al. Unintended consequences of not specifying exclusionary illnesses for systemic exertion intolerance disease. *Diagnostics.* 2015;5(2):272-86. doi: 10.3390/diagnostics5020272. Excluded: excluded population.
- Jason LA, Taylor RR. Measuring attributions about chronic fatigue syndrome. *J Chronic Fatigue Syndr.* 2001;8(3-4):31-40. doi: 10.1300/J092v08n03_04. Excluded: excluded population.
- Jason LA, Taylor RR, Kennedy CL, et al. Chronic fatigue syndrome: comorbidity with fibromyalgia and psychiatric illness. *Medicine and Psychiatry.* 2001;4(1):29-34. Excluded: unable to obtain.
- 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. doi: 10.1177/135910530100600105. PMID: 22049238. Excluded: excluded population.
- Jason LA, Torres-Harding S, Maher K, et al. Baseline cortisol levels predict treatment outcomes in chronic fatigue syndrome nonpharmacologic clinical trial. *J Chronic Fatigue Syndr.* 2008;14(4):39-59. doi: 10.1080/10573320802092039. Excluded: excluded outcome.
- 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. Excluded: excluded study design for Key Question.
- Jason LA, Torres-Harding SR, Taylor RR, et al. A comparison of the 1988 and 1994 diagnostic criteria for chronic fatigue syndrome. *J Clin Psychol Med Settings.* 2001;8(4):337-43. doi: 10.1023/A:1011981132735. Excluded: excluded study design for Key Question.
- Jason LA, Zinn ML, Zinn MA. Myalgic encephalomyelitis: symptoms and biomarkers. *Curr Neuropharmacol.* 2015;13(5):701-34. PMID: 26411464. Excluded: excluded study design for Key Question.
- Ji XD, Jiang JX, Chen JD. The clinical observation in the treatment of chronic fatigue syndrome with modulated medium frequency electrotherapy and ciwujia capsule. *Chin J Rehabil.* 2009;24:253-4. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

- Jia H. Treatment of 71 cases of chronic fatigue syndrome by needling four-gate points. *J Liaoning Coll Tradit Chin Med*. 2005;7(4):382-3. Excluded: not English but possibly relevant.
- Jiang Y. Treatment of 56 cases with chronic fatigue syndrome by needling and bleeding the points on shoulder points. *J Pract Tradit Chin Intern Med*. 2005;19(2):181. Excluded: not English but possibly relevant.
- Johnson SK, DeLuca J, Natelson BH. Depression in fatiguing illness: comparing patients with chronic fatigue syndrome, multiple sclerosis and depression. *J Affect Disord*. 1996;39(1):21-30. PMID: 8835650. Excluded: excluded population.
- Jones JF, Lin JM, Maloney EM, et al. An evaluation of exclusionary medical/psychiatric conditions in the definition of chronic fatigue syndrome. *BMC Med*. 2009;7:57. doi: 10.1186/1741-7015-7-57. PMID: 19818157. Excluded: excluded study design for Key Question.
- Jones JF, Nisenbaum R, Solomon L, et al. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. *J Adolesc Health*. 2004;35(1):34-40. PMID: 15193572. Excluded: excluded study design for Key Question.
- Jones K, Probst Y. Role of dietary modification in alleviating chronic fatigue syndrome symptoms: a systematic review. *Aust N Z J Public Health*. 2017;41(4):338-44. doi: 10.1111/1753-6405.12670. PMID: 28616881. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Kaiser JD. A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome. *Int J Clin Exp Med*. 2015;8(7):11064-74. PMID: 26379906. Excluded: excluded study design for Key Question.
- Kakumanu SS, Mende CN, Lehman EB, et al. Effect of topical nasal corticosteroids on patients with chronic fatigue syndrome and rhinitis. *J Am Osteopath Assoc*. 2003;103(9):423-7. PMID: 14527077. Excluded: inadequate duration.
- 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. Excluded: excluded population.
- Kenter EG, Okkes IM, Oskam SK, et al. Tiredness in Dutch family practice. Data on patients complaining of and/or diagnosed with "tiredness". *Fam Pract*. 2003;20(4):434-40. doi: 10.1093/fampra/cm418. PMID: 12876117. Excluded: excluded outcome.
- Kermode-Scott B. Don't worry about the label. Diagnose underlying perpetuating factors in chronic fatigue syndrome. *Can Fam Physician*. 1995;41:1126-8. PMID: 7780320. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Kim JE, Hong KE, Kim HJ, et al. An open-label study of effects of acupuncture on chronic fatigue syndrome and idiopathic chronic fatigue: study protocol for a randomized controlled trial. *Trials*. 2013;14:147. doi: 10.1186/1745-6215-14-147. PMID: 23693129. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Kim JE, Seo BK, Choi JB, et al. Acupuncture for chronic fatigue syndrome and idiopathic chronic fatigue: a multicenter, nonblinded, randomized controlled trial. *Trials*. 2015;16:314. doi: 10.1186/s13063-015-0857-0. PMID: 26211002. Excluded: excluded population.
- Kim KW, Chung WS, Song MY, et al. Complementary and alternative medicine treatments in the management of chronic fatigue syndrome: a systematic review of randomized controlled trials. *Orient Pharm Exp Med*. 2013;13(2):85-93. doi: 10.1007/s13596-012-0096-9. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Appendix D. List of Excluded Studies

- King C, Jason LA. Improving the diagnostic criteria and procedures for chronic fatigue syndrome. *Biol Psychol*. 2005;68(2):87-106. PMID: 15450690. Excluded: excluded population.
- Kirby SB. Methods and outcome reporting in the PACE trial. *Lancet Psychiatry*. 2015;2(4):e10. doi: 10.1016/S2215-0366%2815%2900110-8. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Kirk J, Douglass R, Nelson E, et al. Chief complaint of fatigue: a prospective study. *J Fam Pract*. 1990;30(1):33-9; discussion 9-41. PMID: 2294161. Excluded: excluded outcome.
- Kmietowicz Z. Cognitive behaviour therapy and exercise are the only effective treatments for chronic fatigue, says study. *BMJ*. 2002;324(7349):1298. PMID: 12043728. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Knight SJ, Scheinberg A, Harvey AR. Interventions in pediatric chronic fatigue syndrome/myalgic encephalomyelitis: a systematic review. *J Adolesc Health*. 2013;53(2):154-65. doi: 10.1016/j.jadohealth.2013.03.009. PMID: 23643337. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Knoop H, Prins JB, Stulemeijer M, et al. The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance. *J Neurol Neurosurg Psychiatry*. 2007;78(4):434-6. PMID: 17369597. Excluded: excluded study design for Key Question.
- Knoop H, Stulemeijer M, de Jong LW, et al. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. *Pediatrics*. 2008;121(3):e619-25. doi: 10.1542/peds.2007-1488. PMID: 18310181. Excluded: excluded study design for Key Question.
- Knoop H, Stulemeijer M, Prins JB, et al. Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? *Behav Res Ther*. 2007;45(9):2034-43. PMID: 17451642. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Knottnerus JA, Knipschild PG, van Wersch JW, et al. [Unexplained fatigue and hemoglobin level; a study of family practice patients]. *Ned Tijdschr Geneesk*. 1986;130(9):402-5. PMID: 3960187. Excluded: not English but possibly relevant.
- Koch H, van Bokhoven MA, ter Riet G, et al. Ordering blood tests for patients with unexplained fatigue in general practice: what does it yield? Results of the VAMPIRE trial. *Br J Gen Pract*. 2009;59(561):e93-100. doi: 10.3399/bjgp09X420310. PMID: 19341544. Excluded: excluded outcome.
- 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. Excluded: excluded outcome.
- Koopman FS, Voorn EL, Beelen A, et al. No reduction of severe fatigue in patients with postpolio syndrome by exercise therapy or cognitive behavioral therapy: results of an RCT. *Neurorehabil Neural Repair*. 2016;30(5):402-10. doi: 10.1177/1545968315600271. PMID: 26253175. Excluded: excluded population.
- Kruesi MJ, Dale J, Straus SE. Psychiatric diagnoses in patients who have chronic fatigue syndrome. *J Clin Psychiatry*. 1989;50(2):53-6. PMID: 2536690. Excluded: excluded population.
- Kurek JN. Treatment of chronic fatigue syndrome with methylphenidate. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2001;61(10-B):5569. Excluded: inadequate duration.

Appendix D. List of Excluded Studies

Lai XY. The acupuncture treatment of spirit selection points to the liver depression and spleen deficiency syndrome of chronic fatigue syndrome clinical observation. Nanjing University of Traditional Chinese Medicine Doctor's Thesis. 2014. Excluded: not English but possibly relevant.

Landmark L, Lindgren RM, Sivertsen B, et al. Chronic fatigue syndrome and experience with the lightning process. *Tidsskr Nor Laegeforen*. 2016;136(5):396. doi: 10.4045/tidsskr.15.1214. PMID: 26983138. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Larun L, KG B, J O-J, et al. Exercise therapy for chronic fatigue syndrome. *Cochrane Database Syst Rev*. 2017 (pagination) PMID: 28444695. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Larun L, Malterud K. Identity and coping experiences in chronic fatigue syndrome: a synthesis of qualitative studies. *Patient Educ Couns*. 2007;69(1-3):20-8. PMID: 17698311. Excluded: excluded study design for Key Question.

Larun L, Odgaard-Jensen J, Brurberg KG, et al. Exercise therapy for chronic fatigue syndrome (individual patient data). *Cochrane Database Syst Rev*. 2014;2014(4)doi: 10.1002/14651858.CD011040. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Larun L, Odgaard-Jensen J, Price JR, et al. An abridged version of the cochrane review of exercise therapy for chronic fatigue syndrome. *Eur J Phys Rehabil Med*. 2016;52(2):244-52. PMID: 26375519. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Lattie EG. The effects of telephone-delivered cognitive behavioral stress management on inflammation and symptoms in myalgic encephalomyelitis/chronic fatigue syndrome: a computational immunology approach. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2016;77(1-B(E)):No Pagination Specified. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Lawn T, Kumar P, Knight B, et al. Psychiatric misdiagnoses in patients with chronic fatigue syndrome. *JRSM Short Rep*. 2010;1(4):28. doi: 10.1258/shorts.2010.010042. PMID: 21103120. Excluded: excluded outcome.

Lechky O. Life insurance MDs sceptical when chronic fatigue syndrome diagnosed. *CMAJ*. 1990;143(5):413-5. PMID: 2390755. Excluded: excluded comparator.

Lee JH, Kim SK, Ko SJ, et al. The effect of oriental medicine music therapy on idiopathic chronic fatigue. *J Altern Complement Med*. 2015;21(7):422-9. doi: 10.1089/acm.2014.0271. PMID: 26056862. Excluded: inadequate duration.

Lerner AM, Beqaj S, Fitzgerald JT, et al. Subset-directed antiviral treatment of 142 herpesvirus patients with chronic fatigue syndrome. *Virus Adapt Treat*. 2010;2((Martin Lerner A., amartinlerner@yahoo.com) Department of Medicine, William Beaumont Hospital, Royal Oak, United States):47-57. Excluded: excluded study design for Key Question.

Lerner AM, Beqaj SH, Deeter RG, et al. Valacyclovir treatment in epstein-barr virus subset chronic fatigue syndrome: thirty-six months follow-up. *In Vivo*. 2007;21(5):707-13. PMID: 18019402. Excluded: excluded outcome.

Lerner AM, Zervos M, Chang CH, et al. A small, randomized, placebo-controlled trial of the use of antiviral therapy for patients with chronic fatigue syndrome. *Clin Infect Dis*. 2001;32(11):1657-8. doi: 10.1086/320530. PMID: 11340544. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Lewis I, Pairman J, Spickett G, et al. Is chronic fatigue syndrome in older patients a different disease? - a clinical cohort study. *Eur J Clin Invest*. 2013;43(3):302-8. doi: 10.1111/eci.12046. PMID: 23397955. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

Lewith G, Stuart B, Chalder T, et al. Complementary and alternative healthcare use by participants in the PACE trial of treatments for chronic fatigue syndrome. *J Psychosom Res.* 2016;87:37-42. doi: 10.1016/j.jpsychores.2016.06.005. PMID: 27411750. Excluded: excluded comparator.

Leyton E, Pross H. Chronic fatigue syndrome. Do herbs of homeopathy help? *Can Fam Physician.* 1992;38(SEP.):2021-6. PMID: 21221272. Excluded: excluded study design for Key Question.

Li CD, Chen YL, Huang L. Clinical observation of soothing liver and activating spleen method in treatment of chronic fatigue syndrome. *Liaoning J Tradit Chin Med.* 2011;38:2037-8. Excluded: not English but possibly relevant.

Li H. Clinical research of CFS of "Ganyupixu" kind with the SHU-MU network points acupuncture. Heilongjiang University of Chinese Medicine Master's Thesis. 2007. Excluded: not English but possibly relevant.

Li SZ, Han B, Wang DS, et al. Combination of acupuncture and cupping treatment of 35 cases with chronic fatigue syndrome. *Chin J Tradit Med Sci Technol.* 2006;13(5):323. Excluded: not English but possibly relevant.

Li XG. Clinical research on treating chronic fatigue syndrome by elongated needle penetration needling plus holistic nursing. *Clin J Chin Med.* 2010:18-9. Excluded: not English but possibly relevant.

Li YX. Combination of acupuncture and cupping treatment of 38 cases with chronic fatigue syndrome. *J Extern Ther Tradit Chin Med.* 2002;11(5):54. Excluded: not English but possibly relevant.

Liang YX, Liu Q. Observation on curative effect of acupoint catgut embedding with moxibustion of moxibustion on chronic fatigue syndrome. *J Pract Tradit Chin Med.* 2014:642-3. Excluded: not English but possibly relevant.

Libman E, Creti L, Baltzan M, et al. Sleep apnea and psychological functioning in chronic fatigue syndrome. *J Health Psychol.* 2009;14(8):1251-67. doi: 10.1177/1359105309344895. PMID: 19858344. Excluded: excluded population.

Lin YM. The clinical researches of moxibustion with warming needle for chronic fatigue syndrome. Guangzhou University of Chinese Medicine Master's Thesis. 2010. Excluded: not English but possibly relevant.

Lin YM, Chen WJ, Chen XL, et al. Therapeutic effect of moxibustion with warming needle for chronic fatigue syndrome with heart-spleen deficiency: an observation of 50 cases. *J New Chin Med.* 2012:93-4. Excluded: not English but possibly relevant.

Linder R, Dinsler R, Wagner M, et al. Generation of classification criteria for chronic fatigue syndrome using an artificial neural network and traditional criteria set. *In Vivo.* 2002;16(1):37-43. PMID: 11980359. Excluded: excluded study design for Key Question.

Lindheimer JB, Meyer JD, Stegner AJ, et al. Symptom variability following acute exercise in myalgic encephalomyelitis/chronic fatigue syndrome: a perspective on measuring post-exertion malaise. *Fatigue.* 2017;5(2):69-88. doi: 10.1080/21641846.2017.1321166. Excluded: inadequate duration.

Ling W. Clinical observation on acupuncture and moxibustion at eight confluence points for treatment of chronic fatigue syndrome [J]. *Chin Acupunct Mox.* 2004;8. Excluded: not English but possibly relevant.

Liu CZ, Lei B. [Effect of Tuina on oxygen free radicals metabolism in patients with chronic fatigue syndrome]. *Zhongguo Zhen Jiu.* 2010;30(11):946-8. PMID: 21246855. Excluded: not English but possibly relevant.

Liu FU. The study of thread embedding therapy with shu mu combination by in treatment of liver depression and spleen deficiency of chronic fatigue syndrome. Guangzhou University of Chinese Medicine Master's Thesis. 2014. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

- Liu YY, Sun ZR. Combination of acupuncture and cupping treatment of 40 cases with chronic fatigue syndrome. *J Clin Acupunct Mox.* 2006;22(7):22-3. Excluded: not English but possibly relevant.
- Lloyd A, Hickie I, Wakefield D, et al. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med.* 1990;89(5):561-8. PMID: 2146875. Excluded: excluded population.
- Lloyd AR, Hickie I, Brockman A, et al. Immunologic and psychologic therapy for patients with chronic fatigue syndrome: a double-blind, placebo-controlled trial. *Am J Med.* 1993;94(2):197-203. PMID: 8430715. Excluded: excluded population.
- Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. *Behav Res Ther.* 2012;50(11):719-25. doi: 10.1016/j.brat.2012.08.005. PMID: 22985998. Excluded: excluded population.
- Lloyd S, Chalder T, Sallis HM, et al. "Telephone-based guided self-help for adolescents with chronic fatigue syndrome: a non-randomised cohort study": corrigendum. *Behav Res Ther.* 2013;51(8):518. doi: 10.1016/j.brat.2013.05.008. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Loades ME, Rimes KA, Ali S, et al. The presence of co-morbid mental health problems in a cohort of adolescents with chronic fatigue syndrome. *Clin Child Psychol Psychiatry.* 2018;23(3):398-408. doi: 10.1177/1359104517736357. PMID: 29096528. Excluded: excluded study design for Key Question.
- Loades ME, Sheils EA, Crawley E. Treatment for paediatric chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) and comorbid depression: a systematic review. *BMJ Open.* 2016;6(10):e012271. doi: 10.1136/bmjopen-2016-012271. PMID: 27729349. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Lou MR. Acupuncture and cupping treatment of 30 cases of chronic fatigue syndrome. *J Guangxi Tradit Chin Med Univ.* 2002;5(2):24-5. Excluded: not English but possibly relevant.
- Loy BD, O'Connor PJ, Dishman RK. Effect of acute exercise on fatigue in people with ME/CFS/SEID: a meta-analysis. *Med Sci Sports Exerc.* 2016;48(10):2003-12. doi: 10.1249/MSS.0000000000000990. PMID: 27187093. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Ma TW, Zhu XK. Treatment of 53 cases with chronic fatigue syndrome by combination of acupuncture, moxibustion and cupping. *Zhejiang J Integr Tradit Chin West Med.* 2003;13(2):122-3. Excluded: not English but possibly relevant.
- Macnamara CL, Cvejic E, Parker GB, et al. Personalised relaxation practice to improve sleep and functioning in patients with chronic fatigue syndrome and depression: study protocol for a randomised controlled trial. *Trials.* 2018;19(1)doi: 10.1186/s13063-018-2763-8 PMID: 29996933. Excluded: inadequate duration.
- Maes M, Leunis JC, Geffard M, et al. Evidence for the existence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with and without abdominal discomfort (irritable bowel) syndrome. *Neuro Endocrinol Lett.* 2014;35(6):445-53. PMID: 25433843. Excluded: excluded study design for Key Question.
- Mahjoub F, Salari R, Noras MR, et al. Are traditional remedies useful in management of fibromyalgia and chronic fatigue syndrome? A review study. *J Evid Based Complementary Altern Med.* 2017;22(4):1011-6. doi: 10.1177/2156587217712763. PMID: 28597692. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

Manu P, Lane TJ, Matthews DA. The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. *Ann Intern Med.* 1988;109(7):554-6. PMID: 3421564. Excluded: too old.

Manu P, Lane TJ, Matthews DA. Chronic fatigue and chronic fatigue syndrome: clinical epidemiology and aetiological classification. *Ciba Found Symp.* 1993;173:23-31; discussion -42. PMID: 8491100. Excluded: excluded comparator.

Marlin RG, Anchel H, Gibson JC, et al. An evaluation of multidisciplinary intervention for chronic fatigue syndrome with long-term follow-up, and a comparison with untreated controls. *Am J Med.* 1998;105(3A):110S-4S. PMID: 9790492. Excluded: excluded study design for Key Question.

Maroti D, Molander P, Bileviciute-Ljungar I. Differences in alexithymia and emotional awareness in exhaustion syndrome and chronic fatigue syndrome. *Scand J Psychol.* 2017;58(1):52-61. doi: 10.1111/sjop.12332. PMID: 27686801. Excluded: excluded outcome.

Maroti D, Westerberg AF, Saury JM, et al. Computerized training improves verbal working memory in patients with myalgic encephalomyelitis/chronic fatigue syndrome: a pilot study. *J Rehabil Med.* 2015;47(7):665-8. doi: 10.2340/16501977-1976. PMID: 26035692. Excluded: excluded study design for Key Question.

Marques M, De Gucht V, Leal I, et al. Effects of a self-regulation based physical activity program (the "4-STEPS") for unexplained chronic fatigue: a randomized controlled trial. *Int J Behav Med.* 2015;22(2):187-96. doi: 10.1007/s12529-014-9432-4. PMID: 25187111. Excluded: excluded population.

Marques M, de Gucht V, Leal I, et al. Efficacy of a randomized controlled self-regulation based physical activity intervention for chronic fatigue: mediation effects of physical activity progress and self-regulation skills. *J Psychosom Res.* 2017;94:24-31. doi: 10.1016/j.jpsychores.2016.12.012. PMID: 28183399. Excluded: excluded population.

Marques M, De Gucht V, Maes S, et al. Protocol for the "four steps to control your fatigue (4-STEPS)" randomised controlled trial: a self-regulation based physical activity intervention for patients with unexplained chronic fatigue. *BMC Public Health.* 2012;12:202. doi: 10.1186/1471-2458-12-202. PMID: 22429404. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Marques MM, De Gucht V, Gouveia MJ, et al. Differential effects of behavioral interventions with a graded physical activity component in patients suffering from chronic fatigue (syndrome): an updated systematic review and meta-analysis. *Clin Psychol Rev.* 2015;40:123-37. doi: 10.1016/j.cpr.2015.05.009. PMID: 26112761. Excluded: excluded population.

McCrone P, Ridsdale L, Darbishire L, et al. Cost-effectiveness of cognitive behavioural therapy, graded exercise and usual care for patients with chronic fatigue in primary care. *Psychol Med.* 2004;34(6):991-9. PMID: 15554570. Excluded: excluded outcome.

McCrone P, Sharpe M, Chalder T, et al. Adaptive pacing, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome: a cost-effectiveness analysis. *PLoS ONE.* 2012;7(8):e40808. PMID: 22870204. Excluded: excluded outcome.

McDermott C, Lynch J, Leydon GM. Patients' hopes and expectations of a specialist chronic fatigue syndrome/ME service: a qualitative study. *Fam Pract.* 2011;28(5):572-8. doi: 10.1093/fampra/cmr016. PMID: 21555341. Excluded: excluded intervention.

McDermott C, Richards SC, Thomas PW, et al. A placebo-controlled, double-blind, randomized controlled trial of a natural killer cell stimulant (BioBran MGN-3) in chronic fatigue syndrome. *QJM.* 2006;99(7):461-8. PMID: 16809351. Excluded: inadequate duration.

McDermott C, Richards SCM, Ankers S, et al. An evaluation of a chronic fatigue lifestyle management programme focusing on the outcome of return to work or training. *Br J Occup Ther.* 2004;67(6):269-73. Excluded: excluded comparator.

Appendix D. List of Excluded Studies

- McDermott MR, Bendle C, Griffin M, et al. Does it matter what you call it? Lay beliefs for overcoming chronic fatigue syndrome, myalgic encephalomyelitis, and post-viral fatigue syndrome. *Ethical Hum Psychol Psychiatry*. 2016;18(2):150-62. doi: 10.1891/1559-4343.18.2.150. Excluded: excluded population.
- McKendrick M. Chronic fatigue syndrome: a controlled trial of the efficacy of homoeopathic treatment. *National research register*. 1999. Excluded: unable to obtain.
- Medow MS, Guber K, Chokshi S, et al. The benefits of oral rehydration on orthostatic intolerance in children with postural tachycardia syndrome. *J Pediatr*. 2019 doi: 10.1016/j.jpeds.2019.07.041. PMID: 31405524. Excluded: excluded population.
- Meeus M, Ickmans K, Struyf F, et al. Does acetaminophen activate endogenous pain inhibition in chronic fatigue syndrome/fibromyalgia and rheumatoid arthritis? A double-blind randomized controlled cross-over trial. *Pain Physician*. 2013;16(2):E61-70. PMID: 23511692. Excluded: excluded outcome.
- Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. *Eur J Pain*. 2007;11(4):377-86. PMID: 16843021. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Meeus M, Nijs J, Vanderheiden T, et al. The effect of relaxation therapy on autonomic functioning, symptoms and daily functioning, in patients with chronic fatigue syndrome or fibromyalgia: a systematic review. *Clin Rehabil*. 2015;29(3):221-33. doi: 10.1177/0269215514542635. PMID: 25200878. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Mehta VK, Blume GB. A randomized trial of fluoxetine in a patient with persistent fatigue. *J Am Board Fam Pract*. 1995;8(3):230-2. PMID: 7618502. Excluded: sample size too small.
- Meng H, Friedberg F. Cost-utility of home-based fatigue self-management versus usual care for the treatment of chronic fatigue syndrome. *Fatigue*. 2017 doi: 10.1080/21641846.2017.1343171. PMID: 30931176. Excluded: excluded outcome.
- Meng H, Friedberg F, Castora-Binkley M. Cost-effectiveness of chronic fatigue self-management versus usual care: a pilot randomized controlled trial. *BMC Fam Pract*. 2014;15:184. doi: 10.1186/s12875-014-0184-7. PMID: 25421363. Excluded: excluded outcome.
- Miao M, A GL, He JZ. Treatment of 64 cases of chronic fatigue syndrome by needling body acupoints and press ear acupoints. *Chin Acupunct Mox*. 2005;25(4):292. Excluded: not English but possibly relevant.
- Mikolasek M, Berg J, Witt CM, et al. Effectiveness of mindfulness-and relaxation-based ehealth interventions for patients with medical conditions: a systematic review and synthesis. *Int J Behav Med*. 2018;25(1):1-16. doi: 10.1007/s12529-017-9679-7. PMID: 28752414. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Mitchell WM. Efficacy of rintatolimod in the treatment of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *Expert Rev Clin Pharmacol*. 2016;9(6):755-70. doi: 10.1586/17512433.2016.1172960. PMID: 27045557. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Moore Y, Anderson NME, Crawley E. A systematic review to identify the definitions of recovery for paediatric patients with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) used in studies since 1994. *Arch Dis Child*. 2015;100(28)doi: 10.1136/archdischild-2015-308599.314. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

- Moorkens G, Wynants H, Abs R. Effect of growth hormone treatment in patients with chronic fatigue syndrome: a preliminary study. *Growth Horm IGF Res.* 1998;8 Suppl B:131-3. PMID: 10990148. Excluded: excluded comparator.
- Morch K, Hanevik K, Rivenes AC, et al. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. *BMC Gastroenterol.* 2013;13:28. doi: 10.1186/1471-230X-13-28. PMID: 23399438. Excluded: excluded study design for Key Question.
- Morrison RE, Keating HJ, 3rd. Fatigue in primary care. *Obstet Gynecol Clin North Am.* 2001;28(2):225-40, v-vi. PMID: 11430174. Excluded: excluded comparator.
- Moss-Morris R, Hamilton W. Pragmatic rehabilitation for chronic fatigue syndrome. *BMJ.* 2010;340:c1799. doi: 10.1136/bmj.c1799. PMID: 20418252. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Moss-Morris R, Petrie KJ. Discriminating between chronic fatigue syndrome and depression: a cognitive analysis. *Psychol Med.* 2001;31(3):469-79. PMID: 11305855. Excluded: excluded population.
- Naschitz J, Dreyfuss D, Yeshurun D, et al. Midodrine treatment for chronic fatigue syndrome. *Postgrad Med J.* 2004;80(942):230-2. PMID: 15082846. Excluded: excluded study design for Key Question.
- Natelson BH, Cheu J, Hill N, et al. Single-blind, placebo phase-in trial of two escalating doses of selegiline in the chronic fatigue syndrome. *Neuropsychobiology.* 1998;37(3):150-4. PMID: 9597672. Excluded: inadequate duration.
- Natelson BH, Cheu J, Pareja J, et al. Randomized, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome. *Psychopharmacology.* 1996;124(3):226-30. PMID: 8740043. Excluded: inadequate duration.
- Ng SM, Yiu YM. Acupuncture for chronic fatigue syndrome: a randomized, sham-controlled trial with single-blinded design. *Altern Ther Health Med.* 2013;19(4):21-6. PMID: 23981369. Excluded: inadequate duration.
- Ni KQ. Treatment of 35 cases with chronic fatigue syndrome by combination of acupuncture and herbs. *J Fujian Coll Tradit Chin Med.* 2002;12(4):22-3. Excluded: not English but possibly relevant.
- Nicolson GL, Ellithorpe R. Lipid replacement and antioxidant nutritional therapy for restoring mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. *J Chronic Fatigue Syndr.* 2006;13(1):57-68. doi: 10.1300/J092v13n01_06. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Fatigue in teenagers on the interNET-the FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. *BMC Neuro.* 2011;11:23. doi: 10.1186/1471-2377-11-23. PMID: 21333021. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Nijs J, Malfliet A. Rehabilitation for patients with myalgic encephalomyelitis/chronic fatigue syndrome: time to extent the boundaries of this field. *J Intern Med.* 2016;279(3):265-7. doi: 10.1111/joim.12431. PMID: 26374087. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Nijs J, Zwinnen K, Meeusen R, et al. Comparison of two exercise testing protocols in patients with chronic fatigue syndrome. *J Rehabil Res Dev.* 2007;44(4):553-9. PMID: 18247252. Excluded: excluded outcome.
- Nilsson MKL, Zachrisson O, Gottfries CG, et al. A randomised controlled trial of the monoaminergic stabiliser (-)-OSU6162 in treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *Acta Neuropsychiatrica.* 2018;30(3):148-57. doi: 10.1017/neu.2017.35. PMID: 29212562. Excluded: inadequate duration.

Appendix D. List of Excluded Studies

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 1 year of follow-up. *Clin Rheumatol*. 2011;30(3):381-9. doi: 10.1007/s10067-010-1677-y. PMID: 21234629. Excluded: excluded outcome.

Oka T, Tanahashi T, Sudo N. Effect of isometric yoga on chronic fatigue syndrome: a randomized controlled trial. *Psychother Psychosom*. 2013;82:78-9. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Oka T, Tanahashi T, Sudo N, et al. Changes in fatigue, autonomic functions, and blood biomarkers due to sitting isometric yoga in patients with chronic fatigue syndrome. *Biopsychosoc Med*. 2018;12(3):1-11. doi: 10.1186/s13030-018-0123-2. PMID: 29643935. Excluded: inadequate duration.

Oka T, Wakita H, Kimura K. Development of a recumbent isometric yoga program for patients with severe chronic fatigue syndrome/myalgic encephalomyelitis: a pilot study to assess feasibility and efficacy. *Biopsychosoc Med*. 2017;11(5):1-9. doi: 10.1186/s13030-017-0090-z. PMID: 28270860. Excluded: excluded outcome.

Oleske JM, Friedman KJ, Kaufman KR, et al. Chronic fatigue syndrome in children and adolescents. *J Chronic Fatigue Syndr*. 2006;13(2-3):97-115. doi: 10.1300/J092v13n02_07. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Olson LG, Ambrogetti A, Sutherland DC. A pilot randomized controlled trial of dexamphetamine in patients with chronic fatigue syndrome. *Psychosomatics*. 2003;44(1):38-43. PMID: 12515836. Excluded: inadequate duration.

Palacios N, Fitzgerald KC, Komaroff AL, et al. Incidence of myalgic encephalomyelitis/chronic fatigue syndrome in a large prospective cohort of U.S. nurses. *Fatigue*. 2017;5(3):159-66. doi: 10.1080/21641846.2017.1323576. Excluded: excluded study design for Key Question.

Pan CQ, Tang ZG, Tan GB. Summary on treatment of 35 cases with chronic fatigue syndrome by combination of electro-acupuncture and acupoint-injection. *Hunan J Tradit Chin Med*. 2005;21(6):22-3. Excluded: not English but possibly relevant.

Pang YH, Liu JP. Therapeutic effect of shengmai powder plus modified xiaoyao powder for treatment of chronic fatigue syndrome. *J Guangzhou Univ Tradit Chin Med*. 2013;30:316-9. Excluded: not English but possibly relevant.

Pardaens K, Haagdorens L, Van Wambeke P, et al. How relevant are exercise capacity measures for evaluating treatment effects in chronic fatigue syndrome? Results from a prospective, multidisciplinary outcome study. *Clin Rehabil*. 2006;20(1):56-66. PMID: 16502751. Excluded: excluded study design for Key Question.

Pardini M, Cordano C, Benassi F, et al. Agomelatine but not melatonin improves fatigue perception: a longitudinal proof-of-concept study. *Eur Neuropsychopharmacol*. 2014;24(6):939-44. doi: 10.1016/j.euroneuro.2014.02.010. PMID: 24636462. Excluded: excluded intervention.

Pardini M, Guida S, Primavera A, et al. Amisulpride vs. fluoxetine treatment of chronic fatigue syndrome: a pilot study. *Eur Neuropsychopharmacol*. 2011;21(3):282-6. doi: 10.1016/j.euroneuro.2010.10.008. PMID: 21112746. Excluded: excluded intervention.

Park SB, Kim KN, Sung E, et al. Human placental extract as a subcutaneous injection is effective in chronic fatigue syndrome: a multi-center, double-blind, randomized, placebo-controlled study. *Biol Pharm Bull*. 2016;39(5):674-9. doi: 10.1248/bpb.b15-00623. PMID: 26911970. Excluded: inadequate duration.

Paterson ET. Staged management for chronic fatigue syndrome. *J Orthomol Med*. 1995;10(2):70-8. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

Patrick DM, Miller RR, Gardy JL, et al. Lyme disease diagnosed by alternative methods: a phenotype similar to that of chronic fatigue syndrome. *Clin Infect Dis*. 2015;61(7):1084-91. doi: 10.1093/cid/civ470. PMID: 26082507. Excluded: excluded population.

Pearn JH. Chronic fatigue syndrome: chronic ciguatera poisoning as a differential diagnosis. *Med J Aust*. 1997;166(6):309-10. PMID: 9087189. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Perry SE, Santhouse AM. Chronic fatigue syndrome. *Medicine*. 2016;44(12):711-4. doi: 10.1016/j.mpmed.2016.09.015. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Peterson PK, Pheley A, Schroepel J, et al. A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome. *Arch Intern Med*. 1998;158(8):908-14. PMID: 9570178. Excluded: inadequate duration.

Petrovics G, Szigeti G, Hamvas S, et al. Controlled pilot study for cancer patients suffering from chronic fatigue syndrome due to chemotherapy treated with BioBran (MGN-3-Arabinoxylane) and targeted radiofrequency heat therapy. *Eur J Integr Med*. 2016;8:29-35. doi: 10.1016/j.eujim.2016.10.004. Excluded: excluded population.

Pinxsterhuis I, Hellum LL, Aannestad HH, et al. Development of a group-based self-management programme for individuals with chronic fatigue syndrome: a pilot study. *Scand J Occup Ther*. 2015;22(2):117-25. doi: 10.3109/11038128.2014.985608. PMID: 25581161. Excluded: excluded comparator.

Plioplys AV. Chronic fatigue syndrome should not be diagnosed in children. *Pediatrics*. 1997;100(2 Pt 1):270-1. PMID: 9240812. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology*. 1997;35(1):16-23. PMID: 9018019. Excluded: inadequate duration.

Porter NS, Jason LA, Boulton A, et al. Alternative medical interventions used in the treatment and management of myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia. *J Altern Complement Med*. 2010;16(3):235-49. doi: 10.1089/acm.2008.0376. PMID: 20192908. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Price EJ, Venables PJ. Dry eyes and mouth syndrome-a subgroup of patients presenting with sicca symptoms. *Rheumatology*. 2002;41(4):416-22. PMID: 11961172. Excluded: excluded population.

Price JR, Mitchell E, Tidy E, et al. Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev*. 2009 (2). Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet*. 2001;357(9259):841-7. PMID: 11265953. Excluded: excluded population.

Prins JB, Elving LD, Koning H, et al. Diagnosing chronic fatigue syndrome: comparison of a protocol and computerised questionnaires. *Neth J Med*. 2003;61(4):120-6. PMID: 12852720. Excluded: excluded outcome.

Randall DC, Cafferty FH, Shneerson JM, et al. Chronic treatment with modafinil may not be beneficial in patients with chronic fatigue syndrome. *J Psychopharmacol*. 2005;19(6):647-60. PMID: 16272188. Excluded: inadequate duration.

Appendix D. List of Excluded Studies

Rao AV, Bested AC, Beaulne TM, et al. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog.* 2009;1(1):1-6. doi: 10.1186/1757-4749-1-6. PMID: 19338686. Excluded: inadequate duration.

Rao XM, Luo ZN, Wang WL. Treatment of 33 cases of chronic fatigue syndrome by heat-sensitive moxibustion. *J Tradit Chin Med.* 2011;66-7. Excluded: not English but possibly relevant.

Rawson KM, Rickards H, Haque S, et al. Pharmacological treatments for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev.* 2007 (4)doi: 10.1002/14651858.CD006813. Excluded: not English but possibly relevant.

Reeves WC, Wagner D, Nisenbaum R, et al. Chronic fatigue syndrome-a clinically empirical approach to its definition and study. *BMC Med.* 2005;3:19. PMID: 16356178. Excluded: excluded outcome.

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. Excluded: excluded outcome.

Richardson G, Epstein D, Chew-Graham C, et al. Cost-effectiveness of supported self-management for CFS/ME patients in primary care. *BMC Fam Pract.* 2013;14:12. doi: 10.1186/1471-2296-14-12. PMID: 23327355. Excluded: excluded outcome.

Richardson G, Epstein D, Wearden A. Cost-effectiveness versus patient acceptability: the exemplar of CFS/ME. *Value in health.* 2012;15(7):A464. doi: 10.1016/j.jval.2012.08.1487. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Richardson J, Costa DC. Relationship between SPECT scans and buspirone tests in patients with ME/CFS. *J Chronic Fatigue Syndr.* 1998;4(3):23-38. doi: 10.1300/J092v04n03_04. Excluded: excluded intervention.

Ridsdale L, Evans A, Jerrett W, et al. Patients with fatigue in general practice: a prospective study. *BMJ.* 1993;307(6896):103-6. doi: 10.1136/bmj.307.6896.103. PMID: 8343705. Excluded: excluded outcome.

Ridsdale L, Godfrey E, Chalder T, et al. Chronic fatigue in general practice: is counselling as good as cognitive behaviour therapy? A UK randomised trial. *Br J Gen Pract.* 2001;51(462):19-24. PMID: 11271868. Excluded: excluded population.

Ridsdale L, Hurley M, King M, et al. The effect of counselling, graded exercise and usual care for people with chronic fatigue in primary care: a randomized trial. *Psychol Med.* 2012;42(10):2217-24. doi: 10.1017/S0033291712000256. PMID: 22370004. Excluded: excluded population.

Riedl A, Schmidtman M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res.* 2008;64(6):573-82. doi: 10.1016/j.jpsychores.2008.02.021. PMID: 18501257. Excluded: excluded population.

Rimes KA, Chalder T. Treatments for chronic fatigue syndrome. *Occup Med.* 2005;55(1):32-9. PMID: 15699088. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Roman P, Carrillo-Trabalón F, Sánchez-Labraca N, et al. Are probiotic treatments useful on fibromyalgia syndrome or chronic fatigue syndrome patients? A systematic review. *Benef Microbes.* 2018;9(4):603-11. doi: 10.3920/BM2017.0125. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Rosenberg BR. Cognitive behavioral treatment of juvenile primary fibromyalgia syndrome. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2005;66(2-B):1184. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Appendix D. List of Excluded Studies

- Rowe KS. Five-year follow-up of young people with chronic fatigue syndrome following the double blind randomised controlled intravenous gammaglobulin trial. *J Chronic Fatigue Syndr.* 1999;5(3-4):97-107. doi: 10.1300/J092v05n03_08. Excluded: excluded study design for Key Question.
- Rowe PC, Calkins H, DeBusk K, et al. Fludrocortisone acetate to treat neurally mediated hypotension in chronic fatigue syndrome: a randomized controlled trial. *JAMA.* 2001;285(1):52-9. PMID: 11150109. Excluded: inadequate duration.
- Russell C, Kyle SD, Wearden AJ. Do evidence based interventions for chronic fatigue syndrome improve sleep? A systematic review and narrative synthesis. *Sleep Med Rev.* 2017;33:101-10. doi: 10.1016/j.smr.2016.05.001. PMID: 27524207. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Sabes-Figuera R, McCrone P, Hurley M, et al. Cost-effectiveness of counselling, graded-exercise and usual care for chronic fatigue: evidence from a randomised trial in primary care. *BMC Health Serv Res.* 2012;12:264. doi: 10.1186/1472-6963-12-264. PMID: 22906319. Excluded: excluded outcome.
- Saez-Francas N, Alegre J, Calvo N, et al. Attention-deficit hyperactivity disorder in chronic fatigue syndrome patients. *Psychiatry Res.* 2012;200(2-3):748-53. doi: 10.1016/j.psychres.2012.04.041. PMID: 22648008. Excluded: excluded study design for Key Question.
- Saez-Francas N, Calvo N, Alegre J, et al. Childhood trauma in chronic fatigue syndrome: focus on personality disorders and psychopathology. *Compr Psychiatry.* 2015;62:13-9. doi: 10.1016/j.comppsy.2015.06.010. PMID: 26343462. Excluded: excluded outcome.
- Sampalli T, Berlasso E, Fox R, et al. A controlled study of the effect of a mindfulness-based stress reduction technique in women with multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. *J Multidiscip Healthc.* 2009;2:53-9. doi: 10.2147/JMDH.S5220. Excluded: excluded population.
- Santaella ML, Font I, Disdier OM. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J.* 2004;23(2):89-93. PMID: 15377055. Excluded: excluded intervention.
- Sathyapalan T, Beckett S, Rigby AS, et al. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. *Nutr J.* 2010;9:55. doi: 10.1186/1475-2891-9-55. PMID: 21092175. Excluded: inadequate duration.
- Saxty M, Hansen Z. Group cognitive behavioural therapy for chronic fatigue syndrome: a pilot study. *Behav Cogn Psychother.* 2005;33(3):311-8. doi: 10.1017/S1352465805002092. Excluded: excluded study design for Key Question.
- Scheeres K, Wensing M, Bleijenberg G, et al. Implementing cognitive behavior therapy for chronic fatigue syndrome in mental health care: a costs and outcomes analysis. *BMC Health Serv Res.* 2008;8:175. doi: 10.1186/1472-6963-8-175. PMID: 18700975. Excluded: excluded study design for Key Question.
- Scheeres K, Wensing M, Knoop H, et al. Implementing cognitive behavioral therapy for chronic fatigue syndrome in a mental health center: a benchmarking evaluation. *J Consult Clin Psychol.* 2008;76(1):163-71. doi: 10.1037/0022-006X.76.1.163. PMID: 18229994. Excluded: excluded study design for Key Question.
- Schreurs KM, Veehof MM, Passade L, et al. Cognitive behavioural treatment for chronic fatigue syndrome in a rehabilitation setting: effectiveness and predictors of outcome. *Behav Res Ther.* 2011;49(12):908-13. doi: 10.1016/j.brat.2011.09.004. PMID: 21982345. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

- Schroder A, Ornbol E, Jensen JS, et al. Long-term economic evaluation of cognitive-behavioural group treatment versus enhanced usual care for functional somatic syndromes. *J Psychosom Res.* 2017;94:73-81. doi: 10.1016/j.jpsychores.2017.01.005. PMID: 28183406. Excluded: excluded outcome.
- Scott LV, Burnett F, Medbak S, et al. Naloxone-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. *Psychol Med.* 1998;28(2):285-93. PMID: 9572086. Excluded: excluded intervention.
- Semalty A, Semalty M, Panda VS, et al. Herbal drugs in chronic fatigue syndrome: an overview. *Schweizerische Zeitschrift für GanzheitsMedizin.* 2012;24(3):155-68. doi: 10.1159/000339011. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Sharpe MC, Archard LC, Banatvala JE, et al. A report-chronic fatigue syndrome: guidelines for research. *J R Soc Med.* 1991;84(2):118-21. PMID: 1999813. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Shen J, Tang X, Zou K. Quality assessment of the reporting of randomized controlled trials of traditional Chinese medicine for chronic fatigue syndrome. *Chinese Journal of Evidence-Based Medicine.* 2007;7(5):385-91. Excluded: not English but possibly relevant.
- Shi LY. Acupuncture treatment of 56 cases of chronic fatigue syndrome. *Liaonong J Tradit Chin Med.* 2001;28(5):304. Excluded: not English but possibly relevant.
- Shi YL, Fu RH. Treatment of 52 cases with chronic fatigue syndrome by knocking and stabbing the three meridians of governing vessel meridian and bilateral urinary bladder meridian on the area of head. *Zhejiang J Tradit Chin Med.* 2004;10:448. Excluded: not English but possibly relevant.
- Shlaes J, Jason L. A buddy/mentor program for PWCs. *Cfids Chronicle.* 1996:21-5. Excluded: excluded population.
- Shu Q, Wang H, Litscher D, et al. Acupuncture and moxibustion have different effects on fatigue by regulating the autonomic nervous system: a pilot controlled clinical trial. *Sci Rep.* 2016;6:37846. doi: 10.1038/srep37846. PMID: 27886247. Excluded: inadequate duration.
- Skapinakis P, Lewis G, Meltzer H. Clarifying the relationship between unexplained chronic fatigue and psychiatric morbidity: results from a community survey in Great Britain. *Int Rev Psychiatry.* 2003;15(1-2):57-64. PMID: 12745311. Excluded: excluded study design for Key Question.
- Smith ME, Haney E, McDonagh M, et al. Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a national institutes of health pathways to prevention workshop. *Ann Intern Med.* 2015;162(12):841-50. doi: 10.7326/M15-0114. PMID: 26075755. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Sollie K, Naess ET, Solhaug I, et al. Mindfulness training for chronic fatigue syndrome: a pilot study. *Health Psychology Report.* 2017;5(3):240-50. doi: 10.5114/hpr.2017.65469. Excluded: excluded study design for Key Question.
- Solomon-Moore E, Jago R, Beasant L, et al. Physical activity patterns among children and adolescents with mild-to-moderate chronic fatigue syndrome/myalgic encephalomyelitis. *BMJ Paediatr Open.* 2019;3(1):e000425. doi: 10.1136/bmjpo-2018-000425. PMID: 31206075. Excluded: excluded intervention.
- Spath M, Welzel D, Farber L. Treatment of chronic fatigue syndrome with 5-HT3 receptor antagonists-preliminary results. *Scand J Rheumatol Suppl.* 2000;113:72-7. PMID: 11028837. Excluded: inadequate duration.

Appendix D. List of Excluded Studies

- Staud R, Boissoneault J, Craggs JG, et al. Task related cerebral blood flow changes of patients with chronic fatigue syndrome: an arterial spin labeling study. *Fatigue*. 2018;6(2):63-79. doi: 10.1080/21641846.2018.1453919. Excluded: excluded outcome.
- Steinberg P, McNutt BE, Marshall P, et al. Double-blind placebo-controlled study of the efficacy of oral terfenadine in the treatment of chronic fatigue syndrome. *J Allergy Clin Immunol*. 1996;97(1 Pt 1):119-26. PMID: 8568124. Excluded: inadequate duration.
- Stoll SVE, Crawley E, Richards V, et al. What treatments work for anxiety in children with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)? Systematic review. *BMJ Open*. 2017;7(9):e015481. doi: 10.1136/bmjopen-2016-015481. PMID: 28877941. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Stouch BC, Strayer D, Carter W. Cardiac toxicity in chronic fatigue syndrome: results from a randomized 40-week multicenter double-blind placebo control trial of rintatolimod. *J Appl Res*. 2010;10(3):80-7. Excluded: excluded outcome.
- Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. *N Engl J Med*. 1988;319(26):1692-8. PMID: 2849717. Excluded: inadequate duration.
- Sudhakaran P. Acupuncture for chronic fatigue. *Med Acupunct*. 2014;26(1):5-14. doi: 10.1089/acu.2013.1009. Excluded: excluded study design for Key Question.
- Sullivan A, Nord CE, Evengard B. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. *Nutr J*. 2009;8:4. doi: 10.1186/1475-2891-8-4. PMID: 19171024. Excluded: excluded study design for Key Question.
- Sun M, He X, Li SZ. Treatment of 40 cases with chronic fatigue syndrome by knocking and stabbing governing vessel meridian. *China Sci Technol Inform*. 2005;9:126. Excluded: not English but possibly relevant.
- Sun Y, Li HJSZZ. Observation on the curative effect of channel-unblocking Back-Shu and Front-Mu points prescription on chronic fatigue syndrome. 2006;25(11):3-4. Excluded: not English but possibly relevant.
- Sutar R, Yadav S, Desai G. Yoga intervention and functional pain syndromes: a selective review. *Int Rev Psychiatry*. 2016;28(3):316-22. doi: 10.1080/09540261.2016.1191448. PMID: 27291934. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Takken T, Henneken T, van de Putte E, et al. Exercise testing in children and adolescents with chronic fatigue syndrome. *Int J Sports Med*. 2007;28(7):580-4. PMID: 17357961. Excluded: excluded study design for Key Question.
- Tang BY. Acupuncture treatment of 39 chronic fatigue syndrome cases. *Shanghai J Acupunct Mox*. 2005;24(1):11-2. Excluded: not English but possibly relevant.
- Taylor R, Jason LA, Kennedy CL, et al. Effect of physician-recommended treatment on mental health practitioners' attributions for chronic fatigue syndrome. *Rehabil Psychol*. 2001;46(2):165-77. doi: 10.1037/0090-5550.46.2.165. Excluded: excluded population.
- Taylor RR, Jason LA, Curie CJ. Prognosis of chronic fatigue in a community-based sample. *Psychosom Med*. 2002;64(2):319-27. PMID: 11914449. Excluded: excluded outcome.
- Taylor RR, Thanawala SG, Shiraishi Y, et al. Long-term outcomes of an integrative rehabilitation program on quality of life: a follow-up study. *J Psychosom Res*. 2006;61(6):835-9. PMID: 17141674. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

- Teitelbaum J. Effective treatment of chronic fatigue syndrome. *Integrative Medicine*. 2005;4(4):24-9. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Teitelbaum JE, Bird B, Greenfield RM, et al. Effective treatment of chronic fatigue syndrome and fibromyalgia - a randomized, double-blind, placebo-controlled, intent-to-treat study. *J Chronic Fatigue Syndr*. 2001;8(2):3-28. doi: 10.1300/J092v08n02_02. Excluded: not a study (letter, editorial, non-systematic review article, no original data). Teitelbaum J, Bird B. Effective treatment of severe chronic fatigue: a report of a series of 64 patients. *J Musculoskelet Pain*. 1995;3(4):91-110. doi: 10.1300/J094v03n04_11. Excluded: excluded study design for Key Question.
- Teitelbaum JE, Johnson C, St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med*. 2006;12(9):857-62. PMID: 17109576. Excluded: excluded study design for Key Question.
- The GK, Bleijenberg G, Buitelaar JK, et al. The effect of ondansetron, a 5-HT₃ receptor antagonist, in chronic fatigue syndrome: a randomized controlled trial. *J Clin Psychiatry*. 2010;71(5):528-33. doi: 10.4088/JCP.08m04719whi. PMID: 20122367. Excluded: inadequate duration.
- The GK, Prins J, Bleijenberg G, et al. The effect of granisetron, a 5-HT₃ receptor antagonist, in the treatment of chronic fatigue syndrome patients-a pilot study. *Neth J Med*. 2003;61(9):285-9. PMID: 14692441. Excluded: excluded study design for Key Question.
- The GK, Verkes RJ, Fekkes D, et al. Tryptophan depletion in chronic fatigue syndrome, a pilot cross-over study. *BMC Res Notes*. 2014;7:650. doi: 10.1186/1756-0500-7-650. PMID: 25227994. Excluded: sample size too small.
- Theoharides TC, Asadi S, Weng Z, et al. Serotonin-selective reuptake inhibitors and nonsteroidal anti-inflammatory drugs-important considerations of adverse interactions especially for the treatment of myalgic encephalomyelitis/chronic fatigue syndrome. *J Clin Psychopharmacol*. 2011;31(4):403-5. doi: 10.1097/JCP.0b013e318225848c. PMID: 21694612. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Thomas MA, Smith AP. An investigation of the long-term benefits of antidepressant medication in the recovery of patients with chronic fatigue syndrome. *Hum Psychopharmacol*. 2006;21(8):503-9. PMID: 16981220. Excluded: excluded intervention.
- Thomas M, Sadlier M, Smith A. The effect of multi convergent therapy on the psychopathology, mood and performance of chronic fatigue syndrome patients: a preliminary study. *Couns Psychother Res*. 2006;6(2):91-9. doi: 10.1080/14733140600711955. Excluded: excluded study design for Key Question.
- Thomas MA, Sadlier MJ, Smith AP. A multiconvergent approach to the rehabilitation of patients with chronic fatigue syndrome: a comparative study. *Physiotherapy*. 2008;94(1):35-42. doi: 10.1016/j.physio.2007.04.013. Excluded: excluded study design for Key Question.
- Tiev KP, Demette E, Ercolano P, et al. RNase L levels in peripheral blood mononuclear cells: 37-kilodalton/83-kilodalton isoform ratio is a potential test for chronic fatigue syndrome. *Clin Diagn Lab Immunol*. 2003;10(2):315-6. PMID: 12626460. Excluded: excluded outcome.
- Tirelli U, Lleshi A, Berretta M, et al. Treatment of 741 Italian patients with chronic fatigue syndrome. *Eur Rev Med Pharmacol Sci*. 2013;17(21):2847-52. PMID: 24254550. Excluded: excluded study design for Key Question.
- Togo F, Natelson BH, Cherniack NS, et al. Sleep is not disrupted by exercise in patients with chronic fatigue syndromes. *Med Sci Sports Exerc*. 2010;42(1):16-22. doi: 10.1249/MSS.0b013e3181b11bc7. PMID: 20010134. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

Torjesen I. Tackling fear about exercise produces long term benefit in chronic fatigue syndrome. *BMJ*. 2015;351:h5771. doi: 10.1136/bmj.h5771. PMID: 26511755. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Torjesen I. Tackling fears about exercise is important for ME treatment, analysis indicates. *BMJ*. 2015;350:h227. doi: 10.1136/bmj.h227. PMID: 25589087. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Tuller D. Trial by error: a letter to archives of disease in childhood. *Virology Blog*; 2018. <http://www.virology.ws/2018/01/30/trial-by-error-a-letter-to-archives-of-disease-in-childhood/>. Accessed July 8, 2019. Excluded: not a study (letter, editorial, non-systematic review article, no original data).

Turkington D, Hedwat D, Rider I, et al. Recovery from chronic fatigue syndrome with modafinil. *Hum Psychopharmacol*. 2004;19(1):63-4. PMID: 14716715. Excluded: excluded study design for Key Question.

Unger ER, Lin JS, Tian H, et al. Multi-site clinical assessment of myalgic encephalomyelitis/chronic fatigue syndrome (MCAM): design and implementation of a prospective/retrospective rolling cohort study. *Am J Epidemiol*. 2017;185(8):617-26. doi: 10.1093/aje/kwx029. PMID: 28338983. Excluded: excluded outcome.

Valdini A, Steinhardt S, Feldman E. Usefulness of a standard battery of laboratory tests in investigating chronic fatigue in adults. *Fam Pract*. 1989;6(4):286-91. PMID: 2632306. Excluded: excluded outcome.

Van Cauwenbergh D, De Kooning M, Ickmans K, et al. How to exercise people with chronic fatigue syndrome: evidence-based practice guidelines. *Eur J Clin Invest*. 2012;42(10):1136-44. doi: 10.1111/j.1365-2362.2012.02701.x. PMID: 22725992. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Van Damme S, Crombez G, Van Houdenhove B, et al. Well-being in patients with chronic fatigue syndrome: the role of acceptance. *J Psychosom Res*. 2006;61(5):595-9. PMID: 17084136. Excluded: excluded outcome.

van Heukelom RO, Prins JB, Smits MG, et al. Influence of melatonin on fatigue severity in patients with chronic fatigue syndrome and late melatonin secretion. *Eur J Neurol*. 2006;13(1):55-60. PMID: 16420393. Excluded: excluded study design for Key Question.

Van Hoof E, De Meirleir K. Chronic fatigue syndrome and myalgic encephalomyelitis: are both conditions on the same continuum? *N Am J Psychol*. 2005;7(2):189-204. Excluded: excluded study design for Key Question.

Van Oosterwijk J, Meeus M, Paul L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *Clin J Pain*. 2013;29(10):873-82. doi: 10.1097/AJP.0b013e31827c7a7d. PMID: 23370076. Excluded: excluded population.

Vancoppenolle A, Vanderfaeillie J, Lampo A, et al. The chronic fatigue syndrome in children and adolescents: results after one year centre of reference. *Tijdschrift voor Geneeskunde*. 2005;61(18):1257-63. Excluded: not English but possibly relevant.

Vital Durand D, Francois S, Nove-Josserand R, et al. [Haemochromatosis screening in 120 patients complaining with persistent fatigue]. *Rev Med Interne*. 2004;25(9):623-8. doi: 10.1016/j.revmed.2004.04.016. PMID: 15363617. Excluded: not English but possibly relevant.

Vos-Vromans D, Evers S, Huijnen I, et al. Economic evaluation of multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome: a randomized controlled trial. *PLoS ONE*. 2017;12(6):e0177260. doi: 10.1371/journal.pone.0177260. PMID: 28574985. Excluded: excluded outcome.

Appendix D. List of Excluded Studies

- Vos-Vromans DC, Huijnen IP, Koke AJ, et al. Differences in physical functioning between relatively active and passive patients with chronic fatigue syndrome. *J Psychosom Res.* 2013;75(3):249-54. doi: 10.1016/j.jpsychores.2013.05.001. PMID: 23972414. Excluded: excluded outcome.
- Vos-Vromans DC, Huijnen IP, Rijnders LJ, et al. Treatment expectations influence the outcome of multidisciplinary rehabilitation treatment in patients with CFS. *J Psychosom Res.* 2016;83:40-5. doi: 10.1016/j.jpsychores.2016.02.004. PMID: 27020075. Excluded: excluded comparator.
- Vos-Vromans DC, Smeets RJ, Huijnen IP, et al. Multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome: a randomized controlled trial. *J Intern Med.* 2016;279(3):268-82. doi: 10.1111/joim.12402. PMID: 26306716. Excluded: excluded comparator.
- Vos-Vromans DC, Smeets RJ, Rijnders LJ, et al. Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomised controlled trial (FatiGo). *Trials.* 2012;13:71. doi: 10.1186/1745-6215-13-71. PMID: 22647321. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Waldman PN. Vitamin therapy in the treatment of depression associated with chronic fatigue syndrome. *Dissertation Abstracts International: Section B: The Sciences and Engineering.* 2001;61(10-B):5232. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Wallman KE, Morton AR, Goodman C, et al. Exercise prescription for individuals with chronic fatigue syndrome. *Med J Aust.* 2005;183(3):142-3. PMID: 16053417. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Walwyn R, Potts L, McCrone P, et al. A randomised trial of adaptive pacing therapy, cognitive behaviour therapy, graded exercise, and specialist medical care for chronic fatigue syndrome (PACE): statistical analysis plan. *Trials.* 2013;14:386. doi: 10.1186/1745-6215-14-386. PMID: 24225069. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Wang H, Liu X, Lv B, et al. Reliable multi-label learning via conformal predictor and random forest for syndrome differentiation of chronic fatigue in traditional Chinese medicine. *PLoS ONE.* 2014;9(6):e99565. doi: 10.1371/journal.pone.0099565. PMID: 24918430. Excluded: excluded study design for Key Question.
- Wang HT. Observation on curative effect of warm acupuncture and moxibustion at back - shu points on chronic fatigue syndrome. *Chin J Clin Rotation Drug Use.* 2010. Excluded: not English but possibly relevant.
- Wang HW. Clinical study on electroacupuncture treatment of chronic fatigue syndrome. Chengdu University of TCM Doctor's Thesis. 2007. Excluded: not English but possibly relevant.
- Wang JH, Chai TQ, Lin GH, et al. Effects of the intelligent-turtle massage on the physical symptoms and immune functions in patients with chronic fatigue syndrome. *J Tradit Chin Med.* 2009;29(1):24-8. PMID: 19514184. Excluded: inadequate duration.
- Wang JJ, Song YJ, Wu ZC, et al. Randomized controlled clinical trials of acupuncture treatment of chronic fatigue syndrome. *Zhen Ci Yan Jiu.* 2009;34(2):120-4. Excluded: not English but possibly relevant.
- Wang JZ, Fang B, Zhang HF, et al. Clinical study of Fuzheng Jiayu prescription in treatment of chronic fatigue syndrome. *Chin J Inf Tradit Chin Med.* 2007;14:75-6. Excluded: not English but possibly relevant.
- Wang Q, Xiong JX. [Clinical observation on effect of electro-acupuncture on back-shu points in treating chronic fatigue syndrome]. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2005;25(9):834-6. PMID: 16248250. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

- Wang T, Xu C, Pan K, et al. Acupuncture and moxibustion for chronic fatigue syndrome in traditional Chinese medicine: a systematic review and meta-analysis. *BMC Complement Altern Med*. 2017;17(1):163. doi: 10.1186/s12906-017-1647-x. PMID: 28335756. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Wang T, Zhang Q, Xue X, et al. A systematic review of acupuncture and moxibustion treatment for chronic fatigue syndrome in China. *Am J Chin Med*. 2008;36(1):1-24. PMID: 18306446. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Wang WH, Duan YJ, Zhu YJ, et al. Clinical observation on treatment of chronic fatigue syndrome by combined acupuncture and cupping. *Shanghai J Acupunct Mox*. 2001;20(1):23-4. Excluded: not English but possibly relevant.
- Wang XZ. Treatment of 12 cases with chronic fatigue syndrome by combination of acupuncture and herbs. *Shanghai J Acupunct Mox*. 2004;23 (6):42. Excluded: not English but possibly relevant.
- Wang Y, Xiao W, Wang J. Therapeutic observation on thunder-fire moxibustion for chronic fatigue syndrome. *Shanghai J Acupunct Mox*. 2013:827-8. Excluded: not English but possibly relevant.
- Wang YL, Wang J, Yang L. Treatment of chronic fatigue syndrome by combination of acupuncture and massage. *J China-Japan Friendship Hosp*. 2003;17(4):252. Excluded: not English but possibly relevant.
- Wang YY, Li XX, Liu JP, et al. Traditional Chinese medicine for chronic fatigue syndrome: a systematic review of randomized clinical trials. *Complement Ther Med*. 2014;22(4):826-33. doi: 10.1016/j.ctim.2014.06.004. PMID: 25146086. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Ward MH, DeLisle H, Shores JH, et al. Chronic fatigue complaints in primary care: incidence and diagnostic patterns. *J Am Osteopath Assoc*. 1996;96(1):34-46, 1. PMID: 8626230. Excluded: excluded study design for Key Question.
- Watson SP, Ruskin AS, Simonis V, et al. Identifying defining aspects of chronic fatigue syndrome via unsupervised machine learning and feature selection. *Int J Mach Learn Comput*. 2014;4(2):133-8. doi: 10.7763/IJMLC.2014.V4.400. Excluded: excluded study design for Key Question.
- Wearden AJ, Riste L, Dowrick C, et al. Fatigue Intervention by Nurses Evaluation-the FINE Trial. A randomised controlled trial of nurse led self-help treatment for patients in primary care with chronic fatigue syndrome: study protocol. *BMC Med*. 2006;4:9. PMID: 16603058. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- White AT, Light AR, Hughen RW, et al. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology*. 2010;47(4):615-24. doi: 10.1111/j.1469-8986.2010.00978.x. PMID: 20230500. Excluded: excluded study design for Key Question.
- White E, Sherlock C. The effect of nutritional therapy for yeast infection (candidiasis) in cases of chronic fatigue syndrome. *J Orthomol Med*. 2005;20(3):193-209. Excluded: excluded study design for Key Question.
- White P, Chalder T, Sharpe M. The PACE trial: results of a large trial of nonpharmacological treatments. *J Psychosom Res*. 2011;70(6):622. Excluded: unable to obtain.
- White PD, Cleary KJ. An open study of the efficacy and adverse effects of moclobemide in patients with the chronic fatigue syndrome. *Int Clin Psychopharmacol*. 1997;12(1):47-52. PMID: 9179634. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

- White PD, Naish VA. Graded exercise therapy for chronic fatigue syndrome. *Physiotherapy*. 2001;87(6):285-8. doi: 10.1016/S0031-9406(05)60762-6. Excluded: excluded study design for Key Question.
- White PD, Sharpe MC, Chalder T, et al. Protocol for the PACE trial: a randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/ myalgic encephalomyelitis or encephalopathy. *BMC Neuro*. 2007;7(6) PMID: 17397525. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Whitehead L, Campion P. Can general practitioners manage chronic fatigue syndrome? A controlled trial. *J Chronic Fatigue Syndr*. 2002;10(1):55-64. doi: 10.1300/J092v10n01_05. Excluded: excluded intervention.
- Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *Pain*. 2004;109(3):497-9. PMID: 15157711. Excluded: excluded study design for Key Question.
- Whiting P, Bagnall AM, Sowden AJ, et al. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. *JAMA*. 2001;286(11):1360-8. PMID: 11560542. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.
- Wiborg JF, Knoop H, Frank LE, et al. Towards an evidence-based treatment model for cognitive behavioral interventions focusing on chronic fatigue syndrome. *J Psychosom Res*. 2012;72(5):399-404. doi: 10.1016/j.jpsychores.2012.01.018. PMID: 22469284. Excluded: excluded outcome.
- Wiborg JF, Knoop H, Prins JB, et al. Does a decrease in avoidance behavior and focusing on fatigue mediate the effect of cognitive behavior therapy for chronic fatigue syndrome? *J Psychosom Res*. 2011;70(4):306-10. doi: 10.1016/j.jpsychores.2010.12.011. PMID: 21414449. Excluded: excluded population.
- Wiborg JF, Knoop H, Stulemeijer M, et al. How does cognitive behaviour therapy reduce fatigue in patients with chronic fatigue syndrome? The role of physical activity. *Psychol Med*. 2010;40(8):1281-7. doi: 10.1017/S0033291709992212. PMID: 20047707. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Wiborg JF, Knoop H, Wensing M, et al. Therapist effects and the dissemination of cognitive behavior therapy for chronic fatigue syndrome in community-based mental health care. *Behav Res Ther*. 2012;50(6):393-6. doi: 10.1016/j.brat.2012.03.002. PMID: 22504122. Excluded: excluded outcome.
- Wilshire C, Kindlon T, McGrath S. PACE trial claims of recovery are not justified by the data: a rejoinder to Sharpe, Chalder, Johnson, Goldsmith and White (2017). *Fatigue*. 2017;5(1):62-7. doi: 10.1080/21641846.2017.1299358. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Wittkowski A, Toye K, Richards HL. A cognitive behaviour therapy group for patients with chronic fatigue syndrome: a preliminary investigation. *Behav Cogn Psychother*. 2004;32(1):107-12. doi: 10.1017/S1352465804001109. Excluded: excluded study design for Key Question.
- 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. Excluded: excluded outcome.
- Worm-Smeitink M, Nikolaus S, Goldsmith K, et al. Cognitive behaviour therapy for chronic fatigue syndrome: differences in treatment outcome between a tertiary treatment centre in the United Kingdom and the Netherlands. *J Psychosom Res*. 2016;87:43-9. doi: 10.1016/j.jpsychores.2016.06.006. PMID: 27411751. Excluded: excluded study design for Key Question.

Appendix D. List of Excluded Studies

- Wu DD. The clinical research of eight meridian confluence points with auricular therapy treatment of chronic fatigue syndrome of liver depression and spleen. Heilongjiang University of Chinese Medicine Master's Thesis. 2010. Excluded: not English but possibly relevant.
- Wu DD, Li Y. The treatment of both heart and spleen deficiency type of chronic fatigue syndrome by eight confluent points with ear acupuncture. *J Clin Acupunct Mox.* 2010;31-3. Excluded: not English but possibly relevant.
- Wyller VB, Saul JP, Walloe L, et al. Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. *Eur J Appl Physiol.* 2008;102(6):623-32. PMID: 18066580. Excluded: excluded study design for Key Question.
- Wyller VB, Thaulow E, Amlie JP. Treatment of chronic fatigue and orthostatic intolerance with propranolol. *J Pediatr.* 2007;150(6):654-5. PMID: 17517256. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Xi HP. Treatment of 50 cases with chronic fatigue syndrome by combination of acupuncture, massage and herbs. *Chin J Tradit Med Sci Technol.* 2004;11(4):202. Excluded: not English but possibly relevant.
- Xie SY. The clinical study of combined therapy of electro- and auricular acupuncture in the treatment of chronic fatigue syndrome. Guangzhou University of Chinese Medicine Master's Thesis. 2009. Excluded: not English but possibly relevant.
- Xiong J. The clinical researchers of electro-therapy treatment for chronic fatigue syndromes. Guangzhou University of Chinese Medicine Master's Thesis. 2005. Excluded: not English but possibly relevant.
- Xu D, Dong YX, Yang XQ. Effect observation of JiaweiNaoxinkang in treatment of chronic fatigue syndrome in 40 patients. *J Changchun Univ Tradit Med.* 2013;29:281-2. Excluded: not English but possibly relevant.
- Xu W, Zhou RH, Li L, et al. Observation on therapeutic effect of chronic fatigue syndrome treated with Panlongci (coiling dragon needling) and moving cupping on back. *World J Acupunct Moxibustion.* 2012;22(4):27-31. doi: 10.1016/S1003-5257(13)60024-0. Excluded: inadequate duration.
- Xu ZH, Wang ZX. Chaihu plus lugumuli tang in treatment of chronic fatigue syndrome in 42 patients. *Henan Tradit Chin Med.* 2013;33:847-8. Excluded: not English but possibly relevant.
- Yagi A, Ataka S. Putative prophylaxes of aloe vera juice with L-arginine to chronic fatigue syndrome. *J Gastroenterol Hepatol Res.* 2016;5(2):1950-6. doi: 10.17554/j.issn.2224-3992.2016.5.603. Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Yan H, Li ZR. Clinical study on treatment of chronic fatigue syndrome with acupuncture and moxibustion based on differentiation of syndromes. *Chin Acupunct Mox.* 2003;23(4):197-9. Excluded: not English but possibly relevant.
- Yang CD, Boa JL, Song JC, et al. Clinical observation of 80 CFS cases treated with catgut embedment in acupoints. *World Chin Med.* 2009:154-5. Excluded: not English but possibly relevant.
- Yang PL. Treatment of chronic fatigue syndrome with round-shaped magnetic needle. *J Extern Ther Tradit Chin Med.* 2001;10(2):52. Excluded: not English but possibly relevant.
- Yao H, Qin HG, Wang RX, et al. Quality assessment of methodology and reporting of clinical trials involving Xiaoyao San for chronic fatigue syndrome. *Chinese Journal of Evidence-Based Medicine.* 2015;15(4):471-8. doi: 10.7507/1672-2531.20150078. Excluded: not English but possibly relevant.
- Yao RM, Qiu MY. Clinical observation of chronic fatigue syndrome treated by Chinese medicine in Hong Kong. *Shanghai J Tradit Chin Med.* 2005;39(6):12-3. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

Ye DN. The effective observation of curing liver depression and spleen deficiency of chronic fatigue syndrome by acupuncture. University of Chinese Medicine Master's Thesis. 2009. Excluded: not English but possibly relevant.

Yin LH. Observation on treatment of chronic fatigue syndrome by combination of acupuncture, spine-massage and music therapy. *J Clin Acupunct Mox.* 2005;21(8):9-10. Excluded: not English but possibly relevant.

Yiu YM, Ng SM, Tsui YL, et al. A clinical trial of acupuncture for treating chronic fatigue syndrome in Hong Kong. *Journal of Chinese Integrative Medicine.* 2007;5(6):630-3. doi: 10.3736/jcim20070606. Excluded: not English but possibly relevant.

Yoshiuchi K, Cook DB, Ohashi K, et al. A real-time assessment of the effect of exercise in chronic fatigue syndrome. *Physiol Behav.* 2007;92(5):963-8. PMID: 17655887. Excluded: excluded study design for Key Question.

Young JL. Use of lisdexamfetamine dimesylate in treatment of executive functioning deficits and chronic fatigue syndrome: a double blind, placebo-controlled study. *Psychiatry Res.* 2013;207(1-2):127-33. doi: 10.1016/j.psychres.2012.09.007. PMID: 23062791. Excluded: inadequate duration.

Yu J. Clinical research on treatment of chronic fatigue syndrome by acupuncture on back points. Dalian Medical University Master's Thesis. 2013. Excluded: not English but possibly relevant.

Yuemei L, Hongping L, Shulan F, et al. The therapeutic effects of electrical acupuncture and auricular-plaster in 32 cases of chronic fatigue syndrome. *J Tradit Chin Med.* 2006;26(3):163-4. PMID: 17078435. Excluded: inadequate duration.

Yuemei L, Hongping L, Shulan F, et al. The therapeutic effects of electrical acupuncture and auricular-plaster in 32 cases of chronic fatigue syndrome. *J Tradit Chin Med.* 2006;26(3):163-4. PMID: 17078435. Excluded: not English but possibly relevant.

Zala J. Diagnosing myalgic encephalomyelitis. *Practitioner.* 1989;233(1471):916-9. PMID: 2594656. Excluded: excluded study design for Key Question.

Zalewski P, Finkelmeyer A, Frith J, et al. Liver volume is lower and associates with resting and dynamic blood pressure variability in chronic fatigue syndrome. *Fatigue.* 2018;6(3):141-52. doi: 10.1080/21641846.2018.1488525. Excluded: excluded population.

Zeng Z, Liu YX. Acupuncture and moxibustion treatment of 38 cases of chronic fatigue syndrome. *Shanghai J Acupunct Mox.* 1999;18(3):24. Excluded: not English but possibly relevant.

Zhang CJ. Effectiveness observation on treatment of 30 cases with chronic fatigue syndrome by knocking and stabbing with dermal needle and cupping. *J Clin Acupunct Mox.* 2004;20(12):37-8. Excluded: not English but possibly relevant.

Zhang D, ZHou C, Liu L. Clinical observation of chronic fatigue syndrome treated by warm acupuncture and moxibustion at jiaji. *Chin Acupunct Mox.* 2007:61-2. Excluded: not English but possibly relevant.

Zhang R, Li J, Chen J, et al. Clinical observation of Shenqi recovery tang in treatment of chronic fatigue syndrome. *Chinese Journal of Information on TCM.* 2004;11(2). Excluded: not English but possibly relevant.

Zhang RF. A randomized controlled study on treating chronic fatigue syndrome by acupuncturing acupoints on meridians; 2012. Excluded: not English but possibly relevant.

Zhang TH, Chen JL. The influence on immune function of patients with chronic fatigue syndrome by moxibustion tonification acupoints. *Shenzhen J Integr Tradit Chin West Med.* 2006;16(4):226-7. Excluded: not English but possibly relevant.

Appendix D. List of Excluded Studies

- Zhang W. Clinical study on acupuncture at Back-Shu points for chronic fatigue syndrome: a report of 22 cases. *J Tradit Chin Med.* 2010;139-41. Excluded: not English but possibly relevant.
- Zhang W, Wu T, Peng W. Acupuncture for chronic fatigue syndrome. *Cochrane Database Syst Rev.* 2011 (9). Excluded: not a study (letter, editorial, non-systematic review article, no original data).
- Zhang Y. Clinical observation on treatment of 38 cases of chronic fatigue syndrome with acupuncture. *Chin Acupunct Mox.* 2002;22(1):17-8. Excluded: not English but possibly relevant.
- Zhang Z, Cai Z, Yu Y, et al. Effect of Lixujieyu recipe in combination with five elements music therapy on chronic fatigue syndrome. *J Tradit Chin Med.* 2015;35(6):637-41. PMID: 26742307. Excluded: inadequate duration.
- Zhang ZX, Wu LL, Chen M. [Effect of lixu jieyu recipe in treating 75 patients with chronic fatigue syndrome]. *Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi.* 2009;29(6):501-5. Excluded: not English but possibly relevant.
- Zhao R. Clinical observation on acupuncture and cupping treatment of 35 cases of chronic fatigue syndrome. *Tianjin J Tradit Chin Med.* 2004;21(4):280. Excluded: not English but possibly relevant.
- Zhen SH, Zhen SZ, Jiao JK, et al. Effect of acupuncture and moxibustion of Shu-Mu points on quality of life of patients with chronic fatigue syndrome. *Guiding J Tradit Chin Med Pharm.* 2011;66-8. Excluded: not English but possibly relevant.
- Zheng SH, Zheng SZ, Jiao JK, et al. Randomized controlled trial of acupuncture of yumu points in treatment of chronic fatigue syndrome. *Liaoning J Tradit Chin Med.* 2012;39:726-8. Excluded: not English but possibly relevant.
- Zhong WQ, Li SC, Gu TT. Observation on curative effect of warming acupuncture on chronic fatigue syndrome. *Shanghai J Acu-mox.* 2014:206-8. Excluded: not English but possibly relevant.
- Zhou L, Feng ZG. Efficacy of chronic fatigue syndrome treated by acupoint catgut-embedding. *J Clin Acupunct Mox.* 2014:31-3. Excluded: not English but possibly relevant.
- Zhou TT. The clinical effects and immune mechanism research of moxibustion with warming needle for chronic fatigue syndrome with deficiency of heart and spleen. *Guangzhou University of Chinese Medicine Doctor's Thesis.* 2013. Excluded: not English but possibly relevant.
- Zhu WG. Abdomen acupuncture treatment of 35 cases of chronic fatigue syndrome. *Henan Tradit Chin Med.* 2004;24(12):56. Excluded: not English but possibly relevant.
- Zhu YH, Liang FR. Randomized controlled trials of electroacupuncture on Shenshu and Zusanli in treatment of chronic fatigue syndrome. *SHJTCM.* 2008;42:48-50. Excluded: not English but possibly relevant.
- Zhu YM. Abdominal acupuncture for treatment of chronic fatigue syndrome a randomized clinical trial. *Nanjing University of Chinese Medicine Doctor's Thesis.* 2012. Excluded: not English but possibly relevant.
- Zou L, Pan Z, Yeung A, et al. A review study on the beneficial effects of baduanjin. *J Altern Complement Med.* 2018;24(4):324-35. doi: 10.1089/acm.2017.0241. PMID: 29227709. Excluded: systematic reviews, secondary analyses, or meta-analyses used as a source document only to identify individual studies.

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non-ME/CFS condition
Brimmer, 2013 ¹	CFS Registry USA	<p>N=104 patients referred to CFS registry over the course of 1 year</p> <p>Referral criteria: Include: Medically unexplained, severe fatigue persisting for one month or longer and at least one month's duration of sleep, or problems with memory or concentration, or unexplained joint or muscle pain; BMI <40; Age 12-69</p> <p>Exclusion (using lab or history): Pregnancy within 12 months Stroke with no full recovery Parkinson's disease COPD or congestive heart failure Insulin-dependent diabetes Uncontrolled diabetes type II Anemia Uncontrolled hypo- or hyperthyroidism Uncontrolled hypertension Sickle cell anemia Cancer within 5 years Untreated depression Substance abuse within 2 years Anorexia or bulimia within 5 years Schizophrenia, bipolar disorder, dementia Hepatitis B or C</p>	<p>CFS vs. Insufficient fatigue vs. Exclusion condition</p> <p>Age: <18: 3% vs. 16% vs. 2% 18-20: 0% vs. 0% vs. 6% 21-30: 8% vs. 16% vs. 4% 31-40: 24% vs. 16% vs. 11% 41-50: 16% vs. 6% vs. 16% 51-60: 32% vs. 33% vs. 39% 61-70: 16% vs. 11% vs. 22% Female: 89% vs. 72% vs. 96% Race: Black: 8% vs. 0% vs. 14% White: 89% vs. 100% vs. 82% Previous CFS Diagnosis (does not include adolescents): 54% vs. 56% vs. 56%</p>	<p>Using Fukuda, 1994 criteria: CFS: 37/104 (36%) Insufficient fatigue: 18/104 (17%) Exclusionary condition: 49/104 (47%) Active inflammation: 4.1% Alcohol abuse: 8.2358.2% Anemia: 6.1% Anorexia: 2.0% Autoimmune disorder: 2.0% Bipolar: 4.1% Spinal disease: 2.0% Diabetes mellitus: 16.3% Hepatitis C virus: 2.0% High blood urea: 4.1% High C-reactive protein: 20.4% Hypertension: 2.0% Hypothyroidism: 20.4% Depression: 8.2% Mitochondrial myopathy: 2.0% Obesity: 4.1% Obstructive sleep apnea: 4.1% Osteoarthritis: 4.1% Narcolepsy: 2.0% Restless legs syndrome: 6.1% Rheumatoid arthritis: 2.0% Sleep problems: 2.0% Schizophrenia: 2.0% Sickle cell: 2.0% Substance abuse: 6.1% Uncontrolled high blood pressure: 2.0% Urinary tract infection: 8.2%</p>

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non- ME/CFS condition
Devasahayam, 2012 ²	Medical Record Review United Kingdom	N=250 Unclear criteria for referral/diagnosis. Patients referred from general practice to CFS specialty clinic with diagnosis of CFS, confirmed in clinical evaluation at CFS specialty clinic.	Characteristics not reported	<p>CFS diagnosis confirmed: 137/250 (54%)</p> <p>Psychiatric diagnoses: 54/250 (22%) Depression: 27/250 (11%) Anxiety: 14/250 (7%) Stress-related disorders: 6/250 (2%) Somatoform disorders: 3/250 (1%) Other psychiatric disorders: 4/250 (1.6%)</p> <p>Medical diagnoses: 53/250 (21%) Sleep disorders: 15/250 (6%) Pain disorders: 6/250 (2%) Endocrine disorders: 7/250 (3%) Nutritional disorders: 7/250 (3%) Musculo-skeletal disorders: 3/250 (1%) Gastro-intestinal disorders: 5/250 (2%) Neurological disorders: 3/250 (1%) Others (cardiac disorders and infections): 6/250 (2%)</p> <p>Miscellaneous reasons: 6/250 (2.4%) Fatigue not meeting CFS criteria: 3/250 (1%) Recovered from CFS: 2/250 (1%) No conclusive diagnosis: 1/250 (0.4%)</p>

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non- ME/CFS condition
Mariman, 2013 ³	Prospective cohort Belgium, the Netherlands	N=279 Patients referred for evaluation of unexplained chronic fatigue. Diagnosis based on Fukuda criteria.	Age, mean: 38.8 % Female: 84.9 Race: not reported Duration of symptoms: not reported Comorbidities: not reported	Final Diagnosis: Patients with ≥4 minor Fukuda criteria (n=224): Unequivocal CFS: n=65 CFS with comorbidity: n=59 CFS +psychiatric disorder: n=7 CFS +sleep disorder: n=45 CFS +both: n=7 CFS excluded: n=100 Psychiatric disorder: n=35 Sleep disorder: n=18 Psychiatric + sleep disorder: n=41 Internal disease: n=4 Other conditions: n=2 Patients with <4 minor Fukuda criteria (n=55) Psychiatric disorder: n=18 Sleep disorder: n=9 Psychiatric + sleep disorder: n=17 Internal disease: n=2 Other condition: n=2 No final diagnosis: n=7
Newton, 2010 ⁴	Retrospective medical record review United Kingdom	N=260 patients referred to CFS specialist service between 2008 and 2009.	Not reported	Reviewed medical notes of patients referred 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%).

Appendix E1. Evidence Table for Key Question 1

Author, year	Study Design Country	N/population Referral criteria?	Population Characteristics: Age Sex Race Criteria used for diagnosis Duration of symptoms Comorbidities	Results: Proportion of patients with non- ME/CFS condition
Nijrolder, 2009 ⁵	Prospective cohort the Netherlands	N=571 patients presenting with fatigue to primary care provider	Age, mean: 43 % Female: 73.9 Race: not reported Criteria used for diagnosis: not reported Duration of symptoms: <1 month: 8.1% 1 to 3 months: 15.9% 3 to 6 months: 17.9% 6 to 12 months: 18.9% >1 year: 39.2%	Diagnosis during 1-year followup after initial presentation for fatigue: Chronic Fatigue Syndrome: 4/571 (0.7%) Musculoskeletal diagnosis: 111/571 (19.4%) Psychological or social: 94/57 (16.5%) Digestive: 46/571 (8.1%) Neurologic: 38/571 (6.7%) General (includes CFS): 28/571 (4.9%) Infection: 104/571 (18.2%) Respiratory: 28/571 (4.9%) Endocrine: 16/571 (2.8%) Cardiovascular: 11/571 (1.9%) Female genital organs: 6/571 (1.1%) Malignant disease: 4/571 (0.7%) Skin: 3/571 (0.5%)
Stadje, 2016 ⁶	Systematic Review Germany	Systematic review of diagnosis of tiredness, three of the included studies presented estimates of the frequency of CFS	Studies included patients presenting with tiredness	Rates of CFS in three studies: 1.9% (95% CI 0.00 to 10.3%) 0.7% (95% CI 0.2 to 1.8%) 31.2% (95% CI 23.7 to 39.5%)- inclusion criteria for study included 2 of the diagnostic criteria for CFS, and explains the higher prevalence.

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Al-Haggar, 2006 ⁷ High	Egypt Single center 2002 to 2005 Specialty clinic recruited from schools and primary care	Adolescents ≥10 years Fukuda, 1994 criteria No other organic diseases	CBT + biofeedback (n=50): 40 to 60 sessions over 18 months, once to twice weekly, then tapered. Patients trained to perform relaxation exercises, to identify circumstances that trigger their symptoms, to avoid or cope well with these stressful events, to change their habits, and even to have the ability of self-control. Symptomatic treatment (n=46): not described

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		Number enrolled, analyzed	Attrition
Al-Haggar, 2006 ⁷ High	Population characteristics Age, mean years: 13.1 vs. 11.9 % Female: 39 vs. 35 Race: not reported Duration of illness, mean weeks: 27.9 vs. 24.5 Severity of fatigue, checklist score %: 54.8 vs. 51.9 No significant differences	Enrolled: 159 Analyzed: 92 (42 vs. 50)	Lost to follow-up: 63 Switched groups, not included in analysis: 4

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
	Benefits
Al-Haggar, 2006 ⁷ High	<p>School attendance, mean (SD) hours per month: 92.8 (18.4) vs. 66.6 (22.8), p=0.004</p> <p>Fatigue severity, mean (SD) checklist score: 32.2 (3.8) vs. 46.5 (14.2), p=0.02</p> <p>Patient-reported outcomes, mean (SD) on 4-point Likert scale:</p> <p>Unrefreshing sleep: 2.12 (0.88) vs. 3.32 (1.14), p=0.002</p> <p>Headache: 2.54 (0.84) vs. 2.86 (0.81), p= 0.03</p> <p>Myalgia: 2.16 (1.12) vs. 2.96 (0.92), p= 0.005</p> <p>Joint pains: 2.34 (1.14) vs. 2.34 (1.26), p > 0.05</p> <p>Tender glands: 1.81 (0.82) vs. 2.22 (0.92), p > 0.05</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Al-Haggar, 2006 ⁷ High	Not reported	Not reported

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Arnold, 2015 ⁸ RCT Medium	United States Single center 2006 to 2012 Outpatient research center	<p>"Revised" CDC (Fukuda, 1994) criteria: at least 6 months of persistent fatigue that substantially reduces the person's level of activity; 4 or more of the following symptoms that must occur with fatigue in a 6-month period: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches, unrefreshing sleep, and postexertional fatigue; other medical conditions that may explain the fatigue; and psychiatric disorders (as diagnosed by the investigator, including eating disorders, psychotic disorders, bipolar disorder, and melancholic depression, are excluded, as well as substance use disorders within 2 years of the onset of fatigue.</p> <p>Inclusion: General fatigue score ≥ 13 on the Multidimensional Fatigue Inventory (MFI) at screening and randomization.</p> <p>Exclusion: Current or past melancholic major depressive disorder or previous diagnosis of psychosis, eating disorder, or bipolar disorder; history of substance abuse or dependence within the past year; patients refractory to treatment; unstable medical illness; abnormal thyroid stimulating hormone concentrations; uncontrolled narrow-angle glaucoma; previously treated with duloxetine; use of herbal medications with central nervous system effects or analgesics (except acetaminophen or NSAIDs); alternative therapies.</p>	<p>Duloxetine (n=30): 30 mg once daily for 1 week, then 60 mg once daily for 3 weeks, then 90 mg for 4 weeks (as tolerated), then 120 mg (as tolerated) for remaining 4 weeks. Patients received a minimum dose of 60 mg once a day if higher doses were intolerable. At the end of 12 weeks, patients were tapered by a reduction of 30 mg daily until discontinuation.</p> <p>Placebo (n=30): Matching placebo</p> <p>Duration of treatment: 12 to 13 weeks</p> <p>Duration of followup: End of 12 week treatment phase</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Arnold, 2015 ⁸ RCT Medium	Duloxetine vs. placebo Mean age (years): 43.0 vs. 44.3 % Female: 86.7 (26/30) vs. 86.7 (26/30) Race, % (n/N): 86.7 (26/30) vs. 83.3 (25/30) white, 13.3 (4/30) vs. 13.3 (4/30) African American, 0 vs. 3.3 (1/30) other Duration of illness: NR (all at least 6 months) Severity of symptoms: <i>CDC Symptom Inventory CFS case definition symptom score (0 to 152 range with lower scores indicating better health)</i> : 39.3 vs. 40.6 <i>Clinical Global Impression of Severity (CGS-S)</i> : Score of 4 (moderately ill) %: 86.2 (25/29) vs. 90.0 (27/30) Score of 5 (markedly ill): 13.7 (4/29) vs. 10.0 (3/10) Comorbidities: NR	Number randomized: 60 Number analyzed: 57	Overall: 5% (3/60) Duloxetine vs. placebo: 3.3% (1/30) vs. 6.6% (2/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Arnold, 2015 ⁸ RCT Medium	<p>Duloxetine vs. placebo</p> <p>Overall Function: <i>SF-36 Medical Outcomes Study Short Form-36 Health Survey</i>, range 0 to 100, mean change (SD): 14.3 (22.6) vs. 7.5 (27.4), between group difference: 6.8 (95% CI, -8.5 to 22.0) p=0.38</p> <p>SF-36 physical function (0 to 100): NS 14.3 (22.6) vs. 7.5 (27.4); difference: 6.8, 95% CI -8.5 to 22.0, p=0.38</p> <p>Quality of Life: <i>Clinician Global Impression of Severity</i>, observed mean change (SD): -1.1 (1.2) vs. -0.4 (1.0), model-based difference between groups: -0.1 (95% CI, -0.3 to 0.0), p=0.02</p> <p><i>Patient Global Impression of Improvement</i>, observed mean change (SD): -1.1 (1.2) vs. -0.4 (1.0), model based difference between groups: -0.8 (95% CI, -1.7 to 0.0), p=0.06</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Multidimensional Fatigue Inventory (4 to 20, lower scores indicate better health)</i>:</p> <p>General fatigue, observed mean change (SD): -3.3 (4.2) vs. -1.8 (2.8), model-based difference between groups: -1.0 (95% CI, -2.8 to 0.7), p=0.23</p> <p>Physical fatigue, observed mean change (SD): -2.4 (4.4) vs. -1.0 (2.7), model-based difference between groups: -0.9 (95% CI, -2.7 to 0.7), p=0.32</p> <p>Reduced activity, observed mean change (SD): -2.1 (4.4) vs. -1.5 (3.2), model-based difference between groups: 0.0 (95% CI, -1.8 to 1.8), p=0.37</p> <p>Reduced motivation, observed mean change (SD): -2.6 (4.1) vs. -1.6 (3.8), model-based difference between groups: -0.8 (95% CI, -2.6 to 1.1), p=0.37</p> <p>Mental fatigue, observed mean change (SD): -3.8 (4.0) vs. -1.4 (3.3), model-based difference between groups: -2.5 (95% CI, -4.4 to -0.6), p=0.01</p> <p>Outcomes related to associated symptoms: <i>Brief Pain Inventory, 0 to 10 scales: Average pain severity</i>, mean (SD): -1.6 (1.5) vs. -0.8 (2.3), model-based differences between groups (log transformation used): 0.73 (95% CI, 0.54 to 1.00), p=0.05</p> <p>Average pain interference, mean (SD): -1.9 (1.3) vs. -1.1 (2.8), model-based difference between groups (log transformation used): 0.70 (95% CI, 0.51 to 0.96), p=0.03</p> <p>CDC Symptoms Inventory, CFS Questions, mean change (SD): -9.7 (13.1) vs. -8.2 (14.6), between-group difference at endpoint: -1.5 (95% CI, -9.9 to 6.9), p=0.72</p> <p>HADS-Depression, change from baseline: -1.6 (2.9) vs. -1.9 (3.0), p=0.67</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Arnold, 2015 ⁸ RCT Medium	<p>Duloxetine vs. placebo</p> <p>Adverse Events: Events that differed % (n/N):</p> <p>Nausea: 65.5 (19/29) vs. 20.0 (6/30), p≤0.001</p> <p>Somnolence: 41.3 (12/29) vs. 10.0 (3/30), p≤0.01</p> <p>Dizziness: 31.0 (9/29) vs. 6.7 (2/30), p≤0.05</p> <p>Headache: 10.3 (3/29) vs. 40.0 (12/30), p≤0.05</p> <p>Dry mouth: 20.7 (6/29) vs. 3.3 (1/30), p≤0.05</p> <p>Withdrawals due to adverse event: 3, all in treatment group: suicidal ideation (1), somnolence (1), and constipation (1).</p> <p>Serious Adverse Events: 1 suicidal ideation in treatment group</p>	Eli Lilly and Company Investigator-Initiated Trial Program, drug provided by Eli Lilly and Company

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Blacker, 2004 ⁹ RCT Medium	United Kingdom, United States, The Netherlands, Sweden, Belgium 35 centers 1997 to 1999 Specialty clinic	CDC (Fukuda, 1994) criteria Inclusion: Ages 18 to 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; neurological disease; known 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.	Galantamine 7.5 (n=89): Galantamine 2.5 mg three times per day Galantamine 15 (n=86): Galantamine 5 mg three times per day Galantamine 22.5 (n=91): Galantamine 7.5 mg three times per day Galantamine 30 (n=86): Galantamine 10 mg three times per day Placebo (n=82): Identical placebo three times per day <i>Note:</i> For intervention groups doses were titrated over 3 to 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 Duration of treatment: 16 weeks (8 weeks at full-dose) Duration of followup: 4 weeks after final dose
Blockmans, 2003 ¹⁰ Crossover RCT Medium	Belgium Single Center 1999 to 2001 Specialty clinic: Tertiary care university clinic	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 or abnormal laboratory screening examination.	Hydrocortisone (n=50): Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day Placebo (n=50): Placebo Both groups received an injection of 250 µg of adrenocorticotrophic hormone three times: once at baseline and before each treatment period. Duration of treatment: Two 3-month treatment periods with no washout between Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Blacker, 2004 ⁹ RCT Medium	<p>Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo</p> <p>Mean ages (years): 39 vs. 39 vs. 39 vs. 37 vs. 38</p> <p>% Female: 72 (64/89) vs. 71 (61/86) vs. 62 (56/91) vs. 62 (53/86) vs. 62 (51/82)</p> <p>% White: 99 (88/89) vs. 92 (79/86) vs. 98 (89/91) vs. 95 (82/86) vs. 94 (77/82)</p> <p>Duration of illness: <7 years, not reported by group</p> <p>Severity of symptoms: Fibromyalgia impact questionnaire global well-being score range 356 to 390; not reported at baseline by group</p> <p>Comorbidities: NR</p>	<p>Number randomized: 434</p> <p>Number analyzed: 423</p>	<p>Overall: 30% (130/434)</p> <p>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)</p>
Blockmans , 2003 ¹⁰ Crossover RCT Medium	<p>For 80 patients who completed the study:</p> <p>Mean age: 38 years</p> <p>% Female: 91 (73/80)</p> <p>Race: NR</p> <p>Duration of illness: mean (range): 30 (16 to 60) months</p> <p>Severity of symptoms: Number of criteria for chronic fatigue syndrome: 6 (SD 2)</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 100</p> <p>Number analyzed: 80</p>	<p>20% (20/100)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Blacker, 2004 ⁹ RCT Medium	<p>Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo:</p> <p>Overall Function: NR</p> <p>Quality of Life: Improved <i>Clinician Global Impression Scores</i>, %: 45% (36/80) vs. 35% (22/63) vs. 36% (25/69) vs. 41% (28/68) vs. 30% (20/67); all comparisons are NS between groups</p> <p><i>FIQ least square mean change from baseline</i></p> <p>Global Well Being (composite): -77.84 vs. -88.65 vs. -29.92 vs. -60.67 vs. -53.89</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Chalder Fatigue Rating Scale least square mean change from baseline (positive changes indicate better health)</i></p> <p>Physical: 9.25 vs. 8.77 vs. 11.02 vs. 9.99 vs. 9.86</p> <p>Mental: 6.46 vs. 5.89 vs. 7.74 vs. 6.60 vs. 6.80</p> <p>Outcomes related to associated symptoms: <i>Pittsburgh Sleep Quality Index Total score (0-21, higher score indicates worse sleep)</i>: -1.60 vs. -2.28 vs. -1.43 vs. -1.73 vs. -2.02 all comparisons are NS between groups</p>
Blockmans , 2003 ¹⁰ Crossover RCT Medium	<p>Hydrocortisone vs. placebo, results prior to crossover portion of the study Mean (SD)</p> <p>Overall Function: <i>SF-36 (0-100 scale, higher scores indicate better health)</i></p> <p>Physical functioning: 31.7 (18.2) vs. 30.4 (18.1); p=0.34</p> <p>Quality of Life: <i>Visual Analog Scale (0-10)</i></p> <p>Degree of well-being: 5.0 (2.4) vs. 4.6 (2.6); p=0.14</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Visual Analog Scale (0-10)</i></p> <p>Degree of fatigue: 6.6 (2.0) vs. 6.7 (2.1); p=0.76</p> <p><i>Abbreviated Fatigue Questionnaire score (4-28, higher scores indicate better health)</i>: 8 (5) vs. 7 (5); p=0.69</p> <p>Outcomes related to associated symptoms:</p> <p><i>Hospital Anxiety and Depression Scale (0-21, lower scores indicate better health) (n=75)</i></p> <p>Depression score: 8 (5) vs. 9 (4); p=0.04 (but not significant after Bonferroni correction)</p> <p>Anxiety score: 9 (4) vs. 10 (4); p=0.28</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Blacker, 2004 ⁹ RCT Medium	<p>Galantamine 7.5 vs. 15 vs. 22.5 vs. 30 vs. placebo; Adverse Events: 90% (389) reported adverse events; Depression, nausea and headache most common in both groups Withdrawals due to adverse events: Total: 23% (88/389) By group: 14% (12/89) vs. 23% (20/86) vs.24% (22/91) vs. 26% (22/86) vs.15% (12/82) Serious Adverse Events: 2% (8/389) none attributed to the study drug</p>	Shire Pharmaceutical Development Limited
Blockmans , 2003 ¹⁰ Crossover RCT Medium	<p>Hydrocortisone vs. placebo Adverse Events: 1 acne and weight gain Withdrawals due to Adverse Event: 1 acne and weight gain Serious Adverse Events: None</p>	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Bourke, 2014 ¹¹ PACE companion	See White, 2011	See White, 2011	See White, 2011
Burgess, 2012 ¹² RCT Medium	United Kingdom Single center Study year(s) NR Research center	<p>CDC (Fukuda, 1994) and Oxford (Sharpe, 1991) criteria</p> <p>Inclusion: Ages 18 to 65 years, met both CDC and Oxford criteria, had CFS for <10 years, able to attend the hospital or have telephone sessions every two weeks.</p> <p>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.</p>	<p>Face-to-face (n=35): Up to 15 sessions of face-to-face CBT, first 2 sessions were 1.5 hours long with additional sessions lasting from 50 to 60 minutes.</p> <p>Telephone (n=45): 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.</p> <p><i>Note:</i> 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 manage 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.</p> <p>Duration of treatment: Varied</p> <p>Duration of followup: 12 months after end of treatment</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Bourke, 2014 ¹¹ PACE companion	See White, 2011	See White, 2011	See White, 2011
Burgess, 2012 ¹² RCT Medium	<p>Face-to-face vs. telephone</p> <p>Mean age (SD): 38.4 (9.7) vs. 36.7 (10.5) years</p> <p>% Female: 74 (26/35) vs. 82 (37/45)</p> <p>% White: 90 overall (NR per group)</p> <p>% With job to return to: 22 (7/35) vs. 45 (20/45)</p> <p>Duration of illness: Mean (SD): 4.20 (2.21) vs. 3.80 (2.09) years</p> <p>Severity of symptoms: NR</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 80 (35 face-to-face, 45 telephone)</p> <p>Number analyzed at 12 month followup: 43 (23 face-to-face, 20 telephone)</p>	<p>Face-to-face vs. telephone: 34% (12/35) vs. 56% (25/45)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Bourke, 2014 ¹¹ PACE companion	<p>Benefits</p> <p>APT vs. CBT vs. GET vs. control Significantly less muscle pain: CBT vs. control (mean difference=0.38 unit change in frequency, p=0.02) GET vs. control (0.42, p=0.01) GET versus APT (0.37, p=0.01) Significantly less joint pain: CBT versus APT (0.35, p=0.02) GET versus APT (0.36, p=0.02)</p>
Burgess, 2012 ¹² RCT Medium	<p>Face-to-face vs. telephone</p> <p>Overall Function: <i>Mean (SD) Medical Outcomes Survey Short Form physical functioning scale scores (0-100 scale, higher scores indicate better health)</i> 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, all other p-values NS</p> <p><i>Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)</i> 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</p> <p>Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR</p> <p>Fatigue: <i>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</i> 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)</p> <p>Outcomes related to associated symptoms: <i>Global improvement scores (% much better or very much better)</i> 6 months: 60 (15/25) vs. 40 (8/20) 12 months: 57 (13/23) vs. 55 (11/20)</p> <p>Depression: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Bourke, 2014 ¹¹ PACE companion	See White, 2011	See White, 2011
Burgess, 2012 ¹² RCT Medium	Face-to-face vs. telephone Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Chalder, 2010 ¹³ Lloyd, 2012 ¹⁴ Medium	United Kingdom Single center 2000 to 2003 Specialty clinic	Adolescents 11 to 18 years Oxford or Fukuda (Sharpe, 1991; Fukuda, 1994) Anti-depressants were acceptable if on a stable dose for 3 months prior to entering the trial Excluded alternative causes for fatigue, major depression, somatization disorder, conversion disorder, history of self-harm, or identifiable disease that could have contributed to their illness	CBT (n=32): 13 1-hour sessions of family- focused CBT every 2 weeks Psycho-education (n=27): 4 didactic sessions over 6-month period. Involved discussion, information giving, and problem solving but did not include homework assignments and cognitive restructuring. Duration of follow up: 24 months
Chan, 2013 ¹⁵ Ho, 2012 ¹⁶ RCT Medium	Hong Kong Special Administrative Region of China Single center 2010 to 2011 Setting NR	Fukuda (Fukuda, 1994) criteria, but diagnosis of CFS-like illness, not CFS, was used Inclusion: Ages 18 to 55, unexplained fatigue over 6 months which was of new onset (not lifelong), with ≥ 4 of 8 following symptoms: impaired memory or concentration, post-exertional malaise, 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	Qigong (n=77): 2 hour Qigong sessions including 1 hour of exercise training twice a week for 5 weeks, followed by 12 weeks of ≥ 30 minutes daily home Qigong exercise. Waitlist (n=77): Wait list; refrained from qigong exercise. Duration of treatment: 4 months (5 weeks training in Qigong exercise and 12 weeks of qigong exercise at home) Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
<p>Chalder, 2010¹³</p> <p>Lloyd, 2012¹⁴</p> <p>Medium</p>	<p>Age, median: 15 vs. 15</p> <p>% Female: 65.6 vs. 71.0</p> <p>Race: Not reported</p> <p>Duration of fatigue, median months: 30 vs. 22</p> <p>Oxford criteria, %: 100 vs. 93.5</p> <p>CDC criteria, %: 68.8 vs. 71.0</p> <p>Comorbid psychiatric diagnosis: 46.9% vs. 22.6%</p>	<p>Enrolled: 63</p> <p>Analyzed: 59 (32 vs. 27)</p>	<p>Lost to follow up: 0 vs. 4</p>
<p>Chan, 2013¹⁵</p> <p>Ho, 2012¹⁶</p> <p>RCT</p> <p>Medium</p>	<p>Qigong vs. waitlist</p> <p>Mean age: 42.4 vs. 42.5 years</p> <p>% Female: 72 (52/72) vs. 82 (53/65)</p> <p>Race: NR</p> <p>% Employed full-time: 76 (55/72) vs. 80 (52/65)</p> <p>% Employed part-time: 4.2 (3/72) vs. 1.5 (1/65)</p> <p>% Unemployed: 5.6 (4/72) vs. 1.5 (1/65)</p> <p>% Housewife: 13 (9/72) vs. 15 (10/65)</p> <p>% Regularly exercise: 26 (19/72) vs. 26 (17/65)</p> <p>Mean number of reported fatigue symptoms (SD): 6.3 (1.4) vs. 6.3 (1.4)</p> <p>Duration of illness: ≥6 months</p>	<p>Number enrolled: 154</p> <p>Number analyzed: 137 (72 qigong, 65 waitlist)</p>	<p>Overall: 28% (43/154)</p> <p>Qigong vs. waitlist: 31% (24/77) vs. 25% (19/77)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
<p>Chalder, 2010¹³</p> <p>Lloyd, 2012¹⁴</p> <p>Medium</p>	<p>Benefits</p> <p>6-month follow up: School attendance: % of expected over 2-week period, mean: 73.4 vs. 64.9; mean difference: 8.5 (-12.3 to 29.3), p=0.42 ≥70% vs. <70%: adjusted OR: 0.87, 95% CI 0.29 to 2.63</p> <p>Chalder fatigue Likert score (scale 0 to 33), mean (SD): 13.3 (5.9) vs. 14.2 (8.4), mean difference: 0.24, 95% CI -3.61 to 4.10</p> <p>Child- reported global improvement, % good outcome: 88.9 vs. 89.7; OR 1.08, 95% CI 0.20 to 5.89</p> <p>Mother-reported global improvement, % good outcome: 89.7 vs. 79.2; OR 2.28, 95% CI 0.48 to 10.73</p> <p>Independent global improvement, % good outcome: 93.1 vs. 74.1; OR 4.73, 95% CI 0.89 to 25.2</p> <p>No significant differences: Physical functioning, social adjustment, Strengths and Difficulties Questionnaire scores, treatment satisfaction</p> <p>24-month follow up (n=24 vs. 20): School attendance, mean % achieving ≥ 70%, 6-months vs. 24-months: CBT groups: 65.6 vs. 90.0; Psycho-education: 66.7 vs. 84.2 Improvement over time: CBT: p=0.06 vs. Psycho-education: p=0.38; OR 1.286, 95% CI 0.183 to 9.021 Maternal-reported Strengths and Difficulties Questionnaire, total score mean at 24-months: 8.16 (5.69) vs. 14.00 (4.94), Group x Time F(df,1)=10.42, p<0.001 Social Adjustment Scale, median impairment at 24 months: 0.60 vs. 1.60, p=0.58 for group differences; CBT over time: p=0.01; Psycho-education over time: p=0.03 No significant effects of group x time (6 and 24 months) in fatigue, SF-36 physical functioning, global functioning, satisfaction, or recovery</p>
<p>Chan, 2013¹⁵</p> <p>Ho, 2012¹⁶</p> <p>RCT</p> <p>Medium</p>	<p>Qigong vs. waitlist</p> <p>Overall Function: <i>Mean (SD) QOL SF-12 mental functioning score (6 items scored from 0 to 100, higher scores indicate better health)</i> From 64 patient subset analysis: 42.7 (7.2) vs. 35.7 (9.5); p=0.001</p> <p><i>Mean (SD) QOL SF-12 physical functioning score (6 items scored from 0 to 100, higher scores indicate better health)</i> From 64 patient subset analysis: 40.1 (6.9) vs. 37.8 (5.6); p=0.484</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) Chalder fatigue scale total fatigue scores (0 to 56 scale, lower score indicates better health)</i> From entire study: 26.6 (13.6) vs. 33.2 (6.3); p<0.001</p> <p><i>Mean (SD) Chalder fatigue scale physical fatigue scores (0-32 scale, lower score indicates better health)</i> From entire study: 15.9 (8.0) vs. 20.8 (5.7); p<0.001</p> <p><i>Mean (SD) Chalder fatigue scale mental fatigue scores (0-24 scale, lower score indicates better health)</i> From entire study: 10.6 (6.1) vs. 12.4 (4.9); p=0.05</p> <p>Outcomes related to associated symptoms: <i>Mean (SD) telomerase activity (arbitrary unit)</i> From 64 patient subset: 0.178 (0.201) vs. 0.104 (0.059), p=0.029, between groups over time</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Chalder, 2010 ¹³ Lloyd, 2012 ¹⁴ Medium	Not reported	NHS Executive London Region Office
Chan, 2013 ¹⁵ Ho, 2012 ¹⁶ RCT Medium	Adverse Events: None reported Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Centre on Behavioral Health Research Fund, University of Hong Kong

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Clark, 2017 ¹⁷ RCT Medium	United Kingdom 2 centers 2012 to 2015 Secondary care clinics for chronic fatigue	NICE/NHS Inclusion: Diagnosed with CFS, meeting NICE criteria, placed on a wait list for therapy, Exclusion: <18 years old, current suicidal thoughts or comorbid psychiatric conditions requiring exclusion, had previously read the GES guide or already received GET, or physical contraindications to exercise.	Graded exercise therapy (n=107): Given and encouraged to use a self-help booklet with a 6-week program of graded exercise self-management, based off of the PACE trial and on NICE recommendations. Six steps outlined included: stabilizing a daily routine, starting regular stretching, deciding on a physical activity goal and choosing a type of activity with which to start, increasing the duration and then the intensity of physical activity. One 30 minute in-person, Skype, or telephone session with a physiotherapist after randomization to answer questions from the participants was given within 5 days of the randomization, then 3 20 minute appointments were offered over the next 8 weeks via Skype or telephone. These patients also received specialist medical care. Control (n=104): Specialist medical care. Duration of treatment: ~8 weeks Duration of followup: 12 weeks after randomization, ~4 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Clark, 2017 ¹⁷ RCT Medium	<p>Graded exercise therapy vs. control</p> <p>Mean age: 38.1 vs. 38.7</p> <p>% female: 82 vs. 76</p> <p>% white: 88 vs. 90</p> <p>Duration of illness, mean (range): 46 (23 to 114) vs. 42 (25 to 99) months</p> <p>Severity of symptoms: % meeting CDC criteria: 68 vs. 74</p> <p>% meeting Oxford criteria: 78 vs. 84</p> <p><i>Mean SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health): 47.3 vs. 50.1</i></p> <p><i>Mean Chalder fatigue scale scores (0-56 scale, lower score indicates better health): 26.3 vs. 26.0</i></p> <p>Comorbidities: % with current major depressive disorder: 9 (10/107) vs. 11 (10/104)</p>	<p>Number enrolled: 211</p> <p>Number analyzed: 199</p>	<p>Overall: 6% (12/211)</p> <p>Graded exercise therapy vs. control: 9% (10/107) vs. 2% (2/104)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Clark, 2017 ¹⁷ RCT Medium	<p>Benefits</p> <p>Graded exercise therapy vs. control</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health):</i> Overall: 55.7 (23.3) vs. 50.8 (25.3), AMD: 6.3 (95% CI, 1.8 to 10.8) p=0.006</p> <p>Meeting CDC criteria (n=141), mean difference in SF-36: 6.3 (95% CI, 1.1 to 11.6) p=0.019</p> <p>Meeting Oxford criteria (n=159), mean difference in SF-36: 5.6 (95% CI, 0.8 to 10.4) p=0.024</p> <p>Work and social adjustment scale mean score at 12 weeks, mean (SD): 23.4 (8.6) vs. 25.4 (8.3)</p> <p>Work and social adjustment scale mean difference at 12 weeks: -1.9 (95% CI, -3.7 to -0.2) p=0.033</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower score indicates better health):</i> 19.1 (7.6) vs. 22.9 (6.9), AMD: -4.2 (95% CI, -6.1 to -2.3) p<0.0001</p> <p>Meeting CDC criteria (n=138), mean difference in Chalder fatigue scale score: -4.1 (95% CI, -6.5 to -1.7) p=0.001</p> <p>Meeting Oxford criteria (n=141), mean difference in Chalder fatigue scale score: -3.5 (95% CI, -5.7 to -1.3) p=0.002</p> <p>Outcomes related to associated symptoms: International Physical Activity Questionnaire 12 week results % (n/N):</p> <p>Low: 34 (33/97) vs. 47 (46/102)</p> <p>Moderate: 36 (35/97) vs. 33 (33/102)</p> <p>High: 30 (29/97) vs. 20 (20/102)</p> <p>Odds ratio: 3.2 (95% CI, 1.8 to 5.8) p<0.0001</p> <p>Depression: <i>Hospital Anxiety and Depression Scale, mean (SD):</i> 7.4 (4.3) vs. 8.6 (4.7), mean difference: -1.1 (-2.0 to -0.3), p=0.006</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Clark, 2017 ¹⁷ RCT Medium	<p>Graded exercise therapy vs. control</p> <p>Adverse Events: 28% (27/97) vs. 23% (23/101)</p> <p>Withdrawals due to adverse event: None</p> <p>Serious Adverse Events: 1% (1/97) vs. 2% (2/101), not suspected to be reactions: 1 fall on arm, 1 twisted knee, 1 with numbness in leg and arm</p>	<p>United Kingdom National Institute for Health Research Research for Patient Benefit Programme and the Sue Estermann Fund</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Crawley, 2018 ¹⁸ RCT Medium	United Kingdom Single center 2010 to 2013 Tertiary care clinic	NICE (2007) diagnostic criteria Inclusion: Aged 12 to 18 years, meeting CFS/ME diagnosis Exclusion: Housebound, unable to speak English	Lightning process (n=51): Phil Parker Lighting Process; trademarked intervention developed from osteopathy, life coaching, and neuolinguistic programming to train patients to recognize and avoid stimulating or triggering unhelpful psychological responses. 3 group sessions on consecutive days. Included specialist medical care. Control (n=49): Specialist medical care; children and their families were offered a variety of treatment options centered around graded activity and sleep improvement Duration of treatment: 3 days Duration of followup: 12 months for most outcomes, but 6 months for SF-36 (primary outcome)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Crawley, 2018 ¹⁸ RCT Medium	<p>Lightning process vs. control:</p> <p>Mean age (SD): 14.7 (1.4) vs. 14.5 (1.6)</p> <p>% Female: 74.5 (38/51) vs. 77.6 (38/49)</p> <p>Race: NR</p> <p>Duration of illness, median months, IQR: 12 (8.0, 18.0) vs. 12 (7.0, 22.0)</p> <p>Severity of symptoms:</p> <p>Median Chalder fatigue score (0 to 33), (SD): 25.0 (4.2) vs. 25.1 (4.2)</p> <p>Median SF-36 physical function (0 to 100), (SD): 53.0 (18.8) vs. 56.0 (21.5)</p> <p>School attendance in the previous week, n:</p> <p>None: 6 vs. 7</p> <p>0.5 day: 5 vs. 7</p> <p>1 day: 3 vs. 3</p> <p>2 days: 8 vs. 8</p> <p>3 days: 12 vs. 12</p> <p>4 days: 12 vs. 9</p> <p>15 days: 4 vs. 3</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 100</p> <p>Number analyzed: 81 (at 6 months)</p>	<p>Lightning process vs. control at 6 months:</p> <p>10% (5/51) vs. 22% (11/49)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Crawley, 2018 ¹⁸ RCT Medium	<p>Benefits</p> <p>Lightning process vs. control</p> <p>Overall Function, Mean SF-36 at 6 months: 81.7 vs. 70.2, adjusted (based on age, gender and baseline outcome) difference in means: 12.5 (95% CI, 4.5 to 20.5), p=0.003</p> <p>Quality of Life: NR, only reported in quality-adjusted life years</p> <p>Mean School Days attended in the previous week: 6 months: 3.2 vs. 2.6, adjusted difference in means: 0.7 (95% CI, 0.0 to 1.4), p=0.064</p> <p>Mean School Days attended in the previous week: 12 months: 4.1 vs. 3.1, adjusted difference in means: 0.9 (95% CI, 0.2 to 1.6), p=0.018</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue, Mean Chalder Fatigue Scale (0 to 33) 6 months: 14.4 vs. 19.8, adjusted difference in means: -4.7 (95% CI, -7.9 to 1.6), p=0.003</p> <p>Fatigue, Mean Chalder Fatigue Scale (0 to 33) 12 months: 12.3 vs. 15.7, adjusted difference in means: -3.2 (95% CI, -6.3 to 0.10), p=0.045</p> <p>Outcomes related to associated symptoms: Mean Pain VAS 6 months: 23.4 vs. 32.8, adjusted difference in means: -11.3 (95% CI, -23.0 to 0.3), p=0.057</p> <p>Mean Pain VAS 12 months: 21.8 vs. 32.0, adjusted difference in means: -9.4 (95% CI, -21.5 to 2.7), p=0.125</p> <p>Depression: HADS-Depression, mean:</p> <p>6 months: 4.2 vs. 5.9, p=0.141</p> <p>12 months: 2.8 vs. 4.6, p=0.033</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Crawley, 2018 ¹⁸ RCT Medium	Lightning process vs. control Adverse Events: 3 vs. 2, but one was related to a parent Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Linbury Trust, Ashden Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Deale, 1997 ¹⁹ Deale, 2001 ²⁰ RCT Medium	United Kingdom Single center Study year(s) NR Hospital clinic specializing in CFS	Oxford (Sharpe, 1991), CDC (Fukuda, 1994) 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 (n=30): 13 individual weekly or biweekly counseling sessions over 4-6 months with the aim of showing patients that activity could be increased steadily and safely without exacerbating symptoms. Graded activity was introduced in session 4, and increased for the duration of the study. Cognitive strategies were introduced in session 8, while the graded activity program continued. Relaxation (n=30): 13 individual weekly or biweekly sessions over 4-6 months teaching progressive muscle relaxation, visualization, and rapid relaxation skills. Duration of treatment: 4 to 6 months Duration of followup: Deale, 1997: 6 months after end of treatment Deale, 2001: 5 years after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
<p>Deale, 1997¹⁹</p> <p>Deale, 2001²⁰</p> <p>RCT</p> <p>Medium</p>	<p>CBT vs. relaxation</p> <p>Mean age (SD): 31 (9) vs. 38 (11) years</p> <p>% Female: 70 (21/30) vs. 67 (20/30)</p> <p>Race: NR</p> <p>Duration of illness: Mean (SD): 3.4 (2.1) vs. 4.6 (3.3) years</p> <p>Severity of symptoms: "The whole group had near maximum scores on the measures of functional impairment and fatigue"</p> <p>% Unemployed: 63 (19/30) vs. 77 (23/30)</p> <p>% On disability benefits: 53 (16/30) vs. 67 (20/30)</p> <p>Comorbidities: % Current psychiatric diagnosis: 37 (11/30) vs. 40 (12/30)</p> <p>Five patients had additional diagnoses of dysthymia, nine had major depression, three had anxiety disorders, and six had both depression and an anxiety disorder; not listed by group.</p>	<p>Number enrolled: 60 (30 CBT, 30 relaxation)</p> <p>Number analyzed: 60 (30 CBT, 30 relaxation) in Deale, 1997; 53 (25 CBT, 28 relaxation) in Deale, 2001</p>	<p>CBT vs. relaxation: 10% (3/30) vs. 13% (4/30)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Deale, 1997 ¹⁹ Deale, 2001 ²⁰ RCT Medium	<p>CBT vs. relaxation</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)</i> Posttreatment: 56.2 (26.2) vs. 34.6 (28.3); 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) <i>Mean (SD) Work and social adjustment scale scores (0-8 scale, lower scores indicate better health)</i> Posttreatment: 4.1 (1.9) vs. 5.2 (1.8) 6 month followup: 3.3 (2.2) vs. 5.4 (1.8); p<0.001 for between group differences over time Quality of Life: NR Work/School Days: % With full- or part-time employment at 5 year followup: 56 (14/25) vs. 39 (11/28); p=0.28 <i>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</i> Proportion full/part-time work: NR Fatigue: <i>Mean (SD) fatigue problem rating scores (0-8 scale, lower scores indicate better health)</i> Posttreatment: 4.1 (1.9) vs. 5.5 (1.4) 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 to 11, scores of ≥4 indicate caseness or excessive fatigue, lower scores indicate better health) Posttreatment: 7.2 (4.0) vs. 7.5 (4.1) 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 Outcomes related to associated symptoms: Beck Depression Inventory, mean (SD): Posttreatment: 8.9 (5.6) vs. 11.9 (7.4) 6-month follow up: 10.1 (6.9) vs. 12.3 (8.5), p>0.30 % 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</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Deale, 1997 ¹⁹ Deale, 2001 ²⁰ RCT Medium	CBT vs. relaxation Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	South East Thames Regional Health Authority Locally Organized Research Scheme; South Thames Small Project Grant Scheme, Wellcome Trust grant

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Dybwad, 2007 ²¹ RCT Medium	Norway Single center 2005 Hospital clinic	CDC (Fukuda, 1994) criteria Inclusion: Diagnosis with Fukuda criteria by a medical doctor especially experienced with the condition, duration of condition ≥ 2 years Exclusion: Antidepressive drugs, other conditions that could give fatigue	Qigong (n=15): Qigong exercises once a week for 2 hours with a certified instructor, over 15 weeks. Sessions consisted of simple principles of anatomy and physiology (30 minutes), qigong practice (1 hour), and breathing exercises, relaxation and mediation including non-structured conversation among participants (30 minutes) Control (n=16): No Qigong training Both groups were encouraged to not start any new treatments during the intervention period. Duration of treatment: 6 months Duration of followup: End of treatment
Fluge, 2011 ²² RCT Medium	Norway Single center 2008 to 2010 Tertiary referral center	CDC (Fukuda, 1994) criteria Inclusion: Diagnosis of CFS by a neurologist, according to Fukuda 1994 criteria; aged 18 to 65 years; and written informed consent. Exclusion: fatigue and not fulfilling CFS criteria; previous malignant disease (except basal cell carcinoma and cervical dysplasia); previous long-term immunosuppressive treatment; previous Rituximab treatment; endogenous depression; lack of ability to adhere to protocol; or evidence of ongoing infection.	Rituximab 500 mg/m², maximum 1,000 mg (15): diluted in saline to a concentration of 2 mg/mL, given two weeks apart Placebo (15): Equal volume of saline given two weeks apart Both groups were given oral cetirizine 10 mg, paracetamol 1 g, and dexamethazone 8 mg prior to infusion. Duration of treatment: two weeks (two treatments) Duration of followup: 12 months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Dybwad, 2007 ²¹ RCT Medium	Qigong vs. control Mean age: 43.2 vs. 45.4 % Female: 80 (12/15) vs. 88 (14/16) Race: NR Duration of illness: 6.5 vs. 9.7 years Severity of symptoms: Mean FSS entire group (n=31): 6.5 Mean SF-36 physical function entire group (n=31): 48 Comorbidities: NR	Enrolled: 31 Analyzed: 28	9.7% (3/31) (1 qigong and 1 control) 1 in qigong group became ill and dropped out before intervention started 1 in control group had a fractured leg and was unable to participate in followup bicycle testing of work capacity 1 had aggravated symptoms from baseline exercise testing
Fluge, 2011 ²² RCT Medium	Rituximab vs. placebo Mean age (years): 37.3 vs. 31.5 % Female: 80 (12/15) vs. 60 (9/15) Race: NR Duration of illness: mean (range): 5.1 (1.0 to 13.0) vs. 8.1 (0.7 to 18.0) years Severity of symptoms: <i>SF-36 physical function (percent, lower score denotes increasing symptoms)</i> , mean (SD): 34 (6) vs. 35 (7) <i>VAS fatigue score (0 to 10, 10 most severe)</i> , mean (range): 8.1 (7.3 to 9.8) vs. 7.9 (6.0 to 9.3) Cognitive score, mean (range): 7.7 (5.0 to 9.7) vs. 7.2 (4.0 to 9.3) Pain score, mean (range): 6.5 (4.0 to 9.3) vs. 6.2 (1.3 to 9.0) "Other symptoms" score, mean (range): 7.8 (5.5 to 10.0) vs. 7.9 (5.0 to 10.0) Rnase L genotype 462 Q/Q: 5 vs. 6 Rnase L genotype 462 Q/R: 10 vs. 7 Rnase L genotype 462 R/R: 0 vs. 2 XMRV PCR: 0/15 vs. 0/15 XMRV Coculture: 0/4 vs. 0/5	Number enrolled: 30 Number analyzed: 30	0 (0/30)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Dybwad, 2007 ²¹ RCT Medium	<p>Benefits</p> <p>Qigong vs. control</p> <p>Overall Function: Mean SF-36 physical function differences in both groups from baseline to retest (SD), 1.3 (16) vs. 4.7 (13) p=0.34 (adjusted for baseline value)</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean change in FSS score (SD): -0.44 (0.60) vs. 0 (0.6), p=0.04, adjusted for baseline values</p> <p>Mean difference: -0.5, 95% CI -0.9 to -0.02; all participants in both groups still clinically fatigued</p> <p>Outcomes related to associated symptoms:</p> <p>Hospital anxiety and depression scale: No significant changes observed after intervention within or between groups, data NR</p> <p>Visual analog scale: Mean change: -1.4 vs. "similar", p=0.05 for between group differences</p>
Fluge, 2011 ²² RCT Medium	<p>Rituximab vs. placebo</p> <p>Overall function: <i>SF-36 physical function, (perfect, lower score denotes increasing symptoms), max change %, mean (SD): 39 (33) vs. 11 (22)</i></p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Major clinical responses: 9 (60%) vs. 7 (7%), p=0.002</p> <p>Moderate clinical responses: 1 (7%) vs. 1 (7%)</p> <p>Overall, 95% CI: 10 (67%) (95% CI, 41% to 85%) vs. 2 (13%) (95% CI, 4% to 38%), p=0.003</p> <p>Response duration: weeks, mean (range): 25 (8 to >44), n=10 vs. 41 (34 to >48), n=2</p> <p>Difference between groups in self reported fatigue score at 40 to 52 weeks: 0.63 (95% CI, -0.09 to 1.34), adjusted p value: 0.25</p> <p>Difference in physician-assessed fatigue score at 12 months after intervention: 0.62 (95% CI, -0.09 to 1.34), adjusted p-value: 0.17</p> <p>Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Dybwad, 2007 ²¹ RCT Medium	Qigong vs. control Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	EXTRA funds from the Norwegian Foundation for Health and Rehabilitation and NAFKAM
Fluge, 2011 ²² RCT Medium	Rituximab vs. placebo Adverse Events: Infusion-related complaints: Palpitations: 1 (7%) vs. 1 (7%) Slight itching: 2 (13%) vs. 0 Nausea: 0 vs. 1 (7%) Discomfort: 2 (13%) vs. 2 (13%) Irregular menstrual bleeding the first two months: 2 (13%) vs. 0 Feeling uneasy and sleepless at 6 to 8 months: 1 (7%) vs. 0 Feeling uneasy and sleepless at 2 to 7 months: 1 (7%) vs. 0 Slight facial acne: 1 (7%) vs. 0 Psoriasis worsening at 2 to 12 months: 2 (13%) vs. 0 Low back pain and balanitis at 5 to 7 months: 1 (7%) vs. 0 Withdrawals due to Adverse Event: None Serious Adverse Events: None	Helse Vest and the legacy of Torstein Hereid.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Fluge, 2019 ²³ RCT Low	Norway 5 centers 2014 to 2017 4 University hospitals an 1 general hospital	Canadian consensus (Caruthers, 2003) criteria Inclusion: ME/CFS according to Canadian consensus criteria; aged 18 to 65 years; had disease for a least 2 years (or ≥5 years if disease was mild), but less than 15 years. Exclusion: Patients with very severe disease (completely bedridden and in need of care, WHO class IV).	Rituximab 500 mg/m², maximum 1,000 mg (77): diluted in saline to a concentration of 2 mg/mL, given two weeks apart Placebo (75): Equal volume of saline with added human albumin (0.4 mg/ML) given two weeks apart In the maintenance phase, patients received a 500 mg fixed dose of rituximab or an equal volume of saline with human albumin at 3, 6, 9 and 12 months. Both groups were given oral cetirizine 10 mg, paracetamol 1 g, and dexamethazone 8mg one hour before infusions. Duration of treatment: 12 months Duration of followup: 24 months
Friedberg, 2016 ²⁴ RCT Medium	United States Recruited from 5 centers nationwide 2011 to 2014 Large tertiary care practices, but intervention took place in participants' homes	CDC (Fukuda, 1994) criteria Inclusion: Note from physician confirming CFS diagnosis, aged between 18 and 65 years, considered physically capable of doing the self-management program (e.g. walking assignments), ≥6 months of persistent fatigue, 4 of 8 secondary symptoms (sore throat, muscle pain, joint pain, headaches, sleep difficulties, post-exertional malaise, tender or sore lymph glands, concentration difficulties). Exclusion: Pregnancy, fatigue clearly attributable to self-reported medical conditions, self-reported psychosis, substance or alcohol abuse in the 2 years prior to illness onset, concurrent or past depression with melancholic or psychotic features within the 5 years prior to illness onset.	FSM:ACT (n=45): Fatigue self management with Web Diaries and Actigraphs; high-tech intervention FSM:CTR (n=44): Fatigue self management with paper diaries and step counters; low-tech intervention Usual care (n=48): Usual care plus web diaries and actographs. Duration of treatment: 12 weeks Duration of followup: 12 months All participants in FSM groups received a program to educate patient about diagnosis and casual factors in CFS in addition to stress factors and behaviors that play a role in disturbed sleep patterns, post-exertional symptoms, and push-crash activities was delivered by booklet and audio CDs. No face to face visits or clinical contacts (phone, email, etc.) with an interventionist. Assignments included a daily diary to identify baseline activities, symptoms, and stress levels. The self-management text included behavioral coping strategies. The program encouraged individualized self-scheduling of home-based activities, rest/sleep assignments, and cognitive coping skills.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Fluge, 2019 ²³ RCT Low	Rituximab vs. placebo Mean age (years): 37.8 vs. 35.5 % Female: 83.1 (64/77) vs. 81.1 (60/74) Race: NR Duration of illness: Mean duration (SD): 8.4 (3.1) vs. 7.6 (2.9) years 2 to <5 years: 14.3% (11/77) vs. 24.3% (18/74) 5 to <10 years: 58.4% (45/77) vs. 59.5% (44/74) 10 to 15 years: 27.3% (21/77) vs. 75.7% (56/74) Severity of symptoms: <i>Baseline SF-36 physical function (scale 0 to 100)</i> (mean): 35.24 vs. 32.45 Baseline fatigue score (0 to 6 scale): 3.0 vs. 3.0 Comorbidities: Hypothyroidism: 5.2% (4/77) vs. 5.4% (4/74) Allergy: 40.3% (31/77) vs. 41.9 (31/74) Fibromyalgia: 7.8% (6/77) vs. 6.8% (5/74) Depression: 9.1% (7/77) vs. 8.1% 6/74 Anxiety: 11.7% (9/77) vs. 10.8% (8/74) Other (unspecified): 27.3% (21/77) vs. 23.0% (17/74)	Number enrolled: 152 Number analyzed: 151	0 (0/152)
Friedberg, 2016 ²⁴ RCT Medium	FSM: ACT vs. FSM:CTR vs. Usual care Mean age: 48.01 vs. 46.99 vs. 50.03 years % Female: 84.4 (38/45) vs. 93.2 (41/44) vs. 87.5 (42/48) Race: % Caucasian: 93.3 (42/45) vs. 84.1 (37/44) vs. 97.9 (47/48) % Hispanic/Latino: 2.2 (1/45) vs. 11.4 (5/44) vs. 0 % African American: 2.2 (1/45) vs. 0 vs. 0 % Other: 2.2 (1/45) vs. 4.5 (2/44) vs. 2.1 (1/48) Duration of illness: 12.57 vs. 13.71 vs. 17.26 years Severity of symptoms: Mean SF-36 physical function: 38.22 vs. 36.59 vs. 38.89 % Employment status is disabled: 57 (26/45) vs. 43 (19/44) vs. 63 (30/48) Comorbidities: NR	Number enrolled: 137 Number analyzed: 127 (41 FSM:ACT, 40 FSM:CTR, 46 Usual Care)	Overall: 7.3%

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Fluge, 2019 ²³ RCT Low	<p>Rituximab vs. placebo</p> <p>Overall Function: SF-36 physical function score (0 to 100 range) at 18 months: 45.67 vs. 45.23, mean difference: 0.42 (95% CI, -8.12 to 8.96), p=0.52</p> <p>Function level, % at 16 to 20 months: 25.25 vs. 25.93, mean difference: -0.68 (95% CI, -5.90 to 4.54), p=0.31</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Fatigue score (range 0 to 6), at 16 to 20 months: 3.12 vs. 3.18, mean difference: -0.06 (95% CI, -0.51 to 0.39), p=0.79</p> <p>Fatigue Severity Scale Score (range 9 to 63, higher scores indicate worse symptoms), mean at 18 months: 55.98 vs. 56.05, mean difference: -0.07 (95% CI, --3.21 to 3.08), p=0.68</p> <p>Outcomes related to associated symptoms: Mean steps per 24 hours, 17 to 21 months: 3,777 vs. 3,904, mean difference: -127 (95% CI, -1004 to 749), p=0.58</p>
Friedberg, 2016 ²⁴ RCT Medium	<p>FSM: ACT vs. FSM:CTR vs. Usual care</p> <p>Overall function: Mean SF-36 physical function (SE):</p> <p>3 months: 43.25 (3.20) vs. 43.75 (3.32) vs. 37.26 (3.13), all comparisons p>0.05</p> <p>12 months: 46.50 (3.68) vs. 45.75 (3.68) vs. 44.07 (3.47), all comparisons p>0.05</p> <p>Quality of life: NR</p> <p>Work/school days: NR</p> <p>Proportion full/part time work: NR</p> <p>Fatigue: Mean fatigue severity scale (SE):</p> <p>3 months: 6.12 (0.11) vs. 5.92 (0.11) vs. 6.42 (0.10), FSM:ACT vs. FSM:CTR p<0.05, other comparisons p>0.05</p> <p>12 months: 6.00 (0.13) vs. 6.10 (0.13) vs. 6.42 (0.12), all comparisons p>0.05</p> <p>Outcomes related to associated symptoms: Mean Beck Depression Inventory (SE):</p> <p>3 months: 14.40 (1.65) vs. 14.98 (1.65) vs. 19.36 (1.55), all comparisons p>0.05</p> <p>12 months: 13.08 (1.48) vs. 14.42 (1.48) vs. 18.64 (1.39), Usual care vs. both other arms p<0.05, intervention arms vs. each other p>0.05</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Fluge, 2019 ²³ RCT Low	Rituximab vs. placebo Adverse Events: Any: 81.8% (63/77) vs. 64.9% (48/74) Withdrawals due to Adverse Event: None Serious Adverse Events: 26.0% (20/77) vs. 18.9 (14/74)	Kavli Trust, Norwegian Research Council, Norwegian Regional Health Trusts, the MEandYou Foundation, Norwegian ME Association, and the legacy of Torstein Hereid.
Friedberg, 2016 ²⁴ RCT Medium	FSM: ACT vs. FSM:CTR vs. Usual care Adverse events: NR Withdrawals due to adverse events: NR Serious adverse events: NR	National Institutes of Health, National Institute of Nursing Research

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Fulcher, 1997 ²⁵ Crossover RCT Medium	United Kingdom Single center Study year(s) NR Chronic fatigue clinic in a general hospital department of psychology	Oxford (Sharpe, 1991) criteria Inclusion: Patients meeting the Oxford criteria Exclusions: Patients excluded for current psychiatric disorders, not including simple phobias, using the clinical interview for the DSM-III-R or for co-morbid symptomatic insomnia. Physical screenings and investigations into records were carried out when appropriate to ensure exclusion of other disorders	Graded exercise (n=33): Exercise treatment, weekly for 12 weeks of supervised treatment, adapted to the patient's current capacity, with a prescription to exercise at home (mainly by walking, but biking and swimming were also encouraged) 5 days a week starting at 15 minutes per session and increasing to a maximum of 30 minutes per session. Patients were given heart monitors and advised to stay within a maximum of peak oxygen consumption, starting at 40% and increasing to 60% Flexibility/relaxation (n=33): 12 weeks of weekly in-person flexibility and relaxation sessions and prescriptions to do sessions at home 5 days a week starting at 10 minutes per session and increasing to 30 minutes per session. Advice to avoid doing any extra physical activities Duration of treatment: 12 weeks, then crossover. Duration of followup: 1 year survey was done, data from after first 12 week period only

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		Number enrolled, analyzed	Attrition
Fulcher, 1997 ²⁵ Crossover RCT Medium	<p>Population characteristics</p> <p>Graded exercise vs. flexibility/relaxation</p> <p>Mean age (SD): 37.2 (10.7) years overall, unreported by arm</p> <p>% Female: 74 (49/66) overall, unreported by arm</p> <p>Race: NR</p> <p>Duration of illness: Median (range): 2.7 (0.6 to 19.0) years overall, unreported by arm</p> <p>Severity of symptoms: <i>Mean Chalder fatigue score (0 to 42) (SD): 28.9 (7.1) vs. 30.5 (5.6)</i></p> <p><i>Mean (SD) SF-36 physical function score: 48.5 (22.1) vs. 47 (18.7)</i></p> <p>Comorbidities: NR</p>	<p>Number enrolled: 66</p> <p>Number analyzed: 59 (29 exercise, 30 control)</p>	<p>Overall: 12% (7/59)</p> <p>Graded exercise vs. flexibility/relaxation: 14% (4/29) vs. 10% (3/30)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Fulcher, 1997 ²⁵ Crossover RCT Medium	<p>Benefits</p> <p>Graded exercise vs. flexibility/relaxation</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)</i></p> <p>12 weeks: 69 (18.5) vs 55 (21.8); p=0.01</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: Exercise vs. all participants (due to control allowed to crossover to exercise)</p> <p>Working full- or part-time at 1 year followup: 66% (31/47) vs. 39% (26/66); (95% CI, 9% to 44%); p=NR</p> <p>Fatigue: <i>Mean (SD) Chalder fatigue scale scores (0-42 scale, lower score indicates better health)</i></p> <p>12 weeks: 20.5 (8.9) vs. 27.4 (7.4); p=0.004</p> <p><i>Mean (SD) Visual analog scale total fatigue score (summed score, 200 noted as 'normal', lower scores indicate better health)</i></p> <p>12 weeks: 253 (48) vs. 286 (67); p=0.04</p> <p><i>Mean (SD) Visual analog scale physical fatigue score (100mm, 100 noted as 'normal', lower scores indicate better health)</i></p> <p>12 weeks: 130 (28) vs. 154 (34); p=0.006</p> <p><i>Mean (SD) Visual analog scale mental fatigue score (100mm, 100 noted as 'normal', lower scores indicate better health)</i></p> <p>12 weeks: 124 (31) vs. 132 (39); p=0.38</p> <p>Outcomes related to associated symptoms: Self-rated CGI score after 12 weeks</p> <p>% Very much better: 31 (9/29) vs. 7 (2/30)</p> <p>% Much better: 24 (7/29) vs. 20 (6/30)</p> <p>% A little better: 38 (11/29) vs. 60 (18/30)</p> <p>% No change: 3 (1/29) vs. 10 (3/30)</p> <p>% A little worse: 3 (1/29) vs. 0 (0/30)</p> <p>% Much worse: 0 (0/29) vs. 3 (1/30)</p> <p>% Very much worse: 0 (0/29) vs. 0 (0/30)</p> <p>p=0.05 for between groups comparison</p> <p>Median (IQR) peak O2 consumption (ml/kg/minute)</p> <p>After 12 weeks: 35.8 (30.8-40.7) vs. 29.8 (24.7-34.9); p=0.03</p> <p>Median increase in peak O2 consumption: 13% vs. 6%</p> <p>Median increase in isometric strength: 26% vs. 15%; p=0.20</p> <p>Graded exercise group completers only: Rated self as better at 1 year followup: 74% (35/47)</p> <p>Depression: Mean (IQR) <i>Hospital Anxiety and Depression Scale</i>: 5.5 (2.9 to 8.1) vs. 4 (0.6 to 7.4), p=0.92</p> <p>Anxiety: Mean (IQR) <i>Hospital Anxiety and Depression Scale</i>: 5.5 (3.0 to 8.0) vs. 7 (3.5 to 1.05), p=0.46</p> <p>Sleep: Mean (IQR) <i>Pittsburgh Sleep Quality Index</i>: 5.0 (3.5 to 6.5) vs. 6 (4.1 to 7.9), p=0.49</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Fulcher, 1997 ²⁵ Crossover RCT Medium	Graded exercise vs. flexibility/relaxation Adverse Events: NR/unclear ("minimal adverse effects" but no number reported) Withdrawals due to adverse event: NR Serious Adverse Events: NR	Linbury Trust, a Sainsbury charitable trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Hobday, 2008 ²⁶ RCT High	United Kingdom Single center Study year(s) NR Chronic fatigue clinic	CDC (Fukuda, 1994) criteria Inclusion: Diagnosis of CFS, no other criteria described. Exclusion: Pregnant, taking oral contraceptives, hormone therapy, steroids, NSAID, antibiotics or immunosuppressants; already following significant dietary changes; taking vitamin and mineral supplements above recommended dose; or diagnosed with an eating disorder.	Low sugar/low yeast (n=25): 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 (n=27): High fiber, 5 servings of fruit and vegetables per day, reduced fat and refined carbohydrate, fish 2 times a week. Duration of treatment: 24 weeks Duration of followup: End of treatment
Huanan, 2017 ²⁷ RCT Medium	China Single center 2014 to 2015 Hospital clinic	CDC (Fukuda, 1994) criteria Inclusion: Aged 18 to 60 years, meeting CDC diagnosis of CFS. Exclusion: Cardiovascular, cerebrovascular, liver, kidney, lung, or hematopoietic-system disease; severe hypotension or diabetes mellitus; mental disorders; pregnant or breastfeeding; combined thrombocytopenia and coagulation disorders; severe obesity	Abdominal tuina (n=40): Four steps of abdominal tuina, including pressing, kneading, pushing and pulling. Five sessions were given daily each week, with 2 consecutive days of no treatment between weeks. Acupuncture (n=40): Acupuncture using chosen acupoints. Five sessions were given daily each week, with 2 consecutive days of no treatment between weeks. Duration of treatment: 4 weeks Duration of followup: 3 months after treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Hobday, 2008 ²⁶ RCT High	Low sugar/low yeast vs. healthy eating Mean age: 44 vs. 42 years % Female: 88 (22/25) vs. 78 (21/27) Race: NR Duration of illness: NR Severity of symptoms: <i>Chalder Fatigue Scale</i> 23.0 vs. 22.5 Comorbidities: NR	Number enrolled: 52 Number analyzed: 39	Overall: 25% (13/52) Low sugar/low yeast vs. healthy eating: 24% (6/25) vs. 26% (7/27)
Huanan, 2017 ²⁷ RCT Medium	Abdominal tuina vs. acupuncture Mean age: 41.8 vs. 42.6 % Female: 44 (17/39) vs. 37 (14/38) Race NR, conducted in China Duration of illness: 10.4 vs. 10.6 months Severity of symptoms: Mean FS-14 score: 8.9 vs. 9.3 Comorbidities: NR	Number enrolled: 80 Number analyzed: 72 (37 abdominal tuina, 35 acupuncture)	Overall: 10% (8/80) 2 abdominal tuina patients lost to followup 1 abdominal tuina patients lost to absent contact details. 2 acupuncture patients underwent additional treatments prohibited in the protocol. 2 acupuncture patients lost to a time constraint. 1 acupuncture patient lost to another reason.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Hobday, 2008 ²⁶ RCT High	<p>Benefits</p> <p>Low sugar/low yeast vs. healthy eating</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health): 42.3 (29.2) vs. 52.2 (24.1); mean difference 9.90, 95% CI -7.43 to 27.23</i></p> <p><i>social functioning subscale, mean: 42.0 (29.3) vs. 50.6 (29.4), mean difference 8.60, 95% CI -10.45 to 27.65</i></p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) Chalder Fatigue Scale scores (scores of ≥4 indicate caseness for fatigue, lower score indicates better health)</i></p> <p>24 weeks: 16.0 (8.2) vs. 17.7 (10.0); mean difference -1.7, 95% CI -7.5 to 4.1</p> <p><i>Medial Outcomes Survey SF-36 vitality subscale scores (0-100 scale, higher score indicates better health) Mean (SD)</i></p> <p>24 weeks: 29.8 (20.7) vs. 36.2 (26.4); p=0.39</p> <p>Outcomes related to associated symptoms: <i>Hospital Anxiety and Depression Score Mean (SD); Anxiety: 8.5 (5.2) vs. 7.3 (4.1); p=0.43; Depression: 6.5 (3.6) vs. 5.4 (3.7); mean difference 1.1, 95% CI -1.2 to 3.5</i></p>
Huanan, 2017 ²⁷ RCT Medium	<p>Abdominal tuina vs. acupuncture</p> <p>Overall Function: NR</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean FS-14 (SD): 6.6 (1.8) vs. 7.6 (2.1), mean difference 1.0, 95% CI 0.11 to 1.88</i></p> <p>Outcomes related to associated symptoms:</p> <p><i>Mean self-rating anxiety scale (SD): 47.0 (4) vs. 49 (5), mean difference 2.0, 95% CI -0.05 to 4.05</i></p> <p><i>Mean Hamilton rating scale for depression (SD): 5.6 (1.3) vs. 6.3 (1.2), mean difference 0.70, 95% CI 0.13 to 1.27</i></p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Hobday, 2008 ²⁶ RCT High	Low sugar/low yeast vs. healthy eating Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	Nurses, Midwives and Allied Health Research Fund (Barts and the London NHS Trust), the ME Association and Department Nutrition and Dietetics (Barts and the London NHS Trust).
Huanan, 2017 ²⁷ RCT Medium	Abdominal tuina vs. acupuncture Adverse Events: Persistent pain for 1 hour during first treatment: 1 vs. 0 Hematoma at needling site: 0 vs. 2 Withdrawals due to AE: None reported Serious Adverse Events: None reported	National Natural Science Foundation

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Janse, 2018 ²⁸ RCT Medium	The Netherlands Single center 2013 to 2015 Tertiary care facility in a hospital	<p>CDC (Fukuda, 1994) criteria</p> <p>Inclusion: Referred to clinic, including examination to rule out medical explanation for fatigue. At least 18 years of age, score of ≥ 35 on fatigue subscale of CIS, severely disabled (SIP-8 score ≥ 700), able to use computer and access to internet.</p> <p>Exclusion: Psychiatric comorbidity that could explain the fatigue, involved in legal procedures concerning disability benefit claims, participation in other CFS research.</p>	<p>iCBT with protocol feedback (n=80): 7 online modules based on a face-to-face CBT for CFS protocol, tailored to each patients' current activity pattern. Patients were asked by their therapists to report on their progress by email at least fortnightly, according to a prescribed schedule. The therapist provided feedback and sent reminders if needed.</p> <p>iCBT with feedback on demand (n=80): Same as above, except patients only received feedback when they asked for advice. Patients received no reminders.</p> <p>Control (n=80): Wait list</p> <p>Duration of treatment: 6 months</p> <p>Duration of followup: End of treatment</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Janse, 2018 ²⁸ RCT Medium	<p>iCBT with protocol feedback vs. iCBT with feedback on demand vs. control</p> <p>Mean age: 36.6 vs. 36.4 vs. 39.9 years % Female: 68 (54/80) vs. 58 (46/80) vs. 56 (45/80) Race NR Duration of illness, median (IQR): 4 (7.8) vs. 4.5 (9.5) vs. 6.5 (7.8) years Severity of symptoms: CIS mean: 50.7 vs. 49.9 vs. 49.5 CDC symptoms, median number (IQR): 7 (2) vs. 7 (2) vs. 7 (2) Comorbidities: Any depressive disorder, %: 11 (9/80) vs. 9 (7/80) vs. 10 (8/80) Any anxiety disorder, %: 9 (7/80) vs. 6 (5/80) vs. 10 (8/80) Other psychiatric disorder, %: 1 (1/80) vs. 1 (1/80) vs. 4 (3/80)</p>	<p>Number enrolled: 240 Number analyzed: 240</p>	<p>3% (6/240) lost to followup iCBT with protocol feedback vs. iCBT with feedback on demand vs. control 1 vs. 1 vs. 4 4 participants in iCBT with protocol feedback group did not start treatment 6 participants in iCBT with feedback on demand group did not start treatment</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Janse, 2018 ²⁸ RCT Medium	<p>iCBT with protocol feedback vs. iCBT with feedback on demand vs. control</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning scale scores (0 to 100 scale, higher scores indicate better health):</i> 73.3 (25.9) vs. 77.0 (21.3) vs. 70.8 (21.0)</p> <p>Difference compared with control: iCBT with protocol feedback: 2.4 (-3.6 to 8.4), p=0.44; iCBT with feedback on demand: 5.8 (0.6 to 11.0), p=0.030</p> <p>Quality of life: NR</p> <p>Work/school Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) CIS fatigue severity scores (8 to 56 scale, lower scores indicate better health):</i> 36.3 (14.6) vs. 37.0 (13.1) vs. 43.9 (10.5)</p> <p>Mean difference compared with control (97.5% CI): iCBT with protocol feedback: -8.3 (-12.7 to -3.9), p<0.0001; iCBT with feedback on demand: -7.2 (-11.3 to -3.1), p<0.0001</p> <p>Outcomes related to associated symptoms:</p> <p>Overall impairment: Mean Sickness Impact Profile 8 (SD): 867.8 (670.4) vs. 885.0 (658.9) vs. 1322.5 (720.8)</p> <p>Mean difference compared with control (95% CI): iCBT with protocol feedback: -338.3 (-514.7 to -161.9), p=0.0002; iCBT with feedback on demand: -356.0 (-530.0 to -182.0), p<0.0001</p> <p>Psychological distress: Mean Symptom Checklist-90 (SD): 135.0 (36.4) vs. 140.3 (45.0) vs. 154.8 (47.6)</p> <p>Mean difference compared with control (95% CI): iCBT with protocol feedback: -14.2 (-24.7 to -3.8), p=0.0075; iCBT with feedback on demand: -12.6 (-23.6 to -1.6), p=0.0247</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Janse, 2018 ²⁸ RCT Medium	iCBT with protocol feedback vs. iCBT with feedback on demand vs. control Adverse events: NR Withdrawals due to adverse events: None Serious adverse events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
<p>Jason, 2007²⁹</p> <p>Jason, 2009³⁰</p> <p>Hlavaty, 2011³¹</p> <p>RCT</p> <p>Medium</p>	<p>United States</p> <p>Single site</p> <p>Study year(s) NR</p> <p>Setting not described</p>	<p>CFS Questionnaire based on CDC (Fukuda, 1994) criteria, psychiatric assessment for DSM-IV diagnosis, and medical assessment</p> <p>Inclusion: Ages ≥18 years, not pregnant, able to read and speak English, considered to be physically capable of attending the scheduled sessions.</p> <p>Exclusion: Persons who used wheelchairs and who were bedridden or housebound; lifelong fatigue; >4 secondary symptoms of CFS; BMI >45; melancholic depression or bipolar depression; alcohol or substance abuse disorder; autoimmune thyroiditis; cancer; lupus; or rheumatoid arthritis.</p>	<p>CBT (n=29): 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.</p> <p>Cognitive therapy (COG) (n=28): 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.</p> <p>Anaerobic activity therapy (ACT) (n=29): 13 sessions, held once every 2 weeks, of anaerobic activity therapy focused on developing individualized, constructive and pleasurable activities with reinforcement.</p> <p>Relaxation (n=28): 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.</p> <p>Duration of treatment: 6 months</p> <p>Duration of followup: 1 year</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
<p>Jason, 2007²⁹</p> <p>Jason, 2009³⁰</p> <p>Hlavaty, 2011³¹</p> <p>RCT</p> <p>Medium</p>	<p>Mean age: 43.8 years</p> <p>% Female: 83 (95/114)</p> <p>% White: 88 (100/114)</p> <p>% Black: 4 (5/114)</p> <p>% Latino: 4 (5/114)</p> <p>% Asian-American: 4 (4/114)</p> <p>CBT vs. COG vs. ACT vs. Relaxation:</p> <p>% Working full or part time: 45 vs. 50 vs. 41 vs. 46</p> <p>Overall:</p> <p>% On disability: 25 (28/114)</p> <p>% Unemployed: 24 (27/114)</p> <p>% Working part-time: 20 (23/114)</p> <p>% Working full-time: 19 (22/114)</p> <p>% Retired: 6 (7/114)</p> <p>% Part-time student: 4 (5/114)</p> <p>% Full-time student: 1 (1/114)</p> <p>% Working part-time and on disability: 1 (1/114)</p> <p>No statistically significant socio-demographic differences between the groups at baseline</p> <p>Duration of illness: NR, all ≥6 months</p> <p>Severity of symptoms:</p> <p>CBT vs. COG vs. ACT vs. Relaxation</p> <p>Mean (SD) FSS scores (1 to 7, lower score indicates better health):</p> <p>6.05 (0.60) vs. 6.25 (0.60) vs. 6.23 (0.85) vs. 5.82 (0.74)</p> <p>Comorbidities: % Lifetime axis I diagnosis: 62 (71/114)</p> <p>% Current axis I diagnosis: 39 (44/114)</p>	<p>Number enrolled: 114 (29 CBT, 28 COG, 29 ACT, 28 Relaxation)</p> <p>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</p>	<p>Average drop out rate: 25%, but NR per group</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
<p>Jason, 2007²⁹</p> <p>Jason, 2009³⁰</p> <p>Hlavaty, 2011³¹</p> <p>RCT</p> <p>Medium</p>	<p>Benefits</p> <p>CBT vs. COG vs. ACT vs. Relaxation</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, higher score indicates better health)</i> 12 months: 58.64 (30.44) vs. 61.09 (23.74) vs. 39.72 (27.63) vs. 61.20 (27.70)</p> <p>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=0.49</p> <p>Jason, 2009 data: comparison by energy envelope (data estimated from figure)</p> <p>Stayed within envelope vs. outside envelope</p> <p>6 months: 58 vs. 48; p=NR 12 months: 65 vs. 42 Change at 12 months from baseline: 17 vs. 0; p=0.03</p> <p>Hlavaty, 2011 data: comparison by homework compliance level</p> <p>Minimum vs. moderate vs. maximum</p> <p>Change in SF-36 physical functioning score at 12 months from baseline: 6.99 (19.30) vs. 7.55 (18.85) vs. 17.50 (18.09); p=NR Quality of Life: <i>Mean (SD) QLS scores (16-112 scale, higher score indicates better health)</i> 12 months: 69.10 (18.99) vs. 72.52 (10.84) vs. 63.00 (13.86) vs. 72.00 (19.70); p=NR Work/School Days: NR Proportion full/part-time work: % Employed at 12 month followup: 62 vs. 56 vs. 33 vs. 43; p=NS Fatigue: <i>Mean (SD) FSS scores (1-7 scale, lower score indicates better health)</i> 12 months: 5.37 (1.19) vs. 5.87 (1.01) vs. 5.77 (1.43) vs. 5.62 (1.06); p=NR</p> <p>Jason, 2009 data: comparison by energy envelope (data estimated from figure)</p> <p>Stayed within envelope vs. outside envelope</p> <p>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</p> <p>Hlavaty, 2011 data: comparison by homework compliance level</p> <p>Minimum vs. moderate vs. maximum</p> <p>Change in score at 12 months from baseline: -0.17 (0.73) vs. -0.51 (1.00) vs. -0.54 (1.09); p=NR Outcomes related to associated symptoms: Depression outcomes at 12-month followup (<i>Beck Depression Inventory, 21- item, lower scores indicate better outcome</i>), mean (SD): 13.95 (13.08) vs. 11.86 (7.36) vs. 16.94 (11.82) vs. 13.50 (9.97), p<0.001</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
<p>Jason, 2007²⁹</p> <p>Jason, 2009³⁰</p> <p>Hlavaty, 2011³¹ RCT Medium</p>	<p>CBT vs. COG vs. ACT vs. Relaxation</p> <p>Adverse Events: NR</p> <p>Withdrawals due to adverse event: NR</p> <p>Serious Adverse Events: NR</p>	<p>NIAID (Grant Number AI 49720)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
<p>Knoop, 2008³²</p> <p>Tummers, 2010³³</p> <p>Tummers, 2013³⁴</p> <p>Block randomized RCT</p> <p>Medium</p>	<p>The Netherlands</p> <p>Single center</p> <p>2006 to 2007</p> <p>Tertiary care facility</p>	<p>CDC (Fukuda, 1994) criteria</p> <p>Inclusion: Patients referred for CBT, age ≥18 years, spoke and read Dutch, not engaged in a legal procedure concerning disability-related financial benefits, medically and psychiatrically evaluated to exclude other causes of fatigue; scored ≥35 on the CIS fatigue severity subscale; total score of >700 on SIP-8.</p> <p>Exclusion: NR</p> <p><i>Tummers, 2010</i> used same population and randomized groups from Knoop 2008 after the end of that trial.</p> <p><i>Tummers, 2013: secondary analysis of Knoop trial and the trial listed under Tummers 2012 (see below)</i></p>	<p>Self-instruction (n=85): 16 weeks or more program of self-instruction booklet containing information about CFS and weekly assignments.</p> <p>Wait list (n=86): Wait list control for 6 to 12 months.</p> <p>Duration of treatment: 16 weeks or more</p> <p>Duration of followup: 6 to 12 months depending on length of treatment</p> <p><i>Tummers, 2010</i></p> <p>Stepped care (n=84): Self-instruction as described above, then up to 14 sessions of individual CBT over 6 months</p> <p>Care as usual (n=85): Wait list as described above, then up to 14 sessions of individual CBT over 6 months</p> <p>For both interventions there were 2 treatment protocols, depending on physical activity of the patient (measured by an ankle actometer). Passive patients worked to achieve a base level of activity spread over the day. active patients immediately began graded activity program.</p> <p>Duration of treatment: 6 months</p> <p>Duration of followup: End of treatment</p> <p><i>Tummers, 2013: secondary analysis of Knoop trial and the trial listed under Tummers 2012 (see below)</i></p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
<p>Knoop, 2008³²</p> <p>Tummers, 2010³³</p> <p>Tummers, 2013³⁴</p> <p>Block randomized RCT</p> <p>Medium</p>	<p>Stepped care vs. care as usual</p> <p>Mean age (SD): 37.6 (10.0) vs. 38.5 (10.6) years</p> <p>% Female: 82 (69/84) vs. 76 (65/85)</p> <p>Race: NR</p> <p>Duration of illness: Median (range): 72 (12 to 420) vs. 96 (12 to 420) months</p> <p>Severity of symptoms: Mean (SD) Number of CDC symptoms: 7.1 (1.6) vs. 7.3 (1.6)</p> <p>Mean (SD) SIP-8 total score: 1,659 (648) vs. 1,515 (545)</p> <p>Mean (SD) CIS Fatigue Severity: 49.1 (5.2) vs. 49.9 (5.6)</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 171 (85 self-instruction, 86 wait list)</p> <p>Number analyzed: 169 (84 self-instruction, 85 wait list)</p>	<p>Stepped care vs. care as usual</p> <p>Did not want to continue with CBT: 57% (48/84) vs. 22% (19/85)</p> <p>Excluded because of medical explanation of fatigue: 1 person in each arm of the Knoop study.</p> <p>Diagnoses were constriction of the coronary arteries and Hashimoto's thyroiditis.</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Knoop, 2008 ³² Tummers, 2010 ³³ Tummers, 2013 ³⁴ Block randomized RCT Medium	<p>Benefits</p> <p>Self-instruction vs. wait list Overall Function: <i>Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)</i> Second assessment: 65.9 (23.2) vs. 60.2 (23.7); p=0.011 <i>Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)</i> Second assessment: 1,079 (690) vs. 1,319 (619); p<0.001 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)</i> 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 Outcomes related to associated symptoms: NR</p> <p>Tummers, 2010 Stepped care vs. care as usual <i>Overall Function: Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)</i> Posttreatment: 71.6 (23.2) vs. 72.3 (24.3); difference -1.1 (95% CI -7.2 to 5.0); p=0.72 <i>Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)</i> Posttreatment: 826 (655) vs. 819 (653); difference 30.2 (95% CI -178 to 238); p=0.77 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)</i> 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 1.00 (95% CI 0.53 to 1.89); p=1.00 Outcomes related to associated symptoms: 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</p> <p>Tummers, 2013 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 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 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</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Knoop, 2008 ³² Tummers, 2010 ³³ Tummers, 2013 ³⁴ Block randomized RCT Medium	Self-instruction vs. wait list Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR Tummers, 2010 Stepped care vs. care as usual Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Li, 2015 ³⁵ Open label pilot RCT High	China 3 centers 2012 to 2014 Hospital clinics	<p>CDC criteria (unspecified), requiring 4 or more of the following 8 symptoms: 1) Post-exertion malaise lasting more than 24 hours; 2) Unrefreshing sleep; 3) Significant impairment of short-term memory or concentration; 4) Muscle pain; 5) Multi-joint pain without swelling and redness; 6) Headaches of a new type, pattern, or severity; 7) Tender cervical or axillary lymph nodes; 8) Frequent or recurrent sore throat.</p> <p>Inclusion: Meeting CDC criteria above and a patient in one of the 3 hospital clinics</p> <p>Exclusion: Current or past use of antidepressants for any psychiatric condition; concurrent DSM-IV Axis 1 disorder, vegetarians, nursing or pregnant, use of psychotropic medication in the past month, previous or current engagement in CFS research, substance dependence or abuse, clinically significant or unstable mental illness.</p>	<p>Dengzhanshengmai (n=134): Below therapy SSRI therapy, plus one 1.08 g Dengzhanshengmai capsule containing 4 ingredients: erigeron breviscapus herba, ginseng herba, schisandra herba and ophiopogon japonicus herba once daily.</p> <p>SSRI (n=134): Selective serotonin reuptake inhibitor alone: Seraxat 10 to 30 mg per day, Zoloft 25 to 100 mg per day, or Citalopram 10 to 30 mg per day for the first 4 weeks, and then standard doses were given.</p> <p>Duration of treatment: 12 weeks</p> <p>Duration of followup: End of treatment</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		Number enrolled, analyzed	Attrition
Li, 2015 ³⁵ Open label pilot RCT High	<p>Population characteristics</p> <p>Dengzhanshengmai vs. SSRI</p> <p>Mean age: 35.1 vs. 36.8 years</p> <p>% Female: 56 (75/134) vs. 63 (84/134)</p> <p>Race: NR, conducted in China</p> <p>Duration of illness, Mean: 15.7 vs. 14.5 months</p> <p>Severity of symptoms: <i>Multidimensional fatigue inventory subscales (4 to 20, higher scores indicating worse symptoms), mean:</i></p> <p>General fatigue: 10.7 vs. 10.2</p> <p>Physical fatigue: 9.6 vs. 9.4</p> <p>Mental fatigue: 7.6 vs. 7.4</p> <p>Reduced activity: 8.9 vs. 8.6</p> <p>Reduced motivation: 7.3 vs. 7.2</p> <p>Comorbidities: Current psychiatric comorbidities excluded, otherwise NR.</p>	<p>Number enrolled: 268</p> <p>Number analyzed: 223 possibly, but unclear whether an intention to treat approach was used for efficacy analysis</p> <p>45 patients (24 vs. 21) didn't complete the study due to drug unavailability in the pharmacy</p>	<p>Unclear</p> <p>Loss to followup and other reasons for dropout: 3.0% vs. 2.2%</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Li, 2015 ³⁵ Open label pilot RCT High	<p>Benefits</p> <p>Dengzhanshengmai vs. SSRI</p> <p>Overall Function: NR</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Multidimensional fatigue inventory subscales (4 to 20, higher scores indicating worse symptoms)</i>, mean improvement:</p> <p>Improvement from week 2 to end of treatment</p> <p>General Fatigue : 1.3 (0.7) vs. 0.8 (0.6), p<0.01</p> <p>Physical Fatigue: 1.0 (0.4) vs. 0.6 (0.3), p<0.01</p> <p>Reduced Activity: 1.3 (0.6) vs. 1.0 (0.5), p<0.01</p> <p>Improvement from week 8 to end of treatment</p> <p>Reduced Motivation: 2.4 (1.0) vs. 2.1 (0.8), p<0.01</p> <p>No improvement</p> <p>Mental Fatigue: data not shown, p>0.05</p> <p>Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Li, 2015 ³⁵ Open label pilot RCT High	<p>Dengzhanshengmai vs. SSRI</p> <p>Adverse Events: 55 vs. 56; Hypertension: 8 vs. 2, p=0.05 All others NS between groups Withdrawals due to adverse events: 13 vs. 10 Serious adverse events: None</p>	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Lopez, 2011 ³⁶ Pilot RCT High	United States Single center Study year(s) NR Setting not described	CDC (Fukuda, 1994) criteria Inclusion: 18 to 60 years of age, ≥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, were undergoing psychotherapy, had a history of substance or drug use within 2 years of the onset of CFS, or a history of major psychiatric illness.	Group CBT (n=44): 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 (n=25): 1 half-day session of psychoeducation summarizing strategies from the 12 week intervention, given during the 6th week of the CBT intervention. Duration of treatment: 12 weeks Duration of followup: End of treatment
Malaguarnera, 2007 ³⁷ RCT Medium	Italy Single center 2000 to 2001 University hospital clinic	CDC (Holmes, 1988) and (Fukuda, 1994) criteria Inclusion: >70 years of age recruited from clinic or residing in a nursing home with ≥4 of the Holmes major criteria or ≥6 of the Fukuda minor criteria Exclusion: Infections, anemia, electrolyte imbalances, metabolic or endocrine disorders, or malignancies	ALC (n=48): 2g acetyl L-carnitine twice per day Placebo (n=48): Matching placebo Patients in both groups received a special diet for 2 weeks prior to randomization, and had clinical visits once a week during the study. A diet diary was given thrice per week Duration of treatment: 180 days Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Lopez, 2011 ³⁶ Pilot RCT High	<p>Mean age (SD): 45.9 (9.3) years</p> <p>% Female: 88 (61/69)</p> <p>% White: 77 (53/69)</p> <p>% Latino: 17 (12/69)</p> <p>% Caribbean Islander: 1 (1/69)</p> <p>% Biracial: 1 (1/69)</p> <p>% Another ethnic group: 3 (2/69)</p> <p>% Working full-time: 13 (9/69)</p> <p>% Working part-time: 19 (13/69)</p> <p>% Unemployed: 16 (11/69)</p> <p>% Retired: 4 (3/69)</p> <p>% Student: 3 (2/69)</p> <p>% On disability: 45 (31/69)</p> <p>Duration of illness: NR</p> <p>Severity of symptoms: Number of CFS symptoms, Mean (SD): 12.14 (2.89)</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 69 (44 group CBT, 25 control)</p> <p>Number analyzed: 58 (38 group CBT, 20 control)</p>	<p>Overall: 15.9% (11/69)</p> <p>Group CBT vs. control: 13.6% (6/44) vs. 20% (5/25)</p>
Malagueira, 2007 ³⁷ RCT Medium	<p>ALC vs. placebo</p> <p>Mean age: 76.2 vs. 78.4</p> <p>% Female: 52 (25/48) vs. 50 (24/48)</p> <p>Race: NR</p> <p>Duration of illness: NR</p> <p>Severity of symptoms:</p> <p>Mean Physical fatigue: 13.4 vs. 13.1</p> <p>Fatigue severity scale: 50.4 vs. 50.1</p> <p>Comorbidities: % Sleep disorders: 90 vs. 88</p>	<p>Enrolled: 96</p> <p>Analyzed: 96</p>	<p>Unclear</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Lopez, 2011 ³⁶ Pilot RCT High	<p>Benefits</p> <p>Group CBT vs. control</p> <p>Overall Function: NR</p> <p>Quality of Life: <i>Mean (SD) QOLI scores</i> <i>Category score (range 1-4, lower scores indicate better health)</i></p> <p>After treatment: 2.81 (1.15) vs. 3.26 (0.87); p=0.02</p> <p>Raw score after treatment: 1.17 (1.83) vs. 0.82 (1.37); p=0.05</p> <p>T score after treatment: 39.28 (14.17) vs. 36.42 (10.56); p=0.05</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) POMS-Fatigue subscale (0-28 scale, lower scores indicate better health)</i></p> <p>After treatment: 17.85 (7.34) vs. 20.09 (6.99); p=0.06</p> <p>Outcomes related to associated symptoms: <i>Mean (SD) Total CDC Symptom Severity scores</i></p> <p>After treatment: 2.01 (0.33) vs. 2.08 (0.39); p=0.04</p> <p>Depression: NR</p>
Malaguarnera, 2007 ³⁷ RCT Medium	<p>ALC vs. placebo</p> <p>Overall Function: Mean functional limitation PF score (SD): 86.9 (17.40 vs. 70.8 (19.1), mean difference: 16.1, 95% CI 8.70 to 23.50</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue:</p> <p>Mean physical fatigue (SD), Wessely and Powell Scale: 6.4 (2.2) vs. 12.6 (2.4), mean difference: -6.2, 95% CI -7.1 to 5.3</p> <p>Mean mental fatigue (SD), Wessely and Powell Scale: 4.4 (1.6) vs. 7.2 (1.9), mean difference -2.8, 95% CI -3.5 to -2.1</p> <p>Mean Fatigue severity scale (SD): 27.9 (9.7) vs. 48.9 (6.9), mean difference: -21.00, 95% CI -24.41 to 17.59</p> <p>Likelihood of prolonged post-exercise fatigue: 48% vs. 96%, RR 0.50, 95% CI 0.37 to 0.68</p> <p>Likelihood of activity reduction >50%: 56% vs. 75%, RR 0.75 (0.56 to 1.01)</p> <p>Outcomes related to associated symptoms:</p> <p>Painful throat: 77% vs. 77%, RR 1.00 (0.80 to 1.24)</p> <p>Painful lymph nodes: 16% vs. 12%, RR 1.33 (0.50 to 3.55)</p> <p>Muscle pain: 67% vs. 90%, RR 0.74 (0.60 to 0.93)</p> <p>Neuropsychiatric complaints: 52% vs. 71%, RR 0.74 (0.53 to 1.02)</p> <p>Spreading arthralgias: 80% vs. 83%, RR 0.95 (0.78 to 1.15)</p> <p>Headaches: 61% vs. 61%, RR 1.00 (0.72 to 1.38)</p> <p>Sleep disorders: 62% vs. 84%, RR 0.75 (0.58 to 0.97)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Lopez, 2011 ³⁶ Pilot RCT High	Group CBT vs. control Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NIH
Malaguarnera, 2007 ³⁷ RCT Medium	ALC vs. placebo Adverse Events: None reported Withdrawals due to AE: None reported Serious Adverse Events: None reported	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
McKenzie, 1998 ³⁸ RCT McKenzie, 2000 ³⁹ Medium	United States Single center 1992 to 1996 Specialty clinic	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, medical or psychiatric condition that required medication, severe active depression	Hydrocortisone (n=35): Oral hydrocortisone 20-30 mg every morning and 5 mg every afternoon (for total dose of 16 mg/m ² daily) Placebo (n=35): Placebo Duration of treatment: 12 weeks Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
McKenzie, 1998 ³⁸ RCT McKenzie, 2000 ³⁹ Medium	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) Duration of illness: Mean: 47 vs. 60 months; p=0.07 Severity of symptoms: <i>Self-rating Wellness score (0 to 100, 0 most severe)</i> : 38.8 vs. 37.6; p=0.50 Comorbidities: Depression: 1 vs. 3; p=0.36 Somatoform pain disorder: 20 vs. 20; p>0.99 Somatization disorder: 3 vs. 6; p=0.31 Major depressive episode: 1 vs. 1; p>0.99 Generalized anxiety disorder: 1 vs. 0; p=0.50 Phobic disorder: 2 vs. 3; p=0.68 Posttraumatic stress disorder: 1 vs. 2; p=0.62 Obsessive-compulsive disorder: 1 vs. 0; p=0.50	Number enrolled: 70 Number analyzed: 70 Number enrolled in bone mineral density assessment published in 2000: 30 Number analyzed: 23 (11 hydrocortisone and 12 placebo)	10% (7/70)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
McKenzie, 1998 ³⁸ RCT McKenzie, 2000 ³⁹ Medium	<p>Hydrocortisone vs. placebo</p> <p>Overall Function: <i>Mean change (SD) in Activity Scale (10 point scale)</i>: 0.3 (1.1) vs. 0.7 (1.4); p=0.32</p> <p>Quality of Life: <i>Global Wellness scale (0-100, lower score most severe)</i></p> <p>Improvement: 20/30 (67%) vs. 19/35 (54%); p=0.31</p> <p>Mean change: 6.3 (11.7) vs. 1.7 (8.8); p=0.06</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean Change in POMS subscales</i></p> <p>Fatigue (negative changes indicate better health): -3.6 (5.3) vs. -1.8 (4.5); p=0.21</p> <p>Vigor (positive changes indicate better health): 1.2 (3.3) vs. 0.7 (3.3); p=0.45</p> <p>Outcomes related to associated symptoms: <i>Beck Depression Inventory (0-63, higher most severe)</i> change: -2.1 (5.1) vs. -0.4 (4.1); p=0.17</p> <p>Symptom Checklist-90-R general severity index (0-360, improvement is reflected by a negative change) mean change: -0.1 (0.2) vs. -0.1 (0.2); p=0.20</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
McKenzie, 1998 ³⁸ RCT McKenzie, 2000 ³⁹ Medium	<p>Hydrocortisone vs. placebo</p> <p>Adverse Events: Increased appetite: 17 vs. 8; p=0.02 Weight gain: 19 vs. 8; p=0.006 Difficulty sleeping: 17 vs. 8; p=0.02 Suppression of adrenal glucocorticoid responsiveness: 12 vs. 0; p<0.001 Any reaction: 31/35 vs. 27/35; p=0.17 Withdrawals due to adverse event: 1 rash with placebo Serious Adverse Events: None</p> <p>Bone mineral density assessments after 12 weeks in a subset of patients:</p> <p>Hydrocortisone (n=11) Lateral spine mean percentage change: -2.0% (95% CI, -3.5 to -0.6), p=0.03 AP spine mean percentage change: -0.8% (95% CI, -1.5 to -0.1), p=0.06 Lateral spine median percentage change: -1.1% (range -5.7 to 1.30%) AP spine median percentage change: -0.6% (range -3.0 to 0.8%)</p> <p>Placebo (n=12) Lateral spine mean percentage change: +1.0% (95% CI, -1.0 to 3.0), p=0.34 AP spine mean percentage change: +0.2% (95% CI, -1.4 to 1.5), p=0.76 Lateral spine median percentage change: 1.5% (range -5.0 to 7.2) AP spine median percentage change: 1.0% (range -2.96 to 4.3)</p> <p>Hydrocortisone vs. placebo: Percentage change in lateral spine: p=0.03 Percentage change in AP: p=0.22</p>	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Montoya, 2013 ⁴⁰ RCT Medium	United States Single center 2007 to 2008 Specialty clinic	CDC (Fukuda, 1994) criteria Inclusion: Age 18 and older; suspected viral onset of CFS; elevated antibody titer meeting additional criteria. Exclusion: low antibody titers on repeat testing, hypothyroidism, uncontrolled major depression, hepatitis C, conflicting medication	Valganciclovir (n=20): Oral valganciclovir 900 mg twice a day for 21 days, then 900 mg once daily for total of 6 months Placebo (n=10): Placebo Duration of treatment: 6 months Duration of followup: 6 months followup after treatment discontinuation (unblinding and outcomes measured at 9 months)
Montoya, 2018 ⁴¹ RCT Medium	United States 4 centers 2013 to 2014 ME/CFS research sites	CDC (Fukuda, 1994) criteria Inclusion: Between 18 and 59 years of age, meeting CDC criteria for ME/CFS, complaining of alertness and/or concentration deficits, in otherwise good health based on medical history and screening evaluation, willing to abstain from nutritional, herbal, or caffeine-containing products during the trial. Exclusion: Major depression defined by Zung Depression Score >60, daily use of anxiety medications, daily concurrent use of more than 1 antidepressant, use of medications such as monoamine oxidase inhibitors, other CNS stimulants, and narcotic opioids.	Methylphenidate hydrochloride (n=67): 5 mg methylphenidate hydrochloride with a mitochondrial modulator (containing vitamins, minerals, amino acids, and antioxidants) twice daily for week 1 and 10 mg twice daily for weeks 2 through 12. Subjects were allowed to decrease dosage to 5 mg for tolerability issues Placebo (n=68): Matched placebo twice daily Duration of treatment: 12 weeks Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Montoya, 2013 ⁴⁰ RCT Medium	<p>Valganciclovir vs. placebo</p> <p>Mean age: 50 vs. 48 years</p> <p>% Female: 75 (15/20) vs. 50 (5/10)</p> <p>Race: NR</p> <p>Duration of illness: Mean: 12.7 vs. 13.5 years; p=0.820</p> <p>Severity of symptoms: <i>Multidimensional Fatigue Inventory total score (20-100, 100 is most severe)</i>: 81.25 vs. 76.00; p=0.447</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 30</p> <p>Number analyzed: 30 (20 valganciclovir, 10 placebo)</p>	<p>1 from each group</p>
Montoya, 2018 ⁴¹ RCT Medium	<p>Methylphenidate hydrochloride vs. placebo</p> <p>Mean age: 42.8 vs. 42.3</p> <p>% Female: 78 (49/63) vs. 66 (43/65)</p> <p>% Race: 90 (57/63) vs. 91 (59/65) white, 3 (2/63) vs. 0 Asian, 5 (3/63) vs. 8 (5/65) African American, 5 (3/63) vs. 2 (1/65) other</p> <p>Duration of illness %: 52 (33/63) vs. 54 (35/65) <10 years, 48 (30/63) vs. 46 (30/65) ≥10 years</p> <p>Severity of symptoms: <i>Mean CIS total score (ranges from 20 to 140, higher scores indicate worse health)</i>: 112.2 vs. 112.4</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 135</p> <p>Number analyzed: 128</p>	<p>Overall: 27% (37/135)</p> <p>Methylphenidate hydrochloride vs. placebo</p> <p>34% (23/67) vs. 21% (14/68)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Montoya, 2013 ⁴⁰ RCT Medium	<p>Valganciclovir vs. placebo</p> <p>Overall Function: <i>Change in self-reported physical function (positive change indicates better health)</i> 1.02 vs. 0.46; p=0.217</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Change in MFI-20 (negative changes indicate better health)</i> Baseline to 9 months : -6.15 vs. -1.10; p=0.224</p> <p>Change in FSS (negative changes indicate better health) -0.06 vs. 0.02; p=0.006</p> <p>Outcomes related to associated symptoms: <i>CDC Symptom inventory</i>: NS</p>
Montoya, 2018 ⁴¹ RCT Medium	<p>Methylphenidate hydrochloride vs. placebo</p> <p>Overall Function: NR</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean CIS total score (ranges from 20 to 140, higher scores indicate worse health):</i> 95.3 vs 98.6, mean change from baseline: -16.9 (±23.52) vs. -13.8 (±22.15), (95% CI, -11.1 to 4.0), p=0.359</p> <p>Mean VAS fatigue change from baseline: -18.2 mm (±25.05) vs. -11.1 mm (±22.08), (95% CI, -11.5 to 2.3), p=0.189</p> <p>Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Montoya, 2013 ⁴⁰ RCT Medium	Valganciclovir vs. placebo Adverse Events: 0 Withdrawals due to adverse event: 0 Serious Adverse Events: 1 patient with cancer in each group considered not related to intervention	Hoffman-La Roche
Montoya, 2018 ⁴¹ RCT Medium	Methylphenidate hydrochloride vs. placebo Adverse Events: Headache: 5 vs. 5 Anxiety: 4 vs. 5 Fatigue: 9 vs. 4 Dizziness: 4 vs. 1 Nausea: 3 vs. 3 All differences p=NS Withdrawals due to adverse event: 8 vs. 3 Serious Adverse Events: Pyelonephritis (thought to be unrelated, resolved after 3 days of onset with appropriate treatment): 1 vs. 0	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Moss-Morris, 2005 ⁴² RCT Medium	New Zealand Single center Study year(s) NR CFS private general practice	CDC (Fukuda, 1994) criteria Inclusion: Interested in a graded exercise study, ages 18 to 65 years and meeting Fukuda criteria. Exclusion: Patients unable to exercise for medical reasons including obesity or patients already performing regular exercise.	Graded exercise (n=25): Graded exercise therapy, increasing from 10 to 15 minutes 4 to 5 times a week to 30 minutes per day 5 days per week. Intensity was measured using heart rate and was increased through the duration of the intervention. Exercise participants also received standard medical care. Usual care (n=24): Standard medical care alone. Duration of treatment: 12 weeks Duration of followup: End of treatment
Nijhof, 2012 ⁴³ ³ Nijhof, 2013 ⁴⁴ ⁴ Crawley, 2012 ⁴⁵ RCT Medium	The Netherlands Two center Study year(s) NR Pediatric hospital and treatment coordinating center	CDC (Fukuda, 1994) criteria Inclusion: Adolescents aged 12 to 18 years, access to a computer with internet connection, meeting CDC CFS criteria. Exclusion: Primary depression, anxiety disorder or suicidal risk assessed with computerized self-report questionnaires.	FITNET (n=68): 21 interactive CBT modules and support from a trained cognitive behavioral psychotherapist, solely through e-consults every other week or immediately in the case of emergencies. Parents followed a parallel program, with the same frequency of email contacts, and access to the module's content, psychoeducation, and e-consult application. Patients and parents had separate accounts and could not see each others' responses. The parents of patients younger than 15 were asked to coach the patients, but the parents of older patients were asked to encourage their children to take responsibility of their treatment. The aim of treatment was return to full-time education. FITNET participants agreed not to undergo any other treatments. Usual care (n=67): Individual or group-based rehabilitation programs, cognitive behavioral therapy face-to-face, or graded exercise programs, or both. Records were kept of the care that was given. This group was given the opportunity to use FITNET after 6 months. Duration of treatment: 6 months Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Moss-Morris, 2005 ⁴² RCT Medium	Graded exercise vs. usual care Mean age (SD): 36.7 (11.8) vs. 45.5 (10.4) years; p=0.009 % Female: 60 (15/25) vs. 79 (19/24) Race: NR Duration of illness: Median (range): 2.7 (0.60 to 20) vs. 5.0 (0.5 to 45) years Severity of symptoms, Mean (SD): Physical fatigue: 14.55 (5.40) vs. 14.61 (4.86) Mental fatigue: 9.90 (3.74) vs. 10.74 (3.90) Total fatigue score: 24.45 (8.79) vs. 25.35 (8.05) SF-36 Physical functioning: 53.10 (18.39) vs. 45.65 (21.07) 22.4% of patients overall were unemployed and unable to work due to disability Comorbidities: Diagnosed cases NR	Number enrolled: 49 Number analyzed: 43 (22 exercise, 21 control)	Overall: 12% (6/49) Graded exercise vs. usual care: 12% (3/25) vs. 13% (3/24)
Nijhof, 2012 ⁴ ³ Nijhof, 2013 ⁴ ⁴ Crawley, 2012 ⁴⁵ RCT Medium	FITNET vs. usual care Mean age (SD): 15.9 (1.3) vs. 15.8 (1.3) % Female: 79 (54/68) vs. 85 (57/67) Race NR Mean duration of illness (range): 16.0 (6 to 84) vs. 19.0 (6 to 108) months Severity of symptoms: Fatigue severity: Mean CIS-20, range 8 to 56, (SD): 51.2 (4.4) vs. 51.6 (4.6) Comorbidities: NR	Number enrolled: 135 Number analyzed at 6 months: 131 (67 FITNET, 64 usual care) Number analyzed at 12 months: 127 (64 FITNET, 63 usual care)	Overall: 6 months: 3.0% (4/135) FITNET vs. usual care: 1.5% (1/68) vs. 4.5% (3/67) Overall: 12 months: 5.9% (8/135) FITNET vs. usual care: 5.9% (4/68) vs. 6.0% (4/67)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Moss-Morris, 2005 ⁴² RCT Medium	<p>Graded exercise vs. usual care</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale score (0-100 scale, higher scores indicate better health)</i> 12 weeks: 69.05 (21.94) vs. 55.00 (22.94); p=0.49</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) Chalder fatigue scale total fatigue scores (0 to 42 scale, lower scores indicate better health)</i> 12 weeks: 13.91 (10.88) vs. 24.41 (9.69); p=0.02</p> <p><i>Mean (SD) Chalder fatigue scale physical fatigue subscale scores (0 to 32 scale, lower score indicates better health)</i> 12 weeks: 7.91 (7.06) vs. 14.27 (5.75); p=0.02</p> <p><i>Mean (SD) Chalder fatigue scale mental fatigue subscale scores (0 to 24 scale, lower score indicates better health)</i> 12 weeks: 6.00 (4.06) vs. 10.14 (4.27); p=0.03</p> <p>Outcomes related to associated symptoms: <i>Self-rated CGI at 6 months</i> % Much or very much improved: 54 (12/22) vs. 24 (5/21); p=0.04; NNT=3.2</p>
Nijhof, 2012 ⁴³ Nijhof, 2013 ⁴⁴ Crawley, 2012 ⁴⁵ RCT Medium	<p>FITNET vs. usual care</p> <p>Overall Function: Physical functioning (CHQ-CF87 cutoff score of 85% or more) at 6 months: 78% (52/67) vs. 20% (13/64), RR 3.8 (95% CI, 2.3 to 6.3), NNT 1.8, p<0.0001</p> <p>Quality of Life: NR</p> <p>Work/School Days: Full school attendance at 6 months (10% absence or less): 75% (50/67) vs. 16% (10/64), RR 4.8 (95% CI, 2.7 to 8.9), NNT 1.7, p<0.0001</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Fatigue severity at 6 months, CIS-20, cutoff score <40: 85% (57/67) vs. 27% (17/64), RR 3.2 (95%CI, 2.1 to 4.9), NNT 1.7, p<0.0001</p> <p>Outcomes related to associated symptoms: Self-rated improvement at 6 months (answer "yes" to statement "I have completely recovered" or "I feel much better but still experience some symptoms"): 78% (52/67) vs. 27% (17/64), RR 2.9 (95% CI, 1.9 to 4.5), NNT 2.0, p<0.0001</p> <p>Recover at 12 months (some patients in usual care group crossed over to FITNET group at the 6 month point): 64% (41/64) vs. 8% (5/63)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Moss-Morris, 2005 ⁴² RCT Medium	Graded exercise vs. usual care Adverse Events: 2% (1/49) 10 of 25 patients refused to repeat fitness test as felt initial test harmful Withdrawals due to adverse event: 1 patient withdrew due to injured calf Serious Adverse Events: NR	University of Auckland Staff Grants
Nijhof, 2012 ⁴³ Nijhof, 2013 ⁴⁴ Crawley, 2012 ⁴⁵ RCT Medium	FITNET vs. usual care Adverse Events: None reported Withdrawals due to adverse event: None reported Serious Adverse Events: None reported	Netherlands Organisation for Health Research and Development

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Öckerman, 2000 ⁴⁶ Crossover RCT High	Sweden Number of centers: NR Study year(s): NR Setting: NR	CDC (Fukuda, 1994) criteria Inclusion: Ages 18 to 70 years, symptom score ≥ 49 for 13 symptoms and ≥ 5 for total well being. Exclusion: smokers, active dental treatment, electrical hypersensitivity, pollen allergy, use of drugs or antioxidants and other medial diseases and/or treatment.	Pollen (n=22): Antioxidant extract of pollen (Polbax), 7 tablets taken at one time per day. Placebo (n=22): Placebo <i>Note:</i> 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. Duration of treatment: 3 months Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Öckerman, 2000 ⁴⁶ Crossover RCT High	Mean age: 50 years % Female: 86 (19/22) Race: NR Duration of illness: NR	Number enrolled: 22 Number analyzed: 22	Overall: 4.5% (1/22)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
	Benefits
Öckerman, 2000 ⁴⁶ Crossover RCT High	<p>Pollen vs. placebo, results both pre- and post-crossover with each participant represented in both groups</p> <p>Overall Function: NR</p> <p>Quality of Life: <i>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)</i> 5.48 vs. 6.45; p=NR</p> <p>Change from baseline: -1.66 vs. -0.21; p<0.01</p> <p><i>Change in total well-being after treatment</i>; p value NR</p> <p>Worse: 9.5% (2/21) vs. 18% (4/22)</p> <p>No change: 29% (6/21) vs. 59% (13/22)</p> <p>Better: 62% (13/21) vs. 23% (5/22)</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean fatigue score (Likert scale 0=no problem to 10=extremely serious symptom)</i> 7.52 vs. 7.14; p=NR</p> <p>Change from baseline: -0.43 vs. -0.18; p<0.05</p> <p>Outcomes related to associated symptoms: <i>Mean depression score (Likert scale 0=no problem to 10=extremely serious symptom)</i> 5.16 vs. 6.60; p=NR</p> <p>Change from baseline: -0.74 vs. -0.10; p<0.001</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		
	Harms	Sponsor
Öckerman, 2000 ⁴⁶ Crossover RCT High	Pollen vs. placebo Adverse Events: Gastrointestinal - 1 or 2 patients Withdrawals due to AE: None Serious Adverse Events: None	NR

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
O'Dowd, 2006 ⁴⁷ RCT Medium	United Kingdom Single Center 2000 to 2002 Health psychology department of a general hospital	<p>CDC (Fukuda, 1994) criteria</p> <p>Inclusion: Presentation consistent with ME/CFS described by Fukuda; NHS patients; able to read and understand patient information leaflet.</p> <p>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.</p>	<p>Group CBT (n=52): 8 2-hour group CBT sessions every other week over a 16 week period 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. Physical structured incremental group exercise sessions were included before a break midway through the session.</p> <p>Group Support (n=50): 8 2-hour group education and support sessions every other week over a 16 week period focusing on sharing of experiences and learning of basic relaxation skills.</p> <p>Usual care (n=51): Managed in primary care and received no other intervention.</p> <p>Duration of treatment: 16 weeks</p> <p>Duration of followup: 12 months</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
O'Dowd, 2006 ⁴⁷ RCT Medium	<p>Group CBT vs. group support vs. usual care</p> <p>Mean age (SD): 41.6 (12.0) vs. 38.8 (11.8) vs. 42.9 (11.6) years</p> <p>% Female: 54 (28/52) vs. 76 (38/50) vs. 71 (36/51)</p> <p>Race: NR</p> <p>% Discontinued main occupation due to CFS: 77 (36/52) vs. 63 (29/50) vs. 70 (35/51)</p> <p>Duration of illness: % With symptoms for >60 months: 42 (21/50) vs. 50 (25/50) vs. 54 (27/50)</p> <p>% Diagnosed >12 months before study: 57% (28/49) vs. 45% (20/44) vs. 62% (29/47)</p> <p>Severity of symptoms: Mean number of symptoms (IQR): 7 (6.5-9) vs. 9 (8-10) vs. 9 (7-10)</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 153 (52 CBT, 50 support, 51 usual care)</p> <p>Number analyzed: 153 (52 CBT, 50 support, 51 usual care)</p>	<p>Group CBT vs. group support vs. usual care:</p> <p>25% (13/52) vs. 8% (4/50) vs. 14% (7/51)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
O'Dowd, 2006 ⁴⁷ RCT Medium	<p>Group CBT vs. group support vs. usual care</p> <p>Overall Function: Group CBT vs. group support vs. usual care <i>Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health); all p values are NS</i></p> <p>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) <i>% Reporting SF-36 score in normal range (score was on or above the 5th centile for the distribution, estimated as the mean -1.645 x SD for the gender-specific age group)</i></p> <p>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 <i>% Reporting ≥15% increase from baseline</i></p> <p>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 group 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) for usual care vs. group support <i>Mean incremental shuttle walking test; shuttles walked (number of complete 10 meter shuttles)</i></p> <p>6 months: 28.5 vs. 25.6 vs. 23.6 12 months: 28.9 vs. 24.1 vs. 24.2 <i>Difference between groups from baseline to 12 months</i></p> <p>CBT vs. group support: 1.16 (95% CI 0.94 to 1.43); CBT vs. usual care: 1.20 (95% CI 0.99 to 1.45) Group 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 5 and/or 12 months: 11.58 (0.71) vs. 9.82 (0.53) vs. 8.76 (0.47); p=0.006</p> <p>Continued below</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
O'Dowd, 2006 ⁴⁷ RCT Continued	<p>Difference between groups from baseline to 12 months</p> <p>CBT vs. group support: 1.77 (95% CI 0.025 to 3.51); p=0.0055</p> <p>CBT vs. usual care: 2.83 (95% CI 1.12 to 5.53); p=0.0055</p> <p>Group support vs. usual care: 1.06 (-0.37 to 2.49); p=0.15</p> <p>Quality of Life: Mean (SD) health related quality of life utility scores (higher scores indicate better health); all p values are NS</p> <p>6 months: 0.43 (0.28) vs. 0.34 (0.32) vs. 0.41 (0.25)</p> <p>12 months: 0.45 (0.34) vs. 0.34 (0.35) vs. 0.46 (0.30)</p> <p>Difference between groups from baseline at 12 months</p> <p>CBT vs. group support: 0.023 (95% CI -0.065 to 0.11); CBT vs. usual care: 0.029 (95% CI -0.052 to 0.11)</p> <p>Group support vs. usual care: 0.006 (95% CI -0.082 to 0.095)</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean (SD) Chalder fatigue scale (0 to 33 scale, lower scores indicate better health)</p> <p>6 months: 17.9 (8.41) vs. 21.4 (7.55) vs. 21.8 (6.90); p=0.19</p> <p>12 months: 17.4 (7.32) vs. 21.4 (7.79) vs. 18.8 (7.19); p=0.19</p> <p>Difference between groups from baseline at 6 and 12 months pooled</p> <p>CBT vs. group support: -3.16 (95% CI -5.59 to -0.74); p=0.011</p> <p>CBT vs. usual care: -2.61 (95% CI -4.92 to -0.30); p=0.027*</p> <p>Support vs. usual care: 0.55 (95% CI -1.56 to 2.66); p=NR</p> <p>*Note: this number is -2.16 in the text and -2.61 in the table</p> <p>Outcomes related to associated symptoms:</p> <p>HADS-Depression:</p> <p>6 months: 6.84 (3.46) vs. 8.20 (3.81) vs. 7.78 (3.76)</p> <p>12 months: 6.82 (3.80) vs. 7.74 (4.02) vs. 7.44 (4.42)</p> <p>Mean difference, adjusted for baseline: -0.13 (-1.13 to 0.87) vs. -0.56 (-1.69 to 0.58) vs. -0.43 (-1.56 to 0.70), p=0.52</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
O'Dowd, 2006 ⁴⁷ RCT Medium	Group CBT vs. group support vs. usual care Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	National Health Service Health Technology Assessment Program

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Oka, 2014 ⁴⁸ RCT Medium	Japan Single center Study year(s) NR Hospital department of psychosomatic medicine	CDC (Fukuda, 1994) criteria Inclusion: Outpatients with CFS; fatigue did not improve sufficiently with ordinary treatment including pharmacotherapy, psychotherapy, and GET for at least 6 months; aged 20 to 70 years; level of fatigue serious enough to cause an absence from school or workplace at least several days a month but not serious enough to require assistance with the activities of daily living; able to fill out questionnaire without assistance; able to sit for at least 30 minutes; able to visit hospital regularly every 2 to 3 weeks. Exclusion: Fatigue due to a physical disease, had previously practiced yoga, or having idiopathic chronic fatigue.	Yoga (n=15): 1-on-1 sitting isometric yoga with an instructor for 20 minutes, once every 2 to 3 weeks, along with pharmacotherapy. Yoga program was designed to avoid exacerbation of symptoms and post-exertion malaise, while providing some reconditioning exercise therapy. It included abdominal breathing practice. Participants were asked to practice the program on non-class days if they could, and were given a videodisc and a booklet. All patients received at least 4 sessions with the instructor, mean=5.6. Control (n=15): Conventional pharmacotherapy alone, and wait-list for yoga. Duration of treatment: Approximately 2 months (9.2±2.5 weeks) Duration of followup: 2 months after end of treatment
Ostojic, 2016 ⁴⁹ Crossover RCT High	Serbia Single center 2014 to 2015 Setting NR	CDC (Fukuda, 1994) criteria Inclusion: Fulfilling CDC CFS criteria and aged >18 years. Exclusion: Psychiatric comorbidity, use of any dietary supplement within 4 weeks prior to study commencing, unwillingness to return for followup, or pregnancy.	Guanidinoacetic acid (n=NR): 2.4 grams daily orally Placebo (n=NR): Cellulose daily orally Patients in both groups were asked not to use any dietary supplements during the study. Duration of treatment: 3 months, then washout before crossover (NR here) Duration of followup: End of first treatment period; 3 months after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Oka, 2014 ⁴⁸ RCT Medium	Yoga vs. control Mean age: 38.0 vs. 39.1 % Female: 80 (12/15) vs. 80 (12/15) Race NR, conducted in Japan Duration of illness: NR Severity of symptoms: Chalder's fatigue scale: Mean physical fatigue: 16.4 vs. 16.5 Mean mental fatigue: 9.5 vs. 9.7 Mean total score: 25.9 vs. 26.1 Comorbidities: at least 2 patients in yoga group had fibromyalgia, NR overall	Number enrolled: 30 Number analyzed: 30	None
Ostojic, 2016 ⁴⁹ Crossover RCT High	Overall: Mean age: 39.3 years % Female: 100 (21/21) Race NR, conducted in Serbia Duration of illness: NR Severity of symptoms: Mean MFI Physical fatigue: 11.2 Comorbidities: NR	Enrolled: 21 Analyzed: 14	7 participants lost during the intervention period due to reasons not connected to the study

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Oka, 2014 ⁴⁸ RCT Medium	<p>Benefits</p> <p>Yoga vs. control</p> <p>Overall Function: SF-8</p> <p>Physical functioning: Only reported as pre-post change in yoga group: 39.6 vs. 42.5, p=NS</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Chalder's fatigue scale:</p> <p>Mean physical fatigue (SD): 12.3 (3.8) vs. 16.1 (3.6), p=0.009; mean difference 3.80, 95% CI 1.03 to 6.57</p> <p>Mean mental fatigue (SD): 6.9 (4.4) vs. 9.7 (3.1), p=0.007; mean difference 2.80, 95% CI -2.83 to 8.43</p> <p>Mean total score (SD): 19.2 (7.5) vs. 25.8 (5.9), p=0.003; mean difference 6.6, 95% CI 1.55 to 11.65</p> <p>Outcomes related to associated symptoms: NR</p>
Ostojic, 2016 ⁴⁹ Crossover RCT High	<p>Guanininoacetic acid vs. placebo</p> <p>Overall Function: NR</p> <p>Quality of Life: Health-related quality of life, mean score (SD), p is for ANOVA treatment vs. time interaction:</p> <p>Physical common score: 55.2 (2.8) vs. 52.8 (4.2), mean difference 2.4, p=0.04</p> <p>Mental common score: 51.1 (5.5) vs. 45.8 (6.5), mean difference 5.3, p<0.005</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean <i>MFI</i>, <i>higher scores indicate worse fatigue</i> (SD), p is for ANOVA treatment vs. time interaction:</p> <p>General fatigue: 11.6 (1.3) vs. 11.8 (1.5), mean difference -0.2, p=0.44</p> <p>Physical fatigue: 11.7 (1.2) vs. 11.6 (1.4), mean difference 0.1, p=0.99</p> <p>Reduced activity: 13.9 (1.2) vs. 11.7 (1.8), mean difference -2.2, p<0.005</p> <p>Reduced motivation: 13.1 (1.9) vs. 15.0 (1.8), mean difference -1.9, p=0.03</p> <p>Mental fatigue: 12.2 (1.7) vs. 14.0 (0.9), mean difference -1.8, p=0.01</p> <p>Outcomes related to associated symptoms:</p> <p>Musculoskeletal soreness at rest, mean score (SD), p is for ANOVA treatment vs. time interaction: 1.2 (1.0) vs. 1.4 (1.3), p=0.31</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Oka, 2014 ⁴⁸ RCT Medium	Yoga vs. control Adverse Events: Dizziness: 1 vs. 0 Tiredness: 2 vs. 0 Lightheadedness: 2 vs. 0 Withdrawals due to AE: None reported Serious Adverse Events: None reported	Health and Labour Sciences Research Grant for integrative medicine
Ostojic, 2016 ⁴⁹ Crossover RCT High	Guanininoacetic acid vs. placebo Adverse Events: None reported Withdrawals due to AE: None reported Serious Adverse Events: None reported	Serbian Ministry of Science, National Strength and Conditioning Association International, Faculty of Sport and Physical Education

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Peterson, 1990 ⁵⁰ RCT Medium	United States Single center 1988 Specialty clinic	CDC (Holmes, 1988) criteria Inclusion: Diagnosis of CFS Exclusion: No evidence of underlying psychopathology as an explanation of chronic fatigue found during interview by psychiatric co-investigator	IgG (n=15): IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) Placebo (n=15): IV placebo (1% albumen solution) every 30 days for 6 months (6 infusions) Duration of treatment: 6 months Duration of followup: End of treatment
Pinxsterhuis, 2017 ⁵¹ RCT Medium	Norway 6 centers 2011 to 2012 Hospitals, specific settings NR	CDC (Fukuda, 1994) and Canadian (Carruthers, 2003) criteria Inclusion: Ages ≥18, CFs diagnosis by medical specialist, meeting CDC and Canadian diagnostic criteria, physically able to attend the program. Exclusion: Pregnancy.	Self-management (n=73): 8 2.5 hour group meetings held every other week conducted by a peer counselor (experienced individual with chronic fatigue syndrome) and occupational therapist, after participating in a 3 day program. Participants were taught how to take greater initiative in coping with their illness and for dealing with healthcare professionals and significant others, through educational presentations, the exchange of experiences among participants, modeling of self-management skills, guided mastery practice, and informative feedback. There was one meeting for relatives consisting of a presentation about chronic fatigue, the content of the self-management program, and an exchange of experiences among relatives. Control (n=73): Treatment as usual, not standardized in Norway. Duration of treatment: 16 weeks Duration of followup: 1 year after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Peterson, 1990 ⁵⁰ RCT Medium	IgG vs. placebo Mean age: 45 vs. 36 % Female: 73 (22/30); NR by group Race: NR Duration of illness: Mean: 3.8 years; NR by group Severity of symptoms: Number of CFS symptoms 8.8; NR by group Comorbidities: NR	Number enrolled: 30 Number analyzed: 28	7% (2/30)
Pinxsterhuis, 2017 ⁵¹ RCT Medium	Self-management vs. control Mean age: 44.0 vs. 43.8 % Female: 94.4 (67/71) vs. 81.1 (54/66), p=0.022 Race: NR Duration of illness: Median time diagnosed (range): 3 (1 to 21) vs. 3 (0 to 17) years Severity of symptoms: Mean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability): 45.8 (18.2) vs. 46.2 (20.2) Mean (SD) Fatigue Severity Scale Score (9 to 63 scale with higher scores indicating greater disability): 56.6 (5.6) vs. 58.0 (4.5) Comorbidities: NR	Number enrolled: 146 Number analyzed at 6 months: 125 (63 self-management, 62 usual care) Number analyzed at 12 months: 118 (59 self-management, 59 usual care)	Self-management vs. control 13.9% overall Did not receive treatment: 2/73 vs. 7/73 Did not complete 6 month followup: 10/73 vs. 11/73 Did not complete 12 month followup: 14/73 vs. 14/73

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Peterson, 1990 ⁵⁰ RCT Medium	<p>Benefits</p> <p>IgG vs. placebo Overall Function: <i>Medical Outcome Study Short Form (0-100 scale, higher scores indicate better health)</i> Mean (SD) Physical: 56.0 (23.2) vs. 51.8 (22.2); p=NS Social: 5.2 (5.5) vs. 9.4 (7.9); p<0.05 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR</p>
Pinxsterhuis, 2017 ⁵¹ RCT Medium	<p>Self-management vs. control Overall Function: <i>Mean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability):</i> 6 months: 47.5 (21.2) vs. 50.5 (23.7); p=NS; Mean change from baseline (95% CI): 0.6 (-2.9, 4.0) vs. 4.3 (-0.4, 8.9) 12 months: 48.9 (17.7) vs. 46.3 (22.3); p=NS; Mean change from baseline (95% CI): 0.8 (-4.2, 5.7) vs. -0.3 (-5.4, 4.9) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>Mean (SD) Fatigue Severity Scale Score (9 to 63 scale with higher scores indicating greater disability):</i> 6 months: 56.0 (6.8) vs. 55.5 (8.2); p=0.039; Mean change from baseline (95% CI): -0.2 (-1.7, 1.3) vs. -2.7 (-4.7, -0.7) 12 months: 56.4 (6.9) vs. 57.1 (6.7); p=NS; Mean change from baseline (95% CI): 0.4 (-1.4, 2.2) vs. -1.4 (-3.0, 0.1) Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Peterson, 1990 ⁵⁰ RCT Medium	IgG vs. placebo Adverse Events: 20% overall Headaches: 93% vs. 60%; p=0.03 Withdrawals due to adverse event: 2 (1 in each group) Serious Adverse Events: 2 IgG and 3 placebo	Baxter Healthcare Corporation.
Pinxsterhuis, 2017 ⁵¹ RCT Medium	Self-management vs. control Adverse Events: NR Withdrawals due to adverse event: 1 vs. 1 lost due to ill health after starting allocated treatment 1 vs. 1 lost due to ill-health Serious Adverse Events: NR	The Norwegian Foundation for Health and Rehabilitation and The National Advisory Unit for CFS/ME

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Powell, 2001 ⁵² Bentall, 2002 ⁵³ Powell, 2004 ⁵⁴ RCT Medium	United Kingdom Single center Study year(s) NR Outpatient clinic	Oxford (Sharpe, 1991) criteria Inclusion: Referred to a chronic fatigue or infectious diseases clinic; aged 15 to 55 years; CFS diagnosis using Oxford criteria confirmed; scoring <25 on the physical functioning subscale of the SF-36. Exclusion: Undergoing further investigations or taking other treatments, including antidepressants (unless the same dose had been taken for ≥3 months without improvement); psychotic illness; somatization disorder; eating disorder; history of substance misuse; confinement to a wheelchair or bed.	Graded Exercise (Minimum) (n=37): Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. Graded Exercise (Telephone) (n=39): Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. These were followed up by 7 planned 30-minute telephone contacts over 3 months. Graded Exercise (Maximum) (n=38): Medical assessment followed by 2 face-to-face evidence-based explanations of symptoms that encouraged graded activity. A graded exercise program was designed in collaboration with each patient and tailored to current functional abilities. The role of psychosocial factors was discussed. These were followed up by 7 1-hour face-to-face treatment sessions over 3 months. Standard medical care (Control) (n=34): Standard medical care: a medical assessment, advice, and a booklet that encouraged graded activity and positive thinking, but gave no explanation for the symptoms. These patients were offered the intervention at 1 year, and 30 completed the intervention. Duration of treatment: Up to 3 months Duration of followup: 1 year (Powell 2001), 2 years for treatment groups, but one year after treatment for original control group (Powell 2004)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Powell, 2001 ⁵² Bentall, 2002 ⁵³ Powell, 2004 ⁵⁴ RCT Medium	Minimum vs. telephone vs. maximum vs. control Mean age: 34 vs. 32 vs. 33 vs. 34 % Female: 76% (28/37) vs. 85% (33/39) vs. 82% (31/38) vs. 71% (24/34) Race: NR Mean duration of illness: 51.2 vs. 51.5 vs. 55.0 vs 48.6 months Severity of symptoms: Mean SF-36 physical functioning (95% CI): 16.0 (15.0 to 17.0) vs. 15.8 (14.6 to 17.0) vs. 16.0 (14.8 to 17.0) vs. 16.3 (12.2 to 17.5) Fatigue scale (range 0 to 11, with higher scores indicating worse fatigue), mean scores (95% CI): 19.4 (10.0 to 10.7) vs. 9.9 99.2 to 10.6) vs. 10.2 (9.9 to 10.6) vs. 10.6 (10.4 to 10.9) Comorbidities: NR	Enrolled: 148 Analyzed: 148 Powell 2004 analyzed: 144	Powell 2001 14% dropped out (21/148), 19 were in intervention groups 2 participants did not complete the questionnaire at 3 months and 1 did not complete the questionnaire at 1 year, but last obtained values were carried forward Powell 2004 5 more lost at 2 years: 2 lost to followup, 2 developed other medical conditions, 1 died by suicide.

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Powell, 2001 ⁵² Bentall, 2002 ⁵³ Powell, 2004 ⁵⁴ RCT Medium	<p>Minimum vs. telephone vs. maximum vs. control</p> <p>Overall Function: <i>Mean (95% CI) SF-36 physical functioning (score range 10 to 30, where 30 is best physical functioning):</i></p> <p>3 months: 22.8 (21.1 to 24.4) vs. 22.3 (20.6 to 24.0) vs. 22.8 (21.2 to 24.3) vs. 16.3 (14.9 to 17.7)</p> <p>6 months: 24.0 (22.4 to 25.6) vs. 23.0 (21.2 to 24.7) vs. 24.1 (22.6 to 25.6) vs. 17.2 (15.6 to 18.7)</p> <p>1 year: 24.1 (23.3 to 26.8) vs. 24.3 (22.5 to 26.0) vs. 24.9 (23.4 to 26.4) vs. 16.9 (15.4 to 18.4), p<0.001 (initial scores and depression scores used as covariates)</p> <p>2 year (Powell 2004) Mean score, (SD): 24.11 (5.94) vs. 23.64 (6.39) vs. 25.45 (4.72) vs. 22.47 (7.02)</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (95% CI) Fatigue scale (score range 0 to 11 with higher scores indicating worse fatigue):</i></p> <p>3 months: 5.0 (3.4 to 6.6) vs. 3.7 (2.3 to 5.2) vs. 4.3 (2.9 to 5.8) vs. 10.4 (10.1 to 10.8)</p> <p>6 months: 3.8 (2.5 to 5.2) vs. 4.0 (2.5 to 5.5) vs. 3.4 (2.2 to 4.6) vs. 9.9 (9.1 to 10.8)</p> <p>1 year: 3.2 (1.8 to 4.7) vs. 3.5 (2.1 to 4.9) vs. 3.1 (1.8 to 4.4) vs. 10.1 (9.3 to 10.8), p<0.001 (initial scores and depression scores used as covariates)</p> <p>2 year (Powell 2004) Mean score, (SD): 4.46 (4.78) vs. 3.59 (4.69) vs. 2.84 (3.67) vs. 6.07 (4.60)</p> <p>Outcomes related to associated symptoms:</p> <p>Depression: <i>Mean hospital anxiety and depression scale depression score (95% CI) (score range to 21 with higher scores indicating worse depression)</i></p> <p>3 months: 6.1 (4.7 to 7.4) vs. 5.9 (4.5 to 7.3) vs. 5.8 (4.8 to 6.9) vs. 11.2 (9.6 to 12.9)</p> <p>6 months: 5.4 (3.9 to 6.9) vs. 5.6 (4.3 to 6.9) vs. 5.0 (3.8 to 6.2) vs. 11.0 (9.2 to 12.9)</p> <p>12 months: 4.2 (3.0 to 5.5) vs. 4.6 (3.2 to 6.0) vs. 4.2 (2.9 to 5.5) vs. 10.1 (8.4 to 11.7), p<0.001 (initial scores used as a covariate)</p> <p>2 year (Powell 2004) Mean score, (SD): 5.11 (5.12) vs. 4.77 (4.67) vs. 4.08 (4.33) vs. 8.37 (5.75)</p> <p>Anxiety: <i>Mean hospital anxiety and depression scale anxiety score (95% CI) (score range to 21 with higher scores indicating worse anxiety)</i></p> <p>3 months: 9.2 (7.3 to 10.7) vs. 7.7 (6.1 to 9.2) vs. 8.7 (7.2 to 10.1) vs. 11.4 (9.8 to 13.1)</p> <p>6 months: 8.7 (7.1 to 10.2) vs. 7.5 (6.0 to 9.0) vs. 7.7 (6.2 to 9.2) vs. 10.6 (8.8 to 12.4)</p> <p>12 months: 7.1 (5.8 to 8.5) vs. 6.5 (5.1 to 7.9) vs. 7.7 (6.1 to 9.3), p<0.01 (initial scores and depression scores used as covariates)</p> <p>2 year (Powell 2004) Mean score, (SD): 7.65 (4.78) vs. 7.03 (5.07) vs. 7.13 (4.47) vs. 9.17 (4.80)</p> <p>Sleep problem questionnaire: <i>Mean score (95% CI) (score range 0 to 20 with higher scores indicating worse sleep problems):</i></p> <p>3 months: 9.0 (7.4 to 10.5) vs. 10.1 (8.2 to 11.9) vs. 8.7 (7.2 to 10.3) vs. 11.6 (9.8 to 13.5)</p> <p>6 months: 7.4 (5.7 to 9.1) vs. 9.1 (7.2 to 11.0) vs. 8.2 (6.6 to 9.9) vs. 12.1 (10.1 to 14.1)</p> <p>12 months: 6.7 (5.0 to 8.4) vs. 8.6 (6.8 to 10.3) vs. 7.1 (5.6 to 10.3) vs. 11.5 (9.7 to 13.4), p<0.001 (initial scores and depression scores used as covariates)</p> <p>2 year (Powell 2004) Mean score, (SD): 7.62 (5.30) vs. 8.15 (5.59) vs. 7.92 (5.50) vs. 10.07 (6.06)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Powell, 2001 ⁵² Bentall, 2002 ⁵³ Powell, 2004 ⁵⁴ RCT Medium	Minimum vs. telephone vs. maximum vs. control Adverse Events: NR Withdrawals due to AE: 1 dropped out due to dissatisfaction with treatment Serious Adverse Events: NR	Linbury Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Rimes, 2013 ⁵⁵ Pilot RCT High	United Kingdom Single center Study year(s) NR, recruitment process was conducted on 2 separate occasions, 1 year apart Tertiary care facility	CDC (Fukuda, 1994) or Oxford (Sharpe, 1991) criteria Inclusion: Adults with CFS who had completed CBT in the previous year at a National Health Service CFS Unit and who had been diagnosed as still having CFS according to CDC or Oxford criteria. Exclusion: Therapist determined interpersonal difficulties which would make group participation unsuitable for patient or other participants, current major depression, not interested, not able to attend regularly.	MBCT (n=18): Introductory session of mindfulness-based cognitive therapy, followed by 8 weekly sessions, lasting 2.25 hours. Conducted in 2 groups, the first had 11 participants and the second had 7 participants. Mindfulness meditation practices also undertaken at home using compact discs. Each class included group discussion including problem solving and awareness. Participants were also offered a 2 month followup mindfulness course. Control (n=19): Wait list group was informed that their MBCT intervention would begin in 4 months. Duration of treatment: 8 weeks Duration of followup: 2 months after end of 8 week treatment
Roerink, 2017 ⁵⁶ RCT Low	The Netherlands Single center 2014 to 2016 Specialty clinic	CDC (Fukuda, 1994) criteria Inclusion: Women aged 18 to 59 years with CFS and severe fatigue leading to functional impairment (CIS-fatigue ≥ 40 and SIP ≥ 700). Exclusion: Use of medication (except oral contraceptives and acetaminophen), use of psychotropic medication in the past month, psychiatric comorbidity (major depression, psychosis, eating disorders, anxiety disorders, bipolar disease, and posttraumatic stress disorder), evident somatic comorbidity that explains fatigue, fatigue lasting >10 years without recent progression, substance abuse within the past 3 months, current engagement in legal procedure with respect to disability claims	Anakinra (n=25): 100 mg subcutaneously daily for 28 days Placebo (n=25): subcutaneously daily for 28 days Duration of treatment: 4 weeks Duration of followup: 20 weeks after treatment ended

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Rimes, 2013 ⁵⁵ Pilot RCT High	MBCT vs. control Mean age: 41.4 vs. 45.2 % Female: 25 (4/16) vs. 11 (2/19) % White UK: 94 (15/16) vs. 63 (12/19) % Other white: 6 (1/16) vs. 26 (5/19) % Black African: 0 vs. 5 (1/19) % Other (not specified): 0 vs. 5 (1/19) Duration of illness: Mean (SD): 8.5 (4.4) vs. 6.1 (4.8) years Severity of symptoms: NR Comorbidities: NR	Randomized: 37 Analyzed: 35 (16 MBCT, 19 control)	MBCT vs. control 5% (2/37) overall Did not receive treatment: 1/18 vs. 0/19 Discontinued treatment after 1 session: 1/18 vs. 0/19
Roerink, 2017 ⁵⁶ RCT Low	Anakinra vs. placebo Mean age: 30 vs. 32 100% female Race: NR Duration of illness: Median (range): 44 (7 to 109) vs. 38 (9 to 108) months Severity of symptoms: Mean fatigue severity <i>CIS-fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue)</i> : 52 vs. 51 Mean functional impairment <i>SIP (ranges from 0 to 5799, higher scores indicate worse health)</i> : 1647 vs. 1706 Comorbidities: NR	Number enrolled: 50 Number analyzed: 50	0% (0/50)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Rimes, 2013 ⁵⁵ Pilot RCT High	<p>Benefits</p> <p>MBCT vs. control</p> <p>Overall Function: 2 months Mean Physical Functioning PF-10, higher scores indicate better functioning (SD): 65.6 (26.3) vs. 55.9 (23.3) 2 months Mean Work and Social Adjustment Scale, 0 to 40 scale with lower scores indicating better health (SD): 20.0 (10.4) vs. 25.8 (6.7) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: 2 months Mean Modified Chalder Fatigue Scale, 0 to 33 with lower scores indicating better health (SD): 21.3 (6.2) vs. 25.0 (6.1) Outcomes related to associated symptoms: NR HADS-Depression, mean (SD): 2 month follow up: 5.6 (2.9) vs. 7.7 (4.6); p=0.153</p>
Roerink, 2017 ⁵⁶ RCT Low	<p>Anakinra vs. placebo</p> <p>Overall Function: <i>SF-36 physical functioning (0 to 100, higher scores indicate better functioning)</i>: 4 weeks: 58.2 vs. 61.2, p=0.53 24 weeks: 60.8 vs. 64.8, p=0.47 <i>SIP (ranges from 0 to 5799, higher scores indicate worse health)</i>: 4 weeks: 1472.2 vs. 1353.7, p=0.47 24 weeks: 1351.5 vs. 1260.4, p=0.62 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>CIS-fatigue score (ranges from 8 to 56, higher scores indicate worse fatigue)</i>: 4 weeks: 46.7 vs. 45.1, p=0.59 24 weeks: 45.3 vs. 44.0, p=0.69 Outcomes related to associated symptoms: Pain: 4 weeks: 7.4 (6.5 to 8.3) vs. 6.3 (5.4 to 7.2), p=0.104 24 weeks: 6.9 (5.9 to 7.9) vs. 6.6 (5.6 to 7.6), p=0.63 Symptom Checklist-90: 4 weeks: 144.4 (136.6 to 152.2) vs. 139.9 (132.1 to 147.7), p=0.42 24 weeks: 143.5 (135.3 to 151.7) vs. 140.5 (132.3 to 148.7), p=0.63</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Rimes, 2013 ⁵⁵ Pilot RCT High	MBCT vs. control Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: None reported	UK Department of Health via National Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley NHS Foundation Trust and the Institute of Psychiatry
Roerink, 2017 ⁵⁶ RCT Low	Anakinra vs. placebo Adverse Events: 24 vs. 14 Injection site reaction: 17 vs. 1 Infection: 6 vs. 4 Withdrawals due to adverse event: 1 vs. 0 1 from Anakinra group discontinued treatment due to a skin infection Serious Adverse Events: None	Interleukin Foundation and an independent anonymous donor

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Rowe, 1997 ⁵⁷ RCT Medium	Australia Single center Study year(s) NR Children's hospital clinic	CDC (Fukuda, 1994) criteria Inclusion: Adolescents 11 to 18 years old meeting Fukuda criteria Exclusion: Receiving steroid medication, non-steroidal anti-inflammatory drugs, immunomodulatory agents, or had received IV immunoglobulin at any point; psychological or family issues salient in presenting symptomatology; improving at such a rate that they would be functioning by the end of the trial	Intragram (n=36): 3 once monthly IV infusions of 1 gm/kg (maximum 1 liter of 6 gm/100 mL) gammaglobulin in 10% weight by volume maltose solution Rowe 1999 also included 19 participants who all received study drug in pilot studies. Placebo (n=35): 3 once monthly IV infusions of 10% weight by volume maltose with 1% albumin solution, volume administered was calculated by patient weight For both groups, frusemide (40 mg orally) was given with infusions greater than 500 mL. Both groups received information about available services such as a visiting teacher service, distance education, social security support, and support groups. Duration of treatment: 3 months Duration of followup: 6 months after final infusion
See, 1996 ⁵⁸ Double-blind crossover study High	United States Single center Study year(s) NR	CDC (Holmes, 1988) criteria Inclusion: Referral by an internist or school of medicine faculty and fulfilling CDC diagnostic criteria Exclusion: Received immunologic therapy in the past year, diagnosis of a chronic infection, immunologic disorder, multiple sclerosis, thyroid disease, IgG deficiency or primary psychiatric illness	Alfa-2a Interferon (n=15): 3 million units subcutaneously 3 times per week after drinking 16 ounces of water. 650mg of acetaminophen was taken 2 hours following the dose. Placebo (n=15): 0.9% sodium chloride solution administered on the same schedule in the same way, with the same dose of acetaminophen. Duration of treatment: 12 weeks Duration of followup: End of treatment (post-crossover data NR here)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Rowe, 1997 ⁵⁷ RCT Medium	Intragran vs. placebo Mean age: 15.3 vs. 15.6 years % Female: 58 (21/36) vs. 80 (28/35) Race: NR Mean duration of illness: 19.5 vs. 16.9 months Severity of symptoms: <i>Percentage functional score, calculated based on attendance at school or work, proportion of school or work attempted, proportion of normal physical activities attempted and proportion of normal social activities attempted, checked against records from parents and schools when possible</i> : 23.9 vs. 25.9 Comorbidities: NR	Number enrolled: 71 Number analyzed: 70	1% (1/71) for 6-month outcomes 1 placebo group
See, 1996 ⁵⁸ Double- blind crossover study High	Overall Mean age: 37.2 years % Female: 80 (24/30) Race: NR Mean duration of illness: 4.6 years (range 1 to 12) Severity of symptoms: NR Comorbidities: NR	Number enrolled: 30 Number analyzed: 26	None

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Rowe, 1997 ⁵⁷ RCT Medium	<p>Intragram vs. placebo</p> <p>Overall Function: Returned to full function at 6 months, %: 25 (9/36) vs. 11 (4/34), p<0.04 Not improved (<25% mean functional improvement from baseline) at 3 months, %: 47.2 (17/36) vs. 68.6 (24/35) Improved (>25% mean functional improvement from baseline) at 3 months, %: 52 (19/36) vs. 31 (11/35) Not improved (<25% mean functional improvement from baseline) at 6 months, %: 27.8 (10/36) vs. 55.9 (19/34) Improved (>25% mean functional improvement from baseline) at 6 months, %: 72.2 (26/36) vs. 44.1 (15/34) Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR</p>
See, 1996 ⁵⁸ Double- blind crossover study High	<p>Alfa-2a Interferon (n=26) vs. placebo (n=13)</p> <p>Overall Function: NR Quality of Life: Mean QOL score: difference between groups=NS Work/School Days: NR Proportion full/part-time work: NR Fatigue: NR Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Rowe, 1997 ⁵⁷ RCT Medium	<p>Intragram vs. placebo</p> <p>Adverse Events: Severe headache following first infusion, %: 64 vs. 20, p<0.01 Significant differences between % of infusions in each group experiencing a ≥3 day headache after the first infusion, a ≥3 day fatigue or weakness after the second and third infusions, and a ≥3 day nausea after the third infusion Count of all: 145 vs. 98 Withdrawals due to adverse event: Serious Adverse Events: NR</p>	<p>Study drug and placebo provided by The Commonwealth Serum Laboratories Research supported by MR Society (Victoria) and The Commonwealth Serum Laboratories Research</p>
See, 1996 ⁵⁸ Double-blind crossover study High	<p>Alfa-2a Interferon vs. placebo</p> <p>Adverse Events: Flu-like symptoms: 4, all in interferon group at the time Diarrhea: 2, all in interferon group at the time Withdrawals due to adverse event: 4 (2 for neutropenia, 1 for palpitations, 1 for worsened fatigue), all in interferon group at the time Serious Adverse Events: None reported</p> <p>It is not clear which of these events occurred pre- or post- crossover.</p>	<p>NR Study drug obtained from Roche Pharmaceuticals</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sharpe 2015 ⁵⁹ pre-specified long-term followup of PACE trial	United Kingdom 2008 to 2011 By mail, with nonresponders reminded by telephone	<p>Included: PACE trial participants who hadn't withdrawn from data collection or long-term followup.</p> <p>Excluded: Contact details not available.</p>	<p>31 median (range 24 to 53) month time from randomization to return of survey.</p> <p>After completing final trial outcome assessment 1 year after randomization, trial participants were offered an additional PACE therapy if they were still unwell, they wanted more treatment, and their PACE doctor agreed this was appropriate. The choice of treatment offered (APT, CBT or GET) was made by the patient's doctor, taking into account the patient's preference and their own opinion of which would be most beneficial. These choices were made with knowledge of the individual patient's treatment allocation, but before the overall trial findings were known.</p> <p>Patients were free to choose additional or different therapies from original assignments 1 year after randomization, and 44% (210/479) received at least 1 additional treatment session.</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sharpe 2015 ⁵⁹ pre-specified long-term followup of PACE trial	<p>Nature and amount of any additional PACE therapies that participants had received for CFS since their 1 year outcome assessment:</p> <p>Overall; specialist medical care vs. APT vs. CBT vs. GET</p> <p>Participants who received any additional sessions, n=479 (2 participants provided incomplete data; 1 in CBT group had additional GET and 1 in APT group had additional APT), %: 44 (210/479); 63 (73/115) vs. 50 (60/119) vs. 31 (36/118) vs. 32 (41/127), p<0.0001</p> <p>Median number of additional sessions received (IQR): 0 (0 to 8); 6 (0 to 12) vs. 1 (0 to 8) vs. 0 (0 to 3) vs. 0 (0 to 6), p<0.0001</p> <p>Participants who received an adequate number of (≥10) sessions of an additional therapy after 12 month trial, %:</p> <p>Received APT: 3 (15/479); 5 (6/115) vs. 0 (0/119) vs. 2 (2/118) vs. 6 (7/127), p=0.016</p> <p>Received CBT: 14 (65/479); 20 (23/115) vs. 17 (20/119) vs. 2 (2/118) vs. 16 (20/127), p<0.0001</p> <p>Received GET: 5 (26/479); 12 (14/115) vs. 6 (7/119) vs. 4 (5/118) vs. 0 (0/127), p=0.0001</p>	<p>Surveys sent to all 604 participants of the PACE trial, 481 (75% of full cohort and 80% of eligible participants) returned questionnaires:</p> <p>115 originally assigned to specialist medical care alone</p> <p>120 originally assigned to APT</p> <p>119 originally assigned to CBT</p> <p>127 originally assigned to GET</p> <p>Proportion of participants who returned questionnaires did not differ between treatment groups, p=0.37</p>	<p>122 questionnaires not returned, and 1 patient withdrew consent</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Sharpe 2015 ⁵⁹ pre-specified long-term followup of PACE trial	<p>Original assignments: Specialist medical care vs. specialist medical care with APT vs. CBT vs. GET</p> <p>Overall Function: <i>SF-36 physical functioning subscale (higher scores indicate better functioning)</i>, mean score (SD): 57.4 (27.9) vs. 52.8 (30.2) vs. 62.2 (27.2) vs. 59.8 (27.6), mean difference between 52 weeks and long-term followup (95% CI): 7.1 (4.0 to 10.3), p<0.0001 vs. 8.5 (4.5 to 12.5), p<0.0001 vs. 3.3 (0.02 to 6.7), p=0.049 vs. 0.5 (-2.7 to 3.6), p=0.78</p> <p>Compared with specialist medical care, mean (95% CI): APT: -3.6 (-9.6 to 2.4), p=0.24 vs. CBT 2.8 (-3.2 to 8.8), p=0.36 vs. GET 2.0 (-4.0 to 7.9, p=0.51; Compared with APT, mean (95% CI): CBT 6.4 (0.4 to 12.4, p=0.035 vs. 5.6 (-0.3 to 11.5), p=0.064</p> <p>Self-rated impairment of daily activities: <i>Participant-rated work and social adjustment scale (range 0 to 40, with lower scores indicating less impairment)</i> mean (SD): 21.1 (11.5) vs. 22.9 (11.7) vs. 19.7 (10.2) vs. 19.4 (10.8); Compared with specialist medical care, mean difference (95% CI): APT 1.3 (-1.2 to 3.7), p=0.30 vs. CBT -1.1 (-3.6 to 1.4), p=0.38 vs. GET -0.8 (-3.2 to 1.6), p=0.51; Compared with APT, mean difference (95% CI): CBT -2.4 (-4.85 to 0.1), p=0.06 vs. GET -2.1 (-4.5 to 0.3), p=0.09</p> <p>Quality of Life: Perceived change in overall health since trial enrollment: <i>Participant-rated clinical global impression of change score</i>: Positive change %: 42 (48/115) vs. 38 (45/118) vs. 42 (50/119) vs. 48 (61/127); Compared with specialized medical care, OR (95% CI): APT 0.8 (0.4 to 1.3), p=0.32 vs. CBT 0.9 (0.5 to 1.5), p=0.62 vs. GET 1.1 (0.6 to 1.8), p=0.85; Compared with APT, OR (95% CI): CBT 1.2 (0.7 to 2.0), p=0.59 vs. 1.4 (0.8 to 2.3), p=0.22</p> <p>Minimum change %: 50 (58/115) vs. 38 (45/118) vs. 48 (57/119) vs. 47 (59/127)</p> <p>Negative change %: 8 (9/115) vs. 12 (14/118) vs. 10 (12/119) vs. 6 (7/127); Compared with specialized medical care, OR (95% CI): APT 1.8 (0.7 to 4.5), p=0.23 vs. CBT 1.6 (0.6 to 4.3), p=0.37 vs. GET 0.8 (0.3 to 2.2), p=0.67; Compared with APT, OR (95% CI): CBT 0.9 (0.4 to 2.2), p=0.81 vs. GET 0.5 (0.2 to 1.1), p=0.09</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Chalder Fatigue Questionnaire (lower scores indicate better health)</i>, mean score (SD): 20.2 (8.6) vs. 20.5 (8.4) vs. 18.4 (8.5) vs. 19.1 (7.8), mean difference between 52 weeks and long-term followup (95% CI): -3.9 (-5.3 to -2.6), p<0.0001 vs. -3.0 (-4.4 to -1.6), p<0.0001 vs. -2.2 (-3.7 to -0.6), p=0.006 vs. -1.3 (-2.7 to -0.1), p=0.059</p> <p>Compared with specialist medical care, mean (95% CI): APT 0.3 (-1.7 to 2.3), p=0.78 vs. CBT -1.4 (-3.4 to 0.7), p=0.19 vs. GET -0.8 (-2.8 to 1.2), p=0.43; Compared with APT, mean (95% CI): CBT -1.6 (-3.6 to 0.3), p=0.11 vs. GET -1.1 (-3.0 to 0.9), p=0.28</p> <p>Outcomes related to associated symptoms: NR</p> <p>No adjustment/penalty due to multiple analyses, so significant p-values are likely to be chance findings.</p> <p>Findings were similar in sensitivity analysis, which controlled for varying duration of followup, data NR.</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sharpe 2015 ⁵⁹ pre- specified long-term followup of PACE trial	No significant worsening in perceived health occurred during the followup period after any of the trial treatments.	United Kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions, National Institute for Health and Research, National Institute for Health and Research Biomedical Research Centre for Mental Health at South London, Maudsley National Health Services Foundation Trust, King's College London

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sharpe, 1996 ⁶⁰ Block randomized RCT Medium	United Kingdom 2 centers Study years NR Hospitals, specific settings NR	Oxford (Sharpe 1991) criteria Inclusion: Ages 18 to 60 years, with major complaint of fatigue and symptoms unexplained by organic disease. 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 (n=30): 16 1-hour sessions of individual CBT over 4 months emphasizing cognitive techniques questioning a simple disease explanation chronic fatigue syndrome and considering the role of psychological and social factors. It included strategies to reduce excessive perfectionism and self criticism, and an active problem solving approach to interpersonal and occupational difficulties was also employed. Patients were invited to evaluate the effect of gradual and consistent increases in activity and to try strategies other than avoidance. Control (n=30): Patients were followed by their General Practitioner in their usual way. Duration of treatment: 4 months Duration of followup: 12 months after entry into study
Strayer, 1994 ⁶¹ RCT Medium	United States 4 centers Study years NR Specialty clinics	CDC (Holmes,1988) criteria Inclusion: CFS diagnosed ≥12 months before study; severe debilitation (Karnofsky Performance Score 20 to 60). Exclusion: Diagnostic workup, brain MRI, and CSF analyses were performed to exclude other disorders.	Rintatolimod (n=45): IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks Placebo (n=47): IV saline twice weekly for 6 months Duration of treatment: 6 months (24 weeks) Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sharpe, 1996 ⁶⁰ Block randomized RCT Medium	<p>CBT vs. control</p> <p>Mean age (SD): 34 (9.1) vs. 38 (11.8) years</p> <p>% Female: 60 (18/30) vs. 77 (23/30)</p> <p>Race: NR</p> <p>Duration of illness: Mean (SD): 33.6 (9.1) vs. 29.7 (24.1) months</p> <p>Severity of symptoms: Mean disability on Karnofsky scale (SD): 71 (3.3) vs. 72 (3.4)</p> <p>Number of days in bed each week (SD): 3.3 vs. 1.6 (1.5)</p> <p>Fatigue severity (patient rated on a 1-10 scale): 7.8 (1.5) vs. 7.9 (1.9)</p> <p>% Not working or studying: 87 (26/30) vs. 50 (15/30)</p> <p>Comorbidities: % Major depressive disorder: 20 (6/30) vs. 20 (6/30)</p> <p>% Any depressive disorder: 53 (16/30) vs. 57 (17/30)</p> <p>% Any anxiety disorder: 47 (14/30) vs. 50 (15/30)</p> <p>% Any anxiety or depression disorder: 67 (20/30) vs. 67 (20/30)</p> <p>% Somatization disorder: 10 (3/30) vs. 10 (3/30)</p>	<p>Number approached: NR</p> <p>Number screened: 123</p> <p>Number eligible: 62</p> <p>Number enrolled: 60 (30 CBT, 30 control)</p> <p>Number analyzed: 60 (30 CBT, 30 control)</p>	<p>1/60 did not complete 12 month followup</p>
Strayer, 1994 ⁶¹ RCT Medium	<p>Rintatolimod vs. placebo</p> <p>Mean age: NR, groups "well matched"</p> <p>% Female: 64 (29/45) vs. 85 (40/47); p=0.003</p> <p>Race: NR</p> <p>Duration of illness: Mean: 6.1 vs. 4.4 years</p> <p>Severity of symptoms: <i>Karnofsky Performance Score (100 to 0, 0 is most severe)</i> mean: 51 to 50; p=0.64</p> <p>Comorbidities: Prior Depression %: 24 (11/45) vs. 23 (11/47); p=0.91</p> <p>MRI abnormality % (n=89): 38 vs. 43 (n by group NR); p=0.60</p> <p>HHV-6-infected giant cells % (n=39): 68 vs. 71 (n by group NR); p=0.82</p>	<p>Number enrolled: 92</p> <p>Number analyzed: 76 to 84 varies by outcome</p>	<p>9% (8/92)</p> <p>4 from each group</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Sharpe, 1996 ⁶⁰ Block randomized RCT Medium	<p>CBT vs. control</p> <p>Overall Function: <i>Achieved KPS score of ≥80</i></p> <p>5 months: 27% (8/30) vs. 20% (6/30); difference of 7 (95% CI, -15 to 28)</p> <p>8 months: 53% (16/30) vs. 30% (9/30); difference of 23 (95% CI, 0 to 48)</p> <p>12 months: 73% (22/30) vs. 27% (8/30); difference of 47 (95% CI, 24 to 69); p<0.001</p> <p><i>Improvement of ≥10 points on KPS</i></p> <p>5 months: 23% (7/30) vs. 7% (2/30); difference of 17 (95% CI, 0 to 34)</p> <p>8 months: 60% (18/30) vs. 20% (6/30); difference of 40 (95% CI, 17 to 63)</p> <p>12 months: 73% (22/30) vs. 23% (7/30); difference of 50 (95% CI, 28 to 72); p<0.001</p> <p>Quality of Life: NR</p> <p>Work/School Days: Improvement in work status at 12 months, %: 63 (19/30) vs. 20 (6/30)</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Fatigue severity (0 to 10), mean: 12 months: 4.3 vs. 6.3</p> <p>Change from baseline, -3.5 vs. -1.6; difference 1.9, 95% CI 0.5 to 3.3</p> <p>Outcomes related to associated symptoms: HADS-Depression: 12 months: 3.6 vs. 5.8</p> <p>Change from baseline: -3.1 vs. -1.0; difference 2.0, 95% CI 0.0 to 4.1</p> <p>Control group outcomes: One patient was referred to behavioral psychotherapy and was prescribed full-dose antidepressants, one patient was diagnosed as suffering from celiac disease and began a gluten free diet, two were referred to psychiatry services and received supportive psychotherapy.</p>
Strayer, 1994 ⁶¹ RCT Medium	<p>Rintatolimod vs. placebo</p> <p>Overall Function: % change in <i>KPS score from baseline (0-100 scale, higher scores indicate better health)</i></p> <p>+20 vs. 0; p=0.023</p> <p>% change in <i>Activities of Daily Living score from baseline (0-100 scale, higher scores indicate better health)</i></p> <p>+23.1 vs. 14.1; p=0.034</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Exercise duration</i></p> <p>% change from baseline: +10.3 vs. +2.1; p=0.007</p> <p><i>Exercise work</i></p> <p>% change from baseline: +11.8 vs. +5.8; p=0.011</p> <p>Outcomes related to associated symptoms:</p> <p>SCL-90-R changes were similar between groups (scoring NR)</p> <p>Decreased used of medications for relief of CFS symptoms declined for rintatolimod but not compared with placebo; p<0.05</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sharpe, 1996 ⁶⁰ Block randomized RCT Medium	CBT vs. control Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Wellcome Trust
Strayer, 1994 ⁶¹ RCT Medium	Rintatolimod vs. placebo Adverse Events: 706 vs. 711 events; $p > 0.90$ Insomnia more frequent among placebo and dry skin among rintatolimod; $p < 0.05$ Withdrawals due to adverse event: None Serious Adverse Events: None	HEM Pharmaceuticals Corporation

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Strayer, 2012 ⁶² Crossover RCT Medium	United States 12 centers 1998 to 2004 Specialty clinics	<p>CDC (Holmes,1988) and (Fukuda, 1994) criteria</p> <p>Inclusion: Adults 18 to 60 years of age with diagnosis of CFS \geq 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.</p> <p>Exclusion: 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, ability to exercise >18 minutes during baseline exercise tolerance tests, history of alcohol or substance abuse within 2 years before the onset of CFS or anytime afterward, history of suicidal ideation, past or current diagnosis of major depressive disorder, schizophrenia, bipolar affective disorder, delusional disorders, dementia, or eating disorder.</p>	<p>Rintatolimod (n=117): IV rintatolimod 200 mg twice weekly for 2 weeks, followed by 400 mg twice weekly for 40 weeks</p> <p>Placebo (n=117): Placebo IV saline solution twice weekly for 42 weeks <i>Block randomization by treadmill duration (\leq 9 minutes vs. >9 minutes)</i></p> <p>Duration of treatment: 42 weeks</p> <p>Duration of followup: End of treatment</p>
Stubhaug, 2008 ⁶³ Medium	Norway Single center 2001 Specialty clinic	<p>Diagnostic criteria: 65/72 (90%) patients met Oxford, 29/72 (40%) patients met Fukuda criteria</p> <p>Included: Chronic fatigue complaints, ICD-10 code F48.0 for neurasthenia Allowed mild depressive or anxiety symptoms independent or secondary to fatigue symptoms</p>	<p>Mirtazapine first 12 weeks (n=28) plus comprehensive CBT after 12 weeks (n=22)</p> <p>Placebo first 12 weeks (n=24) plus comprehensive CBT after 12 weeks (n=24)</p> <p>Comprehensive CBT first 12 weeks (n=23, same individuals in C and D), mirtazapine only second 12 weeks (n=11)</p> <p>Comprehensive CBT first 12 weeks (n=23, same individuals in C and D), placebo only second 12 weeks (n=12)</p> <p>Duration of follow up: 24 weeks</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Strayer, 2012 ⁶² Crossover RCT Medium	Rintatolimod vs. placebo Mean age: 43 vs. 44 years % Female: 67 (79/117) vs. 78 (91/117) % white: 93 (109/117) vs. 92 (107/117) Duration of illness: Mean: 9.6 vs. 9.7 years Severity of symptoms: NR Comorbidities: NR	Number enrolled: 240 Number analyzed: 201	19.2% (46/240)
Stubhaug, 2008 ⁶³ Medium	Marzipatine vs. placebo vs. CBT/marzipatine vs. CBT/placebo Age, mean years: 45 vs. 45 vs. 47 vs. 51 % Female: 76 vs. 88 vs. 82 vs. 83 Race: not reported Duration of illness: not reported Severity of symptoms: Fatigue scale score (Chalder 0 to 33), mean: 24.76 vs. 25.54 vs. 24.91 vs. 24.33	Enrolled: 72 Analyzed: 72	All patients included in data analysis, using last observation carried forward

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Strayer, 2012 ⁶² Crossover RCT Medium	<p>Benefits</p> <p>Rintatolimod vs. placebo, results prior to crossover portion of the study</p> <p>Overall Function: KPS score, Activities of Daily Living scores, Vitality Score (SF-36), and General Health Perception (SF-36) measured with some significant differences pre and post, but not compared between rintatolimod and placebo groups</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Cardiopulmonary exercise tolerance (primary outcome)</i></p> <p>Increase from baseline: 36.5% vs. 15.2%; p=0.047</p> <p>Outcomes related to associated symptoms: Decreased used of medications for relief of CFS symptoms: 68% vs. 55%; p=0.048</p>
Stubhaug, 2008 ⁶³ Medium	<p>12- week follow up, mean (95% CI)</p> <p>Marzipatine vs. placebo vs. CBT/marzipatine+CBT/placebo:</p> <p>CGI score: 4.0 (3.7 to 4.3) vs. 4.4 (3.9 to 4.9) vs. 4.4 (3.9 to 4.9), A vs. C+D p=0.046, B vs. C+D, p=0.001</p> <p>Fatigue Scale score: 22.7 (21.4 to 24.1) vs. 23.7 (21.0 to 26.5) vs. 23.7 (21.0 to 26.5), A vs. C+D p=0.34, B vs. C+D, p=0.014</p> <p>HRSD (Hamilton Rating Scale for Depression): 12.6 (11.4 to 13.8) vs. 13.5 (10.9 to 16.1) vs. 13.5 (10.9 to 16.1), A vs. C+D , p=0.36, B vs. C+D, p=0.54</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Strayer, 2012 ⁶² Crossover RCT Medium	Rintatolimod vs. placebo Adverse Events: 99% rintatolimod and 97% placebo reported symptoms, flu-like syndrome, chills, vasodilatation, and dyspnea were more frequent in rintatolimod vs. placebo ($p < 0.05$) Withdrawals due to adverse event: 4 (2 in each group) Serious Adverse Events: 3 in each group with no differences between rintatolimod and placebo	Hemispherx Biopharma
Stubhaug, 2008 ⁶³ Medium	Mirtazapine vs. Placebo At least one adverse event: 100% vs. 45% Sedation: 56% vs. 11% Increased appetite: 31% vs. not reported Weight increase: 33% vs. 11% Restless leg syndrome: 19% vs. not reported Headache: not reported vs. 17% Insomnia: not reported vs. 11%	Organon AS provided unrestricted grant, medication, and placebo

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Stulemeijer, 2005 ⁶⁴ RCT Medium	The Netherlands Single center 1999 to 2002 Pediatric outpatient clinic in department of child psychology	CDC (Fukuda, 1994) criteria Inclusion: Aged 10 to 17.2 years, referred to clinic for complaint of fatigue and meeting CDC criteria for CFS. Exclusion: Psychiatric comorbidity.	CBT (n=36): 10 individual sessions of cognitive behavioral therapy administered by a child therapist. These patients agreed to undertake no further treatments or assessments during therapy. Therapy differed for physically active and physically passive patients; active patients were taught to reduce their levels of activity to respect their limitations, then build the activity level in a controlled way. Passive patients began activity building immediately, with no regard to reinforcing the patients' need to respect limitations. Both groups included active involvement from parents, and focused on the specific developmental tasks of adolescents. The goal was a return to full-time school. Control (n=35): Waiting list for therapy, with no limitations on other assessments or therapies. Duration of treatment: 5 months Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Stulemeijer, 2005 ⁶⁴ RCT Medium	CBT vs. control Mean age: 15.6 vs. 15.7 years % Female: 89 (31/35) vs. 91 (31/34) Race: NR Duration of illness: 16.0 vs. 18.0 months Severity of symptoms: Fatigue Severity (Checklist individual strength): 52.5 vs. 51.6 Comorbidities: NR	Number randomized: 71 Number analyzed: 69 (35 CBT, 34 control)	13% (9/71) overall CBT: 19% (6/36) Control: 8.6% (3/35)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Stulemeijer, 2005 ⁶⁴ RCT Medium	<p>Benefits</p> <p>CBT vs. control</p> <p>Overall Function: Mean (SD) <i>physical functioning subscale of the SF-36 (0 to 100 range with higher scores indicating better functioning)</i>: 69.4 (28.0) vs. 55.3 (21.1), treatment effect 14.5 (95% CI, 7.4 to 21.6), p=0.001</p> <p>Quality of Life: NR</p> <p>Work/School Days: Mean (SD) school attendance (number of hours attended divided by the number of hours that should have been attended) (2 participants were left out of the analysis because they'd completed final exams and weren't required to attend school for 5 months): 74.7 (37.8) vs. 66.7 (36.0), treatment effect 18.2 (95% CI, 0.8 to 35.5), p=0.040</p> <p>Proportion full/part-time work: NA</p> <p>Fatigue: Mean (SD) Fatigue severity subscale of the checklist of individual strength: 30.2 (16.8) vs. 44.0 (13.4), treatment effect 17.3 (95% CI, 6.2 to 28.4), p=0.003</p> <p>Outcomes related to associated symptoms: Mean patient-indicated symptom scores (SD):</p> <p>Unrefreshing sleep: 2.5 (1.1) vs. 3.2 (0.8), treatment effect -1.2 (-1.8 to -0.6), p=0.001</p> <p>Muscle pain: 2.4 (1.0) vs. 2.4 (0.8), treatment effect -1.1 (95% CI, -1.6 to -0.6), p=0.001</p> <p>Impaired concentration: 2.4 (1.2) vs. 2.7 (0.8), treatment effect -1.1 (95% CI, -1.5 to -0.65), p=0.001</p> <p>Tiredness after exercise: 2.5 (1.1) vs. 2.9 (0.3), treatment effect -1.0 (95% CI, -1.5 to -0.5), p=0.001</p> <p>Headache: 2.6 (0.9) vs. 2.5 (0.8), treatment effect -0.05 (95% CI, -0.9 to 0.0), p=0.033</p> <p>Impaired memory: 1.8 (1.1) vs. 2.4 (1.0), treatment effect -0.4 (95% CI, -0.93 to 0.1), p=0.12</p> <p>Multi-joint pain: 2.0 (1.2) vs. 2.3 (0.9), treatment effect -0.2 (95% CI, -0.7 to 0.3), p=0.38</p> <p>Sore throat: 1.6 (0.8) vs. 1.9 (0.7), treatment effect 0.2 (95% CI, -0.3 to -0.7), p=0.40</p> <p>Sensitive lymph nodes: 1.6 (0.9) vs. 1.5 (0.9), treatment effect 0.0 (95% CI, -0.4 to 0.6), p=0.72</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		
	Harms	Sponsor
Stulemeijer, 2005 ⁶⁴ RCT Medium	CBT vs. control Adverse Events: NR Withdrawals due to AE: NR Serious Adverse Events: NR	Foundation for Children's Welfare Stamps Netherlands and the ME Society

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sulheim 2014 ⁶⁵ Combined cross-sectional and RCT Medium	Norway Single center 2010 to 2012 Referral center recruiting nationwide from all 20 pediatric hospital departments in Norway, assessments made at one single research unit	CDC (Fukuda, 1994) criteria, only 75% met criteria Inclusion: Patients with CFS (3 months of unexplained, disabling, chronic/relapsing fatigue of new onset) aged 12 to 18 years. Exclusion: Psychiatric or medical disorder that might explain the fatigue, concurrent demanding life event.	Clonadine (n=60): Clonadine hydrochloride in lactose capsules (25µg or 50µg twice daily for body weight <35kg or >35kg respectively. A half-dose was given for the first 3 days and for the last week. Placebo (n=60): Empty lactose capsules twice daily Duration of treatment: 9 weeks Duration of followup: 30 weeks
Surawy, 2005 ⁶⁶ RCT High	United Kingdom Single center Study year(s) NR Hospital clinic	Oxford (Sharpe, 1991) criteria Inclusion: Patients with a diagnosis of CFS and meeting the Oxford criteria, following a thorough initial screening for infections and physical diseases who were assessed for suitability for CBT and placed on the waiting list, due to wait more than 3 months Exclusion: Did not have a primary diagnosis of CFS, unable to travel to the group, or had a diagnosis of major depression or schizophrenia	CBT (n=9): 8 weekly group sessions, given at the same time each week Control (n=9): Waiting list for therapy, including standard care that may have included visits to the general practitioner and alternative therapies such as homeopathy and acupuncture, but not CBT or mindfulness. Questionnaires were sent by mail to the control group. Duration of treatment: 8 weeks Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sulheim 2014 ⁶⁵ Combined cross-sectional and RCT Medium	Clonidine vs. placebo Mean age: 15.2 vs. 15.5 % Female: 78 (47/60) vs. 65 (39/60) Race: 98% Scandinavian overall Median duration of illness: 17.5 vs. 18 months Severity of symptoms: Mean Functional Disability Inventory: 24.0 vs. 23.1 Mean Chalder Fatigue Questionnaire 11-item (0 to 33): 19.1 vs. 19.2 Comorbidities: % Adhering to Fukuda criteria: 76 (45/60) vs. 74 (43/60)	Number enrolled: 120 Number analyzed at 30 weeks: Modified intention to treat analysis; 120	None
Surawy, 2005 ⁶⁶ RCT High	CBT vs. control Mean age: NR % Female: 44 (4/9) vs. 44 (4/9) Race: NR Duration of illness: NR Severity of symptoms: Mean (SD) <i>Chalder Fatigue Scale</i> (14-item, 0 to 42, with higher scores indicating worse fatigue): 21.25 (9.16) vs. 25.33 (6.24) Comorbidities: NR; major depression and schizophrenia excluded	Number randomized: 18 Number analyzed: 17 (9 CBT, 8 control)	5.6% (1/18) overall CBT: 0 Control: 11% (14/9)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Sulheim 2014 ⁶⁵ Combined cross- sectional and RCT Medium	<p>Clonidine vs. placebo</p> <p>Overall Function: Mean Functional Disability Inventory at 30 weeks: 17.5 vs. 16.8, difference 0.2, 95% CI: -13.3 o 13.6, p=0.98</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean Chalder Fatigue Questionnaire at 30 weeks: 11.1 vs. 13.5, difference 0.5, 95% CI: -14.7 to 15.7, p=0.95</p> <p>Outcomes related to associated symptoms:</p> <p>Pain (BPI):</p> <p>8 weeks: 17.9 vs. 16.4, p=0.24</p> <p>30 weeks: 11.1 vs. 13.5, p=0.95</p> <p>NS at week 8 and 10-week follow-up</p> <p>Sleep (KSQ Insomnia Score):</p> <p>8 weeks: 3.7 vs. 3.8, p=0.54</p> <p>30 weeks: 3.6 vs. 3.6, p=0.74NS at week 8 and 10-week follow-up</p>
Surawy, 2005 ⁶⁶ RCT High	<p>CBT vs. control</p> <p>Overall Function: Mean (SD) <i>physical function subscale of the SF-36 (0 to 100 range with higher scores indicating better functioning)</i>: 40.00 (16.78) vs. 35.50 (27.00), p=0.58</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean (SD) <i>Chalder Fatigue Scale (14-item, 0 to 42, with higher scores indicating worse fatigue)</i>: 18.56 (8.13) vs. 20.38 (8.26), p=0.08</p> <p>Outcomes related to associated symptoms: HADS Anxiety mean (SD): 8.22 (2.99) vs. 8.63 (4.57), p=0.01</p> <p>HADS Depression mean (SD): 8.33 (1.66) vs. 9.50 (3.96), p=0.28</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias		
	Harms	Sponsor
Sulheim 2014 ⁶⁵ Combined cross- sectional and RCT Medium	<p>Clonidine vs. placebo</p> <p>Adverse Events: Total: 75% (43/57) vs. 65% (33/51), p=0.223</p> <p>Dizziness when rising: 28% (16/57) vs. 10% (5/51), p=0.17 (although 23 adverse event analyses were performed)</p> <p>Withdrawals due to adverse event:</p> <p>Headache: 2 vs. 0</p> <p>Syncope: 1 vs. 0</p> <p>Suspected suicidality: 0 vs. 1</p> <p>Abdominal discomfort: 0 vs. 1</p> <p>Serious Adverse Events: NR</p>	<p>Health South-East Hospital Trust, University of Oslo, Oslo and Akershus University College of Applied Sciences, the Norwegian Competence Network of Paediatric Pharmacotherapy, Simon Fougner Hartmann's Family Foundation, Eckbo's Family Foundation</p>
Surawy, 2005 ⁶⁶ RCT High	<p>CBT vs. control</p> <p>Adverse Events: NR</p> <p>Withdrawals due to AE: NR</p> <p>Serious Adverse Events: NR</p>	<p>Linbury Trust</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Sutcliffe, 2010 ⁶⁷ Pilot RCT Medium	United Kingdom Number of centers NR Study year(s) NR Setting NR, exercises performed in home	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.	Orthostatic training (n=19): Daily training consisting of 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 (n=19): 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. Duration of treatment: 6 months Duration of followup: End of treatment
Taylor, 2004 ⁶⁸ RCT Medium	United States Single center Study year(s) NR Center for independent living	CDC (Fukuda, 1994) Inclusion: Adults with CFS by Fukuda criteria Exclusion: Psychiatric illness that would rule out CFS diagnosis, untreated hyperthyroidism	Counseling (n=23): 8 sessions of a group illness-management program using empowerment theory occurring every other week over 4 months. These sessions consisting of check-ins, reporting of self-monitored goal attainment, educational lecture and discussion of participant-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. After a post-group assessment that occurred during a 1 month break period, participants received 7 months of 1-on-1 peer counseling, which consisted of self-advocacy training, continued monitoring of goal attainment, and ongoing case coordination services. \$300 was also given to each participant after they supplied statements of how their planned expenditure would facilitate their goal attainment and independent living. Wait list (n=24): On waiting list for 12 months, then given program as described above. Results of this group after they received the program are NR. Duration of treatment: 12 months Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Sutcliffe, 2010 ⁶⁷ Pilot RCT Medium	Orthostatic training vs. control Mean age: 48 vs. 48 years % Female: 79 (15/19) vs. 84 (16/19) Race: NR Duration of illness: NR Severity of symptoms: NR Comorbidities: NR	Number enrolled: 38 Number analyzed: 36 (18 orthostatic training, 18 control)	Overall: 26% (10/38) Orthostatic training vs. control: NR
Taylor, 2004 ⁶⁸ RCT Medium	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) Duration of illness: NR Severity of symptoms: <i>Mean symptom severity (scale NR, higher ratings indicate worse health) (SD): 15.1 (3.0) vs. 14.2 (2.8)</i> Comorbidities: NR	Number enrolled: 47 (23 counseling, 24 wait list) Number analyzed: 47 (23 counseling, 24 wait list)	None dropped out

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Sutcliffe, 2010 ⁶⁷ Pilot RCT Medium	<p>Benefits</p> <p>Orthostatic training vs. control</p> <p>Overall Function: 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</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Improvement of ≥10 points on FIS at 6 months: 50% (7/14) vs. 38% (5/13); p=NR</p> <p>Outcomes related to associated symptoms: NR</p>
Taylor, 2004 ⁶⁸ RCT Medium	<p>Counseling vs. wait list</p> <p>Overall Function: NR</p> <p>Quality of Life: <i>Mean (SD) QLI scores (0-30 scale, higher scores indicate better life quality)</i></p> <p>Overall at 4 months: 13.2 (3.8) vs. 14.6 (4.8)</p> <p>Overall at 12 months: 15.7 (3.7) vs. 14.6 (4.1)</p> <p>Change in score at 12 months from baseline: 2.6 vs. 0.6; p<0.05</p> <p>Health and function subscale at 4 months: 12.8 (1.8) vs. 13.6 (2.1)</p> <p>Health and function subscale at 12 months: 14.1 (1.7) vs. 13.6 (1.8)</p> <p>Social and economic subscale at 4 months: 15.2 (0.8) vs. 15.5 (1.0)</p> <p>Social and economic subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9)</p> <p>Psychological and spiritual subscale at 4 months: 15.0 (1.1) vs. 15.2 (1.3)</p> <p>Psychological and spiritual subscale at 12 months: 15.5 (1.1) vs. 15.1 (1.2)</p> <p>Family subscale at 4 months: 15.4 (1.0) vs. 15.5 (1.0)</p> <p>Family subscale at 12 months: 15.6 (0.8) vs. 15.5 (0.9)</p> <p>Change in score at 12 months from baseline: 0.2 vs. -0.2; p<0.05</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: NR</p> <p>Outcomes related to associated symptoms: <i>Mean symptom severity (scale NR, higher ratings indicate worse health) (SD):</i></p> <p>4 months: 14.4 (3.5) vs. 14.3 (2.7)</p> <p>12 months: 13.9 (3.5) vs. 14.8 (2.8)</p> <p>Change in score at 12 months from baseline: -1.2 vs. 0.6; p<0.05</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Sutcliffe, 2010 ⁶⁷ Pilot RCT Medium	Orthostatic training vs. control Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Northern Regional CFS/ME Clinical Network
Taylor, 2004 ⁶⁸ RCT Medium	Counseling vs. wait list Adverse Events: NR Withdrawals due to adverse event: None Serious Adverse Events: NR	U.S. Department of Education National Institute on Disability and Rehabilitation Research Grant #H133G000097

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
The, 2007 ⁶⁹ RCT Medium	The Netherlands Single center 2003 to 2005 Specialty clinic	CDC (Fukuda, 1994) criteria Inclusion: Ages 18 to 65 years, IGFBP3/IGF1 ratio >2.5 Exclusion: Psychiatric comorbidities, pregnant or lactating women, lactose intolerance, or taking psychotropic drugs or experimental medications. <i>Note: Healthy controls were included to compare hormone blood levels, outcome NR here</i>	Acclidyne (n=30): Acclidyne (increases IGF1 levels) capsules on a decreasing dosage schedule (from 1,000 mg every day to 250 mg every 2 days) with amino acid supplement Placebo (n=27): Placebo capsules with placebo amino acid supplement Duration of treatment: 14 weeks Duration of followup: End of treatment
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ RCT Medium	The Netherlands Single center Study year(s) NR Tertiary care facility	CDC (Fukuda, 1994) criteria Inclusion: Age 18 to 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; BMI >40.	Self-instruction (n=62): 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, sleep routine setting, physical activity level adapted for either relatively-active person or a low-active person, gradually asked to increase activity or divide activities more evenly, 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, learn how to communicate about CFS, gradually increase mental and social activities, and relapse prevention and improve self control. Wait list (n=61): Waitlist control for duration of intervention. Duration of treatment: 20 or more weeks Duration of followup: 6 months after baseline assessment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
The, 2007 ⁶⁹ RCT Medium	<p>Acclidyne vs. placebo</p> <p>Mean age (SD): 40.9 (9.4) vs. 43.4 (11.2) years</p> <p>% Female: 77 (23/30) vs. 59 (16/27)</p> <p>Race: NR</p> <p>Duration of illness: NR</p> <p>Severity of symptoms: <i>Mean (SD) Checklist Individual Strength-fatigue (8-56 scale, lower scores indicate better health): 46.5 (7.4) vs. 46.2 (7.9)</i></p> <p><i>Mean (SD) Sickness Impact Profile-8 (0-5,799 scale, lower scores indicate better health): 1,484 (520.4) vs. 1,317 (481.7)</i></p> <p><i>Mean (SD) CDC symptoms: 7.6 (1.4) vs. 7.5 (1.3)</i></p> <p>Comorbidities: NR</p>	<p>Number enrolled: 57</p> <p>Number analyzed: 57</p>	<p>Overall: 3.5% (2/57)</p> <p>Acclidyne vs. placebo: 3.3% (1/30) vs. 3.7% (1/27)</p>
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ RCT Medium	<p>Self-instruction vs. wait list</p> <p>Mean age (SD): 36.3 (12.1) vs. 36.4 (13.6) years</p> <p>% Female: 74 (46/62) vs. 82 (50/61)</p> <p>Race: NR</p> <p>Mean (range) duration of illness: 48 (6 to 464) vs. 60 (6 to 625) months</p> <p>Severity of symptoms: <i>Mean (SD) CIS Fatigue severity (8 to 56 scale with lower scores indicating less fatigue): 51 (5.3) vs. 51.6 (5.5)</i></p> <p><i>Mean (SD) SF-36 physical functioning (0 to 100 scale with lower score indicating greater disability): 50.0 (22.2) vs. 51.6 (22.6)</i></p> <p><i>Mean (SD) SF-36 social functioning (0 to 100 scale with lower score indicating greater disability): 37.7 (22.3) vs. 41.0 (21.7)</i></p> <p>Comorbidities: NR</p>	<p>Number enrolled: 123 (62 self-instruction, 61 wait list)</p> <p>Number analyzed: 111 (55 self-instruction, 56 wait list)</p>	<p>Self-instruction vs. wait list</p> <p>11% (7/62) vs. 8% (5/61)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
The, 2007 ⁶⁹ RCT Medium	<p>Benefits</p> <p>Acclydine vs. placebo Overall Function: <i>Mean (SD) functional impairment SIP-8 scores (0-5,799 scale, lower scores indicate better health)</i> 14 weeks: 1,228.1 (619.7) vs. 1,120.2 (543.0); 59.1, 95% CI -201.7 to 319.8, p=0.65 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>Mean (SD) CIS-fatigue severity scores (8-56 scale, lower scores indicate better health)</i> 14 weeks: 42.4 (11.6) vs. 43.0 (12.6); mean difference in change from baseline 1.1, 95% CI -4.4 to 6.5, p=0.70 Daily fatigue level: 8.0 vs. 7.0, p=0.76; average daily fatigue rating for 14 days, range 0-16, higher scores indicate more fatigue Outcomes related to associated symptoms: <i>Mean (SD) physical activity level over a 12-day period (measured by actometer attached to the ankle)</i> 14 weeks: 64.9 (23.4) vs. 64.9 (23.5); mean difference in change from baseline 4.1, 95% CI -5.9 to 14.0, p=0.42</p>
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ RCT Medium	<p>Self-instruction vs. wait list Overall Function: <i>Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)</i> Second assessment: 65.4 (24.9) vs. 59.3 (22.9); p=0.08</p> <p>Subanalysis of baseline group with SF-36 physical functioning score ≤70</p> <p>Self-instruction (n=53) vs. wait list (n=50) <i>Mean (SD) SF-36 physical functioning scale (0-100 scale, higher scores indicate better health)</i> Second assessment: 63.0 (25.9) vs. 53.4 (18.7) Change from baseline: 18.5 vs. 9.6, difference: 9.05 (95% CI, 0.2 to 17.9); p<0.05 Quality of Life: NR Work/School Days: NR Proportion full/part-time work: NR Fatigue: <i>Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)</i> 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)</p> <p>Subanalysis of baseline group with SF-36 physical functioning score ≤70</p> <p>Self-instruction (n=53) vs. wait list (n=50) <i>Mean (SD) CIS fatigue severity scores (8-56 scale, lower scores indicate better health)</i> 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 Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
The, 2007 ⁶⁹ RCT Medium	Accliydine vs. placebo Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: None	Optipharma and GlaxoSmithKline
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ RCT Medium	Self-instruction vs. wait list Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Dutch Medical Research Council ZonMW

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ Continued	See Tummers 2012/2013	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996 ⁷¹ RCT Medium	The Netherlands Single center Study year(s): NR Specialty clinic	Oxford (Sharpe, 1991) criteria Inclusion: Fatigue for more than 1 year with substantial impairment in daily life (≥ 35 on subjective fatigue subscale of the checklist individual strength). Exclusion: Score < 16 and > 11 on modified Beck depression inventory, any physical illness the could explain complaints, any psychiatric diagnosis besides major depressive disorder in depressed patients, pregnancy or lactation, lack of contraception in women of childbearing age, exposure to fluoxetine in a clinical trial, previous lack of satisfactory response to an adequate course of fluoxetine, participation in a recent clinical trial, use of any prescribed medication except clinical analgesics that could not be stopped , current psychotherapy.	Fluoxetine (n=54): One 20 mg capsule once a day. Placebo (n=53): Not described. Duration of treatment: 8 weeks Duration of followup: 10 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ Continued	See Tummers 2012/2013	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996 ⁷¹ RCT Medium	<p>Fluoxetine depressed vs. fluoxetine non-depressed vs. placebo depressed vs. placebo non-depressed</p> <p>Mean age (years): 39.9 vs. 39.8 vs. 38.5 vs. 37.8</p> <p>% Female: 83 (15/18) vs. 67 (12/18) vs. 72 (13/18) vs. 53 (10/19)</p> <p>Race NR</p> <p>Mean duration of illness (range): 5 (1 to 30) vs. 5 (1 to 20) vs. 6 (2 to 20) vs. 6 (2 to 30)</p> <p>Severity of symptoms: <i>Subjective fatigue, daily observed fatigue score, measured 4 times a day on a 4-point scale, and combined, with higher scores indicating worse fatigue</i>: 10.2 vs. 8.6 vs. 9.8 vs. 9 (estimated from Figure 2)</p> <p>Comorbidities: Major depressive disorder %: 100 vs. 0 vs. 100 vs. 0</p>	Enrolled: 107 Analyzed: 96	Fluoxetine vs. placebo 10.3% (9/54) vs. 4 (2/53)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ Continued	<p>Benefits</p> <p>Tummers, 2013</p> <p>Interaction tests for potential moderators from linear regression models (95% CI)</p> <p>Age (years): 0.15 (0.01 to 0.045); p<0.05 Depression: 0.15 (0.04 to 1.95); p=0.04 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</p> <p>Interaction tests for potential moderators from logistic regression models (95% CI)</p> <p>Age (years): 1.06 (0.99 to 1.13); p=0.10 Depression: 1.40 (1.08 to 1.82); p=0.01 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</p>
Vercoulen, 1996 ⁷¹ RCT Medium	<p>Fluoxetine depressed vs. fluoxetine non-depressed vs. placebo depressed vs. placebo non-depressed</p> <p>Overall Function: NR</p> <p>Quality of Life: <i>Self-reported change:</i></p> <p>Recovered: 0 vs. 0 vs. 0 vs. 0 Improved, %: 14 (3/21) vs. 21 (5/24) vs. 13 (3/23) vs. 7% (2/28) Unchanged, %: 62 (13/21) vs. 71 (17/24) vs. 52 (12/52) vs. 79 (22/28) Worse, %: 24 (5/21) vs. 8 (2/24) vs. 35 (8/23) vs. 14 (4/28)</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Subjective fatigue, daily observed fatigue score, measured 4 times a day on a 4-point scale, and combined, with higher scores indicating worse fatigue:</i> 10.3 vs. 8.2 vs. 9.2 vs. 8.8 (estimated from figure)</p> <p>Mean difference between fluoxetine and placebo in improvement in fatigue severity: -0.164 (95% CI, 0.64 to 0.31), p=NS</p> <p>Outcomes related to associated symptoms: Mean difference between fluoxetine and placebo in improvement in depression severity: -0.186 (95% CI, 0.35 to 0.02), p=NS</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Tummers, 2012 ⁷⁰ Tummers, 2013 ³⁴ Continued	See Tummers 2012/2013	See Tummers 2012/2013
Vercoulen, 1996 ⁷¹ RCT Medium	<p>Fluoxetine vs. placebo</p> <p>Adverse events: Tremor: NR, but fluoxetine group greater p=0.006 Perspiration: NR, but fluoxetine group greater p=0.008 Withdrawals due to adverse events, %: 15 (8/54) vs. 4 (2/53) Serious adverse events: NR</p>	Eli Lilly, Netherlands

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Vermeulen, 2004 ⁷² Open-label randomized study Medium	The Netherlands Single center Study year(s) NR CFS clinic	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 (n=30): Acetyl-L-carnitine 2g/day Propionyl-L-carnitine (n=30): Propionyl-L-carnitine 2 g/day Combination (n=30): Acetyl-L-carnitine 2g/day + propionyl-L-carnitine 2 g/day Duration of treatment: 24 weeks Duration of followup: 2 weeks after end of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Vermeulen, 2004 ⁷² Open-label randomized study Medium	<p>Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination</p> <p>Mean age (SD): 37 (11) vs. 38 (11) vs. 42 (12) years</p> <p>% Female: 77 (23/30) vs. 77 (23/30) vs. 77 (23/30)</p> <p>Race: NR</p> <p>Duration of illness: Median (range): 5.5 (1.0 to 23.0) vs. 3.0 (0.5 to 25.0) vs. 6.0 (1.0 to 21.0) years</p> <p>Severity of symptoms: <i>Mean (SD) General fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health): 18.6 (1.9) vs. 18.4 (18) vs. 19.1 (1.4)</i></p> <p><i>Mean (SD) Physical fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health): 18.1 (2.6) vs. 17.8 (2.3) vs. 18.5 (1.6)</i></p> <p><i>Mean (SD) Mental fatigue, Multidimensional fatigue inventory-20 (5-20 scale, lower scores indicate better health): 17.0 (3.3) vs. 16.3 (2.5) vs. 15.7 (3.9)</i></p> <p>Comorbidities: NR</p>	<p>Number enrolled: 90</p> <p>Number analyzed: 89</p>	<p>Overall: 20% (18/90)</p> <p>Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination: 27% (8/30) vs. 13% (4/30) vs. 20% (6/30)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
	Benefits
Vermeulen, 2004 ⁷² Open-label randomized study Medium	<p>Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination</p> <p>Overall Function: NR</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) MFI-20 scores (5-20 scale, lower scores indicate better health)</i></p> <p>General fatigue at 24 weeks: 15.9 (4.2) vs. 16.5 (3.1) vs. 17.3 (3.3); mean differences: ALC vs. PLC, 0.60, 95% CI 2.52 to -1.32; ALC vs. ALC/PLC, 1.40, 95% CI 3.37 to -0.57; PLC vs. ALC/PLC, 0.80, 95% CI 2.45 to -0.85</p> <p>Physical fatigue at 24 weeks: 15.7 (4.4) vs. 16.4 (3.2) vs. 16.5 (3.4) mean differences: ALC vs. PLC, 0.70, 95% CI 2.70 to -1.30 ALC vs. ALC/PLC, 0.80, 95% CI 2.85 to -1.25 PLC vs. ALC/PLC, 0.10, 95% CI 1.81 to -1.61</p> <p>Mental fatigue at 24 weeks: 15.1 (3.6) vs. 13.9 (3.5) vs. 14.6 (4.0) mean differences: ALC vs. PLC, -1.20, 95% CI 0.65 to -3.05 ALC vs. ALC/PLC, -0.50, 95% CI 1.49 to -2.49 PLC vs. ALC/PLC, 0.70, 95% CI 2.64 to -1.24</p> <p>Outcomes related to associated symptoms: <i>% Improved on CGI</i></p> <p>24 weeks: 59 (17/29) vs. 63 (16/25) vs. 37 (11/30); ALC vs. PLC, RR 1.02, 95% CI 0.54 to 1.90 ALC vs. ALC/PLC, RR 0.65, 95% CI 0.39 to 1.09 PLC vs. ALC/PLC, RR 0.64, 95% CI 0.38 to 1.09</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Vermeulen, 2004 ⁷² Open-label randomized study Medium	Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination Adverse Events: NR Withdrawals due to adverse event: 10% (3/29) vs. 7% (2/30) vs. 10% (3/30) Overstimulated feeling and sleeplessness Serious Adverse Events: NR	Sigma-Tau Ethifarma

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Vollmer-Conna, 1997 ⁷³ RCT Medium	Australia 2 centers Study year(s): NR Hospital inflammation research units	CDC (Fukuda, 1994) criteria Inclusion: No other explanation of chronic fatigue. Exclusion: Pregnant; taking steroid medication, nonsteroidal anti-inflammatory drugs, immunomodulatory agents, or choline esterase inhibitors; had previously received immunologic therapy; recent history of asthma	Immunoglobulin 0.5 g/kg (n=22): 3 monthly IV infusions each lasting 24 hours Immunoglobulin 1 g/kg (n=28): 3 monthly IV infusions each lasting 24 hours Immunoglobulin 2 g/kg (n=23): 3 monthly IV infusions each lasting 24 hours Placebo (n=26): 1% albumin in 10% weight/volume maltose, 3 monthly IV infusions each lasting 24 hours Duration of treatment: 3 months Duration of followup: 3 months after the final infusion
Walach, 2008 ⁷⁴ Partially-blinded RCT Low	Germany and Austria 14 centers 2001 to 2003 Private practices for environmental medicine specializing in CFS	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, patients with a serious acute illness or hospital admission in the 3 months prior to entry	Distant healing (n=207): 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 (n=206): No healing as "deferred treatment" <i>Note: Patients were also randomized to being blinded or unblinded to treatment allocation:</i> <i>Blinded distant healing n=105</i> <i>Unblinded distant healing n=102</i> <i>Blinded usual care n=95</i> <i>Unblinded usual care n=109</i> Duration of treatment: 6 months Duration of followup: 6 months after end of treatment; 18 months total for patients recruited at beginning of study

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Vollmer-Conna, 1997 ⁷³ RCT Medium	Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo Mean age (years): 41 vs. 40 vs. 38 vs. 40 % Female: 74 (17/23) vs. 79 (22/28) vs. 61 (14/23) vs. 85 (22/26) Race NR Mean duration of illness (years): 6 vs. 7 vs. 5 vs. 7 Severity of symptoms: <i>Mean Karnofsky Performance Scores, 0 to 100 (higher scores indicate better health)</i> : 73 vs. 70 vs. 67 vs. 71, p=NS <i>Profile of Mood States (POMS) energy score (calculated by subtracting the POMS fatigue score from the POMS vigor score for each patient)</i> : -13.0 vs. -9.3 vs. -7.3 vs. -16.0, p=0.005, NS (Bonferroni adjusted p-critical was 0.004 due to multiple comparisons) Comorbidities: NR	Enrolled: 99 Analyzed: 99	4 patients left the study, but were analyzed on an intention-to-treat basis.
Walach, 2008 ⁷⁴ Partially-blinded RCT Low	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 (78/105) vs. 76.5 (78/102) vs. 76.6 (72/94) vs. 75.0 (81/108) 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 Duration of illness: Mean (SD): 11.3 (9.4) vs. 9.6 (6.7) vs. 9.6 (8.6) vs. 11.9 (9.9) years Severity of symptoms: % <i>Severe idiopathic CFS</i> : 7.6 (8/105) vs. 2.9 (3/102) vs. 4.3 (4/94) vs. 3.7 (4/108) <i>Mean (SD) Fatigue severity score (1-7 scale, lower scores indicate better health)</i> : 6.2 (0.9) vs. 6.1 (0.9) vs. 6.1 (1.1) vs. 6.0 (1.1) Comorbidities: NR	Number enrolled: 411 Number analyzed: 409	Overall: 3.6% (15/411) Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care: 1.9% (2/105) vs. 5.9% (6/102) vs. 3.2% (3/95) vs. 3.7% (4/109)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Vollmer-Conna, 1997 ⁷³ RCT Medium	<p>Benefits</p> <p>Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo</p> <p>Overall Function: <i>Investigator-rated Median Karnofsky Performance Score, 0 to 100, higher scores indicate better health</i> : By group, median (1st to 3rd IQR): 80.0 (80 to 70) vs. 80.0 (80 to 70) vs. 75.0 (80 to 70) vs. 77.5 (80 to 70), difference in change between groups: p>0.13</p> <p>Quality of Life: <i>Visual Analog Scale</i>: Trend toward improvement in all groups, but no significant difference between groups, data NR, p>0.09</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Profile of Mood States (POMS) energy score (calculated by subtracting the POMS fatigue score from the POMS vigor score for each patient)</i>: No significant difference between groups, data NR</p> <p>Outcomes related to associated symptoms: Nonsedentary activity hours per day: No significant difference between groups, data NR</p>
Walach, 2008 ⁷⁴ Partially-blinded RCT Low	<p>Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)</i></p> <p>6 months: 34.69 (9.77) vs. 34.79 (10.41) vs. 35.08 (10.01) vs. 33.46 (9.68); p=NR</p> <p>Change from baseline: 3.66 (6.83) vs. 3.04 (7.38) vs. 3.29 (7.28) vs. 0.75 (7.85); p=NR</p> <p><i>Mean (SD) SF-36 mental health subscale scores (0-100 scale, lower score indicates better health)</i></p> <p>6 months: 36.37 (11.98) vs. 36.61 (10.75) vs. 38.44 (12.01) vs. 35.97 (11.56); p=NR</p> <p>Change from baseline: -0.29 (9.54) vs. 1.74 (10.25) vs. 1.16 (11.07) vs. 0.81 (10.45); p=NR</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: NR</p> <p>Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Vollmer-Conna, 1997 ⁷³ RCT Medium	<p>Immunoglobulin 0.5 g/kg vs. Immunoglobulin 1 g/kg vs. Immunoglobulin 2 g/kg vs. Placebo</p> <p>Adverse events: Moderate to severe constitutional symptoms including headache, fatigue, malaise, and concentration impairment typically reported 12 to 2 hours after the completion of the infusion and persisting for up to 10 days, %: 88 (18/22) vs. 71 (20/28) vs. 78 (18/23) vs. 88 (23/26), p=0.49</p> <p>Withdrawals due to adverse events: 3 immunoglobulin patients (group[s] NR) withdrew after either a severe constitutional symptom reaction (2 patients) or a vesiculopapular skin eruption on hands and feet (1 patient) to infusion 1 or 2</p> <p>Serious adverse events: NR</p>	Commonwealth Serum Laboratories and the Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis Society of New South Wales
Walach, 2008 ⁷⁴ Partially-blinded RCT Low	<p>Blinded distant healing vs. unblinded distant healing vs. blinded usual care vs. unblinded usual care</p> <p>Adverse Events: NR</p> <p>Withdrawals due to adverse event: NR</p> <p>Serious Adverse Events: NR</p>	European Commission "Quality of Life and Living Resources" grant, Bundesamt fur Wissenschaft und Bildung, Switzerland, and the Samuelli Institute

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Wallman, 2004 ⁷⁵ RCT High	Australia Single center Study year(s) NR University human performance laboratory	CDC (Fukuda, 1994) criteria Inclusion: Physician's written confirmation of diagnosis using Fukuda criteria. Exclusion: Alternative diagnosis or failure to provide written confirmation of diagnosis	Graded exercise (n=32): Aerobic activity using all the large muscles of the body, beginning with 5 to 15 minutes, with intensity based on mean HR value, every other day unless they had a relapse. Subjects could choose between walking, cycling, or swimming. Flexibility/relaxation (n=29): Relaxation/flexibility therapy; listening to a relaxation tape and stretching exercises every other day over 12 weeks. Requested not to participate in any extra physical activity. Both groups used a diary to record their sessions and were assessed once a week for 4 weeks before and 4 weeks after the intervention, with the average scores used for pre-and post-treatment data. Both groups were contacted by phone every other week to review progress and determine next exercise regimen. Duration of treatment: 12 weeks Duration of followup: End of treatment
Wearden, 2010 ⁷⁶ Wearden, 2012 ⁷⁷ Wearden, 2013 ⁷⁸ FINE Trial Block-randomized and stratified RCT Medium	United Kingdom 186 centers 2005 to 2007 Primary care; therapies delivered in-home	Oxford (Sharpe, 1991) 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 undertaking systemic psychological therapies for CFS/ME; had received pragmatic rehabilitation in the past year. All patients were referred from general practitioners, who performed a list of exclusionary tests based on Fukuda, 1994 criteria.	Graded exercise (pragmatic rehabilitation) (n=95): 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 (n=101): 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 (n=100): 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. Duration of treatment: 18 weeks Duration of followup: 70 weeks total

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wallman, 2004 ⁷⁵ RCT High	<p>Graded exercise vs. flexibility/relaxation</p> <p>Mean age: NR by group, range overall 16 to 74</p> <p>% Female: 84% (27/32) vs. 69% (20/29)</p> <p>Race: NR</p> <p>Duration of illness: "No initial difference," data NR</p> <p>Severity of symptoms: Mental fatigue, maximum score 12, average score (range): 6.3 (5.6 to 7.0) vs. 5.6 (5.0 to 6.1)</p> <p>Physical fatigue, maximum score 21, average score (range): 11.6 (10.1 to 13.0) vs. 11.4 (10.4 to 12.3)</p> <p>Comorbidities: 6 subjects had a major depressive disorder in the previous 12 months, group NR</p> <p>2 subjects had dysthymia, group NR</p>	<p>Number enrolled: 68</p> <p>7 excluded post-randomization, 6 for reasons not associated with the study, and one because her BMI (44) prevented her from participating in the exercise test.</p> <p>Number analyzed: 61 (32 exercise, 29 relaxation/flexibility)</p>	<p>Overall: 10% (7/68)</p> <p>Graded exercise vs. flexibility/relaxation: 6% (2/34) vs. 15% (5/34) patients received neither intervention and were not included in baseline or end of treatment testing</p>
Wearden, 2010 ⁷⁶ Wearden, 2012 ⁷⁷ Wearden, 2013 ⁷⁸ FINE Trial Block-randomized and stratified RCT Medium	<p>Graded exercise vs. supportive listening vs. usual care</p> <p>Mean age: 43.74 vs. 45.13 vs. 44.92 years</p> <p>% Female: 78 (74/95) vs. 79 (80/101) vs. 76 (76/100)</p> <p>Race: NR</p> <p>Duration of illness: Median (range): 7 (0.5-51.7) years</p> <p>Severity of symptoms: All scored ≤70% on SF-36 physical functioning scale and scored ≥4 on 0 to 11 Chalder fatigue scale</p> <p>% Ambulatory: 90 (85/95) vs. 87 (88/101) vs. 88 (88/100)</p> <p>% Met London ME criteria: 30 (28/95) vs. 31 (31/101) vs. 33 (33/100)</p> <p>Comorbidities: % Any anxiety diagnosis: 27 (21/95) vs. 20 (17/101) vs. 26 (22/100)</p> <p>% Any depression diagnosis: 19 (18/95) vs. 15 (15/101) vs. 20 (20/100)</p> <p>% With ≥2 comorbidities: 34 (32/95) vs. 32.7 (33/101) vs. 43 (43/100)</p> <p>% With 1 comorbidity: 22 (21/95) vs. 28 (29/101) vs. 24 (24/100)</p> <p>% With no comorbidities: 44 (42/95) vs. 39 (39/101) vs. 33 (33/100)</p> <p>Comorbidities: musculoskeletal disorders 21% (63/296), gastrointestinal problems including irritable bowel syndrome 5% (45/296), and cardiovascular diseases such as hypercholesterolemia 14% (41/296)</p>	<p>Number enrolled: 296 (95 graded exercise, 101 supportive listening, 100 usual care)</p> <p>Number analyzed: 274 at 20 weeks (85 graded exercise, 97 supportive listening, 92 usual care) and 257 at 70 weeks (81 graded exercise, 90 supportive listening, 86 usual care)</p>	<p>Overall: 13.2% (39/296)</p> <p>Graded exercise vs. supportive listening vs. usual care: 14.7% (14/95) vs. 10.9% (11/101) vs. 14.0% (14/100)</p> <p>1 in supportive listening group subsequently received diagnosis of multiple sclerosis (misdiagnosis)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Wallman, 2004 ⁷⁵ RCT High	<p>Benefits</p> <p>Graded exercise vs. flexibility/relaxation</p> <p>Overall Function: Ratings of perceived exertion (estimated from figure): 1.3 vs. 1.8 (p=0.013)</p> <p>Quality of Life: <i>Self-rated clinical global impression change scores after completing treatment:</i></p> <p>1: Very much better: 16% (5/32) vs. 7% (2/29)</p> <p>2: Much better: 44% (14/32) vs. 34% (10/29)</p> <p>3: A little better: 31% (10/32) vs. 34% (10/29)</p> <p>4: No change: 9% (3/32) vs. 21% (6/29)</p> <p>5: A little worse: 0 vs. 3% (1/29)</p> <p>6: Much worse: 0 vs. 0</p> <p>7: Very much worse: 0 vs. 0</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mental fatigue, maximum score 12, average score (range): 4.5 (3.9 to 5.2) vs. 4.8 (4.2 to 5.5)</p> <p>Physical fatigue, maximum score 21, average score (range): 8.1 (6.9 to 9.4) vs. 9.6 (8.3 to 10.9)</p> <p>Outcomes related to associated symptoms: HADS depression: 4.8 (6 to 5.9) vs. 6.5 (5.5 to 7.6), p=0.041</p>
Wearden, 2010 ⁷⁶ Wearden, 2012 ⁷⁷ Wearden, 2013 ⁷⁸ FINE Trial Block- randomized and stratified RCT Medium	<p>Overall Function: Graded exercise vs. supportive listening vs. usual care</p> <p><i>Mean percentage scores (SD) on SF-36 physical functioning scale (0-100 scale, higher scores indicate better outcomes)</i></p> <p>20 weeks: 39.94 (25.21) vs. 33.28 (22.94) vs. 40.27 (26.45); treatment effect estimate -7.54, 95% CI -12.96 to -2.33; p=0.005 for supportive listening vs. usual care; 70 weeks: 43.27 (27.38) vs. 35.72 (25.94) vs. 39.83 (27.77); p=NS</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Graded exercise vs. supportive listening vs. usual care</p> <p><i>Mean (SD) Chalder fatigue scale scores (items scored dichotomously; lower scores indicate better outcomes)</i></p> <p>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 graded exercise vs. usual care;</p> <p>70 weeks: 8.72 (3.65) vs. 9.39 (3.21) vs. 9.48 (2.71).</p> <p>Graded exercise vs. usual care</p> <p><i>Mean (SD) Chalder fatigue scale scores (items scored 0-3 and summed to total of 0-33; lower scores indicate better outcomes)</i></p> <p>20 weeks: 22.78 (8.56) vs. 26.27 (7.68); 70 weeks: 23.90 (8.34) vs. 26.02 (7.11)</p> <p>Graded exercise vs. usual care vs. supportive listening</p> <p>Outcomes related to associated symptoms: <i>HADS-Depression, mean (SD):</i></p> <p>20 weeks: 7.28 (4.02) vs. 8.48 (4.47) vs. 8.85 (4.01)</p> <p>70 weeks: 7.88 (4.45) vs. 8.06 (4.75) vs. 8.67 (4.51)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wallman, 2004 ⁷⁵ RCT High	<p>Graded exercise vs. flexibility/relaxation</p> <p>Adverse Events: 0 vs. 3% (1/29) felt a little worse after completing treatment</p> <p>Withdrawals due to Adverse Events: NR</p> <p>Serious Adverse Events: NR</p>	NR
Wearden, 2010 ⁷⁶ Wearden, 2012 ⁷⁷ Wearden, 2013 ⁷⁸ FINE Trial Block- randomized and stratified RCT Medium	<p>Adverse Events: Overall: 4 (herpes simplex infection, attempted suicide, bleeding peptic ulcer, and recurrence of cancer; all deemed unrelated to interventions)</p> <p>Withdrawals due to adverse event: Unclear, 2 each in graded exercise and supportive listening withdrew due to nurse therapist or researcher safety concerns, not otherwise described</p> <p>Serious Adverse Events: None reported</p>	United Kingdom Medical Research Council and the United Kingdom Department of Health; and the University of Manchester

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Wearden, 1998 ⁷⁹ RCT Medium	England and Wales Single center 1993 to 1995 University department of medicine out-patient clinic	Oxford (Sharpe, 1991) criteria Inclusion: Ages ≥ 18 years, meeting Oxford criteria, principle complaint of fatigue lasting six months and exacerbated by exercise, impairment in 3 out of 4 areas of activity. Exclusion Medical cause of fatigue; unable to come off of depressants; requiring orthopedic treatment.	GET + fluoxetine (n=33): Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3x/week, with low initial intensity that was gradually increased based on heart rate plus fluoxetine 20 mg daily. Fluoxetine (n=35): Fluoxetine 20 mg daily plus placebo exercise program of being told to keep doing what they were doing, rest when needed, and no other advice. GET (n=34): Preferred aerobic activity (usually walking/jogging, swimming, or cycling) performed for 20 minutes, ≥3x/week, with low initial intensity that was gradually increased based on heart rate plus placebo drug. Attention control (n=34): Placebo drug plus placebo exercise program of being told to keep doing what they were doing, rest when needed, and no other advice. Duration of treatment: 26 weeks Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wearden, 1998 ⁷⁹ RCT Medium	<p>Overall, GET + fluoxetine vs. GET vs. fluoxetine vs. attention control</p> <p>Mean age: 38.7, 38.2 vs. 40.4 vs. 38.8 vs. 37.6 years</p> <p>% Female: 71 (97/136), 67 (22/33) vs. 79 (27/34) vs. 77 (27/35) vs. 62 (21/34)</p> <p>Race: NR</p> <p>Duration of fatigue median: 28.0, 29.5 vs. 34.5 vs. 30.5 vs. 22.0 months</p> <p>Severity of symptoms: <i>Fatigue: Mean (95% CI) Chalder fatigue scale scores (0 to 42, lower scores indicate better health):</i> 35.9 vs. 33.7 vs. 34.4 vs. 34.0</p> <p>Comorbidities: NR by group; % overall:</p> <p>Current psychiatric diagnosis: 46 (62/136)</p> <p>Major depression: 10 (14/136)</p> <p>Either dysthymia or a depressive disorder not otherwise specified: 24 (32/136)</p> <p>Various anxiety disorders: 10 (14/136)</p> <p>Somatization disorder: 2 (2/146)</p>	<p>Number enrolled: 136</p> <p>Number analyzed:</p> <p>ITT: 136 (33 GET + fluoxetine, 34 fluoxetine, 35 GET, 34 attention control)</p> <p>Completed trial: 96 (19 GET + fluoxetine, 23 fluoxetine, 25 GET, 29 attention control)</p>	<p>Overall: 29% (40/136)</p> <p>GET + fluoxetine vs. fluoxetine vs. GET vs. attention control</p> <p>42% (14/33) vs. 32% (11/34) vs. 29% (10/35) vs. 17% (5/29)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Wearden, 1998 ⁷⁹ RCT Medium	<p>Benefits</p> <p>GET + fluoxetine vs. GET vs. fluoxetine vs. attention control</p> <p>Overall Function: <i>Mean (SD) functional work capacity (amount of O2 consumed in the final minute of exercise per kg of body weight)</i></p> <p>0-12 weeks: 2.2 (1.0 to 3.4) vs. 2.6 (1.0 to 4.3) vs. 0.4 (-1.2 to 2.0) vs. 0.4 (-0.9 to 1.7)</p> <p>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)</p> <p><i>Effect of exercise on functional work capacity</i></p> <p>Mean change 0-12 weeks: 2.0 (95% CI 0.60 to 3.49), p=0.005</p> <p>Mean change 0-26 weeks: 1.9 (95% CI 0.15 to 3.69), p=0.03</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (95% CI) Chalder fatigue scale scores (0 to 42, lower scores indicate better health)</i></p> <p>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)</p> <p>26 weeks: -6.0 (-9.7 to -2.3) vs. -5.7 (-9.5 to -1.9) vs. -3.0 (-5.9 to -0.2) vs. -2.7 (-5.4 to 0.01)</p> <p><i>% non-cases of fatigue (Chalder fatigue scale score <4)</i></p> <p>12 weeks: 18 (6/33) vs. 1 (3/34) vs. 1 (3/35) vs. 6 (2/34)</p> <p>26 weeks: 18 (6/33) vs. 18 (6/34) vs. 6 (2/35) vs. 6 (2/34)</p> <p>p=0.025 for exercise interventions combined vs. others</p> <p><i>Exercise improved fatigue scale scores</i></p> <p>Mean change 0 to 12 weeks: 2.1 (95% CI -0.6 to 4.8), p=0.13</p> <p>Mean change 26 weeks: 2.9 (95% CI -0.2 to 6.1), p=0.07</p> <p>Outcomes related to associated symptoms: HADS-Depression, mean change (95% CI) at 26 weeks: -2.0 (3.3 to -0.7) vs. -1.2 (-2.5 to 0.2) vs. -1.7 (-3.0 to -0.5) vs. -1.3 (-2.3 to -0.3)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wearden, 1998 ⁷⁹ RCT Medium	GET + fluoxetine vs. GET vs. fluoxetine vs. attention control Adverse Events: Overall unclear, only reported drop-outs due to adverse events Withdrawals due to adverse event: 11 medication side-effects (2 reported with placebo) Serious Adverse Events: NR	Linbury Trust; study drug provided by Eli Lilly

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Weatherley-Jones, 2004 ⁸⁰ RCT Medium	United Kingdom 2 centers 1998 to 2000 1 specialty clinic in CFS and 1 in infectious disease	Oxford (Sharpe, 1991) criteria Inclusion: Patients over 18 years of age, meeting the Oxford criteria Exclusion: Clinically significant abnormalities in full blood count, liver function tests, thyroid stimulating hormone, acute phase protein, urea and electrolytes; protein or sugar in urine; primary major depression; current engagement in individual psychotherapy or counseling; pregnancy; bipolar disorders; psychosis; eating disorders; substance abuse/dependence; somatization disorders; patients already receiving homeopathy or CBT or who had completed a course of homeopathy of CBT for CFS.	Homeopathy (n=53): Homeopathic prescriptions (including cacinosin, polycrest remedies, antidotes to specific viruses and vaccinations and bowel nosodes) given after approximately monthly 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 (n=50): Placebo prescribed in the same manner as homeopathy Duration of treatment: 6 months Duration of followup: 1 month after end of treatment; 7 months total after randomization

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Weatherley-Jones, 2004 ⁸⁰ RCT Medium	<p>Homeopathy vs. placebo</p> <p>Mean age (SD): 38.9 (10.6) vs. 38.8 (11.2) years</p> <p>% Female: 57 (30/53) vs. 62 (31/50)</p> <p>Race: NR</p> <p>Duration of illness: Mean (SD): 4.8 (4.3) vs. 3.7 (2.4) years</p> <p>Severity of symptoms Mean (SD):</p> <p><i>Multidimensional fatigue inventory (4-20 scale, lower scores indicate better health)</i></p> <p>General fatigue: 18.4 (1.7) vs. 18.1 (2.2)</p> <p>Physical fatigue: 18.0 (2.2) vs. 17.5 (3.1)</p> <p>Mental fatigue: 16.7 (3.7) vs. 16.5 (3.0)</p> <p>Reduced activity: 16.1 (3.1) vs. 13.2 (3.7)</p> <p>Reduced motivation: 13.0 (3.9) vs. 13.2 (3.7)</p> <p><i>Fatigue Impact Scale (0-40 scale, lower scores indicate better health)</i></p> <p>Cognitive dimension: 24.1 (9.0) vs. 24.2 (8.0)</p> <p>Physical dimension: 27.3 (6.8) vs. 27.4 (7.1)</p> <p><i>Functional Limitations Profile, a version of the Sickness Impact Profile (scale unclear, higher scores indicate better health)</i></p> <p>Physical dimension: 20.4 (14.1) vs. 22.1 (14.9)</p> <p>Psychosocial dimension: 35.1 (14.8) vs. 36.3 (15.0)</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 103</p> <p>Number analyzed: 86</p>	<p>Overall: 11% (11/103)</p> <p>Homeopathy vs. placebo: 10% (5/50) vs. 11% (6/53)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Weatherley-Jones, 2004 ⁸⁰ RCT Medium	<p>Homeopathy vs. placebo</p> <p>Overall Function: <i>Mean change from baseline (SD) Functional Limitations Profile scores (scale unclear, higher score indicates better health)</i></p> <p>Physical dimension: 5.11 (8.82) vs. 2.72 (8.40), p=0.04</p> <p>Psychosocial dimension: 9.81 (14.19) vs. 6.76 (10.67); p=0.14</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean change from baseline (SD) MFI-20 scores (4-20 scale, lower score indicates better health); likelihood for improvement (RR, 95% CI)</i></p> <p>General fatigue: 2.70 (3.93) vs. 1.35 (2.66); RR 1.67, 95% CI 0.94 to 2.97</p> <p>Physical fatigue: 2.13 (4.00) vs. 1.28 (2.74); RR 1.42, 95% CI 0.77 to 2.60</p> <p>Mental fatigue: 2.70 (4.01) vs. 2.05 (2.86); RR 1.25, 95% CI 0.76 to 2.07</p> <p>Reduced activity: 2.72 (4.47) vs. 1.81 (2.82); RR 1.27, 95% CI 0.75 to 2.15</p> <p>Reduced motivation: 1.35 (4.15) vs. 1.65 (3.02); RR 0.89, 95% CI 0.53 to 1.50</p> <p><i>Mean change from baseline (SD) FIS (0-40 scale for each subscale, except 0-80 scale for social subscale, lower score indicates better health)</i></p> <p>Cognitive dimension: 4.88 (9.3) vs. 4.21 (7.18); p=0.61</p> <p>Physical dimension: 4.98 (8.5) vs. 5.30 (6.69); p=0.98</p> <p>Social dimension: 7.92 (18.02) vs. 8.20 (14.06); p=0.79</p> <p>Outcomes related to associated symptoms: NR</p> <p>Likelihood of improvement on MFI-20: General fatigue</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Weatherley-Jones, 2004 ⁸⁰ RCT Medium	Homeopathy vs. placebo Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	Linbury Trust grant

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
<p>White, 2011⁸¹</p> <p>White, 2013⁸²</p> <p>Dougall, 2014⁸³</p> <p>PACE Trial RCT</p> <p>Medium</p>	<p>United Kingdom</p> <p>6 centers</p> <p>2005 to 2010</p> <p>Specialist CFS clinics</p>	<p>Oxford (Sharpe, 1991) criteria</p> <p>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).</p> <p>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.</p>	<p>Adaptive pacing therapy + specialist medical care (APT) (n=160): 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.</p> <p>Cognitive behavioral therapy + specialist medical care (CBT) (n=161): 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.</p> <p>Graded exercise + specialist medical care (GET) (n=160): 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. The most commonly chosen exercise was walking.</p> <p>Control (n=160): Specialist medical care (SMC), consisting of information about chronic fatigue syndrome, generic advice, and symptomatic pharmacology.</p> <p>Duration of treatment: 23 weeks</p> <p>Duration of followup: 12 months</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
<p>White, 2011⁸¹</p> <p>White, 2013⁸²</p> <p>Dougall, 2014⁸³ PACE Trial RCT Medium</p>	<p>APT vs. CBT vs. GET vs. control</p> <p>Mean age (SD): 39 (11) vs. 39 (12) vs. 39 (12) vs. 37 (11) years</p> <p>% Female: 76 (121/159) vs. 80 (129/161) vs. 77 (123/160) vs. 76 (122/160)</p> <p>% White: 92 (146/159) vs. 94 (151/161) vs. 93 (148/160) vs. 94 (150/160)</p> <p>Duration of illness: Median (IQR): 33 (16 to 69) vs. 36 (16 to 104) vs. 35 (18 to 67) vs. 25 (15 to 57) months</p> <p>Severity of symptoms: <i>Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower scores indicate better health):</i> 28.5 (4) vs. 27.7 (3.7) vs. 28.2 (3.8) vs. 28.3 (3.6)</p> <p><i>Mean (SD) SF-36 physical functioning subscale scores (0 to 100 scale, higher scores indicate better health):</i> 37.2 (16.9) vs. 39.0 (15.3) vs. 36.7 (15.4) vs. 39.2 (15.4)</p> <p>Comorbidities: % Any depressive disorder: 35 (55/159) vs. 34 (55/161) vs. 34 (54/160) vs. 34 (55/160)</p> <p>% Any psychiatric disorder: 47 (75/159) vs. 47 (75/161) vs. 46 (73/160) vs. 48 (77/160)</p>	<p>Number enrolled: 641 (160 APT, 161 CBT, 160 GET, 160 control)</p> <p>Number analyzed: 630 (159 APT, 155 CBT, 159 GET, 157 control)</p>	<p>Overall: 1.7% (11/641)</p> <p>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)</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
White, 2011 ⁸¹ White, 2013 ⁸² Dougall, 2014 ⁸³ PACE Trial RCT Medium	<p>APT vs. CBT vs. GET vs. control</p> <p>Overall Function: <i>Mean (SD) SF-36 physical functioning subscale scores (0 to 100 scale, higher scores indicate better health)</i></p> <p>12 weeks: 41.7 (19.9) vs. 51.0 (20.7) vs. 48.1 (21.6) vs. 46.6 (20.4)</p> <p>24 weeks: 43.2 (21.4) vs. 54.2 (21.6) vs. 55.4 (23.3) vs. 48.4 (23.1)</p> <p>52 weeks: 45.9 (24.9) vs. 58.2 (24.1) vs. 57.7 (26.5) vs. 50.8 (24.7)</p> <p>Mean difference from control at 52 weeks: APT: -3.4 (-8.4 to 1.6) p=NS; CBT: 7.1 (2.0 to 12.1) p=0.0068; GET: 9.4 (4.4 to 14.4) p=0.0005</p> <p>Mean difference from APT at 52 weeks: CBT: 10.5 (5.4 to 15.6) p=0.0002; GET: 12.8 (7.7 to 17.9) p<0.0001</p> <p>% Improved from baseline (by ≥8 points): 49 (75/153) vs. 71 (105/148) vs. 70 (108/154) vs. 58 (88/152)</p> <p>% Within normal range (score ≥60): 35 (53/153) vs. 52 (77/148) vs. 53 (81/154) vs. 41 (62/152)</p> <p><i>Mean (SD) Work and social adjustment scale scores (0-45 scale, lower scores indicate better health)</i></p> <p>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</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Mean (SD) Chalder fatigue scale scores (0 to 33 scale, lower scores indicate better health)</i></p> <p>12 weeks: 24.2 (6.4) vs. 23.6 (6.5) vs. 22.8 (7.5) vs. 24.3 (6.5)</p> <p>24 weeks: 23.7 (6.9) vs. 21.5 (7.8) vs. 21.7 (7.1) vs. 24.0 (6.9)</p> <p>52 weeks: 23.1 (7.3) vs. 20.3 (8.0) vs. 20.6 (7.5) vs. 23.8 (6.6)</p> <p>Mean difference (95% CI) from control at 52 weeks: APT: -0.7 (-2.3 to 0.9) p=NS; CBT: -3.4 (-5.0 to -1.8) p=0.0001; GET: -3.2 (-4.8 to -1.7) p=0.0003</p> <p>Mean difference (95% CI) from APT at 52 weeks: CBT: -2.7 (-4.4 to -1.1) p=0.0027; GET: -2.5 (-4.2 to -0.9) p=0.0059</p> <p>% Improved from baseline (by ≥2 points): 65 (99/153) vs. 76 (113/148) vs. 80 (123/154) vs. 65 (98/152)</p> <p>% Within normal range (score ≤18): 22 (34/153) vs. 41 (60/148) vs. 33 (51/154) vs. 21 (32/152)</p> <p>Depression: HADS-Depression, mean (SD)</p> <p>52 weeks: 7.2 (4.5) vs. 6.2 (3.7) vs. 6.1 (4.1) vs. 7.2 (4.7); CBT vs. control: p=0.0003; GET vs. control: p=0.0035; CBT vs. APT: p=0.382, GET vs. APT: p=0.23</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
White, 2011 ⁸¹	<p><i>Outcomes related to associated symptoms: Patients with self-rated CGI changes</i></p> <p>12 weeks % Positive change: 13 (20/153) vs. 21 (32/153) vs. 25 (37/151) vs. 5 (7/151)</p> <p>12 weeks % Minimum change: 82 (126/159) vs. 74 (113/161) vs. 74 (111/151) vs. 88 (133/160)</p>
White, 2013 ⁸²	<p>12 weeks % Negative change: 5 (7/153) vs. 5 (8/153) vs. 2 (3/151) vs. 7 (11/151)</p> <p>24 weeks % Positive change: 24 (37/155) vs. 38 (56/149) vs. 37 (54/148) vs. 19 (28/151)</p> <p>24 weeks % Minimum change: 72 (111/155) vs. 55 (82/149) vs. 60 (89/148) vs. 71 (107/151)</p>
Dougall, 2014 ⁸³	<p>24 weeks % Negative change: 5 (7/155) vs. 7 (11/149) vs. 3 (5/148) vs. 11 (16/151)</p> <p>52 weeks % Positive change: 31 (47/153) vs. 41 (61/147) vs. 41 (62/152) vs. 25 (38/152)</p> <p>52 weeks % Minimum change: 63 (96/153) vs. 52 (77/147) vs. 53 (80/152) vs. 66 (100/152)</p>
PACE Trial RCT Medium	<p>52 weeks % Negative change: 7 (10/153) vs. 6 (9/147) vs. 7 (10/152) vs. 9 (14/152)</p> <p>OR (95% CI) positive change vs. negative change</p> <p>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</p> <p>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</p> <p><i>Recovery based on different criteria at 52 weeks</i></p> <p>% 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)</p> <p>% No longer meeting case definitions</p> <p>CDC (Fukuda, 1994) criteria: 49 (74/150) vs. 67 (97/144) vs. 65 (93/144) vs. 51 (76/149)</p> <p>Oxford (Sharpe, 1991) criteria: 43 (64/149) vs. 54 (77/143) vs. 56 (81/144) vs. 41 (62/150)</p> <p>London ME criteria: 68 (100/147) vs. 76 (107/140) vs. 77 (106/138) vs. 66 (97/148)</p> <p><i>Cumulative criteria for recovery at 52 weeks</i></p> <p>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)</p> <p>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)</p> <p><i>Meeting "trial recovery criteria" in subgroups meeting alternate definitions of CFS or ME at baseline</i></p> <p>CDC (Fukuda, 1994) criteria: 9 (9/102) vs. 19 (17/89) vs. 22 (20/93) vs. 6 (6/98)</p> <p>London ME criteria: 11 (8/75) vs. 21 (15/70) vs. 21 (16/75) vs. 10 (7/73)</p> <p>OR (95% CI) for composite "trial recovery" CBT vs. APT: 3.36 (1.64 to 6.88); p=0.001</p> <p>CBT vs. control: 3.69 (1.77 to 7.69); p<0.001</p> <p>GET vs. APT: 3.38 (1.65 to 6.93); p=0.001</p> <p>GET vs. control: 3.71 (1.78 to 7.74); p<0.001</p> <p>APT vs. control: 1.10 (0.47 to 2.58); p=NS</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
White, 2011 ⁸¹ White, 2013 ⁸² Dougall, 2014 ⁸³ PACE Trial RCT Medium	<p>APT vs. CBT vs. GET vs. control</p> <p>Adverse Events: % With ≥1 non-serious adverse event‡: 96 (152/159) vs. 89 (143/161) vs. 93 (149/160) vs. 93 (149/160); p=NS</p> <p>Number of non-serious adverse events‡: 949 vs. 848 vs. 992 vs. 977, p=0.0081 for CBT vs. APT and p=0.0016 for CBT vs. control</p> <p>Median (quartiles) non-serious adverse events‡ per person-year: 4 (2, 9) vs. 4 (2, 7) vs. 5 (2, 8) vs. 4 (3, 8); p=NS</p> <p>% with physical function worse: 25 (39/159) vs. 9 (15/161) vs. 11 (18/160) vs. 18 (28/160); p=0.0007</p> <p>% with worse fatigue: 13 (21/159) vs. 9 (14/161) vs. 7 (11/160) vs. 14 (22/160); p=NS</p> <p>% with worse function and fatigue: 7 (11/159) vs. 2 (4/161) vs. 3 (5/160) vs. 5 (8/160); p=NS</p> <p>Withdrawals due to adverse event: % Withdrawn due to worsening: 2 (3/159) vs. 0 vs. 1 (2/160) vs. <1 (1/160)</p> <p>Serious Adverse Events: % With ≥1 SAE*: 9 (15/159) vs. 4 (7/161) vs. 8 (13/160) vs. 4 (7/160); p=NS</p> <p>Number of serious adverse events: 16 vs. 8 vs. 17 vs. 7, p=0.0433 for GET vs. control</p> <p>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)</p> <p>% With ≥1 serious adverse reactions†: 1 (2/159) vs. 2 (3/161) vs. 1 (2/160) vs. 1 (2/160); p=NS</p> <p>Number of serious adverse reactions†: 2 vs. 4 vs. 2 vs. 2</p> <p>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)</p> <p>*Serious adverse events 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.</p> <p>†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.</p> <p>‡Non-serious adverse events 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.'</p>	United Kingdom Medical Research Council, Department of Health for England, Scottish Chief Scientist Office, Department for Work and Pensions

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Wiborg, 2015 ⁸⁴ RCT Medium	The Netherlands Single center 2008 to 2011 Outpatient clinic	CDC (Fukuda, 1994) criteria Inclusion: ≥18 years of age, referred to clinic for management of chronic fatigue, willing to receive group therapy. Exclusion: In a dispute over a disability pension, already undergoing CBT treatment, clinical reason for exclusion (i.e. they received specifically tailored interventions because they were unsuccessfully treated with CBT for CFS outside the study clinic, or were between 18 and 21 years of age and the family had to be involved in the therapy)	CBT 8/2 (n=68): Cognitive behavioral therapy in a group of 8 patients and 2 therapists. 14 2-hour group sessions over 6 months. Topics covered included personal goal setting, fixing sleep-wake cycles, reducing the focus on bodily symptoms, a systematic challenge of fatigue-related beliefs, regulation and gradual increase in activities, and accomplishment of personal goals. Patients were encouraged to give feedback to fellow participants. CBT 4/1 (n=68): Cognitive behavioral therapy in a group of 4 patients and 1 therapist. 14 2-hour group sessions over 6 months with same topics as those listed above. Wait list (n=68): Wait list for individual CBT Duration of treatment: 6 months Duration of followup: End of treatment
Williams, 2002 ⁸⁵ Crossover RCT Medium	United Kingdom Number of centers unclear Study year(s) NR University hospital	Oxford (Sharpe, 1991) Criteria Inclusion: Patients diagnosed with CFS by the Oxford criteria Exclusion: Anemia, inadequately replaced hypothyroidism, various reasons including diagnostic uncertainty and reluctance to meet the practical demands of the protocol.	Melatonin (n=42): Oral melatonin 5 mg daily Phototherapy (n=42): Phototherapy with 2500 Lux lightbox 30 minutes in morning Duration of treatment: 60 weeks: 12 weeks placebo, 12 weeks treatment, 12 week washout or placebo, then 12 week crossover and 12 week washout or placebo Duration of followup: End of treatment

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Wiborg, 2015 ⁸⁴ RCT Medium	CBT 8/2 vs. CBT 4/1 vs. wait list Mean age: 36.4 vs. 39.9 vs. 37.3 % Female: 75 (51/68) vs. 74 (50/68) vs. 82 (56/68) Duration of illness, mean (SD): 8.6 (9.5) vs. 7.6 (9.7) vs. 10.0 (10.6) years Severity of symptoms: Mean CIS fatigue severity, (SD): 51.4 (4.8) vs. 50.5 (4.5) vs. 49.9 (4.8) Comorbidities: NR	Number enrolled: 204 Number analyzed: 204	Overall: 17% (34/204) CBT 8/2 vs. CBT 4/1 vs. wait list: 15% (10/68) vs. 24% (16/68) vs. 12% (8/68)
Williams, 2002 ⁸⁵ Crossover RCT Medium	Overall, for those completing study Mean age (SD): 44.5 (11.1) years % Female: 57 (17/30) Race: NR Duration of illness: Mean (SD): 3.6 (3.3) years Severity of symptoms: NR Comorbidities: NR	Number enrolled: 42 Number analyzed: 30	Overall: 29% (12/42) Melatonin first vs. phototherapy first: 27% (6/22) vs. 30% (6/20)

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Benefits
Wiborg, 2015 ⁸⁴ RCT Medium	<p>CBT 8/2 plus CBT 4/1 vs. wait list</p> <p>Overall Function: Mean physical functioning (SD): 747.7 (22.0) vs. 63.3 (21.1), treatment effect 14.1 (95% CI, 9.0 to 19.3), p<0.001</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: Mean fatigue severity (SD): 33.5 (13.6) vs. 46.6 (8.5), treatment effect -13.8 (95% CI, -17.2 to -10.3), p<0.001</p> <p>Improvement in fatigue severity: 49.3% (67/139) vs. 8.8% (6/68), OR 10.0 (95 CI, 4.1 to 24.8), p<0.001</p> <p>Normal functioning in fatigue severity: 32.4% (44/136) vs. 2.9% (2/68), OR 15.8 (95% CI, 3.7 to 67.4), p<0.001</p> <p>Outcomes related to associated symptoms: Mean overall impairment (SD): 800 (664) vs. 1,389 (561), treatment effect -623 (95% CI, -788 to -458), p<0.001</p> <p>Mean psychological distress (SD): 135 (32.0) vs. 153 (38.5), treatment effect -22.1 (95% CI, -29.9 to -14.4), p<0.001</p>
Williams, 2002 ⁸⁵ Crossover RCT Medium	<p>Melatonin vs. phototherapy</p> <p>Overall Function: <i>Median (IQR) SF-36 physical functioning subscale scores (0-100 scale, lower score indicates better health)</i></p> <p>After treatment: 42.5 (16.3 to 53.8) vs. 45 (22.5 to 60.0); p=NS</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Median (IQR) visual analog scale score for How fatigued are you? (1-10 scale, lower score indicates better health)</i></p> <p>After treatment: 6.1 (4.8 to 8.0) vs. 7.2 (5.5 to 8.3); p=NS</p> <p><i>Median (IQR) Mental Fatigue Inventory scores (0-36 scale, lower score indicates better health)</i></p> <p>After treatment: 23 (15.0 to 27.0) vs. 24 (21.0 to 29.0); p=NS</p> <p><i>Median (IQR) SF-36 vitality subscale scores (0-100 scale, lower score indicates better health)</i></p> <p>After treatment: 20 (10.0 to 40.0) vs. 20 (10.0 to 25.0); p=NS</p> <p>Outcomes related to associated symptoms: NR</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Wiborg, 2015 ⁸⁴ RCT Medium	CBT 8/2 vs. CBT 4/1 vs. wait list Adverse Events: NR Withdrawals due to adverse event: NR Serious Adverse Events: NR	NR
Williams, 2002 ⁸⁵ Crossover RCT Medium	Melatonin vs. phototherapy Adverse Events: NR Withdrawals due to adverse event: None Serious Adverse Events: NR	Linbury Trust

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Country Number of Centers Study Years Setting (primary care, specialty clinic or other)	Diagnostic criteria Inclusion/ Exclusion criteria	Interventions (n) Duration of treatment Duration of followup
Windthorst, 2017 ⁸⁶ Pilot RCT High	Germany Single center Study year(s) NR Outpatient treatment center	CDC (Fukuda, 1994) criteria Inclusion: Females currently diagnosed with CFS meeting CDC criteria. Exclusion: Somatic or medical conditions explaining fatigue, substance abuse, primary psychiatric disorder, ongoing psychotherapy or activation program, BMI <18.5 or >35.	Graded exercise (n=15): 8 50 minute sessions consisting of 20 to 30 minutes of slow walking adapted to a heart rate at 70% of individual anaerobic threshold, discussion of diary, and review of session. Patients were encouraged to reduce resting and avoiding behavior, but simultaneously to watch carefully for symptoms and feelings of overload. Homework was 2 to 3 20 to 30 minute walking sessions per week at home, controlled by a pulse watch. Heartrate variability biofeedback therapy (n=13): 8 50 minute sessions consisting of 20 to 30 minutes of heartrate variability biofeedback therapy, discussion of diary, and review of biofeedback results. Homework was twice daily 5 to 10 minute practice sessions without the biofeedback device. Participants in both groups kept a daily diary of fatigue intensity, activity, and individual training at home. First session for both groups was introductory only, with no treatment administered. Duration of treatment: 8 weeks Duration of followup: 5 months
Wright, 2005 ⁸⁷ High	United Kingdom Single center Unclear study dates Specialty clinic	Oxford criteria, modified for children with three months fatigue Excluded other fatiguing medical conditions, and pre-existing ongoing CFS treatment	Pacing (n=6): pacing activity to the changing needs and responses of the body, managing energy within an overall limit, resting when necessary, avoiding physically and/or emotionally stressful situations until ready, tailoring return to school to the needs of the young person STAIRway to Health programme (n=7): structured tailored incremental rehabilitation program. Provided holistic understanding of CFS, explaining vicious cycles that exacerbate illness, bolstering adaptive coping strategies. Tailored gradual return to school and normal social activity. Treatment duration of 1 year: weekly for 1 month, every 2 weeks for three months, every 3 weeks for two months, every 4 weeks for six months

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Population characteristics	Number enrolled, analyzed	Attrition
Windthorst, 2017 ⁸⁶ Pilot RCT High	<p>Graded vs. heartrate variability biofeedback therapy</p> <p>Mean age: 50.0 vs. 51.4</p> <p>100% female</p> <p>Duration of illness: >2 years: 100% vs. 84.5% (11/13)</p> <p>>1 year: 0 vs. 7.7% (1/13)</p> <p>6 months: 0 vs. 7.7% (1/13)</p> <p>Severity of symptoms: <i>German Multidimensional Fatigue Inventory total, range 20 to 100, with lower scores indicating better health</i>: 68.8 vs. 61.5, p=NS</p> <p>Comorbidities: NR</p>	<p>Number enrolled: 28</p> <p>Number analyzed: 24 (11 graded exercise training, 13 biofeedback therapy)</p>	<p>Overall: 29% (8/28)</p> <p>Graded exercise vs. heartrate variability biofeedback therapy: NR</p>
Wright, 2005 ⁸⁷ High	<p>Age: 0 to 11: 1; 12 to 14: 7; 15 to 19: 5</p> <p>% Female: 62%</p> <p>Race: not reported</p> <p>Duration of illness, median months: 14.5 vs. 12.0</p>	<p>Enrolled: 13</p> <p>Analyzed: 11</p>	<p>15%</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	
Windthorst, 2017 ⁸⁶ Pilot RCT High	<p>Benefits</p> <p>Graded exercise vs. heartrate variability biofeedback therapy</p> <p>Overall Function: SF-36 Physical mean score (SD): after treatment: 44.8 (9.7) SES=0.92 vs. 45.2 (9.9) SES=0.28</p> <p>5 month follow up: 46.6 (7.1) SES=1.14 vs. 47.1 (12.2) SES=0.49</p> <p>SF-36 Mental mean score (SD): after treatment: 41.7 (10.9) SES=0.06 vs. 48.6 (9.0) SES=0.50</p> <p>5 month follow up: 38.3 (15.3) SES=0.30 vs. 51.0 (8.9) SES=0.73</p> <p>Quality of Life: NR</p> <p>Work/School Days: NR</p> <p>Proportion full/part-time work: NR</p> <p>Fatigue: <i>Multidimensional Fatigue Inventory total (SD), range 20 to 100, with lower scores indicating better health:</i></p> <p>Outcomes related to associated symptoms: after treatment: 56.6 (18.8) SES=1.21 vs. 48.2 (15.9) SES=1.37</p> <p>5 month follow up: 55.6 (21.3) SES=1.31 vs. 43.6 (15.9) SES=1.84</p> <p>Depression: PHQ-9 baseline vs. after treatment vs. 5 month follow up:</p> <p>GET: 8.9 (5.4) vs. 8.3 (4.6) vs. 8.8 (6.0), p=0.656</p> <p>Biofeedback: 7.5 (3.1) vs. 4.3 (3.0) vs. 4.2 (3.1), p=0.006</p>
Wright, 2005 ⁸⁷ High	<p>Differences, with all showing improvement in STAIRway arm than pacing arm:</p> <p>Child Health Questionnaire (1 = excellent, 5 = poor): 21.8 (20.94 to 22.74); F=23.4; p= 0.002</p> <p>School attendance comparing six months prior to study to last six months of treatment (percentage): 45.1 (21.8 to 92.0); F= 4.9; p= 0.057</p> <p>School attendance comparing six months prior to study to six months post study (percentage): 56.1 (6.3 to 105.7); F=6.8; p= 0.032</p> <p>Difficulty doing highly exertional activities (child rated) (0-4, 4 being fully healthy): 1.46 (20.33 to 3.25); F= 3.7; p= 0.095</p> <p>Difficulty doing moderately exertional activities such as swimming (0-4, 4 being fully healthy): 1.56 (20.20 to 2.33); F=4.4; p= 0.075</p> <p>Difficulty walking and climbing several flights of stairs(0-4, 4 being fully healthy): 0.93 (0.02 to 1.84); F= 5.8; p= 0.046</p> <p>Difficulty climbing one flight of stairs(0-4, 4 being fully healthy): 0.71 (20.18 to 1.61); F= 3.5; p= 0.10</p> <p>Difficulty getting in and out of bed(0-4, 4 being fully healthy): 0.31 (20.17 to 0.78); F= 2.4; p= 0.17</p> <p>Young Person Functional Ability Scale (percentage score rated by pediatrician): 17.0 (217.0 to 51.0) F=1.3; p= 0.28</p> <p>HADS Anxiety (0–21 child rated): 21.60 (28.31 to 5.10); F= 0.30; p= 0.60</p> <p>Birleson Depression Rating Scale (0–36): 22.99 (210.0 to 4.06); F= 1.0; p= 0.36</p> <p>Fatigue score (Chalder 0 to 42 14 item version): 25.2 (219.8 to 9.49); F= 0.67; p= 0.44</p>

Appendix E2. Evidence Table for Key Question 3

Author, year Study Design Risk of Bias	Harms	Sponsor
Windthorst, 2017 ⁸⁶ Pilot RCT High	<p>Graded exercise vs. heartrate variability biofeedback therapy</p> <p>Adverse Events: 1 increased appetite and weight gain in graded exercise therapy 1 change in daily routine and role perception in biofeedback therapy, 1 stress from conversations about symptoms and individual issues, 1 development of a depressive episode due to external individual reasons in graded exercise therapy group Withdrawals due to adverse events: NR Serious Adverse Events: NR</p>	Alfred-Teufel Foundation
Wright, 2005 ⁸⁷ High	Not reported	Not reported

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Al-Haggar, 2006 ⁷	Yes	Unclear	Yes	Yes	No	No	Yes	Yes/Yes	Yes	Yes	Yes	High
Arnold, 2015 ⁸	Unclear	Unclear	Yes, except for social functioning, mental health and emotional scores	Unclear	Unclear	Yes	Yes	No/No	No	No	Yes	Medium
Blacker, 2004 ⁹	Yes	NR	Yes	Unclear	Unclear	Unclear	Yes	No/No	Yes	No	Yes	Medium
Blockmans, 2003 ¹⁰	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	No	Yes	Yes	Medium
Burgess, 2012 ¹²	Yes	Yes	Yes	No	No	No	Yes	Yes/Yes	Yes	No	Yes	Medium
Chalder, 2010 ¹³	Yes	Yes	No	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Chan, 2013 ¹⁵ Ho, 2012 ¹⁶	Yes	Unclear	Yes	No	No	No	Yes	No/Yes	Yes	No	Yes	Medium
Clark, 2017 ¹⁷	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Crawley, 2018 ¹⁸	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Deale, 1997 ¹⁹ Deale, 2001 ²⁰	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Dybwad, 2007 ²¹	Yes	Yes	No, duration of illness	Yes ("testing person")	No	No	Yes	No/No	Yes	No	Yes	Medium
Fluge, 2011 ²²	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	No	No	Yes	Medium
Fluge, 2019 ²³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	No	Yes	Low
Friedberg, 2016 ²⁴	Yes	Unclear	Yes	Unclear	No	No	Yes	No/No	Yes	Yes	Yes	Medium
Fulcher, 1997 ²⁵	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Hobday, 2008 ²⁶	Yes	No	Yes	No, outcome assessors were not blinded. Data analysts were	No	No	Yes	Yes	No	Yes	Yes	High
Huanan, 2017 ²⁷	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Medium
Janse, 2018 ²⁸	Yes	Unclear	Yes	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Jason, 2007 ²⁹ Hlavaty, 2011 ³¹ Jason, 2009 ³⁰	Yes	Unclear	Yes	Unclear	No	No	No	Unclear	Yes	No	Yes	Medium
Knoop, 2008 ³² Tummers, 2010 ³³ Tummers, 2013 ³⁴	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Medium
Li, 2015 ³⁵	NR	NR	Yes	No	No	No	Yes	No/No	No	No	Yes	High
Lopez, 2011 ³⁶	Unclear	Unclear	Unclear	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Malaguarnera, 2008 ³⁷	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Yes	No	Yes	Medium
McKenzie, 1998 ³⁸ McKenzie, 2000 ³⁹	Yes	NR	Yes	Unclear	Unclear	Yes	Yes	No	Unclear	No	Yes	Medium
Montoya, 2013 ⁴⁰	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No/No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Montoya, 2018 ⁴¹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No 27% (37/135)/Yes 34% (26/67) vs. 21% (14/68)	No	Yes	Yes	Medium
Moss-Morris, 2005 ⁴²	Yes	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	Medium
Nijhof, 2012 ⁴³ Nijhof, 2013 ⁴⁴ Crawley, 2012 ⁴⁵	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Ockerman, 2000 ⁴⁶	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Yes	No	Yes	High
O'Dowd, 2006 ⁴⁷	Unclear	Yes	No (sex)	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Oka, 2014 ⁴⁸	Yes	Yes	Yes	No	No	No	Yes	No/No	Unclear	No	Yes	Medium
Ostojic, 2016 ⁴⁹	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	High
Peterson, 1990 ⁵⁰	Yes	Yes	Yes, except for age	Yes	Unclear	Yes	Yes	No/No	Yes	No	Yes	Medium
Pinxsterhuis, 2017 ⁵¹	Yes	Unclear	Yes	Yes	No	No	Yes	No/No	No	No	Yes	Medium
Powell, 2001 ⁵² Bentall, 2002 ⁵³ Powell, 2004 ⁵⁴	Yes	Yes	Yes	Unclear	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Rimes, 2013 ⁵⁵	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes/No	Yes	No	Yes	High
Roerink, 2017 ⁵⁶	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Low
Rowe, 1997 ⁵⁷	Unclear	Unclear	Yes, except for sex	Yes	Unclear	Yes	Yes	No	No	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
See, 1996 ⁵⁸	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	Unclear	Yes	High
Sharpe, 1996 ⁶⁰	Yes	Yes	Yes	Unclear	Unclear	No	No	No/No	Yes	No	Yes	Medium
Strayer, 2012 ⁶²	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes	No	Yes	Medium
Strayer, 1994 ⁶¹	Unclear	Yes	Yes, except for sex	Yes	Unclear	Yes	Yes	No	No	No	Yes	Medium
Stubhaug, 2008 ⁶³	Yes	Unclear	Yes	Yes	Yes (to medication only)	Yes (to medication only)	Yes (to medication only)	Yes/Yes	Yes	No	Yes	Medium
Stulemeijer, 2005 ⁶⁴	Yes	Yes	Yes	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Sulheim, 2014 ⁶⁵	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No	No; 20% of randomized subjects did not fulfill all criteria	No	Yes	Medium
Surawy, 2005 ⁶⁶	Unclear	Unclear	Unclear	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Sutcliffe, 2010 ⁶⁷	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	No	Yes	Medium
Taylor, 2004 ⁶⁸	Yes	Unclear	Yes	No	No	No	No	Unclear	Yes	No	Yes	Medium
The, 2007 ⁶⁹	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Medium
Tummers, 2012 ⁷⁰	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	No	Yes	Medium
Vercoulen, 1996 ⁷¹	Unclear	Unclear	Yes, except for sex	NA	Yes	Yes	Yes	No	No	No	Yes	Medium
Vermeulen, 2004 ⁷²	Yes	Yes	Yes	Unclear	No	No	Yes	No	Yes	No	Yes	Medium
Vollmer-Conna, 1997 ⁷³	Yes	Unclear	Yes, except for POMS-fatigue	Unclear	Unclear	Yes	Yes	No	Yes	No	Yes	Medium

Appendix F. Risk of Bias for Randomized Controlled Trials

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition reported	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Outcomes Pre-specified	Risk of Bias
Walach, 2008 ⁷⁴	Yes	Yes	Yes	Yes	Yes	50%, by design	Yes	No	Yes	No	Yes	Low
Wallman, 2004 ⁷⁵	Unclear	Unclear	Yes	Unclear	No	No	Yes	No/No	Yes	No	Yes	High
Wearden, 1998 ⁷⁹	Yes	Unclear	Yes	Unclear	Unclear	Partial (to medication)	Yes	No/No	Yes	No	Yes	Medium
Wearden, 2010 ⁷⁶ Wearden, 2012 ⁷⁷ Wearden, 2013 ⁷⁸	Yes	Yes	Yes	Yes	No	No	Yes	No/No	Yes	No	Yes	Medium
Weatherley-Jones 2004 ⁸⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Medium
White, 2011 ⁸¹ White, 2013 ⁸² Dougall, 2014 ⁸³ Bourke, 2014 ¹¹	Yes	Yes	Yes	Partial (statistician)	No	No	Yes	No/No	Yes	No	Yes	Medium
Wiborg, 2015 ⁸⁴	Yes	Yes	Yes	No	No	No	Yes	Yes/No	Yes	No	Yes	Medium
Williams, 2002 ⁸⁵	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	No	No	Yes	Medium
Windthorst, 2017 ⁸⁶	Unclear	Unclear	Yes	Unclear	No	No	Yes	No	No	No	Yes	High
Wright, 2005 ⁸⁷	Unclear	Yes	Yes	Yes	No	No	No	Unclear	Yes	No	Yes	High

Note: Refer to Appendix G for abbreviations and acronyms.

Appendix G. Abbreviations and Acronyms

Abbreviation	Definition
ACT	anaerobic activity therapy
ADL	activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AMD	adjusted mean difference
ANOVA	analysis of variance
AP	anteroposterior
APT	adaptive pacing therapy
ARD	adjusted risk difference
BMI	body mass index
CBT	cognitive behavioral therapy
CDC	Centers for Disease Control and Prevention
CDs	compact discs
CFS	chronic fatigue syndrome
CGI	Clinical Global Impression of Change
CGS-S	Clinical Global Impression Severity Score
CHQ-CF	child health questionnaire-child form
CI	confidence interval
CIBEROBN	Ventro de Investagacion Biomedica en Red de Fisiopatologia de la Obesidad y Nutricion
CIS	checklist individual strength
CNS	central nervous system
COG	cognitive therapy
COPD	Chronic Obstructive Pulmonary Disease
DF	degrees of freedom
DSM-III-R	Diagnostic Statistical Manual third edition revised
DSM-IV	Diagnostic Statistical Manual IV
EPC	Evidence-based Practice Center
ESS	Epworth Sleepiness Scale
FDA	U.S. Food and Drug Administration
FINE	Fatigue Intervention by Nurses Evaluation
FIQ	Fibromyalgia Impact Questionnaire
FIS	Fatigue Impact Scale
FITNET	fatigue in teenagers on the internet
FSM	fatigue self-management
FSM:ACT	fatigue self-management with web diaries and actigraphs
FSM:CTR	fatigue self-management with paper diaries and step counters
FSS	fatigue severity scale
GAA	guadidinoacetic acid
GES	guided graded exercise self-help
GET	graded exercise therapy
GETSET	guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome
GHQ	general health questionnaire
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-anxiety
HADS-D	Hospital Anxiety and Depression Scale-depression
HHV-6	human herpes virus-6
HRSD	Hamilton Rating Scale
HTA	Health Technology Assessment
iCBT	internet-based cognitive-behavioral therapy
ICD-10	International Statistical Classification of Diseases and Related Health Problems-10th revision

Appendix G. Abbreviations and Acronyms

IGF1	insulin-like growth factor-1
IGFBP3	insulin like growth factor binding protein 3
IgG	immunoglobulin G
IOM	Institute of Medicine
IQR	interquartile range
ITT	intention to treat
IV	intravenous
KFSS	Krupp Fatigue Severity Scale
KPS	Karnofsky Performance Scale
MBCT	mindfulness-based cognitive therapy
MCT	multi convergent therapy
MD	mean difference
MDD	major depressive disorder
ME	myalgic encephalomyelitis
MFI	Multidimensional Fatigue Inventory
M-H	Mantel-Haenszel test
MOS	Medical Outcome Study
MRI	magnetic resonance imaging
NAFKAM	Norway's National Research Center in Complementary and Alternative Medicine
NH&MRC	National Health and Medical Research Council
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NNT	number needed to treat
NR	not reported
NS	not significant
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PACE	pacing, graded activity, cognitive behavior therapy
PF	physical function
PHQ	patient health questionnaire
PICOTS	populations, interventions, comparators, outcomes, timing, and setting/study design
POMS	profile of mood states
QLI	quality of life index
QLS	quality of life score
QOL	Quality of Life
QOLI	quality of life inventory
QOL-SF	quality of life short form
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SCL-90-R	symptom checklist 90-revised
SD	standard deviation
SE	standard error
SEID	systemic exertion intolerance disease
SEM	standard error of the mean
SES	standardized effect sizes
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SGR	support the activities of research groups

Appendix G. Abbreviations and Acronyms

SIP	Sickness Impact Profile
SIP-8	Sickness Impact Profile 8-item
SMC	specialist medical care
SMD	standardized mean difference
SOE	strength of evidence
SSRI	selective serotonin reuptake inhibitor
VAS	visual analogue scale
WMD	weighted mean difference
ZonMW	ZorgOnderzoek Nederland and Medische wetenschappen

References

1. 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. doi: 10.1186/1756-0500-6-309. PMID: 23915640.
2. Devasahayam A, Lawn T, Murphy M, et al. Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: service evaluation survey. *JRSM Short Rep*. 2012;3(1):4. doi: 10.1258/shorts.2011.011127. PMID: 22299071.
3. Mariman A, Delesie L, Tobback E, et al. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. *J Psychosom Res*. 2013;75(5):491-6. doi: 10.1016/j.jpsychores.2013.07.010. PMID: 24182640.
4. 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. doi: 10.4997/JRCPE.2010.404. PMID: 21132135.
5. Nijrolder I, van der Windt D, de Vries H, et al. Diagnoses during follow-up of patients presenting with fatigue in primary care. *CMAJ*. 2009;181(10):683-7. doi: 10.1503/cmaj.090647. PMID: 19858240.
6. Stadje R, Dornieden K, Baum E, et al. The differential diagnosis of tiredness: a systematic review. *BMC Fam Pract*. 2016;17(1):147. PMID: 27765009.
7. Al-Haggag MS, Al-Naggag ZA, Abdel-Salam MA. Biofeedback and cognitive behavioral therapy for Egyptian adolescents suffering from chronic fatigue syndrome. *J Pediatr Neurol*. 2006;4(3):161-9. doi: 10.1055/s-0035-1557320.
8. Arnold LM, Blom TJ, Welge JA, et al. A randomized, placebo-controlled, double-blinded trial of duloxetine in the treatment of general fatigue in patients with chronic fatigue syndrome. *Psychosomatics*. 2015;56(3):242-53. doi: 10.1016/j.psych.2014.12.003. PMID: 25660434.
9. 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.
10. 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.
11. Bourke JH, Johnson AL, Sharpe M, et al. Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. *Psychol Med*. 2014;44(7):1545-52. doi: 10.1017/S0033291713002201. PMID: 23967878.
12. 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. doi: 10.1017/S1352465811000543. PMID: 21929831.
13. Chalder T, Deary V, Husain K, et al. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. *Psychol Med*. 2010;40(8):1269-79. doi: 10.1017/S003329170999153X. PMID: 19891804.
14. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: long-term follow-up of an RCT. *Behav Res Ther*. 2012;50(11):719-25. doi: 10.1016/j.brat.2012.08.005. PMID: 22985998.
15. 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. *Evid Based Complement Alternat Med*. 2013 doi: 10.1155/2013/485341. PMID: 23983785.
16. 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. doi: 10.1007/s12160-012-9381-6. PMID: 22736201.
17. Clark LV, Pesola F, Thomas JM, et al. Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. *Lancet*. 2017;390(10092):363-73. doi: 10.1016/S0140-6736(16)32589-2. PMID: 28648402.

References

18. Crawley EM, Gaunt DM, Garfield K, et al. Clinical and cost-effectiveness of the lightning process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. *Arch Dis Child*. 2018;103(2):155-64. doi: 10.1136/archdischild-2017-313375. PMID: 28931531.
19. Deale A, Chalder T, Marks I, et al. Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. *Am J Psychiatry*. 1997;154(3):408-14. PMID: 9054791.
20. Deale A, Husain K, Chalder T, et al. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry*. 2001;158(12):2038-42. PMID: 11729022.
21. Dybwad M, Frøslie K, Stanghelle J. Work capacity, fatigue and health related quality of life in patients with myalgic encephalopathy or chronic fatigue syndrome, before and after qigong therapy, a randomized controlled study. Nesoddtangen, Norway: Sunnaas Rehabilitation Hospital. 2007.
22. Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PLoS ONE*. 2011;6(10):e26358. doi: 10.1371/journal.pone.0026358. PMID: 22039471.
23. Fluge O, Rekeland IG, Lien K, et al. B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Ann Intern Med*. 2019;170(9):585-93. doi: 10.7326/m18-1451. PMID: 30934066.
24. Friedberg F, Adamowicz J, Caikauskaite I, et al. Efficacy of two delivery modes of behavioral self-management in severe chronic fatigue syndrome. *Fatigue*. 2016;4(3):158-74. doi: 10.1080/21641846.2016.1205876.
25. Fulcher KY, White PD. Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ*. 1997;314(7095):1647-52. doi: 10.1136/bmj.314.7095.1647. PMID: 9180065.
26. Hobday RA, Thomas S, O'Donovan A, et al. Dietary intervention in chronic fatigue syndrome. *J Hum Nutr Diet*. 2008;21(2):141-9. doi: 10.1111/j.1365-277X.2008.00857.x. PMID: 18339054.
27. Huanan L, Wang J, Zhang W, et al. Chronic fatigue syndrome treated by the traditional Chinese procedure abdominal tuina: a randomized controlled clinical trial. *J Tradit Chin Med*. 2017;37(6):819-26. doi: 10.1016/S0254-6272(18)30046-3.
28. Janse A, Worm-Smeitink M, Bleijenberg G, et al. Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. *Br J Psychiatry*. 2018;212(2):112-8. doi: 10.1192/bjp.2017.22. PMID: 29436329.
29. 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.
30. 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. doi: 10.1016/j.pec.2009.02.015. PMID: 19356884.
31. Hlavaty LE, Brown MM, Jason LA. The effect of homework compliance on treatment outcomes for participants with myalgic encephalomyelitis/chronic fatigue syndrome. *Rehabil Psychol*. 2011;56(3):212-8. doi: 10.1037/a0024118. PMID: 21767035.
32. 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. doi: 10.1192/bjp.bp.108.051292. PMID: 18827302.
33. 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. doi: 10.1037/a0020052. PMID: 20873907.
34. Tummers M, Knoop H, van Dam A, et al. Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. *J Psychosom Res*. 2013;74(5):373-7. doi: 10.1016/j.jpsychores.2013.01.007. PMID: 23597323.

References

35. Li DQ, Li ZC, Dai ZY. Selective serotonin reuptake inhibitor combined with dengzhanshengmai capsule improves the fatigue symptoms: a 12-week open-label pilot study. *Int J Clin Exp Med*. 2015;8(7):11811-7. PMID: 26380022.
36. Lopez C, Antoni M, Penedo F, et al. A pilot study of cognitive behavioral stress management effects on stress, quality of life, and symptoms in persons with chronic fatigue syndrome. *J Psychosom Res*. 2011;70(4):328-34. doi: 10.1016/j.jpsychores.2010.11.010. PMID: 21414452.
37. Malaguarnera M, Gargante MP, Cristaldi E, et al. Acetyl L-Carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr*. 2008;46(2):181-90. PMID: 17658628.
38. 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.
39. McKenzie R, Reynolds JC, O'Fallon A, et al. Decreased bone mineral density during low dose glucocorticoid administration in a randomized, placebo controlled trial. *J Rheumatol*. 2000;27(9):2222-6. PMID: 10990237.
40. 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. doi: 10.1002/jmv.23713. PMID: 23959519.
41. Montoya JG, Anderson JN, Adolphs DL, et al. KPAX002 as a treatment for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a prospective, randomized trial. *Int J Clin Exp Med*. 2018;11(3):2890-900.
42. 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.
43. Nijhof SL, Bleijenberg G, Uiterwaal CS, et al. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. *Lancet*. 2012;379(9824):1412-8. doi: 10.1016/S0140-6736(12)60025-7. PMID: 22385683.
44. Nijhof SL, Priesterbach LP, Uiterwaal CS, et al. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. *Pediatrics*. 2013;131(6):e1788-95. doi: 10.1542/peds.2012-2007. PMID: 23669515.
45. Crawley EM. Internet-based cognitive behavioural therapy (FITNET) is an effective treatment for adolescents with chronic fatigue syndrome. *Arch Dis Child Educ Pract Ed*. 2012;97(6):238. PMID: 22952037.
46. Öckerman PA. Antioxidant treatment of chronic fatigue syndrome. *Clin Pract Alternat Med*. 2000;1(2):88-91.
47. 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.
48. Oka T, Tanahashi T, Chijiwa T, et al. Isometric yoga improves the fatigue and pain of patients with chronic fatigue syndrome who are resistant to conventional therapy: a randomized, controlled trial. *Biopsychosoc Med*. 2014;14(27):1-9. doi: 10.1186/s13030-014-0027-8. PMID: 25525457.
49. Ostojic SM, Stojanovic M, Drid P, et al. Supplementation with guanidinoacetic acid in women with chronic fatigue syndrome. *Nutrients*. 2016;8(2):72. doi: 10.3390/nu8020072. PMID: 26840330.
50. 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.
51. Pinxsterhuis I, Sandvik L, Strand EB, et al. Effectiveness of a group-based self-management program for people with chronic fatigue syndrome: a randomized controlled trial. *Clin Rehabil*. 2017;31(1):93-103. doi: 10.1177/0269215515621362. PMID: 26672998.
52. Powell P, Bentall RP, Nye FJ, et al. Randomised controlled trial of patient education to encourage graded exercise in chronic fatigue syndrome. *BMJ*. 2001;322(7283):387-90. PMID: 11179154.

References

53. Bental RP, Powell P, Nye FJ, et al. Predictors of response to treatment for chronic fatigue syndrome. *Br J Psychiatry*. 2002;181:248-52. PMID: 12204931.
54. Powell P, Bental RP, Nye FJ, et al. Patient education to encourage graded exercise in chronic fatigue syndrome. 2-year follow-up of randomised controlled trial. *Br J Psychiatry*. 2004;184:142-6. PMID: 14754826.
55. Rimes KA, Wingrove J. Mindfulness-based cognitive therapy for people with chronic fatigue syndrome still experiencing excessive fatigue after cognitive behaviour therapy: a pilot randomized study. *Clin Psychol Psychother*. 2013;20(2):107-17. doi: 10.1002/cpp.793. PMID: 21983916.
56. Roerink ME, Bredie SJH, Heijnen M, et al. Cytokine inhibition in patients with chronic fatigue syndrome: a randomized trial. *Ann Intern Med*. 2017;166(8):557-64. doi: 10.7326/M16-2391. PMID: 28265678.
57. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res*. 1997;31(1):133-47. PMID: 9201655.
58. See DM, Tilles JG. Alpha-interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest*. 1996;25(1-2):153-64. PMID: 8675231.
59. Sharpe M, Goldsmith KA, Johnson AL, et al. Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial. *Lancet Psychiatry*. 2015;2(12):1067-74. doi: 10.1016/S2215-0366(15)00317-X. PMID: 26521770.
60. 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.
61. 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.
62. 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. doi: 10.1371/journal.pone.0031334. PMID: 22431963.
63. Stubhaug B, Lie SA, Ursin H, et al. Cognitive-behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial. *Br J Psychiatry*. 2008;192(3):217-23. doi: 10.1192/bjp.bp.106.031815. PMID: 18310583.
64. Stulemeijer M, de Jong LW, Fiselier TJ, et al. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. *BMJ*. 2005;330(7481):14. PMID: 15585538.
65. Sulheim D, Fagermoen E, Winger A, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatrics*. 2014;168(4):351-60. doi: 10.1001/jamapediatrics.2013.4647. PMID: 24493300.
66. Surawy C, Roberts J, Silver A. The effect of mindfulness training on mood and measures of fatigue, activity, and quality of life in patients with chronic fatigue syndrome on a hospital waiting list: a series of exploratory studies. *Behav Cogn Psychother*. 2005;33(1):103-9. doi: 10.1017/S135246580400181X.
67. 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. doi: 10.1111/j.1365-2362.2009.02225.x. PMID: 19912315.
68. 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.
69. The GKH, Bleijenberg G, van der Meer JWM. The effect of acclidine in chronic fatigue syndrome: a randomized controlled trial. *PLoS Clin Trials*. 2007;2(5):e19. PMID: 17525791.
70. Tummers M, Knoop H, van Dam A, et al. Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. *Psychol Med*. 2012;42(10):2205-15. doi: 10.1017/S0033291712000232. PMID: 22354999.

References

71. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet*. 1996;347(9005):858-61. PMID: 8622391.
72. 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.
73. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med*. 1997;103(1):38-43. PMID: 9236484.
74. 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. doi: 10.1159/000116609. PMID: 18277062.
75. Wallman KE, Morton AR, Goodman C, et al. Randomised controlled trial of graded exercise in chronic fatigue syndrome. *Med J Aust*. 2004;180(9):444-8. PMID: 15115421.
76. 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. doi: 10.1136/bmj.c1777. PMID: 20418251.
77. 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. doi: 10.1192/bjp.bp.111.107474. PMID: 22844025.
78. 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. doi: 10.1037/a0033561. PMID: 23796316.
79. Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry*. 1998;172:485-90. PMID: 9828987.
80. 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.
81. 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. doi: 10.1016/S0140-6736(11)60096-2. PMID: 21334061.
82. 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. doi: 10.1017/S0033291713000020. PMID: 23363640.
83. 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. doi: 10.1016/j.jpsychores.2014.04.002. PMID: 24913337.
84. Wiborg JF, van Bussel J, van Dijk A, et al. Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. *Psychother Psychosom*. 2015;84(6):368-76. doi: 10.1159/000438867. PMID: 26402868.
85. 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.
86. Windthorst P, Mazurak N, Kuske M, et al. Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: an exploratory pilot study. *J Psychosom Res*. 2017;93:6-13. doi: 10.1016/j.jpsychores.2016.11.014. PMID: 28107894.
87. Wright B, Ashby B, Beverley D, et al. A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents. *Arch Dis Child*. 2005;90(4):369-72. PMID: 15781925.