Annals of Internal Medicine

REVIEW

Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop

M.E. Beth Smith, DO; Elizabeth Haney, MD; Marian McDonagh, PharmD; Miranda Pappas, MA; Monica Daeges, BA; Ngoc Wasson, MPH; Rongwei Fu, PhD; and Heidi D. Nelson, MD, MPH

Background: Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) is a debilitating multisystem condition affecting more than 1 million adults in the United States.

Purpose: To determine benefits and harms of treatments for adults with ME/CFS and identify future research needs.

Data Sources: MEDLINE, PsycINFO, and Cochrane databases (January 1988 to September 2014); clinical trial registries; reference lists; and manufacturer information.

Study Selection: English-language randomized trials of the effectiveness and adverse effects of ME/CFS treatments.

Data Extraction: Data on participants, study design, analysis, follow-up, and results were extracted and confirmed. Study quality was dual-rated by using prespecified criteria; discrepancies were resolved through consensus.

Data Synthesis: Among 35 treatment trials enrolling participants primarily meeting the 1994 Centers for Disease Control and Prevention and Oxford case definitions of CFS, the immune modulator rintatolimod improved some measures of exercise performance compared with placebo in 2 trials (low strength of evidence). Trials of galantamine, hydrocortisone, IgG, valganciclovir, isoprinosine, fluoxetine, and various complementary medicines were inconclusive (insufficient evidence). Counseling therapies and graded exercise therapy compared with no treatment, relaxation, or support improved fatigue, function, global improvement, and work impairment in some trials; counseling therapies also improved quality of life (low to moderate strength of evidence). Harms were rarely reported across studies (insufficient evidence).

Limitation: Trials were heterogeneous and were limited by size, number, duration, applicability, and methodological quality.

Conclusion: Trials of rintatolimod, counseling therapies, and graded exercise therapy suggest benefit for some patients meeting case definitions for CFS, whereas evidence for other treatments and harms is insufficient. More definitive studies comparing participants meeting different case definitions, including ME, and providing subgroup analysis are needed to fill research gaps.

Primary Funding Source: Agency for Healthcare Research and Quality. (PROSPERO: CRD42014009779)

Ann Intern Med. 2015;162:841-850. doi:10.7326/M15-0114 **www.annals.org**
For author affiliations, see end of text.

Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) is a debilitating multisystem condition characterized by chronic and disabling fatigue and several other symptoms, including pain, sleep disturbance, neurologic and cognitive changes, motor impairment, and altered immune and autonomic responses (1–3). Experts consider postexertional malaise and memory or concentration problems to be critical components (4–6), and several diagnostic criteria, including those released by the Institute of Medicine in 2015, require the presence of postexertional malaise (1, 2, 7–9).

There is uncertainty regarding the cause of ME/CFS, whether it is a pathologically discrete syndrome (2, 4), whether ME should be considered a subset of CFS or its own distinct disease (6), and whether symptoms are nonspecific and shared by other disease entities. Some propose that an inciting event initiates an immune response that leads to immune and neuroendocrine dysregulation (10, 11). Viral causes have been studied on the basis of the observation that most patients report a sudden onset of symptoms that were preceded by a febrile illness with enlarged lymph nodes. However, no specific virus or other infectious agent has been identified, and not all patients experience a preceding febrile illness (10).

The Centers for Disease Control and Prevention (CDC) reported a 0.3% prevalence of ME/CFS in the United States in 1997, corresponding to more than 1 million adults (12). Through use of different case definitions or different diagnostic methods, the rate may be as high as 3.3% (13, 14).

Given the multitude of symptoms that patients with ME/CFS experience, treatment approaches have been broad, including immunologic, pharmacologic, and behavioral treatments and complementary and alternative medicine. No medications for the treatment of ME/CFS have been approved by the U.S Food and Drug Administration (FDA); however, many have been used without review and approval (off-label), and some are not approved for any indication in the United States (for example, isoprinosine and rintatolimod). In an FDA survey, patients with ME/CFS identified treatments that fell

See also:

Related articles 834, 860
Editorial comment 871

Web-Only
CME quiz

into 2 broad categories: those intended to treat the cause of the disease and those targeting specific symptoms or perpetuating factors (15). Medications to treat causes include immune modulators, antivirals, and antibiotics. Interventions targeting symptoms include medications to treat specific symptoms, such as pain, fatigue, autonomic dysfunction, and sleep dysfunction, and nondrug therapies, such as yoga, exercise techniques, counseling, pacing strategies, and mental exercises (15). In practice, the clinical management of patients varies widely, and many patients receive a multifaceted approach to treatment.

This systematic review is part of a larger report to inform a research agenda for the National Institutes of Health (NIH) 2014 Pathways to Prevention Workshop, an evidence-based methodology workshop (16). This review evaluates and summarizes research on the benefits and harms of medical and nonmedical treatments for ME/CFS based on trials enrolling patients meeting criteria for ME, CFS, or both and identifies limitations of current studies and needs for future research in this area.

METHODS

Key questions guiding this review were developed in collaboration with the NIH ME/CFS Working Group following a standard protocol, including input from key informants and a technical expert panel, registration in the PROSPERO database for systematic reviews (17), and posting on an Agency for Healthcare Research and Quality (AHRQ) public Web site. Key questions concern the benefits and harms of therapeutic interventions for adults with ME/CFS, how interventions vary by patient subgroups, and characteristics of patients who respond and do not respond to interventions. A technical report details the methods and includes the analytic framework, search strategies, and additional evidence tables (16).

Data Sources and Searches

A research librarian searched the following electronic databases to identify relevant articles published between January 1988 (year of first case definition) and September 2014: MEDLINE (Ovid), PsycINFO, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and National Health Sciences Economic Evaluation Database. Searches were supplemented by references identified from additional sources, including trial registries, scientific information packets from manufacturers, reference lists, and experts.

Study Selection

We included English-language trials that enrolled patients aged 18 years or older who met the criteria for ME, CFS, or both according to at least 1 established case definition. Included were randomized, controlled trials of at least 12 weeks' duration that compared medications, complementary and alternative medicine approaches, counseling and behavior therapies, and exercise therapies with no treatment or other types of treatment. For completeness, we separately summarized additional trials of medications that were designed for shorter durations of treatment. Treatment outcomes were patient centered and included function, fatigue, quality of life, involvement in daily activities, and harms. We did not include studies of the results of laboratory tests or studies focusing on individual symptoms, such as pain.

Two investigators independently evaluated each study to determine inclusion eligibility. Disagreement was resolved by consensus, with a third investigator making the final decision as needed.

Data Extraction and Quality Assessment

From the included studies, one investigator extracted study details and a second investigator reviewed them for accuracy and completeness. Investigators rated the quality (risk of bias) of the individual studies and strength of the body of evidence on the basis of established criteria (18). The strength of evidence consisted of 4 major categories—high, moderate, low, or insufficient—according to the design, quantity, size, and quality of studies; consistency across studies; precision of estimates; and directness of effect. A second investigator reviewed ratings, and disagreements were resolved by consensus, with a third investigator making the final decision as needed.

Data Synthesis

For most treatments, only single trials were available; data were synthesized qualitatively with attention to such factors as patient characteristics and risk of bias. For treatments with more than 2 trials, the appropriateness of statistical meta-analysis was determined by considering internal validity of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. The combined effects were estimated by using a random-effects model based on the profile likelihood method (19). Combined relative risks were calculated for binary outcomes. For continuous outcomes, the combined weighted mean differences were calculated by using the means and SDs at follow-up from each intervention group. The chi-square test based on the Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were used to assess heterogeneity in effects between studies, and sensitivity analyses explored statistical heterogeneity when present. All quantitative analyses were performed by using Stata/IC software, version 13.0 (Stata Corp.).

Role of the Funding Source

The AHRQ funded the review, and a working group convened by the NIH helped develop the review's scope and key questions. Neither had a role in study selection, quality assessment, or synthesis. The investigators are solely responsible for the content.

RESULTS

Among the 6175 abstracts identified by searches, 35 treatment trials in 45 publications met inclusion cri-

teria (**Appendix Figure**, available at www.annals.org). These included 9 trials of medications (20–28), 7 of complementary and alternative medicine (29–35), 14 of counseling or behavioral therapies (8, 36–48), 7 of exercise (23, 48–54), and 4 comparing or combining different therapies (23, 40, 48, 53) (**Appendix Table 1**, available at www.annals.org). Most trials met criteria for fair quality (24 trials) or poor quality (5 trials). Trials enrolled predominantly middle-aged women from ME/CFS specialty clinics; used CFS case definitions, primarily the 1994 CDC (3) or Oxford criteria (56), to determine participant eligibility; had small sample sizes (27 trials had <100 participants); and were conducted in the United States and Western Europe (16). Outcomes varied across trials and included 20 unique measures as well as various Likert scales developed for individual studies. Even when trials used the same outcome, measures and thresholds were often defined differently, thereby limiting comparisons and statistical meta-analysis. In general, harms were rarely reported.

Major limitations of trials included enrollment of fewer than 20 participants in a study group (8, 20, 25, 28–30), dissimilar groups at baseline (31, 43, 50, 52), high loss to follow-up (23, 26, 29, 37, 54), unclear or lack of intention-to-treat analysis (8, 24, 27, 29, 34, 35, 39, 40, 42, 54), no reporting of between-group comparisons for key outcomes (27, 30, 32, 35), unclear randomization process (8, 25, 30, 35, 36, 39, 40, 42, 45), and inadequate blinding (8, 23, 25, 29, 32, 35–37, 39, 41, 44–46, 48, 50–52).

Medications

Nine placebo-controlled trials of medications evaluated the effectiveness of rintatolimod (21, 27), valganciclovir (28), galantamine (26), hydrocortisone (22), hydrocortisone plus fludrocortisone (24), IgG (20), isoprinosine (25), and fluoxetine (23). None of these medications are FDA approved for CSF. Eight trials met criteria for fair quality (20–24, 26–28) and 1 for poor quality (25).

Benefits

Rintatolimod, an investigational intravenous immune modulator and antiviral drug, improved measures of exercise performance compared with placebo in 2 fair-quality trials (n = 324) enrolling severely disabled adults (improved cardiopulmonary exercise test tolerance, 36.5% versus 15.2%, P = 0.047; improved exercise duration, 10.3% versus 2.1%, P = 0.007; improved exercise work, 11.8% versus 5.8%, P = 0.01) (low strength of evidence) (21, 27). The clinical implications of these changes are unclear. One of these 2 trials also reported improvement in measures of function (activities of daily living and Karnofsky Performance Scale score) (21), and the other indicated a reduction in use of other medications to relieve CFS symptoms (27). Attrition ranged from 9% to 19% and adherence, from 83% to 91%. In a small, underpowered trial of valganciclovir that enrolled 30 participants with elevated antibody titers who were suspected of having viral-onset ME/CFS, fatigue was improved in the treatment group compared with the placebo group on the basis of 1 scale, but no statistically significant differences were seen for other measures (28). These trials did not report data for patient subgroups.

Trials of galantamine, hydrocortisone, IgG, isoprinosine, and fluoxetine indicated no beneficial effects but were limited by small numbers of participants. Additional trials enrolling fewer than 30 participants and with durations less than 12 weeks indicated no statistically significant differences compared with placebo for acyclovir (57) and showed improved 36-item Short-Form Survey (SF-36) scores for physical health and function with rituximab (58).

Harms

Differences in total withdrawals, withdrawals due to adverse events, and harms of medications were not reported or did not statistically significantly differ between groups for most medications. Participants taking rintatolimod reported flu-like symptoms, chills, vasodilatation, and dyspnea (27). Galantamine was associated with higher rates of withdrawal and attrition than was placebo, demonstrating a dose-dependent relationship; the highest rates were seen at doses of 15 mg or more per day (26). Overall, 90% of participants in the galantamine trial reported harms, with depression, nausea, and headache most common in both the treatment and placebo groups; 2% experienced serious events, although none was attributed to the study drug (26).

In the 2 corticosteroid trials, attrition rates were 10% (22) and 20% (24). Harms that significantly differed between treatment and placebo groups included suppression of adrenal glucocorticoid responsiveness (34% versus 0%; P < 0.001), increased appetite (48% versus 23%; P = 0.02), weight gain (54% versus 23%; P = 0.006), and difficulty sleeping (48% versus 23%; P = 0.02) (22). Participants taking intravenous IgG (1 g/kg) reported significantly more headaches (93%) than did placebo recipients (60%) (20). Participants taking fluoxetine had more withdrawals from medication-associated adverse events compared with the placebo group (13% versus 3%), although total withdrawals did not differ.

Complementary and Alternative Medicines

Seven trials compared complementary and alternative medicine approaches with usual care, placebo, or another intervention (29–35). Five small trials evaluated dietary approaches or supplements, including a low-sugar/low-yeast diet compared with a healthy diet (29), antioxidant extract of pollen versus placebo (30), acclydine (a supplement proposed to increase biologically active insulin-like growth factor) versus placebo (31), formulations of L-carnitine compared with each other (32), and melatonin versus phototherapy or placebo (35). Additional trials evaluated distant healing (33) and homeopathy (34). One trial met criteria for good quality (31, 33), 5 for fair quality (29, 32, 34, 35), and 1 for poor quality (30).

Benefits

Trials of diets, supplements, or phototherapy indicated no statistically significant differences between treatment and comparison groups. A trial of distant healing that used various techniques of prayer or imagining the transmission of healing energy, light, or power compared with usual care also found no statistically significant differences between groups (33). A trial of homeopathy that used various individualized prescriptions for remedies provided by practitioners versus placebo indicated improved general fatigue for the homeopathy group (Multidimensional Fatigue Inventory, 20-item score, 2.70 versus 1.35; $P = 0.04$) (34). However, the clinical significance of this small change is not clear, and there were no between-group differences for several other outcomes.

Harms

Patients taking formulations of L-carnitine reported sleeplessness and feeling overstimulated (32). No serious harms were reported in the trial of pollen extract (30).

Counseling and Behavioral Therapies

Fourteen trials in 23 publications evaluated the effectiveness of a counseling or behavioral therapy. Therapies included cognitive behavioral therapy (CBT) intended to change behavioral and belief factors that may trigger and maintain symptoms (36–38, 40, 43, 44, 48, 59–61); group or individual counseling wherein participants learned coping and self-sufficiency strategies (8, 45); self-instruction through use of informative booklets with assignments (41, 46, 62); pragmatic rehabilitation that provided strategies to promote a gradual progression of activity (40); and supportive listening providing empathic and nondirective support (47, 63, 64). These therapies were compared with usual care, wait-list control, no treatment, relaxation techniques, adaptive pacing (avoiding activities demanding >70% of a participant's perceived energy), anaerobic therapy that promoted gradual return of pleasurable activities (40, 47, 63, 64), graded exercise therapy (GET) (48), or an alternate form of counseling or behavioral therapy. Five trials met criteria for good quality (44–48), 6 for fair quality (36–38, 40, 41, 43), and 3 for poor quality (8, 39, 42).

Benefits

The effectiveness of counseling and behavior therapies was inconsistent across trials and outcome measures. In some trials, counseling and behavior therapies improved fatigue (8, 38, 39, 41, 43, 46, 48, 62), physical function (Figure 1) (38, 40, 41, 43, 44, 48), quality of life (42, 45), work impairment (38, 48), and the clinical global impression of change scale (38, 48, 59) (low to moderate strength of evidence). No statistically significant differences between counseling and comparison groups were reported for other outcomes. The trials were too heterogeneous to allow us to determine whether one type of counseling intervention was more effective than another, and a small trial comparing face-to-face versus telephone CBT indicated no differences between these therapeutic approaches (37).

A meta-analysis of 4 trials of CBT reporting changes in SF-36 physical function scores indicated no statistically significant difference between intervention and control groups (weighted mean difference, 10.42 [95% CI, −3.86 to 24.69]; $I^2 = 79.6\%$, 4 trials) (Figure 2) (39, 42, 47, 56). However, physical function scores were higher for the intervention group when an outlier study (59) was removed in a sensitivity analysis (weighted mean difference, 6.02 [CI, 1.05 to 10.88]; $I^2 = 0.0\%$; 3 trials) (47, 56, 57).

Harms

Three trials reported harms with counseling or behavioral therapies. In the largest trial comparing CBT with adaptive pacing or usual care (PACE [Pacing, graded Activity and Cognitive behaviour therapy: a randomized Evaluation] trial), the therapy group reported significantly fewer serious and nonserious adverse events than the other groups (6% serious events versus 11%; $P = 0.03$) (48). A trial comparing counseling with a wait-list control group reported no withdrawals due to harms (45), and a trial comparing pragmatic rehabilitation with supportive listening or usual care reported no differences between groups for reported harms or withdrawals due to harms (47).

Exercise Therapies

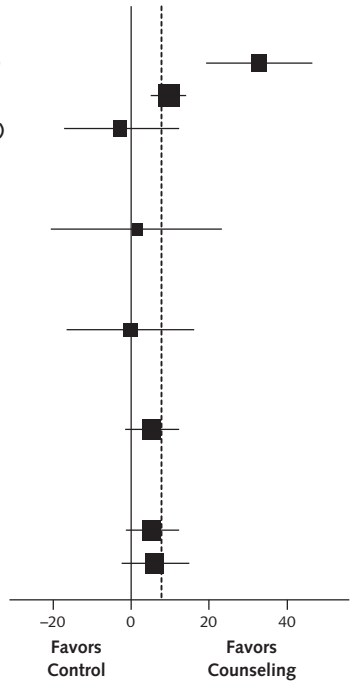
Seven trials evaluated the effectiveness of exercise therapies. These included GET involving an exercise plan with structured incremental increases in exercise over time (23, 48, 50, 52, 53), qigong exercise (49, 51), and home orthostatic training (54). Trials compared one form of exercise with another, standard medical care, adaptive pacing, CBT, or placebo. One trial met criteria for good quality (48) and 6 for fair quality (23, 49–54).

Benefits

GET improved measures of function (SF-36 physical function weighted mean difference, 10.68 [CI, 6.32 to 16.88]; $I^2 = 0\%$; 3 trials) (Figure 3) (48, 50, 52), fatigue (4 trials, $n = 619$), global improvement as measured by the clinical global impression of change score (relative risk, 1.58 [CI, 1.24 to 2.47]; $I^2 = 0\%$; 3 trials) (Figure 4) (48, 50, 52); and work impairment (1 trial, $n = 475$; low to moderate strength of evidence). The largest trial of GET (PACE trial) showed less deterioration of physical function with GET than with control (25% for adaptive pacing versus 18% for usual care versus 11% for GET; $P < 0.001$), but there were no statistically significant differences in serious deterioration measured by a composite score (48, 65). No differences between comparison groups were reported in a trial of 314 participants that compared GET with CBT or in a trial of 115 participants that compared CBT plus GET versus usual care (53).

Figure 1. Effects of various types of counseling therapies on the SF-36 physical function subscale.

Study, Year (Reference)	Counseling Patients, *n*	Counseling Mean SF-36 Score (SD)	Control Patients, *n*	Control Mean SF-36 Score (SD)	Weighted Mean Difference (95% CI)
Individual CBT*					
Deale et al, 2001 (59)	30	71.6 (28)	30	38.4 (26.9)	33.20 (19.31 to 47.09)
White et al, 2011 (48)†	155	58.2 (24.1)	316	48.3 (24.8)	9.90 (5.22 to 14.58)
Jason et al, 2007 (40)†	29	58.64 (30.44)	28	61.2 (27.7)	–2.56 (–17.66 to 12.54)
Group CBT*					
O'Dowd et al, 2006 (43)†	52	35.2 (81.5)	101	33.8 (9.0)	1.40 (–20.82 to 23.62)
Buddy counseling‡					
Jason et al, 2010 (8)	15	36.1 (14.1)	15	36 (29.9)	0.10 (–16.63 to 16.83)
Pragmatic rehabilitation§					
Wearden et al, 2010 (47)†	81	43.27 (27.38)	176	37.7 (26.8)	5.57 (–1.59 to 12.73)
Self-instruction‖					
Knoop et al, 2008 (41)	84	65.9 (23.2)	85	60.2 (23.7)	5.70 (–1.37 to 12.77)
Tummers et al, 2012 (46)†	55	65.4 (24.9)	56	59.3 (22.9)	6.10 (–2.80 to 15.00)

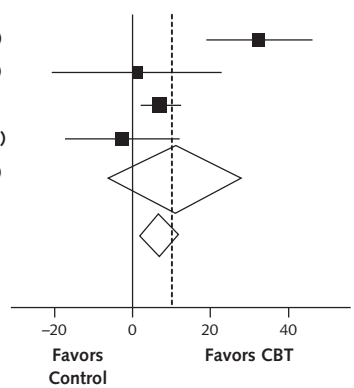


CBT = cognitive behavioral therapy; SF-36 = Short Form-36.
* Therapy intended to change behavioral and belief factors that may trigger and maintain symptoms.
† Compared with all participants in control groups in the trial.
‡ Teaches coping and self-sufficiency strategies.
§ Strategies to promote a gradual progression of activity.
‖ Use of informative booklets with assignments.

A trial enrolling 144 participants in China compared qigong exercise with sham qigong (49, 51). Although some measures of fatigue on the Chalder Fatigue Scale were statistically significantly better with the exercise group, others were not. A trial of 38 patients found no statistically significant differences in measures of fatigue between home orthostatic training compared with usual care or sham orthostatic training (54).

Figure 2. Meta-analysis of trials of the effects of CBT on the SF-36 physical function subscale.

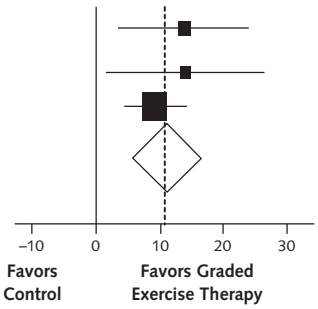
Study, Year (Reference)	CBT Patients, *n*	CBT Mean SF-36 Score (SD)	Control Patients, *n*	Control Mean SF-36 Score (SD)	Weighted Mean Difference (95% CI)
Deale et al, 2001 (59)	30	71.6 (28)	30	38.4 (26.9)	33.20 (19.31 to 47.09)
O'Dowd et al, 2006 (43)*	52	35.2 (81.5)	101	33.8 (9.0)	1.40 (–20.82 to 23.62)
White et al, 2011 (48)	155	58.2 (24.1)	157	50.8 (24.7)	7.40 (1.99 to 12.81)
Jason et al, 2007 (40)	29	58.64 (30.44)	28	61.2 (27.7)	–2.56 (–17.66 to 12.54)
Total (I^2 = 79.6; P = 0.002)					10.46 (–7.47 to 27.77)
Sensitivity analysis excluding Deale et al, 2001					**6.02 (1.05 to 10.99)**
Total (I^2 = 0.00; P = 0.437)					



CBT = cognitive behavioral therapy; SF-36 = Short Form-36.
* Compared with all participants in control groups in the trial.

Figure 3. Meta-analysis of trials of the effects of graded exercise therapy on the SF-36 physical function subscale.

Study, Year (Reference)	Graded Exercise Therapy: Patients, *n*	Graded Exercise Therapy: Mean SF-36 Score (SD)	Control: Patients, *n*	Control: Mean SF-36 Score (SD)	Weighted Mean Difference (95% CI)
Fulcher and White, 1997 (50)	29	69 (18.5)	30	55 (21.8)	14.00 (3.70–24.30)
Moss-Morris et al, 2005 (52)	25	69.05 (21.94)	24	55 (22.9)	14.05 (1.48–26.62)
White et al, 2011 (48)*	159	57.7 (26.5)	316	48.3 (24.8)	9.40 (4.46–14.34)
Total (I^2 = 0.0; P = 0.627)					10.68 (6.32–16.88)



Graded exercise therapy involved an exercise plan with structured incremental increases in exercise over time, qigong exercise, and home orthostatic training. SF-36 = Short Form-36.
* Compared with all participants in control groups in the trial.

Harms

Harms were poorly reported in exercise trials, and no subgroup analyses were performed. One trial reported small but significantly more serious adverse events (17 exercise versus 7 usual care; P = 0.04) and more nonserious adverse events (992 GET versus 977 usual care versus 949 adaptive pacing versus 848 CBT) in the GET versus comparison groups, although adverse reactions attributed to the intervention were similar between groups (48). In a smaller trial of GET compared with placebo or fluoxetine, total withdrawals were greatest with GET (37% versus 22%) (23). In addition, in a trial of GET, 20% of patients declined to repeat exercise testing because of perceived harm of testing (52). There were no differences in total withdrawals in the other 2 trials of GET (50, 52), and no harms were reported in other exercise trials (51, 54).

Characteristics of Responders and Nonresponders

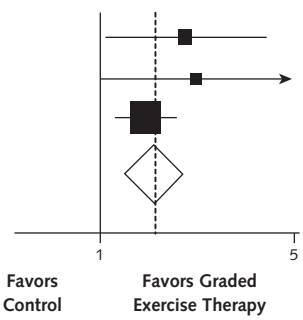
Four trials suggested that younger patients with less impairment, who are less focused on symptoms, adherent to cognitive therapy programs, and avoid over- and underexertion (that is, they stay within their energy envelope) are more likely to improve in some measures of fatigue and function (36, 40, 52, 60, 63).

DISCUSSION

Thirty-five trials evaluated the benefits and harms of treatments for adults meeting case definitions primarily for CFS; however, evidence is inconclusive (Appendix Table 2, available at www.annals.org). Limited evidence indicated that rintatolimod improved measures of exercise performance compared with placebo in severely debilitated participants (low strength of evidence). Counseling, behavior therapies, and GET improved measures of fatigue, function, global improvement, and work impairment; counseling and behavior therapies also improved quality of life (low to moderate strength of evidence). Results of all other interventions and outcomes were from small single trials that provided insufficient strength of evidence. Although adverse effects were rarely reported in most trials, coun-

Figure 4. Meta-analysis of trials of the effects of graded exercise therapy on the clinical global impression of change scale.

Study, Year (Reference)	Improved/Not Improved: Graded Exercise Therapy	Improved/Not Improved: Control	Risk Ratio (95% CI)
Fulcher and White, 1997 (50)	15.95/29	8.1/30	2.04 (1.04–4.00)
Moss-Morris et al, 2005 (52)	13.5/25	5.76/24	2.25 (1.01–5.00)
White et al, 2011 (48)*	62/152	85/305	1.47 (1.13–1.91)
Total (I^2 = 0.0; P = 0.448)			1.58 (1.24–2.47)



Graded exercise therapy involved an exercise plan with structured incremental increases in exercise over time, qigong exercise, and home orthostatic training.
* Compared with all participants in control groups in the trial.

seling and behavior therapies were associated with fewer harms (low strength of evidence) than medications and GET (insufficient evidence).

These results are consistent with those of previous systematic reviews (66–70). A recent systematic review of trials of exercise for patients with CFS found no evidence suggesting that exercise worsens symptoms (70). However, no trials reported harms for participants meeting case definitions for ME or ME/CSF (48), and it remains unclear how more severely disabled patients respond to exercise therapy. One trial considered participants meeting the London criteria for ME (n = 357 of 640 total) and found similar results for outcomes of fatigue and physical function but did not evaluate harms in this subgroup (48). It is possible that adverse effects of exercise therapy could be avoided by careful selection of patients, and additional research is needed to determine which patients would achieve maximal benefits without incurring harm. Although trials of counseling and behavioral therapies reported mixed results, improvements in multiple outcomes are consistent with outcomes seen with similar therapies for other chronic illnesses (68–72).

This systematic review was limited by deficiencies of the trials. Most trials enrolled participants on the basis of case definitions for CFS only. The Oxford CFS case definition is the least restrictive, and its use as entry criteria could have resulted in selection of participants with other fatiguing illnesses or illnesses that resolve spontaneously with time (16, 71). The Institute of Medicine recently released new diagnostic criteria for CFS that require the presence of postexertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance (7, 72). Participants in previous trials did not meet these requirements. In addition, most treatments were evaluated in single trials designed as pilot studies that enrolled small numbers of participants from specialized clinical centers, and outcomes were assessed by using different methods and outcome measures. Some trials were primarily intended to measure intermediate outcomes, such as natural killer cell–mediated cytotoxicity (25), and most were underpowered for the health outcomes relevant to this systematic review. Although several fatigue and function outcomes were based on validated scales and measures, others were not, and the clinical significance of changes in scores over time is not clear for most of them.

This systematic review included only English-language trials. No trials analyzed results by relevant subgroups or compared treatment responders with nonresponders. We could not assess publication bias because of the limited number of trials for each intervention. Whereas this review focused on outcomes that are universal to all case definitions of patients, such as fatigue and function, a review of other types of outcomes, such as postexertional malaise, would also be useful.

Future research would benefit from using consistent clinical criteria and comparing outcomes according to clinical presentation, such as postexertional malaise, neurocognitive status, and autonomic dysfunction. This approach would identify patient subgroups that may respond differently to specific treatments and could provide greater insight into the underlying causes of ME/CFS. Studies should report adverse effects more consistently and completely to improve identification of patients who may be negatively affected. Similarly, stratification of results by patient characteristics, such as age, sex, race, baseline functional status, and intermediate outcomes, would help determine the applicability of different treatments for specific patients and situations.

Definitive treatment trials require larger numbers of participants based on appropriate power calculations for clinically relevant outcomes to determine efficacy, along with more rigorous adherence to methodologic standards, such as blinding of outcome assessors, intention-to-treat analysis, and strategies to minimize patient loss to follow-up. Future trials should enroll more men and racial and ethnic minorities; broader age ranges; and participants with greater disability, such as homebound patients. Given the fluctuating nature of ME/CFS, follow-up periods longer than 1 year would help determine effectiveness and harms over time. The development of a set of core outcome measures, including patient-centered outcomes (such as quality of life, employment, and time spent in activity), would help guide research and facilitate future analyses. Trial registries and collaborations would help consolidate and standardize data. Reporting more information about concomitant treatments and adherence to treatment would improve the applicability of study findings. Given the devastating effect of this condition on patients and families, researchers should consider involving the patient and advocate voice in trial planning and development so that future research is relevant and meaningful to those affected by ME/CFS.

In conclusion, trials of rintatolimod, counseling therapies, and GET suggested benefits for patients with CFS, providing low to moderate strength of evidence. However, these treatments have not been adequately tested in broader patient populations, particularly those meeting more specific case definitions. Other treatments and harms have been inadequately studied. More definitive studies are needed to fill these research gaps.

From Pacific Northwest Evidence-based Practice Center, Oregon Health & Science University, and Providence Cancer Center, Providence Health and Services Oregon, Portland, Oregon.

Acknowledgment: The authors thank following individuals for their contributions to this project: Richard Bryant, MD, for pro-

viding expert consultation throughout the report; Andrew Hamilton, MLS, MS, for conducting literature searches; and Spencer Dandy, BS, for assistance with preparing this report (all are located at the Oregon Health & Science University). They also thank Suchitra Iyer, PhD, Task Order Officer at the Agency for Healthcare Research and Quality; Carmen Green, MD, National Institutes of Health (NIH) Working Group Chair; the NIH Working Group; the Technical Expert Panel; and reviewers of the draft report.

Financial Support: By the Agency for Healthcare Research and Quality (contract 290-2012-00014-I, task order 4), Rockville, Maryland.

Disclosures: Dr. Fu reports funds under contract for the Evidence-based Practice Centers IV Program from Oregon Health & Science University during the conduct of this study. Ms. Daeges reports grants from Agency for Healthcare Research and Quality during the conduct of this study. Dr. Nelson reports grants from Agency for Healthcare Research and Quality during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-0114.

Requests for Single Reprints: M.E. Beth Smith, DO, 3181 SW Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239; e-mail, smithbet@ohsu.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Carruthers BM, Jain AK, de Meirleir KL, Peterson DL, Klimas NG, Lerner A, et al.** Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. J Chronic Fatigue Syndr. 2003;11:7-115.

2. **Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al.** Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270:327-38. [PMID: 21777306] doi:10.1111/j.1365-2796.2011.02428.x

3. **Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A.** The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121:953-9. [PMID: 7978722] doi:

4. **Carruthers BM, van de Sande MI, De Meirleir K, Klimas N, Broderick G, Mitchell T, et al.** Myalgic encephalomyelitis–adult & paediatric: international consensus primer for medical practitioners. 2012. Accessed at http://sacfs.asn.au/download/me_international_consensus_primer_for_medical_practitioners.pdf on 11 February 2015.

5. **Davenport TE, Stevens SR, VanNess MJ, Snell CR, Little T.** Conceptual model for physical therapist management of chronic fatigue syndrome/myalgic encephalomyelitis. Phys Ther. 2010;90:602-14. [PMID: 20185614] doi:10.2522/ptj.20090047

6. **Jason LA, Brown A, Evans M, Sunnquist M, Newton JL.** Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013;1:168-183. [PMID: 23914329]

7. Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: National Academies Pr; 2015.

8. **Jason LA, Roesner N, Porter N, Parenti B, Mortensen J, Till L.** Provision of social support to individuals with chronic fatigue syndrome. J Clin Psychol. 2010;66:249-58. [PMID: 19902489] doi:10.1002/jclp.20648

9. **Dowsett E, Goudsmit E, Macintyre A, Shepherd C.** London Criteria for myalgic encephalomyelitis. In: Report from The National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME). Westcare. 1994. 96-98. Accessed at www.actionforme.org.uk/Resources/Action%20for%20ME/Documents/get-informed/national%20task%20force.pdf on 26 March 2015.

10. **Komaroff AL, Cho TA.** Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. 2011;31:325-37. [PMID: 21964849] doi:http://dx.doi.org/10.1055/s-0031-1287654

11. **Morris G, Maes M.** A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. Metab Brain Dis. 2013;28:523-40. [PMID: 22718491] doi:10.1007/s11011-012-9324-8

12. **Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, et al.** Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003;163:1530-6. [PMID: 12860574]

13. **Jason LA, Brown A, Clyne E, Bartgis L, Evans M, Brown M.** Contrasting case definitions for chronic fatigue syndrome, Myalgic Encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. Eval Health Prof. 2012;35:280-304. [PMID: 22158691] doi:10.1177/0163278711424281

14. **Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, et al.** Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr. 2007;5:5. [PMID: 17559660]

15. **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. Accessed at www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf on 11 Februrary 2015.

16. **Smith M, Nelson H, Haney E, Pappas M, Daeges M, Wasson N, et al.** Diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome. Evidence Report/Technology Assessment No. 219. (Prepared by the Pacific Northwest Evidence-based Practice Center under contract 290-2012-00014-I.) AHRQ Publication No. 15-E001-EF. Rockville, MD: Agency for Healthcare Research and Quality; December 2014. Accessed at http://effectivehealthcare.ahrq.gov/ehc/products/586/2004/chronic-fatigue-report-141209.pdf on 26 March 2015.

17. **Smith ME, Nelson N, Haney E, McDonagh M, Pappas M, Daeges M, et al.** Diagnosis and treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009779 on 11 February 2015.

18. **Owens D, Lohr KN, Atkins D, Treadwell J, Reston J, Bass E, et al.** Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

19. **Hardy RJ, Thompson SG.** A likelihood approach to meta-analysis with random effects. Stat Med. 1996;15:619-29. [PMID: 8731004]

20. **Peterson PK, Shepard J, Macres M, Schenck C, Crosson J, Rechtman D, et al.** A controlled trial of intravenous immunoglobulin G in chronic fatigue syndrome. Am J Med. 1990;89:554-60. [PMID: 2239975]

21. **Strayer DR, Carter WA, Brodsky I, Cheney P, Peterson D, Salvato P, et al.** A controlled clinical trial with a specifically configured RNA drug, poly(I).poly(C12U), in chronic fatigue syndrome. Clin Infect Dis. 1994;18 Suppl 1:S88-95. [PMID: 8148460]

22. **McKenzie R, O'Fallon A, Dale J, Demitrack M, Sharma G, Deloria M, et al.** Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized controlled trial. JAMA. 1998;280:1061-6. [PMID: 9757853]

23. **Wearden AJ, Morriss RK, Mullis R, Strickland PL, Pearson DJ, Appleby L, 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]

24. **Blockmans D, Persoons P, Van Houdenhove B, Lejeune M, Bobbaers H.** 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;114:736-41. [PMID: 12829200]
25. **Diaz-Mitoma F, Turgonyi E, Kumar A, Lim W, Larocque L, Hyde BM.** 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;11:71-93.
26. **Blacker CV, Greenwood DT, Wesnes KA, Wilson R, Woodward C, Howe I, et al.** Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. JAMA. 2004;292:1195-204. [PMID: 15353532]
27. **Strayer DR, Carter WA, Stouch BC, Stevens SR, Bateman L, Cimoch PJ, et al; Chronic Fatigue Syndrome AMP-516 Study Group.** 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:e31334. [PMID: 22431963] doi:10.1371/journal.pone.0031334
28. **Montoya JG, Kogelnik AM, Bhangoo M, Lunn MR, Flamand L, Merrihew LE, 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;85:2101-9. [PMID: 23959519] doi:10.1002/jmv.23713
29. **Hobday RA, Thomas S, O'Donovan A, Murphy M, Pinching AJ.** Dietary intervention in chronic fatigue syndrome. J Hum Nutr Diet. 2008;21:141-9. [PMID: 18339054] doi:10.1111/j.1365-277X.2008.00857.x
30. **Öckerman PA.** Antioxidant treatment of chronic fatigue syndrome. Clin Pract Alternat Med. 2000;1:88-91.
31. **The GK, Bleijenberg G, van der Meer JW.** The effect of acclydine in chronic fatigue syndrome: a randomized controlled trial. PLoS Clin Trials. 2007;2:e19. [PMID: 17525791]
32. **Vermeulen RC, Scholte HR.** Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med. 2004;66:276-82. [PMID: 15039515]
33. **Walach H, Bosch H, Lewith G, Naumann J, Schwarzer B, Falk S, et al.** Effectiveness of distant healing for patients with chronic fatigue syndrome: a randomised controlled partially blinded trial (EUHEALS). Psychother Psychosom. 2008;77:158-66. [PMID: 18277062] doi:10.1159/000116609
34. **Weatherley-Jones E, Nicholl JP, Thomas KJ, Parry GJ, McKendrick MW, Green ST, et al.** A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. J Psychosom Res. 2004;56:189-97. [PMID: 15016577]
35. **Williams G, Waterhouse J, Mugarza J, Minors D, Hayden K.** Therapy of circadian rhythm disorders in chronic fatigue syndrome: no symptomatic improvement with melatonin or phototherapy. Eur J Clin Invest. 2002;32:831-7. [PMID: 12423324]
36. **Bazelmans E, Prins JB, Lulofs R, van der Meer JW, Bleijenberg G; Netherlands Fatigue Research Group Nijmegen.** Cognitive behaviour group therapy for chronic fatigue syndrome: a non-randomised waiting list controlled study. Psychother Psychosom. 2005;74:218-24. [PMID: 15947511]
37. **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;40:175-91. [PMID: 21929831] doi:10.1017/S1352465811000543
38. **Deale A, Chalder T, Marks I, Wessely S.** Cognitive behavior therapy for chronic fatigue syndrome: a randomized controlled trial. Am J Psychiatry. 1997;154:408-14. [PMID: 9054791]
39. **Goudsmit EM, Ho-Yen DO, Dancey CP.** Learning to cope with chronic illness. Efficacy of a multi-component treatment for people with chronic fatigue syndrome. Patient Educ Couns. 2009;77:231-6. [PMID: 19576714] doi:10.1016/j.pec.2009.05.015
40. **Jason LA, Torres-Harding S, Friedberg F, Corradi K, Njoku MG, Donalek J, et al.** Non-pharmacologic interventions for CFS: a randomized trial. J Clin Psychol Med Settings. 2007;14:275-96.
41. **Knoop H, van der Meer JW, Bleijenberg G.** Guided self-instructions for people with chronic fatigue syndrome: randomised controlled trial. Br J Psychiatry. 2008;193:340-1. [PMID: 18827302] doi:10.1192/bjp.bp.108.051292
42. **Lopez C, Antoni M, Penedo F, Weiss D, Cruess S, Segotas MC, 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;70:328-34. [PMID: 21414452] doi:10.1016/j.jpsychores.2010.11.010
43. **O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.** Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme. Health Technol Assess. 2006;10:iii-iv, ix-x, 1-121. [PMID: 17014748]
44. **Sharpe M, Hawton K, Simkin S, Surawy C, Hackmann A, Klimes I, et al.** Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial. BMJ. 1996;312:22-6. [PMID: 8555852]
45. **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;58:35-43. [PMID: 14763634]
46. **Tummers M, Knoop H, van Dam A, Bleijenberg G.** Implementing a minimal intervention for chronic fatigue syndrome in a mental health centre: a randomized controlled trial. Psychol Med. 2012;42:2205-15. [PMID: 22354999] doi:10.1017/S0033291712000232
47. **Wearden AJ, Dowrick C, Chew-Graham C, Bentall RP, Morriss RK, Peters S, et al; Fatigue Intervention by Nurses Evaluation (FINE) trial writing group and the FINE trial group.** Nurse led, home based self help treatment for patients in primary care with chronic fatigue syndrome: randomised controlled trial. BMJ. 2010;340:c1777. [PMID: 20418251] doi:10.1136/bmj.c1777
48. **White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al; PACE trial management group.** 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;377:823-36. [PMID: 21334061] doi:10.1016/S0140-6736(11)60096-2
49. **Chan JS, Ho RT, Wang CW, Yuen LP, Sham JST, Chan CL.** Effects of qigong exercise on fatigue, anxiety, and depressive symptoms of patients with chronic fatigue syndrome-like illness: a randomized controlled trial. Evidence based Complement Alternat Med. 2013;2013:485341. [PMID: 23983785]
50. **Fulcher KY, White PD.** Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. BMJ. 1997;314:1647-52. [PMID: 9180065]
51. **Ho RT, Chan JS, Wang CW, Lau BW, So KF, Yuen LP, 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;44:160-70. [PMID: 22736201] doi:10.1007/s12160-012-9381-6
52. **Moss-Morris R, Sharon C, Tobin R, Baldi JC.** A randomized controlled graded exercise trial for chronic fatigue syndrome: outcomes and mechanisms of change. J Health Psychol. 2005;10:245-59. [PMID: 15723894]
53. **Núñez M, Fernández-Solà J, Nuñez E, Fernández-Huerta JM, Godás-Sieso T, Gomez-Gil E.** 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;30:381-9. [PMID: 21234629] doi:10.1007/s10067-010-1677-y
54. **Sutcliffe K, Gray J, Tan MP, Pairman J, Wilton K, Parry SW, et al.** Home orthostatic training in chronic fatigue syndrome–a randomized, placebo-controlled feasibility study. Eur J Clin Invest. 2010;40:18-24. [PMID: 19912315] doi:10.1111/j.1365-2362.2009.02225.x
55. **Holmes GP, Kaplan JE, Gantz NM, Komaroff AL, Schonberger LB, Straus SE, et al.** Chronic fatigue syndrome: a working case definition. Ann Intern Med. 1988;108:387-9. [PMID: 2829679]
56. **Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, et al.** A report–chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991;84:118-21. [PMID: 1999813]
57. **Straus SE, Dale JK, Tobi M, Lawley T, Preble O, Blaese RM, et al.** Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. N Engl J Med. 1988;319:1692-8. [PMID: 2849717]

58. **Fluge Ø, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D, 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:e26358. [PMID: 22039471] doi:10.1371/journal.pone.0026358
59. **Deale A, Husain K, Chalder T, Wessely S.** Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. Am J Psychiatry. 2001; 158:2038-42. [PMID: 11729022]
60. **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: 212-8. [PMID: 21767035] doi:10.1037/a0024118
61. **Jason L, Benton M, Torres-Harding S, Muldowney K.** The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Educ Couns. 2009;77:237-41. [PMID: 19356884] doi:10.1016/j.pec.2009.02.015
62. **Tummers M, Knoop H, Bleijenberg G.** Effectiveness of stepped care for chronic fatigue syndrome: a randomized noninferiority trial. J Consult Clin Psychol. 2010;78:724-31. [PMID: 20873907] doi:10.1037/a0020052
63. **Wearden AJ, Dunn G, Dowrick C, Morriss RK.** Depressive symptoms and pragmatic rehabilitation for chronic fatigue syndrome. Br J Psychiatry. 2012;201:227-32. [PMID: 22844025] doi:10.1192/bjp.bp.111.107474
64. **Wearden AJ, Emsley R.** Mediators of the effects on fatigue of pragmatic rehabilitation for chronic fatigue syndrome. J Consult Clin Psychol. 2013;81:831-8. [PMID: 23796316] doi:10.1037/a0033561
65. **Dougall D, Johnson A, Goldsmith K, Sharpe M, Angus B, Chalder T, et al.** Adverse events and deterioration reported by participants in the PACE trial of therapies for chronic fatigue syndrome. J Psychosom Res. 2014;77:20-6. [PMID: 24913337] doi:10.1016/j.jpsychores.2014.04.002
66. **Alraek T, Lee MS, Choi TY, Cao H, Liu J.** Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review. BMC Complement Altern Med. 2011;11:87. [PMID: 21982120] doi:10.1186/1472-6882-11-87
67. **Chambers D, Bagnall AM, Hempel S, Forbes C.** Interventions for the treatment, management and rehabilitation of patients with chronic fatigue syndrome/myalgic encephalomyelitis: an updated systematic review. J R Soc Med. 2006;99:506-20. [PMID: 17021301]
68. **Edmonds M, McGuire H, Price J.** Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2004:CD003200. [PMID: 15266475]
69. **Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramírez G.** Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA. 2001;286: 1360-8. [PMID: 11560542]
70. **Larun L, Brurberg KG, Odgaard-Jensen J, Price JR.** Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2015;2:CD003200. [PMID: 25674924] doi:10.1002/14651858.CD003200.pub3
71. **Haney E, Smith ME, McDonagh M, Pappas M, Daeges M, Wasson N, et al.** Diagnostic methods for myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162:834-40. doi:10.7326/M15-0443
72. **Ganiats TG.** Redefining the chronic fatigue syndrome. Ann Intern Med. 2015;162:653-4. [PMID: 25668185] doi:10.7326/M15-03577
73. **Tummers M, Knoop H, van Dam A, Bleijenberg G.** Moderators of the treatment response to guided self-instruction for chronic fatigue syndrome. J Psychosom Res. 2013;74:373-7. [PMID: 23597323] doi:10.1016/j.jpsychores.2013.01.007

CME CREDIT

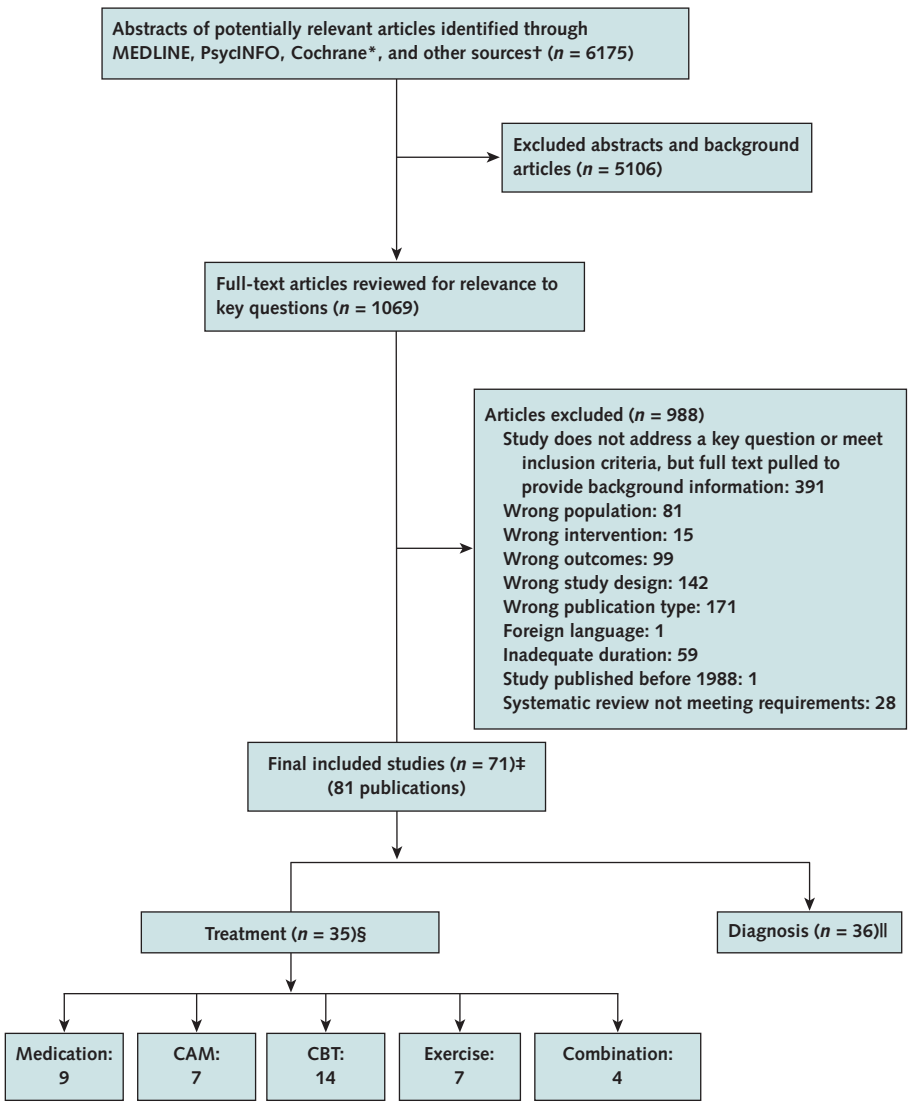
Some *Annals* articles are designated for CME credit and companion CME quizzes are provided at www.annals.org. To access CME questions, click on the CME option under an article's title on the table of contents at www.annals.org, or you may access CME quizzes at www.annals.org/cme. Subscribers and ACP members may take the tests free of charge. For a nominal fee, nonsubscribers can purchase tokens electronically that enable them to take the CME quizzes.

Reviewers who provide timely, high-quality reviews also may get CME credit.

Current Author Addresses: Drs. Smith, Haney, McDonagh, Fu, and Nelson; Ms. Pappas, Ms. Daeges, and Ms. Wasson: 3181 SW Sam Jackson Park Road, Mail Code: BICC, Portland, OR 97239.

Author Contributions: Conception and design: M.E.B. Smith, E. Haney, M. McDonagh, M. Pappas, H.D. Nelson.
Analysis and interpretation of the data: M.E.B. Smith, E. Haney, M. McDonagh, M. Pappas, N. Wasson, R. Fu, H.D. Nelson.
Drafting of the article: M.E.B. Smith, M. McDonagh, M. Pappas, N. Wasson, H.D. Nelson.
Critical revision of the article for important intellectual content: M.E.B. Smith, E. Haney, M. McDonagh, M. Pappas, N. Wasson, R. Fu, H.D. Nelson.
Final approval of the article: M.E.B. Smith, E. Haney, M. McDonagh, M. Pappas, R. Fu, H.D. Nelson.
Provision of study materials or patients: M. Daeges.
Statistical expertise: R. Fu.
Obtaining of funding: M.E.B. Smith, M. McDonagh, H.D. Nelson.
Administrative, technical, or logistic support: M. Pappas, M. Daeges, N. Wasson, H.D. Nelson.
Collection and assembly of data: M.E.B. Smith, E. Haney, M. Pappas, N. Wasson, H.D. Nelson.

Appendix Figure. Summary of evidence search and selection.



CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy.
* Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment, National Health Sciences Economic Evaluation Database, and the Cochrane Database of Systematic Reviews.
† Identified from such sources as reference lists, hand searches, and suggestions by experts.
‡ Studies that provided data and contributed to the body of evidence were considered "included."
§ Studies may be included in more than 1 published article, and this number indicates the number of unique studies included, representing a total of 45 publications. Studies may have provided data for more than 1 type of treatment.
‖ Studies included for the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome are reported in the companion article in this issue (71).

Appendix Table 1. Summary of Trials of Therapies

Study, Year (Reference) Participants Quality Rating	Treatment and Comparison Groups	Diagnostic Criteria	Duration of Follow-up	Outcomes	Benefit	Harm
Medications						
Blacker et al, 2004 (26) N = 423 Fair	A. Galantamine 2.5 mg TID B. Galantamine 5 mg TID C. Galantamine 7.5 mg TID D. Galantamine 10 mg TID E. Placebo	CDC (Fukuda, 1994)	4 months	Fatigue, QOL, CGI	None	More withdrawals, depression, nausea, and headache
Blockmans et al, 2003 (24) N = 80 Fair	A. Hydrocortisone 5 mg/day + 9-alpha fludrocortisone 50 µg/day B. Placebo	CDC (Fukuda, 1994)	3 month treatment; 3 month placebo crossover	Fatigue, QOL, function	None	NR
Diaz-Mitoma et al, 2003 (25) N = 15 Poor	A. Oral isoprinosine 1 g TID in weeks 1, 3, 5, 7, 9, and 11 only on Monday-Friday; and 1 g/day in weeks 2, 4, 6, 8, 10, and 12 only on Monday-Friday B. Placebo	CDC (Holmes, 1988 and Fukuda, 1994)	3 months	Fatigue, ADL scale	None	NR
McKenzie et al, 1998 (22) N = 60-70 varies by outcome Fair	A. Oral hydrocortisone 20-30 mg every morning and 5 mg every evening B. Placebo	CDC (Holmes, 1988 and Fukuda, 1994)	3 months	Fatigue, QOL, function	None	Suppression of adrenal glucocorticoid responsiveness (12 vs. 0; $P < 0.001$); increased appetite (17 vs. 8; $P = 0.02$); weight gain (19 vs. 8; $P = 0.006$); and difficulty sleeping (17 vs. 8; $P = 0.02$).
Montoya et al, 2013 (28) N = 30 Fair	A. Oral valganciclovir 900 mg BID for 21 days, then 900 mg/day for total of 6 months B. Placebo	CDC (Fukuda, 1994)	6 months treatment, 6 month follow-up	Fatigue, function, CDC symptom inventory	Improved fatigue	NR
Peterson et al, 1990 (20) N = 28 Fair	A. IV IgG (1 g/kg) every 30 days for 6 months (6 infusions) B. Placebo	CDC (Holmes, 1988)	6 months	Function	None	Headache
Strayer et al, 1994 (21) N = 76-84 varies by outcome Fair	A. IV rintatolimod 200 mg twice weekly 4 times, then 400 mg twice weekly for a total of 24 weeks B. Placebo	CDC (Holmes, 1988 and Fukuda, 1994)	6 months	Function, exercise, use of medications	Improved function, exercise, reduced use of medications	NR
Strayer et al, 2012 (27) N = 240 Fair	A. IV rintatolimod 400 mg twice weekly for 40 weeks B. Placebo	CDC (Holmes, 1988 and Fukuda, 1994)	10 months	Function, exercise, use of medications	Improved exercise, reduced use of medications	Flu-like syndrome, chills, vasodilatation, and dyspnea
Wearden, et al, 1998 (23) N = 68 Fair	A. Fluoxetine 20 mg/day B. Placebo	Oxford (Sharpe, 1991)	6.5 months	Fatigue, function	None	More withdrawals due to medication side effects

Continued on following page

Appendix Table 1–Continued

Study, Year (Reference) Participants Quality Rating	Treatment and Comparison Groups	Diagnostic Criteria	Duration of Follow-up	Outcomes	Benefit	Harm
Jason et al, 2007 (40) Jason et al, 2009 (61) Hlavaty et al, 2011 (60) N = 114 Fair	A. CBT B. COG C. ACT D. Relaxation	CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment	12 months	Fatigue, function, QOL, employment	Improved function with CBT and COG	NS
Jason et al, 2010 (8) N = 30 Poor	A. Buddy counseling B. Control, no treatment for 4 months	CDC (Fukuda, 1994)	4 months	Fatigue, function	Improved fatigue	NR
Knoop et al, 2008 (41) Tummers et al, 2010 (62) N = 169 Fair	Knoop, 2008 A. Self-instruction B. Wait list control Tummers, 2010 A. Stepped care B. Usual care	CDC (Fukuda, 1994)	6-12 months	Fatigue, function	Improved fatigue and function with self instruction	NR
Lopez et al, 2011 (42) N = 58 Poor	A. Group CBT B. Control, 1 session of psychoeducation summarizing strategies	CDC (Fukuda, 1994)	3 months	Fatigue, QOL	Improved QOL	NR
O'Dowd et al, 2006 (43) N = 153 Fair	A. Group CBT B. Group support C. Usual care	CDC (Fukuda, 1994)	12 months	Fatigue, function, QOL	Improved fatigue with CBT	NR
Sharpe et al, 1996 (44) N = 60 Good	A. CBT B. Usual care	Oxford (Sharpe 1991)	12 months	Function	Improved function	NR
Taylor, 2004 (45) N = 47 Good	A. Counseling B. Wait list	CDC (Fukuda, 1994)	12 months	QOL	Improved QOL	NS
Tummers et al, 2012 (46) N = 111 Good	A. Self-instruction B. Wait list	CDC (Fukuda, 1994)	6 months	Fatigue, function	Improved fatigue	NR
Tummers et al, 2013 (73) Secondary analysis of Knoop et al, 2008 (41) and Tummers et al, 2012 (46) combined	A. Self-instruction B. Wait list	CDC (Fukuda, 1994)	6-12 months	Fatigue	Improved fatigue	NR
Wearden et al, 2010 (47) Wearden et al, 2012 (63) Wearden and Emsley, 2013 (64) N = 257 Good	A. Pragmatic rehab B. Supportive listening C. Usual care	Oxford (Sharpe, 1991)	4.5 months treatment; 17.5 month total follow-up	Fatigue, function	Improved function with supportive listening	NS

Continued on following page

Appendix Table 1–Continued

Study, Year (Reference) Participants Quality Rating	Treatment and Comparison Groups	Diagnostic Criteria	Duration of Follow-up	Outcomes	Benefit	Harm
Complementary and alternative medicine						
Hobday et al, 2008 (29) N = 39 Fair	A. Low sugar/low yeast B. Healthy eating	CDC (Fukuda, 1994)	6 months	Fatigue, function	None	NR
Öckerman, 2000 (30) N = 22 Poor	A. Pollen: Antioxidant extract of pollen (Polbax) B. Placebo	CDC (Fukuda, 1994)	3 month	Fatigue, QOL	None	NR
The et al, 2007 (31) N = 57 Good	A. Acclydine B. Placebo	CDC (Fukuda, 1994)	3.5 months	Fatigue, function	None	NR
Vermeulen and Scholte, 2004 (32) N = 89 Fair	A. Acetyl-L-carnitine B. Propionyl-L-carnitine C. Combination, Acetyl-L-carnitine 2 g/day + propionyl-L-carnitine 2 g/day	CDC (Fukuda, 1994)	6 months	Fatigue, CGI	None	NR
Walach et al, 2008 (33) N = 409 Good	A. Distant healing B. Usual care	CDC (Fukuda, 1994)	6 month, 18 month follow-up	Function	None	NR
Weatherly-Jones et al, 2004 (34) N = 86 Fair	A. Homeopathy B. Placebo	Oxford (Sharpe, 1991)	6 months	Fatigue, function	Improved fatigue	NR
Williams et al, 2002 (35) N = 30 Fair	A. Melatonin B. Phototherapy C. Placebo	Oxford (Sharpe, 1991)	12 months	Fatigue, function	None	NR
Counseling and behavior therapies						
Bazelmans et al, 2005 (36) N = 65 Fair	A. Group CBT B. Wait list control	CDC (Fukuda, 1994)	6 months	Fatigue, function, employment	Improved function	NR
Burgess et al, 2012 (37) N = 43 Fair	A. Face-to-face CBT B. Telephone CBT	CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)	12 months	Fatigue, function, employment, CGI	Improved CGI with face-to-face counseling	NS
Deale et al, 1997 (38) N = 60 Deale et al, 2001 (59) N = 53 Fair	A. CBT B. Relaxation	Oxford (Sharpe, 1991) and United States (Schluederberg, 1992)	6 months (Deale, 1997) and 5 years (Deale, 2001)	Fatigue, function, employment, CGI, recovery, relapses	Improved all outcomes	NR
Goudsmit et al, 2009 (39) N = 44 Poor	A. Counseling B. Wait list	Oxford (Sharpe, 1991)	6 months	Fatigue, function	Improved fatigue	NR

Continued on following page

Appendix Table 1–Continued

Study, Year (Reference) Participants Quality Rating	Treatment and Comparison Groups	Diagnostic Criteria	Duration of Follow-up	Outcomes	Benefit	Harm
White et al, 2011 (48) N = 630 Good	A. APT B. CBT C. GET D. Usual care	Oxford (Sharpe, 1991)	13 months	Fatigue, function, employment, CGI, recovery	Improved all outcomes (CBT, GET) CBT vs. GET NS	Fewest adverse events with CBT
Exercise						
Chan et al, 2013 (49) and Ho et al, 2012 (51) N = 52 Fair	A. Qigong exercise B. Control group	CDC (Fukuda, 1994)	4 months	Fatigue, function	Improved fatigue	NR
Fulcher and White, 1997 (50) N = 59 Fair	A. GET B. Control group	Oxford (Sharpe, 1991)	3 months, 12 month follow-up	Fatigue, function, employment, CGI	Improved all outcomes	NS
Moss-Morris et al, 2005 (52) N = 49 Fair	A. GET B. Control group	CDC (Fukuda, 1994)	3 month, 6 month follow-up	Fatigue, function, CGI	Improved fatigue and CGI	20% refused repeat exercise testing
Núñez et al, 2011 (53) N = 115 Fair	A. CBT + GET B. Usual care	CDC (Fukuda, 1994)	3 months treatment, 12 month follow-up	Fatigue, function	None	NR
Sutcliffe et al, 2010 (54) N = 36 Fair	A. Orthostatic training B. Sham control	CDC (Fukuda, 1994)	6 months	Fatigue, function	None	NR
Wearden, et al, 1998 (23) N = 68 Fair	A. GET + fluoxetine B. GET + drug placebo C. Fluoxetine + exercise placebo D. Placebo control	Oxford (Sharpe,1991)	6.5 months	Fatigue, function	Improved fatigue and function (GET)	Greatest withdrawal GET
White et al, 2011 (48) N = 630 Good	A. APT B. CBT C. GET D. Usual care	Oxford (Sharpe, 1991)	13 months	Fatigue, function, employment, CGI, recovery	Improved all outcomes (CBT, GET) CBT vs. GET NS	Most adverse events with GET

ACT = anaerobic activity therapy; ADL = activities of daily living; APT = adaptive pacing therapy; BID = twice daily; CBT = cognitive behavioral therapy; CDC = Centers for Disease Control and Prevention; CFS = chronic fatigue syndrome; CGI = clinical global impression of change; COG = cognitive therapy; DSM-IV = Diagnostic and Statistical Manual, fourth edition; GET = graded exercise therapy; IV = intravenous; NR = not reported; NS = not significant QOL = quality of life; TID = thrice daily.

Appendix Table 2. Summary of Evidence by Outcomes for Trials With Statistically Significant Between-Group Differences

Outcome	Study Design; Studies, *n*; Participants, *n*	Findings and Direction of Effect	Strength of Evidence Grade
Function			
Rintatolimod	2 RCTs (*n* = 316)	Improved exercise duration (10% vs. 2%, p=0.007), exercise work (12% vs. 6%, p=0.011), and cardiopulmonary exercise tolerance (37% vs. 15%, p=0.047) with rintatolimod.	Low
Counseling therapies	11 RCTs (*n* = 1441)	Improved physical function (36-item Short Form Survey) with cognitive behavioral therapy (weighted mean difference 10.46; 95% CI −7.47 to 27.77; 4 trials).	Low
Graded exercise therapy	4 RCTs (*n* = 619)	Improved physical function (36-item Short Form Survey) with graded exercise therapy (weighted mean difference 10.68; 95% CI 6.32 to 16.88; 3 trials).	Moderate
Fatigue			
Valganciclovir	1 RCT (*n* = 30)	Improved fatigue based on one scale, but no differences for other measures.	Insufficient
Counseling therapies	11 RCTs (*n* = 1439)	Improved fatigue with counseling therapies using various measures (27% to 76% improved with counseling vs. 7% to 65% with controls in 4 trials; results were mixed in 3 trials; and no differences between groups in 4 trials).	Low
Graded exercise therapy	4 RCTs (*n* = 619)	Improved Chalder Fatigue Scale scores with GET in 3 trials (mean total: 13.91 vs. 24.41, p=0.02; physical fatigue: 7.91 vs. 14.27, p=0.02)	Low
Qigong exercise	1 RCT (*n* = 144)	Improved fatigue (Chalder Fatigue Scale) with Qigong exercise (mean difference: total: −13.1 vs. 6.6, p<0.001; physical subscale: −8.8 vs. −3.8, p<0.001; mental subscale: −4.3 vs. −2.7, p=0.05.	Insufficient
Quality of life			
Counseling therapies	4 RCTs (*n* = 343)	Improved quality of life with counseling therapies in 2 trials using various measures (mean QOLS at 12 weeks: 2.81 vs. 3.26, p=0.02; mean change in QLI scores from baseline at 12 months: 2.6 vs. 0.6; p<0.05); no differences in 2 trials.	Low
Global improvement			
Counseling therapies	2 RCTs (*n* = 531)	Improved global impression of change with counseling therapies (41% and 70% improved in CBT vs. 25% and 31% in controls).	Moderate
Graded exercise therapy	3 RCTs (*n* = 583)	Improved global impression of change with GET (RR 1.58; 95% CI 1.24 to 2.47)	Moderate
Work impairment			
Counseling therapies	2 RCTs (*n* = 531)	Improved work impairment with cognitive behavioral therapy using a work and social adjustment scale compared with controls (mean at 6 months: 3.3 vs. 5.4, p<0.001 on scale scored with range 0-8; mean at 1 year: 21.0 vs. 24.5; p=0.0001 on scale scored with range 0-45). No differences in the proportion working full or part time.	Low
Graded exercise therapy	1 RCT (*n* = 475)	Improved work impairment with GET using a work and social adjustment scale compared with adaptive pacing and no treatment at 1 year (20.5 vs. 24.5 vs. 23.9; p=0.0004 and p<0.001, respectively)	Low
Graded exercise therapy	1 RCT (*n* = 59)	Greater proportion working at 1 year with GET (66% vs. 39%; 95% CI 9-44%)	Insufficient
Harms			
Cognitive and behavioral therapy	2 RCTs (*n* = 728)	Fewer total harms [CBT group (848) vs. adaptive pacing (949, p=0.0081) and no treatment (977, p=0.0016), *n* = 471] and fewer serious harms [per 100 person-years (5.0; 95% CI 2.2 to 9.8) vs. adaptive pacing (10.1; 95% CI 5.8 to 16.3), *n* = 471] with CBT compared with other therapies in one trial. No differences in one trial.	Low

CBT = cognitive behavioral therapy; GET = graded exercise therapy; QLI = Quality of Life Inventory; QOLS = Quality of Life Scale; RCT = randomized, controlled trial.