Appendix K. Strength of Evidence

Table K1. Strength of evidence

| **Key Question outcome** | **Study design/number of studies(n)** | **Study limitations** | **Directness** | **Consistency** | **Precision** | **Reporting bias** | **Overall effect** | **Strength of evidence/grade** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment and harms** |   |   |   |   |   |   |   |   |
| **a) What are the benefits of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?** |   |   |   |
| *Galantamine vs. placebo* |   |   |   |   |   |   |   |   |
| Decreased fatigue | 1 RCT (n=423) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Improved quality of life | 1 RCT (n=423) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Global improvement | 1 RCT (n=423) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Improved overall function, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Hydrocortisone vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=68) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Decreased fatigue | 1 RCT (n=68) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Improved quality of life | 1 RCT (n=65) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Hydrocortisone + fludrocortisone vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=80) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Decreased fatigue | 1 RCT (n=80) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Improved quality of life | 1 RCT (n=80) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>  | Insufficient |
| Increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Immunoglobulin G vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=28) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Rintatolimod vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=84) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Increased exercise work capacity | 2 RCT (n=316) | Medium | Direct  | Consistent  | Precise | Undetected | + | Low |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Valganciclovir vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=30) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=30) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Isoprinosine vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=15) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=15) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Fluoxetine vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=68) | Medium | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=68) | Medium | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Acclydine vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=57) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=57) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Increased physical activity (actometer) | 1 RCT (n=57) | High | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Acetyl-L-carnitine vs. propionyl-L-carnitine vs. combination* |   |   |   |   |   |   |   |
| Decreased fatigue | 1 RCT (n=89) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Global improvement | 1 RCT (n=89) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved overall function and quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Pollen extract vs. placebo* |   |   |   |   |   |   |   |   |
| Decreased fatigue | 1 RCT (n=22) | High | Direct  | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved quality of life | 1 RCT (n=22) | High | Direct  | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved overall function, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Low sugar/low yeast diet vs. healthy eating* |   |   |   |   |   |   |   |   |
| Decreased fatigue | 1 RCT (n=39) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life | 1 RCT (n=39) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved overall function, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Distant healing vs. no treatment* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=409) | Medium | Direct | Consistency unknown (single study) | Imprecise | Undetected | <>‖  | Insufficient |
| Decreased fatigue, improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Homeopathy vs. placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=89) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=89) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | - | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Melatonin vs. phototherapy* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT crossover design (n=30) | High | Direct | Consistency unknown (single study) | imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT crossover design (n=30) | High | Direct | Consistency unknown (single study) | imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |

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

| **Key question outcome** | **Study design/number of studies(n)** | **Study limitations** | **Directness** | **Consistency** | **Precision** | **Reporting bias** | **Overall effect** | **Strength of evidence/grade** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *GET vs. no treatment or flexibility/relaxation therapy or adaptive pacing* |   |   |   |   |   |   |
| Improved overall function | 4 RCT(n=619)3 pooled  | Medium | Direct | Consistent | Precise | Undetected | SF-36 physical function WMD 10.29 (95%CI, 6.71 to 13.88) | Moderate |
| Decreased fatigue | 4 RCT(n=619) | Medium | Direct | Consistent | Imprecise | Undetected | +†† | Low |
| Increased proportion working full- or part-time | 1 RCT (n=59) | Medium | Direct | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Decreased work impairment | 1 RCT (n=475) | Low | Direct | Consistency unknown (single study) | Precise | Undetected | + | Low |
| Global improvement | 3 RCT (n=583)3 pooled | Medium | Direct | Consistent | Precise | Undetected | Mean CGI scoresRR 1.58 (95% CI, 1.25 to 1.98) | Moderate |
| Recovery (Chalder fatigue score <18, SF-36 physical function score >60, no longer meeting Oxford case definition criteria, and reporting much or very much improvement on CGI)  | 1 RCT (n=475) | Low | Direct | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved quality of life, increased days spent at work/school | No studies |   |   |   |   |   |   | Insufficient |
| *Home orthostatic training vs. sham home orthostatic training* |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=36) | High | Imprecise | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Decreased fatigue | 1 RCT (n=36) | High | Imprecise | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *Qigong exercise vs. no qigong exercise* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=52) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | +¶ | Insufficient |
| Decreased fatigue | 1 RCT (n=52) | High | Direct | Consistency unknown (single study) | Imprecise | Undetected | + | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |

| **Key question outcome** | **Study design/number of studies(n)** | **Study limitations** | **Directness** | **Consistency** | **Precision** | **Reporting bias** | **Overall effect** | **Strength of evidence/grade** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| *GET vs. fluoxetine vs. combination or placebo* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=136) | Medium | Direct | Consistency unknown (single study) | Precise | Undetected | + | Insufficient |
| Decreased fatigue | 1 RCT (n=136) | Medium | Direct | Consistency unknown (single study) | Precise | Undetected | + | Insufficient |
| Increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| *CBT + GET vs. usual care* |   |   |   |   |   |   |   |   |
| Improved overall function | 1 RCT (n=115) | Low | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Decreased fatigue | 1 RCT (n=115) | Low | Direct | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Improved quality of life, increased days spent at work/school and proportion working full- or part-time | No studies |   |   |   |   |   |   | Insufficient |
| **b) What are the harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?** |   |   |   |
| *Galantamine vs. placebo* |   |   |   |   |   |   |   |   |
| Withdrawals due to harms, rates of harms, total withdrawals, serious harms, and total harms | 1 RCT (n=434) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| *Hydrocortisone vs. placebo* |   |   |   |   |   |   |   |   |
| Withdrawals due to harms, serious harms, other harms | 1 RCT (n=70) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | - | Insufficient |
| Rates of harms, total withdrawals, total harms | No studies |   |   |   |   |   |   | Insufficient |
| *Hydrocortisone + fludrocortisone vs. placebo* |   |   |   |   |   |   |   |   |
| Withdrawals due to harms, serious harms, other harms, total harms  | 1 RCT (n=80) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <> | Insufficient |
| Rates of harms, total withdrawals | No studies | No studies |   |   |   |   |   | Insufficient |
| *Immunoglobulin G vs. placebo* |   |   |   |   |   |   |   |   |
| Withdrawals due to harms, serious harms, other harms, total harms  | 1 RCT (n=28) | Medium | Direct  | Consistency unknown (single study) | Imprecise | Undetected | <>‡‡ | Insufficient |
| Rates of harms, total withdrawals | No studies |   |   |   |   |   |   | Insufficient |

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

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

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

**Key:** + = positive effect; <> = no effect; - = negative effect.
\*5 studies showed overall positive effect, while 2 showed mixed effects using different measures, 1 showed negative effect, and 4 showed no effect.
†9 studies showed positive effects, while 3 showed no effect.
‡2 studies showed positive effects, 2 showed no effect, and 1 showed a positive effect vs. support but not vs. no treatment.
§Significant increase in 1 of 3 trials, 1trial reported a significant increase vs. support but not vs. no treatment.
‖ For those blinded to treatment only, not for comparison of intervention groups.
¶Intervention scored better on mental functioning subscale, but not physical functioning subscale.
\*\*2 of 4 studies showed a benefit, for the intervention group, while 2 showed no differences.

††3 of 4 studies showed a benefit for the intervention group, while 1 showed no differences.
‡‡More headaches in intervention group, but no other differences.
§§Some harms more frequent in intervention group, insomnia more frequent in placebo group, see Appendix G4 for details.
**Abbreviations:** CBT= cognitive behavioral therapy; CFS= chronic fatigue syndrome; CI= confidence interval; CGI= Clinical Global Impression of Change score; GET= graded exercise treatment; ME= myaligc encephalomyelitis; n= sample size; RCT= randomized controlled trial; RR= relative risk; SF-36= 36-item Short Form Survey; WMD= weighted mean difference; vs.= versus.