**Table 31: Clinical evidence profile: Central nervous system stimulants (methylphenidate, modafinil, dexamphetamine, lisdexamphetamine) versus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Central nervous system stimulants (methylphenidate, modafinil, dexamphetamine, lisdexamphetamine) versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Quality of Life: SF36 physical total (follow-up 4-6 weeks; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 70 (methylphenidate or dexamphetamine) | 70 | - | MD 1.63 higher (4.11 lower to 7.37 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of Life: SF36 mental total (follow-up 4-6 weeks; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 70 (methylphenidate or dexamphetamine) | 70 | - | MD 3.51 higher (1.67 lower to 8.69 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of Life: SF36 vitality (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 0.6 lower (15.95 lower to 14.75 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 physical role limitation (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 28 (modafinil) | 14 | - | MD 6.45 lower (26.66 lower to 13.76 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 physical function (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 1.6 lower (19.6 lower to 16.4 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 mental health (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 6.3 lower (16.26 lower to 3.66 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 emotional role limitation (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 28 (modafinil) | 14 | - | MD 19.3 lower (35.88 to 2.72 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 pain (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 2.45 lower (22.61 lower to 17.71 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 social (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 2.4 lower (21.85 lower to 17.05 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of Life: SF36 general health (follow-up 20 days; range of scores: 0-100; Better indicated by higher values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 0.4 lower (14.35 lower to 13.55 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Fatigue: Checklist Individual Strength (CIS) total score (follow-up 4-12 weeks; range of scores: 20-140; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 123 (methylphenidate) | 125 | - | MD 7.12 lower (12.07 to 2.16 lower) | ⊕⊕OO LOW | CRITICAL |
| **Fatigue: Fatigue Severity Scale (follow-up 6 weeks; range of scores: 9-63; Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | very serious[4] | serious[1] | very serious[2] | none | 23 (dexamphetamine or lisdexamphetamine) | 21 | - | MD 7.67 lower (21.75 lower to 6.4 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Fatigue: Chalder Physical Fatigue scale (follow-up 20 days; range of scores: 0-21; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 0.25 lower (4.92 lower to 4.42 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Fatigue: Chalder Mental Fatigue scale (follow-up 20 days; range of scores: 0-12; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 28 (modafinil) | 14 | - | MD 0.4 higher (1.55 lower to 2.35 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Sleep quality: sleep latency (time taken to fall asleep in mins) (follow-up 6 weeks; Better indicated by lower values)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | very serious[2] | none | 10 (dexamphetamine) | 10 | - | MD 1.2 higher (2.91 lower to 5.31 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological status: HADS anxiety (follow-up 4 weeks; range of scores: 0-21; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 60 (methylphenidate) | 60 | - | MD 0.4 lower (1.74 lower to 0.94 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological status: HADS depression (follow-up 4 weeks; range of scores: 0-21; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | no serious imprecision | none | 60 (methylphenidate) | 60 | - | MD 0.4 lower (1.93 lower to 1.13 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological status: Hamilton Anxiety Scale improvement (follow-up 6 weeks; range of scores: 0-56; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 13 (lisdexamphetamine) | 11 | - | MD 5.13 higher (2.08 lower to 12.34 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: AEs leading to discontinuation (follow-up 6-12 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 10/78 (12.8%) (methylphenidate or lisdexamphetamine) | 3/76 (3.9%) | RR 2.91 (0.9 to 9.43) | 75 more per 1000 (from 4 fewer to 333 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: Serious AEs (pyelonephritis) (follow-up 12 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 1/63 (1.6%) (methylphenidate) | 0/65 (0%) | Peto OR 7.63 (0.15 to 384.58) | 20 more per 1000 (from 30 fewer to 60 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: sleepiness (follow-up 4 weeks)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | very serious[2] | none | 21/60 (35%) (methylphenidate) | 23/60 (38.3%) | RR 0.91 (0.57 to 1.46) | 34 fewer per 1000 (from 165 fewer to 176 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: dry mouth (follow-up 4-6 weeks)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 35/75 (46.7%) (methylphenidate or lisdexamphetamine) | 18/71 (25.4%) | RR 1.9 (1.22 to 2.96) | 228 more per 1000 (from 56 more to 497 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: dizziness (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 30/60 (50%) (methylphenidate) | 38/60 (63.3%) | RR 0.79 (0.57 to 1.08) | 133 fewer per 1000 (from 272 fewer to 51 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events: akathisia (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 29/60 (48.3%) (methylphenidate) | 34/60 (56.7%) | RR 0.85 (0.61 to 1.2) | 85 fewer per 1000 (from 221 fewer to 113 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events: abdominal pain (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | very serious[2] | none | 28/60 (46.7%) (methylphenidate) | 23/60 (38.3%) | RR 1.22 (0.8 to 1.85) | 84 more per 1000 (from 77 fewer to 326 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: chest pain (follow-up 4 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 17/60 (28.3%) (methylphenidate) | 25/60 (41.7%) | RR 0.68 (0.41 to 1.12) | 133 fewer per 1000 (from 246 fewer to 50 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events: anorexia (follow-up 6 weeks)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | serious[1] | serious[2] | none | 5/10 (50%) (dexamphetamine) | 1/10 (10%) | RR 5 (0.7 to 35.5) | 400 more per 1000 (from 30 fewer to 1000 more) | ⊕⊕OO LOW | CRITICAL |
| **Adverse events: headache (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 2/15 (13.3%) (lisdexamphetamine) | 1/11 (9.1%) | RR 1.47 (0.15 to 14.21) | 43 more per 1000 (from 77 fewer to 1000 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events: insomnia (follow-up 6 weeks)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | serious[1] | very serious[2] | none | 1/15 (6.7%) (lisdexamphetamine) | 0/11 (0%) | Peto OR 5.66 (0.11 to 299.01) | 70 more per 1000 (from 120 fewer to 250 more) | ⊕OOO VERY LOW | CRITICAL |
| **Adverse events (follow-up 20 days)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | serious[1] | very serious[2] | none | 21/28 (75%) (modafinil) | 8/14 (57.1%) | RR 1.31 (0.79 to 2.17) | 177 more per 1000 (from 120 fewer to 669 more) | ⊕OOO VERY LOW | CRITICAL |
| **Cognitive function: Behaviour Rating Inventory of Executive Function (BRIEF), improvement in global executive composite (follow-up 6 weeks; range of scores: not reported; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | no serious imprecision | none | 13 (lisdexamphetamine) | 11 | - | MD 18.02 higher (8.39 to 27.65 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Pain: McGill pain Questionnaire improvement (follow-up 6 weeks; range of scores: 0-78; Better indicated by lower values)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 13 (lisdexamphetamine) | 11 | - | MD 7.84 higher (0.44 to 15.24 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Symptom scales: Clinical Global Improvement - severity (follow-up 6 weeks; range of scores: 1-7; Better indicated by lower values)** | | | | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[3] | no serious inconsistency | serious[1] | serious[2] | none | 13 (lisdexamphetamine) | 11 | - | MD 1.28 higher (0.3 to 2.26 higher) | ⊕OOO VERY LOW | CRITICAL |

[1] The majority of the evidence included an indirect population (downgraded by one increment) or a very indirect population (downgraded by two increments). Populations were downgraded if the ME/CFS diagnostic criteria used did not include PEM as a compulsory feature
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Heterogeneity, I2=86%, p=0.05, unexplained by subgroup analysis.