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...
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 I² 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, vasodilation, 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), acyclidine (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 imaging 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).
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 1. Effects of various types of counseling therapies on the SF-36 physical function subscale.**

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

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.**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>CBT Patients, n</th>
<th>Mean SF-36 Score (SD)</th>
<th>Control Patients, n</th>
<th>Mean SF-36 Score (SD)</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deale et al, 2001 (59)</td>
<td>30</td>
<td>71.6 (28)</td>
<td>30</td>
<td>38.4 (26.9)</td>
<td>33.20 (19.31 to 47.09)</td>
</tr>
<tr>
<td>O’Dowd et al, 2006 (43)*</td>
<td>52</td>
<td>35.2 (81.5)</td>
<td>101</td>
<td>33.8 (9.0)</td>
<td>1.40 (-20.82 to 23.62)</td>
</tr>
<tr>
<td>White et al, 2011 (48)</td>
<td>155</td>
<td>58.2 (24.1)</td>
<td>157</td>
<td>50.8 (24.7)</td>
<td>7.40 (1.99 to 12.81)</td>
</tr>
<tr>
<td>Jason et al, 2007 (40)</td>
<td>29</td>
<td>58.64 (30.44)</td>
<td>28</td>
<td>61.2 (27.7)</td>
<td>-2.56 (-17.66 to 12.54)</td>
</tr>
<tr>
<td>Total (*I² = 79.6; P = 0.002)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.46 (-7.47 to 27.77)</td>
</tr>
<tr>
<td>Sensitivity analysis excluding Deale et al, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.02 (1.05 to 10.99)</td>
</tr>
<tr>
<td>Total (*I² = 0.00; P = 0.437)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBT = cognitive behavioral therapy; 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 3. Meta-analysis of trials of the effects of graded exercise therapy on the SF-36 physical function subscale.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Graded Exercise Therapy</th>
<th>Control</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulcher and White, 1997 (50)</td>
<td>29</td>
<td>69 (18.5)</td>
<td>14.00 (3.70–24.30)</td>
</tr>
<tr>
<td>Moss-Morris et al, 2005 (52)</td>
<td>25</td>
<td>69.05 (21.94)</td>
<td>14.05 (1.48–26.62)</td>
</tr>
<tr>
<td>White et al, 2011 (48)*</td>
<td>159</td>
<td>57.7 (26.5)</td>
<td>9.40 (4.46–14.34)</td>
</tr>
<tr>
<td>Total ((I^2 = 0.0; P = 0.627))</td>
<td>316</td>
<td>48.3 (24.8)</td>
<td>10.68 (6.32–16.88)</td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Graded Exercise Therapy</th>
<th>Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulcher and White, 1997 (50)</td>
<td>15.95/29</td>
<td>8.1/30</td>
<td>2.04 (1.04–4.00)</td>
</tr>
<tr>
<td>Moss-Morris et al, 2005 (52)</td>
<td>13.5/25</td>
<td>5.76/24</td>
<td>2.25 (1.01–5.00)</td>
</tr>
<tr>
<td>White et al, 2011 (48)*</td>
<td>62/152</td>
<td>85/305</td>
<td>1.47 (1.13–1.91)</td>
</tr>
<tr>
<td>Total ((I^2 = 0.0; P = 0.448))</td>
<td>1.58 (1.24–2.47)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
soring 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 fatigueuing 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.

Disclaimer: The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of the Agency for Healthcare Research and Quality (AHRQ). No statement in this report should be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

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

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

References
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.


**Appendix Figure.** Summary of evidence search and selection.

Abstracts of potentially relevant articles identified through MEDLINE, PsycINFO, Cochrane*, and other sources† (n = 6175)

Excluded abstracts and background articles (n = 5106)

Full-text articles reviewed for relevance to key questions (n = 1069)

Articles excluded (n = 988)
- Study does not address a key question or meet inclusion criteria, but full text pulled to provide background information: 391
- Wrong population: 81
- Wrong intervention: 15
- Wrong outcomes: 99
- Wrong study design: 142
- Wrong publication type: 171
- Foreign language: 1
- Inadequate duration: 59
- Study published before 1988: 1
- Systematic review not meeting requirements: 28

Final included studies (n = 71)‡ (81 publications)

Treatment (n = 35)§
- Medication: 9
- CAM: 7
- CBT: 14
- Exercise: 7
- Combination: 4

Diagnosis (n = 36)‖

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).
<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants</th>
<th>Quality Rating</th>
<th>Treatment and Comparison Groups</th>
<th>Diagnostic Criteria</th>
<th>Duration of Follow-up</th>
<th>Outcomes</th>
<th>Benefit</th>
<th>Harm</th>
</tr>
</thead>
</table>
| 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 fluocorticosterone 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 for 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*
<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Participants</th>
<th>Diagnostic Criteria</th>
<th>Duration of Follow-up</th>
<th>Outcomes</th>
<th>Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jason et al, 2007 (40)</td>
<td>N = 114 Fair</td>
<td>CFS Questionnaire, psychiatric assessment for DSM-IV diagnosis, and medical assessment</td>
<td>12 months</td>
<td>Fatigue, function, QOL, employment</td>
<td>Improved function with CBT and COG</td>
<td>NS</td>
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<tr>
<td>Jason et al, 2009 (61)</td>
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<td>Hlavaty et al, 2011 (60)</td>
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<tr>
<td>Jason et al, 2010 (8)</td>
<td>N = 30 Poor</td>
<td>A. Buddy counseling B. Control, no treatment for 4 months</td>
<td>4 months</td>
<td>Fatigue, function</td>
<td>Improved fatigue</td>
<td>NR</td>
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<tr>
<td>Knoop et al, 2008 (41)</td>
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<tr>
<td>Tummers et al, 2010 (62)</td>
<td>N = 169 Fair</td>
<td>CDC (Fukuda, 1994)</td>
<td>6-12 months</td>
<td>Fatigue, function</td>
<td>Improved fatigue and function with self instruction</td>
<td>NR</td>
</tr>
<tr>
<td>Lopez et al, 2011 (42)</td>
<td>N = 58 Poor</td>
<td>CDC (Fukuda, 1994)</td>
<td>3 months</td>
<td>Fatigue, QOL</td>
<td>Improved QOL</td>
<td>NR</td>
</tr>
<tr>
<td>O’Dowd et al, 2006 (43)</td>
<td>N = 153 Fair</td>
<td>CDC (Fukuda, 1994)</td>
<td>12 months</td>
<td>Fatigue, function, QOL</td>
<td>Improved fatigue with CBT</td>
<td>NR</td>
</tr>
<tr>
<td>Sharpe et al, 1996 (44)</td>
<td>N = 60 Good</td>
<td>Oxford (Sharpe 1991)</td>
<td>12 months</td>
<td>Function</td>
<td>Improved function</td>
<td>NR</td>
</tr>
<tr>
<td>Taylor, 2004 (45)</td>
<td>N = 47 Good</td>
<td>CDC (Fukuda, 1994)</td>
<td>12 months</td>
<td>QOL</td>
<td>Improved QOL</td>
<td>NS</td>
</tr>
<tr>
<td>Tummers et al, 2012 (46)</td>
<td>N = 111 Good</td>
<td>CDC (Fukuda, 1994)</td>
<td>6 months</td>
<td>Fatigue, function</td>
<td>Improved fatigue</td>
<td>NR</td>
</tr>
<tr>
<td>Tummers et al, 2013 (73)</td>
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<tr>
<td>Secondary analysis of Knoop et al, 2008 (41) and Tummers et al, 2012 (46) combined</td>
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<tr>
<td>Wearden et al, 2010 (47)</td>
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<tr>
<td>Wearden et al, 2012 (63)</td>
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<tr>
<td>Wearden and Emsley, 2013 (64)</td>
<td>N = 257 Good</td>
<td>Oxford (Sharpe, 1991)</td>
<td>4.5 months treatment; 17.5 month total follow-up</td>
<td>Fatigue, function</td>
<td>Improved function with supportive listening</td>
<td>NS</td>
</tr>
<tr>
<td>Study, Year (Reference)</td>
<td>Treatment and Comparison Groups</td>
<td>Diagnostic Criteria</td>
<td>Duration of Follow-up</td>
<td>Outcomes</td>
<td>Benefit</td>
<td>Harm</td>
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<tr>
<td>Complementary and alternative medicine</td>
<td>Hobday et al, 2008 (29) N=3 9 Fair</td>
<td>A. Low sugar/low yeast B. Healthy eating</td>
<td>CDC (Fukuda, 1994)</td>
<td>6 months</td>
<td>Fatigue, function</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Ockerman, 2000 (30) N=22 Poor</td>
<td>A. Pollen: Antioxidant extract of pollen (Polbax) B. Placebo</td>
<td>CDC (Fukuda, 1994)</td>
<td>3 months</td>
<td>Fatigue, QOL</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>The et al, 2007 (31) N=57 Good</td>
<td>A. Acyclovir B. Placebo</td>
<td>CDC (Fukuda, 1994)</td>
<td>3.5 months</td>
<td>Fatigue, function</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Vermeulen and Scholte, 2004 (32) N=89 Fair</td>
<td>A. Acetly-L-carnitine B. Propionyl-L-carnitine C. Combination, Acety-L-carnitine 2 g/day and Propionyl-L-carnitine 2 g/day</td>
<td>CDC (Fukuda, 1994)</td>
<td>6 months</td>
<td>Fatigue, CGI</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Walach et al, 2008 (33) N=409 Good</td>
<td>A. Distant healing B. Usual care</td>
<td>CDC (Fukuda, 1994)</td>
<td>6 month, 18 month follow-up</td>
<td>Function</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Weatherly-Jones et al, 2004 (34) N=86 Fair</td>
<td>A. Homeopathy B. Placebo</td>
<td>Oxford (Sharpe, 1991)</td>
<td>6 months</td>
<td>Fatigue, function</td>
<td>Improved fatigue</td>
</tr>
<tr>
<td></td>
<td>Williams et al, 2002 (35) N=30</td>
<td>A. Melatonin B. Phototherapy C. Placebo</td>
<td>Oxford (Sharpe, 1991)</td>
<td>12 months</td>
<td>Fatigue, function</td>
<td>None</td>
</tr>
<tr>
<td>Counseling and behavior therapies</td>
<td>Bazelmans et al, 2005 (36) N=65 Fair</td>
<td>A. Group CBT B. Wait list control</td>
<td>CDC (Fukuda, 1994)</td>
<td>6 months</td>
<td>Fatigue, function, employment</td>
<td>Improved function</td>
</tr>
<tr>
<td></td>
<td>Burgess et al, 2012 (37) N=43 Fair</td>
<td>A. Face-to-face CBT B. Telephone CBT</td>
<td>CDC (Fukuda, 1994) and Oxford (Sharpe, 1991)</td>
<td>12 months</td>
<td>Fatigue, function, employment, CGI</td>
<td>Improved CGI with face-to-face counseling</td>
</tr>
<tr>
<td></td>
<td>Deale et al, 1997 (38) N=60 Deale et al, 2001 (59) N=53 Fair</td>
<td>A. CBT B. Relaxation</td>
<td>Oxford (Sharpe, 1991) and United States (Schuellerberg, 1992)</td>
<td>6 months (Deale, 1997) and 5 years (Deale, 2001)</td>
<td>Fatigue, function, employment, CGI, recovery, relapses</td>
<td>Improved all outcomes</td>
</tr>
<tr>
<td></td>
<td>Goudsmit et al, 2009 (39) N=44 Poor</td>
<td>A. Counseling B. Wait list</td>
<td>Oxford (Sharpe, 1991)</td>
<td>6 months</td>
<td>Fatigue, function</td>
<td>Improved fatigue</td>
</tr>
</tbody>
</table>

Continued on following page
## Appendix Table 1—Continued

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Treatment and Comparison Groups</th>
<th>Diagnostic Criteria</th>
<th>Duration of Follow-up</th>
<th>Outcomes</th>
<th>Benefit</th>
<th>Harm</th>
</tr>
</thead>
</table>
| White et al, 2011 (48)  | A. APT  
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 | A. Qigong exercise  
B. Control group | CDC (Fukuda, 1994) | 4 months | Fatigue, function | Improved fatigue | NR |
| Fulcher and White, 1997 (50)  
N = 59 | 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 | 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 | 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 | A. Orthostatic training  
B. Sham control | CDC (Fukuda, 1994) | 6 months | Fatigue, function | None | NR |
| Wearden, et al, 1998 (23)  
N = 68 | 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 | 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Design; Studies, n; Participants, n</th>
<th>Findings and Direction of Effect</th>
<th>Strength of Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rintatolimod</td>
<td>2 RCTs (n = 316)</td>
<td>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.</td>
<td>Low</td>
</tr>
<tr>
<td>Counseling therapies</td>
<td>11 RCTs (n = 1441)</td>
<td>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).</td>
<td>Low</td>
</tr>
<tr>
<td>Graded exercise therapy</td>
<td>4 RCTs (n = 619)</td>
<td>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).</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>1 RCT (n = 30)</td>
<td>Improved fatigue based on one scale, but no differences for other measures.</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Counseling therapies</td>
<td>11 RCTs (n = 1439)</td>
<td>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).</td>
<td>Low</td>
</tr>
<tr>
<td>Graded exercise therapy</td>
<td>4 RCTs (n = 619)</td>
<td>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)</td>
<td>Low</td>
</tr>
<tr>
<td>Qigong exercise</td>
<td>1 RCT (n = 144)</td>
<td>Improved fatigue (Chalder Fatigue Scale) with Qigong exercise (mean difference: total: −13.1 vs. 6.6; p&lt;0.001; physical subscale: −8.8 vs. −3.8; p&lt;0.001; mental subscale: −4.3 vs. −2.7; p=0.05).</td>
<td>Insufficient</td>
</tr>
<tr>
<td>Quality of life</td>
<td>4 RCTs (n = 343)</td>
<td>Improved quality of life with counseling therapies in 2 trials using various measures (mean QOLS at 12 weeks: 2.81 vs. 3.26; p=0.002; mean change in QLI scores from baseline at 12 months: 2.6 vs. 0.6; p&lt;0.05); no differences in 2 trials.</td>
<td>Low</td>
</tr>
<tr>
<td>Counseling therapies</td>
<td>4 RCTs (n = 531)</td>
<td>Improved global impression of change with counseling therapies (41% and 70% improved in GET vs. 25% and 31% in controls).</td>
<td>Moderate</td>
</tr>
<tr>
<td>Graded exercise therapy</td>
<td>3 RCTs (n = 583)</td>
<td>Improved global impression of change with GET (RR 1.58; 95% CI 1.24 to 2.47)</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Work impairment</strong></td>
<td></td>
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<tr>
<td>Counseling therapies</td>
<td>2 RCTs (n = 531)</td>
<td>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&lt;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.</td>
<td>Low</td>
</tr>
<tr>
<td>Graded exercise therapy</td>
<td>1 RCT (n = 475)</td>
<td>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&lt;0.001, respectively)</td>
<td>Low</td>
</tr>
<tr>
<td>Graded exercise therapy</td>
<td>1 RCT (n = 59)</td>
<td>Greater proportion working at 1 year with GET (66% vs. 39%; 95% CI 9.44%)</td>
<td>Insufficient</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
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<tr>
<td>Cognitive and behavioral therapy</td>
<td>2 RCTs (n = 728)</td>
<td>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.</td>
<td>Low</td>
</tr>
</tbody>
</table>

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