Appendix D Effectiveness evidence

Study	Arnold 2015[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Single outpatient research centre setting
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Revised CDC definition of CFS
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-65; met revised CDC criteria for CFS: at least 6 months of persistent disabling fatigue, 4 or more of impaired memory/concentration, sore throat, tender glands, aching or stiff muscles, multi joint pain, new headaches, unrefreshing sleep and post-exertional fatigue; General fatigue score of >+13 on MFI at baseline
Exclusion criteria	Other medical disorders that could explain the fatigue; psychiatric disorders; substance abuse disorders; women who were pregnant or breastfeeding; women of childbearing potential not using contraceptives; people deemed to be refractory to treatment; people whose response was deemed to be influenced by current or future disability compensation issues; serious unstable medical illness; abnormal TSH levels; uncontrolled narrow angle glaucoma; acute liver injury/severe cirrhosis; suicidal risk; known non-responder to duloxetine; known hypersensitivity to duloxetine; any treatment with investigational drug within 30 days of screening; use of any medications or herbal agents with CNS effects (except occasional sedating antihistamines); treatment with analgesics except OTC NSAIDs and paracetamol; unconventional or alternative therapies.

Recruitment/selection of patients	consecutive referral or via advertisement
Age, gender and ethnicity	Age - Mean (range): duloxetine/placebo: 43/44.3. Gender (M:F): 13.3:86.7. Ethnicity: Duloxetine/placebo: white 86.7%/83.3%; African-American 13.3%/13.3%; other 0%/3.3%
Further population details	-
Extra comments	Duloxetine/placebo: MFI general fatigue 17.3/17.3; MFI general fatigue 14.8/13.9; MFI reduced activity 14.3/14.5;MFI reduced motivation 12.3/12.6; MFI mental fatigue 15.4/15.5; Brief Pain Inventory average pain severity 4/3.8; HADS anxiety 8.1/8.8; HADS depression 6.3/9; Total CDC symptom inventory 63.7/67.8; SF36 physical functioning 63.1/55.9; role physical 25/18.5; social functioning 67.6/54.2; bodily pain 50.2/46.3; mental health 71/55.4; role emotional 74.1/38.3; vitality 17.6/16.7; general health 49.9/52.1; CGI severity - moderate 86.2%/90%
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature
Interventions	(n=30) Intervention 1: antidepressants - serotonin-norepinephrine reuptake inhibitors. Duloxetine hydrochloride - 30mg once a day for 1 week, then 60 mg once a day for the next 3 weeks. The dose then increased to 90mg per day for next 4 weeks (as tolerated). If highest doses not tolerated doses could be as low as 60mg per day. Duration 12 weeks. Concurrent medication/care: At the end of 12 weeks patients had a 1 week tapering phase in which the drug was reduced by 30mg daily until discontinuation. Indirectness: No indirectness (n=30) Intervention 2: placebo. Identical placebo given in same way as study drug. Duration 12 weeks. Concurrent medication/care: At the end of 12 weeks patients had a 1 week tapering phase in which the placebo was reduced by 30mg daily until discontinuation. Indirectness: No indirectness
Funding	Study funded by industry (Eli Lilly and Company Investigator-Initiated Trial program.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 physical functioning at 12 weeks; MD; 6.8 (95%CI -8.5 to 22, SF-36 physical functioning 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 mental health at 12 weeks; MD; -1.1 (95%CI -11.8 to 9.5, SF-36 mental health 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 role emotional at 12 weeks; MD; 4.4 (95%CI -24.2 to 32.9, SF-36 role emotional 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 role physical at 12 weeks; MD; 11 (95%CI -9 to 30.9, SF-36 role physical 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 bodily pain at 12 weeks; MD; 11.4 (95%CI -0.5 to 23.2, SF-36 bodily pain 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 vitality at 12 weeks; MD; 3.3 (95%CI -10.3 to 17, SF-36 vitality 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 general health at 12 weeks; MD; 0 (95%CI -10.8 to 10.7, SF-36 general health 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: SF-36 social functioning at 12 weeks; MD; 0.7 (95%CI -14.7 to 16, SF-36 social functioning 0-100; High=Top is good outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcome 2: Fatigue at longest follow up available

- Actual outcome for adults; severity mixed or unclear: MFI-20 general fatigue at 12 weeks; MD; -1 (95%CI -2.8 to 0.7, Multidimensional fatigue inventory-20 general fatigue subscale range not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: MFI-20 physical fatigue at 12 weeks; MD; -0.9 (95%CI -2.7 to 0.9, Multidimensional fatigue inventory-20 physical fatigue subscale range not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: MFI-20 reduced activity at 12 weeks; MD; 0 (95%CI -1.8 to 1.8, Multidimensional fatigue inventory-20 reduced activity subscale range not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: MFI-20 reduced motivation at 12 weeks; MD; -0.8 (95%CI -2.6 to 1.1, Multidimensional fatigue inventory-20 reduced motivation subscale range not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: MFI-20 mental fatigue at 12 weeks; MD; -2.5 (95%CI -4.4 to -0.6, Multidimensional fatigue inventory-20 mental fatigue subscale range not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS - anxiety at 12 weeks; MD; -0.9 (95%CI -2.4 to 0.6, Hospital anxiety and depression scale anxiety subscale 0-21, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: HADS - depression at 12 weeks; MD; 0.94 (95%CI 0.72 to 1.23, Hospital anxiety and depression scale depression subscale 0-21, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - severity at 12 weeks; MD; -0.73 (95%CI -1 to -0.54, Brief pain inventory severity subscale 0-10, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Brief Pain Inventory - interference at 12 weeks; MD; -0.7 (95%CI -0.96 to -0.51, Brief pain inventory interference subscale 0-10, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0

Protocol outcome 5: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Most frequently reported treatment-emergent adverse events at 12 weeks; Group 1: 131/29, Group 2: 62/30; Comments: Total number of reported treatment-emergent adverse events. Adverse events were those reported by at least 5% of patients in the treatment group. The list of adverse events reported was: nausea, somnolence, dizziness, headache, dry mouth, insomnia, constipation, cold virus, decreased appetite, diarrhoea, light headedness, anxiety, vivid dreams, increased urination, increased yawning, jittery, increased sweating, chills, depression, fever, hot flush, increased appetite, irritability,

pruritus, muscle fasciculation, abdominal pain, sinus infection, vaginal infection, weight gain.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression of Severity at 12 weeks; MD; -0.1 (95%CI -0.3 to 0), Clinical Global Impression of Severity 1-7, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Clinical Global Impression of Improvement at 12 weeks; MD; -0.8 (95%CI -1.7 to 0), Clinical Global Impression of Improvement 1-7, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: CDC symptom inventory at 12 weeks; MD; -2.7 (95%CI -15.5 to 10.1), CDC symptom inventory scale not reported, High=Top is poor outcome. Comments: Model based estimate is the MD in changes from baseline, with adjustment for other covariates.);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Systematically higher SF-36 indices for the duloxetine group. Other outcomes similar.; Blinding details: Self-administered so possible lack of assessor blinding may not have been overly important; Group 1 Number missing: 10, Reason: unclear; Group 2 Number missing: 4, Reason: unclear

Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Blacker 2004[8]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=434)

Countries and setting	Conducted in USA; Setting: Most patients recruited from primary care centres, and some from tertiary care centres
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 20 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Modified US centers for disease control and prevention diagnosis for CFS
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	age 18-65 years; modified US CDC diagnosis for CFS; illness duration; 7 years; those with concurrent fibromyalgia also included.
Exclusion criteria	Concurrent psychiatric diagnoses; any inpatient psychiatric care; previous suicide; IBS; peptic ulcer; severe asthma; endocrine or metabolic disease; HIV; neurological disease; sensitivity to cholinergic agents; exposure to organophosphates; Gulf war syndrome; participation in CBT or GET programmes during the study; pregnancy; concomitant medication during trial except minor analgesics; antidepressants or cholinergics or antihypertensives or corticosteroids or antihistamines within 3 months prior to trial onset; other psychotropic medication within 6 weeks prior to study onset; Domperidone was allowed for anti-emetic use
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 37-39.1. Gender (M:F): 34:66. Ethnicity: White 96%; Black 1.4%; Indian subcontinent 0.5%; Asian 0.025%; Hispanic 2%
Further population details	-
Extra comments	baseline values not provided
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature

Interventions	(n=352) Intervention 1: Galantamine hydrobromide. 3 x 2.5mg per day or 3 x 5mg per day or 3 x 7.5mg per day or 3 x 10mg per day. Duration 16 weeks. Concurrent medication/care: Titrated over a 3-8 week period, commencing at 2.5mg/day, with weekly increments of 2.5 to 7.5mg depending on dose. Target dose maintained for final 8 weeks at least. Indirectness: No indirectness (n=82) Intervention 2: placebo. 3 x daily. Duration 16 weeks. Concurrent medication/care: Titration details not clear. Indirectness: No indirectness
Funding	Study funded by industry (Shire Pharmaceutical Development Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GALANTAMINE HYDROBROMIDE versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue rating scale-physical at 20 weeks; Mean; , Comments: Only mean change from baseline given for the placebo (9.86) and the 4 dose sub-groups (8.77 to 11.02). No measures of variance so not possible to estimate 95% CIs;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines given as range across all arms; result is change from baseline.; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 3, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Chalder fatigue rating scale-mental at 20 weeks; Mean; , Comments: Only mean change from baseline given for the placebo (6.8) and the 4 dose sub-groups (5.89 to 7.74). No measures of variance so not possible to estimate 95% CIs;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines given as range across all arms; result is change from baseline.; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 3, Reason: unclear

Protocol outcome 2: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Computerised cognitive test at 20 weeks; Mean; , Comments: For each of the sub-tests only mean changes from baseline were given without any measure of variance. The values are not given here, as they cannot be usefully used in a meta-analysis; not possible to estimate 95% CIs;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines given as range across all arms; result is change from baseline.; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 3, Reason: unclear

Protocol outcome 3: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Pittsburgh Sleep Quality Index - total score at 20 weeks; Mean; , Comments: Only mean change from baseline

given for the placebo (-2.02) and the 4 dose sub-groups (-2.28 to -1.43). No measures of variance so not possible to estimate 95% CIs;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines given as range across all arms; result is change from baseline.; Group 1 Number missing: 9, Reason: unclear; Group 2 Number missing: 3, Reason: unclear

Protocol outcome 4: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: Clinician global impression scores - no change or worse (>=3) at 20 weeks; Group 1: 169/280, Group 2: 47/67
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: No baseline details given; Group 1 Number missing: 72, Reason: mostly adverse events but generally unclear if related to outcome; Group 2 Number missing: 15, Reason: adverse events but generally unclear if related to outcome

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Blockmans 2006[9]**
Study type	RCT (Patient randomised; Crossover: 1 week (half-life of drug = 2 hours, so likely to be appropriate))
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Belgium; Setting: General Internal medicine Outpatient clinic at a University Hospital in Gasthuisberg, Belgium.
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 4 weeks for each period
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC CFS criteria

Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	1994 CDC criteria; at least 4 minor criteria; at least 6 months of fatigue; ambulant; concentration problems mandatory;
Exclusion criteria	Any abnormalities in biochemical investigation (such as FBC, protein electrophoresis ionogram, calcium, phosphorous, renal function, liver function, glycaemia, muscle enzymes, antinuclear factor, cortisol, thyroid function, hepatitis B and C serology, urine microscopy, chest X-ray and abdominal US); primary psychiatric disorders; addition problems; <18 years; history of stomach/duodenal ulcers, arterial hypertension, glaucoma, DM, cardiac arrhythmia; Tourette's syndrome; use of beta blockers, antidepressant or antipsychotic medication; ongoing pregnancy
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 40 (8). Gender (M:F): 15:45. Ethnicity: unclear
Further population details	-
Extra comments	Median fatigue duration 36 months (IQR 22-74); weight 71.3kg; sbp 128(15) mmHg; dbp 81 mmHg; HR 72(8); sleepless ness 67%; dry mouth 38%; dizziness 70%; akathisia 70%; abdominal pain 53%; chest pain 43%.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=60) Intervention 1: sympathomimetic/central antihypertensive drugs - methylphenidate. 10 mg twice daily (8am and 2pm). Taken for 1 month. Duration 1 months. Concurrent medication/care: Washout period of 1 week (half-life of drug is 2 hours so over 1 week there would be only 1 / [2 to the power of 84] remaining - thus it is an appropriate duration). Patients who stopped the treatment during the first period but who returned after 4 weeks were allowed to start therapy with the second compound. Indirectness: No indirectness (n=60) Intervention 2: placebo. Taken twice daily, but unclear if identical in appearance to study drug. Duration 1 month. Concurrent medication/care: Washout period of 1 week (half-life of drug is 2 hours so over 1 week there would be only 1 / [2 to the power of 84] remaining - thus it is an appropriate duration). Patients who stopped the treatment during the first period but who returned after 4 weeks were allowed to start therapy with the second compound. Indirectness: No indirectness

	Comments: The same 60 patients took both drugs, but in a random order. Thus about half would have had the study drug in the first period, whilst the other half would have had the placebo first. A washout period of 1 week was used before each patient took the alternative compound in the second period of 4 weeks.
Funding	Funding not stated (No report of conflicts of interest or funding)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (RITALIN) (KPAX002) versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-36 Physical composite at 4 weeks; Group 1: mean 52.8 (SD 19); n=60, Group 2: mean 51.2 (SD 18.7); n=60; SF36 physical composite 0-100, High=Top is good outcome. Unclear whether a more appropriate paired analysis was performed. However the current analysis will be conservative in that it will tend to underestimate the precision.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF-36 mental composite at 4 weeks; Group 1: mean 51.8 (SD 16.4); n=60, Group 2: mean 47.3 (SD 16.7); n=60; SF36 physical composite 0-100, High=Top is good outcome. Unclear whether a more appropriate paired analysis was performed. However the current analysis will be conservative in that it will tend to underestimate the precision.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: CIS fatigue total score at 4 weeks; Group 1: mean 102.8 (SD 22.4); n=60, Group 2: mean 112.5 (SD 11.3); n=60; Checklist Individual Strength – fatigue 20-140, High=Top is poor outcome. Unclear whether a more appropriate paired analysis was performed. However the current analysis will be conservative in that it will tend to underestimate the precision.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: HADS Depression at 4 weeks; Group 1: mean 7.3 (SD 3.8); n=60, Group 2: mean 7.7 (SD 3.7); n=60; Hospital anxiety and depression scale depression subscale 0-21, High=Top is poor outcome. Unclear whether a more appropriate paired analysis was performed. However the current analysis will be conservative in that it will tend to underestimate the precision.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: HADS anxiety at 4 weeks; Group 1: mean 8.3 (SD 3.8); n=60, Group 2: mean 8.7 (SD 4.7); n=60; Hospital anxiety

and depression scale anxiety subscale 0-21, High=Top is poor outcome. Unclear whether a more appropriate paired analysis was performed. However the current analysis will be conservative in that it will tend to underestimate the precision. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: sleeplessness at 4 weeks; Group 1: 21/60, Group 2: 23/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: dry mouth at 4 weeks; Group 1: 34/60, Group 2: 18/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: dizziness at 4 weeks; Group 1: 30/60, Group 2: 38/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: Akathisia at 4 weeks; Group 1: 29/60, Group 2: 34/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: Abdominal pain at 4 weeks; Group 1: 28/60, Group 2: 23/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: chest pain at 4 weeks; Group 1: 17/60, Group 2: 25/60 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Fluge 2011[22]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Norway; Setting: Department of oncology, single (tertiary referral) centre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnosis of CFS by a neurologist, according to the Fukuda 1994 criteria; pre-treatment evaluation included thorough clinical examination, standard laboratory tests and further diagnostic tests if pre-treatment evaluation revealed any relevant abnormality that could explain the severe fatigue
Stratum	adults; severity mixed or unclear: age 18–65 years, meeting Fukuda 1994 criteria
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	a diagnosis of CFS by a neurologist, according to the Fukuda 1994 criteria; age 18–65 years; written informed consent
Exclusion criteria	fatigue not fulfilling CFS criteria; previous malignant disease (except basal cell carcinoma and cervical dysplasia); previous long-term immunosuppressive treatment; previous Rituximab treatment; endogenous depression; lack of ability to adhere to protocol; evidence of on-going infection
Recruitment/selection of patients	Most of the participants were recruited from patients referred to Department of Neurology
Age, gender and ethnicity	Age - Mean (SD): Rituximab 37.3 (11.5) years, placebo 31.5 (11.6) years. Gender (M:F): 9/21. Ethnicity: not reported
Further population details	-
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature
Interventions	(n=15) Intervention 1: immunomodulatory drugs - rituximab. Rituximab 500 mg/m² (maximum 1000 mg), diluted in saline to a concentration of 2 mg/ml, or an equal volume of saline, were given twice two weeks apart, with nurse

	surveillance and according to local guidelines used for treating B-cell lymphomas. Infusion bags had double plastic covers to avoid content identification by nurse or patient. Duration 2 weeks. Concurrent medication/care: No additional Rituximab infusions, or other intervention, were given during follow-up. All patients were given oral cetirizine 10 mg, paracetamol 1 g, and dexamethasone 8 mg prior to infusion. Indirectness: No indirectness; Indirectness comment: NA (n=15) Intervention 2: placebo. An equal volume if saline, given twice two weeks apart, with nurse surveillance and according to local guidelines used for treating B-cell lymphomas. Infusion bags had double plastic covers to avoid content identification by nurse or patient. Duration 2 weeks. Concurrent medication/care: No additional infusions, or other interventions, were given during follow-up. All patients were given oral cetirizine 10 mg, paracetamol 1 g, and dexamethasone 8 mg prior to infusion. Indirectness: No indirectness; Indirectness comment: NA
Funding	Academic or government funding (Helse Vest (Western Norway Regional Health Authority); legacy of Torstein Hereid)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RITUXIMAB versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical composite (max % change from baseline) at 10 months ; Group 1: mean 54 (SD 46); n=13, Group 2: mean 26 (SD 17); n=15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baselines, mean (SD): Rituximab 24 (5); Placebo 26 (6); Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 mental composite (max % change from baseline) at 10 months ; Group 1: mean 9 (SD 54); n=13, Group 2: mean 5 (SD 32); n=15
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Baselines, mean (SD): Rituximab 46 (11); Placebo 46 (8); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available;

	Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Hickie 2000[34]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Australia; Setting: Recruited from infectious diseases and immunology outpatient clinics in Sydney, Australia.
Line of therapy	Not applicable
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Lloyd criteria - not a set of criteria based on expert group consensus
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-65; fulfilled diagnostic criteria for CFS by LLoyd et al. (1988) [similar to 1994 CDC comprising chronic, persisting or relapsing fatigue for >6 months with neurological dysfunction including impairment of concentration and/or new onset of short-term memory impairment].
Exclusion criteria	Diagnosis of alternative illness that explains symptoms; steroid medication or other immunomodulatory agents; hepatic dysfunction; recent alcohol or substance abuse; pregnant/breastfeeding/not using contraception.
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 42.3 to 44.9. Gender (M:F): 41:49. Ethnicity: unclear

Further population details	-
Extra comments	moclobemide/placebo: duration of illness 84.2 weeks/90.9 weeks; initial KPI score 74.3/75.9; POMS fatigue 18/18; POMS vigour 8.2/8.8; POMS depression 12.9/14.1; current major depression 30%/40%; current psychological distress 68%/67%; CD4 T cell count 0.87/0.95
Indirectness of population	Serious indirectness: Lloyd 1988 criteria were excluded from the diagnostic criteria review on the basis there was unclear methodology for the development of the criteria and have therefore been downgraded here for indirectness.
Interventions	(n=47) Intervention 1: antidepressants - MAOIs. Moclobemide - a reversible inhibitor of monoamine oxidase (RIMA) - initially given as 150mg tablet twice daily after meals. After 1 week the dose was increased to 2 tablets in morning and 1 tablet at night for a total dose of 450mg/day. This was increased to 600mg/day if tolerated. Duration 6 weeks. Concurrent medication/care: Intermittent night dosages of benzodiazepines allowed for insomnia. Indirectness: No indirectness (n=43) Intervention 2: placebo. Identical 150mg tablet given in same dosages and time points as moclobemide - i.e. initially 300mg/day (in 2 doses) rising to 450mg or 600mg per day. Duration 6 weeks. Concurrent medication/care: Intermittent benzodiazepines allowed for sleep problems. Indirectness: No indirectness
Funding	Funding not stated (No mention of funding or conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MAOIS versus PLACEBO

Protocol outcome 1: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Karnofsky performance index (KPI) - measures level of disability at 6 weeks; Group 1: mean 0.86 standard deviation at baseline (SD 1.2); n=40, Group 2: mean 0.58 standard deviation at baseline (SD 1.3); n=37; Karnofsky performance index - measures level of disability scale not reported, High=Top is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Profile of mood states (POMS) - fatigue at 6 weeks; Group 1: mean -0.05 Units of baseline standard deviation (SD

0.4); n=40, Group 2: mean -0.01 Units of baseline standard deviation (SD 0.3); n=37; Profile of mood states – fatigue 0-28, High=Top is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for adults; severity mixed or unclear: Profile of mood states (POMS) - vigour at 6 weeks; Group 1: mean 0.51 units of baseline standard deviation (SD 1.2); n=40, Group 2: mean 0 units of baseline standard deviation (SD 1.1); n=37; Profile of mood states – vigour 0-32, High=Top is good outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for adults; severity mixed or unclear: Profile of mood states (POMS) - depression at 6 weeks; Group 1: mean -0.06 standard deviations at baseline (SD 1); n=40, Group 2: mean -0.08 standard deviations at baseline (SD 0.7); n=37; Profile of mood states – depression 0-60, High=Top is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Globally improved cases at 6 weeks; Group 1: 24/47, Group 2: 14/43 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Kakumanu 2003[37]**
Study type	RCT (Patient randomised; Crossover: 1 week)
Number of studies (number of participants)	1 (n=28)
Countries and setting	Conducted in USA; Setting: University hospital
Line of therapy	Not applicable

Duration of study	Intervention time: 4 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-65; CDC criteria for CFS; symptoms of rhinitis
Exclusion criteria	sleep apnoea; obesity; nasal polyps; recent URTI; deviated septum; seasonal allergic rhinitis; asthma; other respiratory diseases
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 46.2(31-62). Gender (M:F): 8:20. Ethnicity: unclear
Further population details	-
Extra comments	perennial rhinitis 54%; nonallergic rhinitis 46%;
Indirectness of population	Very serious indirectness: All participants had rhinitis and 1994 CDC criteria used; PEM is not a compulsory feature
Interventions	(n=21) Intervention 1: oral corticosteroids - fludrocortisone/hydrocortisone/other. NASAL (not oral) corticosteroid (Flunisolide) self-administered with two sprays twice daily. Duration 4 weeks - 8 weeks. Concurrent medication/care: This was a hybrid parallel/cross-over trial design. There were 4 groups of 7 who were treated as follows: active throughout; placebo throughout; active then placebo; placebo then active. Thus 21 had the active treatment at one point. In the analysis the results from these 21 people were aggregated without any apparent adjustments for some having had the other treatment (with the possibility of carryover effects). Indirectness: No indirectness (n=21) Intervention 2: placebo. Saline spray - 2 sprays twice daily. Duration 4 weeks - 8 weeks. Concurrent medication/care: This was a hybrid parallel/cross-over trial design. There were 4 groups of 7 who were treated as follows: active throughout; placebo throughout; active then placebo; placebo then active. Thus 21 had the placebo at some point. In the analysis the results from these 21 people were aggregated without any apparent adjustments for

	some having had the other treatment (with the possibility of carryover effects). Indirectness: No indirectness
Funding	Academic or government funding (GCRC grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUDROCORTISONE/HYDROCORTISONE/OTHER versus PLACEBO Protocol outcome 1: Sleep quality at longest follow up available - Actual outcome for adults; severity mixed or unclear: Epworth Sleepiness Scale at 4-8 weeks; MD; -3.18 (95%CI -6.57 to 0.21); Epworth sleepiness scale 0-24, High=poor outcome; Comments: baseline scores not reported Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for adults; severity mixed or unclear: Functional Outcomes of Sleep Questionnaire at 4-8 weeks; MD; 0.89 (95%CI -0.9884 to 2.7716); University of Pennsylvania Functional Outcomes of Sleep Quality of Life Survey scale not reported, High=Top is good outcome; Comments: baseline scores not reported Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Fatigue at longest available follow up - Actual outcome for adults; severity mixed or unclear: Chronic Fatigue Syndrome Severity Rating at 4-8 weeks; MD; -3.17 (95%CI -7.48 to 1.14), Units: unclear, High=poor outcome; Comments: Unclear if this is a validated scale; CIs calculated from SE Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Symptom scales at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Lloyd 1990[44]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)
Countries and setting	Conducted in Australia; Setting: Unclear.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months + 3 months
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: Diagnosed according to Lloyd 1988 criteria. These criteria were not included in the diagnostic criteria review of this guideline and have therefore been downgraded for indirectness. However, the study states that their own criteria emphasize the same features as the criteria published subsequently by the Centers for Disease Control.
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	A diagnosis of CFS required: (1) a history of at least 6 months in duration of marked exercise-aggravated muscle fatigue, with abnormally prolonged recovery time, associated with typical constitutional and neuropsychiatric symptoms; (2) that CFS was producing frequent medical consultation and a substantial reduction in the ability to participate in usual daily activities when com-pared with the subject's pre-morbid status [for ex-ample, considerable time lost from school or work, and inability to participate in sports]. All patients had chronic and persisting symptomatology, rather than a relapsing and remitting course as sometimes reported for this syndrome.
Exclusion criteria	A physical examination and standardized investigation protocol excluded other chronic infectious or immunodeficiency-related disorders.
Recruitment/selection of patients	Unclear.
Age, gender and ethnicity	Age - Mean (SD): Treatment group 39 (10) years; placebo group 33 (12) years. Gender (M:F): 25 males, 24 females. Ethnicity: Not stated.

Further population details	-
Extra comments	All subjects had normal blood cell counts, renal and liver function tests, muscle enzyme assays, thyroid function tests, antinuclear antibodies, rheumatoid factor, total immunoglobulin levels, and serologic tests for syphilis, hepatitis B, and human immunodeficiency virus.
Indirectness of population	Serious indirectness: CFS diagnostic criteria used (Lloyd 1988) were excluded from the diagnostic criteria review on the basis there was unclear methodology for the development of the criteria. The study states that the criteria emphasize the same features as the criteria published subsequently by the Centers for Disease Control.
Interventions	(n=23) Intervention 1: immunomodulatory drugs - IV immunoglobulin G. High-dose intravenous (IV) immunoglobulin G. Immunoglobulin G (Intragam, Commonwealth Serum Laboratories, Melbourne Australia [based on the formulation of Gamimune N, Cutter Laboratories, Berkeley, California]) was administered intravenously by continuous infusion in a dosage of 2 g (IgG)/kg. Three infusions lasting 24 hours were administered at monthly intervals. Duration 3 24-hour infusions over 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=26) Intervention 2: placebo. Placebo (10% w/v maltose) was administered intravenously for 24 hours at an equivalent volume to the IgG infusion. Duration 3 24-hour infusions over 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Academic or government funding (The research was funded by scholarships from the National Health and Medical Research Council of Australia (AL), Canberra, Australia, and the New South Wales Institute of Psychiatry (IH) and Myalgic Encephalomyelitis Society of New South Wales, Sydney, Australia.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IMMUNOGLOBULIN G versus PLACEBO

Protocol outcome 1: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hamilton Depression Scale at 6 months; Group 1: mean 9 (SD 5); n=23, Group 2: mean 10 (SD 3); n=26; Hamilton Depression Scale 0-62 Top=High is poor outcome; Comments: Baselines, mean (SD): Immunoglobulin 10.7 (2.8) Placebo 10.5 (3.4)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: Zung Self-Rating Depression Scale at 6 months; Group 1: mean 41 (SD 11); n=23, Group 2: mean 40 (SD 12); n=26; Zung Self-Rating Depression Scale 0-80 Top=High is poor outcome; Comments: Baselines, mean (SD): Immunoglobulin 42 (8) Placebo 38 (11) Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baselines, mean (SD): Immunoglobulin 42 (8) Placebo 38 (11); Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Return to school or work at longest follow up available - Actual outcome for adults; severity mixed or unclear: Resumption of pre-morbid employment status in full-time occupations or housework. at 6 months; Group 1: 6/23, Group 2: 0/26; Comments: Reported that six of the 13 patients (all from immunoglobulin group) who 'responded' (ie had a marked reduction in symptoms and improvement in functional capacity) resumed their pre-morbid employment status in full-time occupations or housework. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Marked reduction in symptoms and improvement in functional capacity at 6 months; Group 1: 10/23, Group 2: 3/26; Comments: Determined through an evaluation of symptoms and disability by the physician, meeting the criteria for "response". Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Mckenzie 1998[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in USA; Setting: Unclear

Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC 1988 criteria for CFS (all met 1994 criteria as well)
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18 to 55 years who met the CDC1988 criteria for CFS; illness began over a period of 6 weeks or less; use of birth control; negative pregnancy test
Exclusion criteria	Contraindications to systemic steroids; any other acute or chronic condition that required ongoing or intermittent medication; use of any prescribed and OTC drugs (except paracetamol) in 2-6 weeks before enrolment or during study
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: hydrocortisone 36.7yrs, placebo 38.3 yrs. Gender (M:F): 14:56. Ethnicity: Hydrocortisone/placebo; white 97%/94%, black 3%/0, other 0/6%
Further population details	-
Extra comments	Hydrocortisone/placebo: length of illness 46.9/59.9 months; impaired employment 77%/69%; urine cortisol 192/187;resting serum cortisol 425/397; self-rating wellness score 38.8/37.6; BDI 12/9.9; activity scale 4.7/5; SIP 18.7/17.9; profile of mood states (PMS) anger 5.7/4.7; PMS anxiety 8.1/8; PMS confusion 10.7/10; PMS depression 7.7/4.8; PMS fatigue 19.6/17.8; PMS vigor 7.9/7.3; SQ 90-R general severity index 0.61/0.53; positive symptom distress index 1.7/1.8; positive symptom total 29.4/26.2; Hamilton Depression rating Scale 9.8/9.4; concurrent mental disorders 74%/94%
Indirectness of population	Serious indirectness – Holmes 1988 and 1994 CDC criteria used; PEM is not a compulsory feature

Interventions	(n=35) Intervention 1: oral corticosteroids -fludrocortisone/hydrocortisone/other. Hydrocortisone pills - dose of 16mg per square metre of body surface per day (20-30mg every morning at 8am and 5mg every day at 2pm). Duration 12 weeks. Concurrent medication/care: None. Indirectness: No indirectness (n=35) Intervention 2: placebo. Identical placebo at same doses as hydrocortisone group. Duration 12 week. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUDROCORTISONE/HYDROCORTISONE/OTHER versus PLACEBO

Protocol outcome 1: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory (BDI) at 12 weeks; Group 1: mean -2.1 (SD 5.1); n=34, Group 2: mean -0.4 (SD 4.1); n=34; Beck Depression Inventory (BDI) 0-63 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: BDI 12/9.9; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - anger at 12 weeks; Group 1: mean -1.6 (SD 3.9); n=34, Group 2: mean -0.8 (SD 3.8); n=34; Profile of Mood States (POMS) 0-48 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - anxiety at 12 weeks; Group 1: mean -0.8 (SD 2.5); n=34, Group 2: mean -2.1 (SD 3.6); n=34; Profile of Mood States (POMS) 0-46 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - confusion at 12 weeks; Group 1: mean -1.1 (SD 3.3); n=34, Group 2: mean -1.4 (SD 2.9); n=34; Profile of Mood States (POMS) 0-28 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear
- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - depression at 12 weeks; Group 1: mean -1.6 (SD 4.6); n=34, Group 2: mean 0 (SD 3.8); n=34; Profile of Mood States (POMS) 0-60 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - fatigue at 12 weeks; Group 1: mean -3.6 (SD 5.3); n=34, Group 2: mean -1.8 (SD 4.5); n=34; Profile of Mood States (POMS) 0-28 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Profile of Mood States - vigour at 12 weeks; Group 1: mean 1.2 (SD 3.3); n=34, Group 2: mean 0.7 (SD 3.3); n=34; Profile of Mood States (POMS) 0-32 Top=High is good outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Symptom checklist-90-R general severity index at 12 weeks; Group 1: mean -0.1 (SD 0.2); n=34, Group 2: mean -0.1 (SD 0.2); n=34; Symptom checklist-90-R general severity index scale not reported, High=Top is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Symptom checklist-90-R positive symptom distress index at 12 weeks; Group 1: mean 0 (SD 0.3); n=34, Group 2: mean -0.1 (SD 0.3); n=34; Symptom checklist-90-R positive symptom distress index scale not reported, High=Top is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Symptom checklist-90-R positive symptom total at 12 weeks; Group 1: mean -2.6 (SD 10.8); n=34, Group 2: mean -2.4 (SD 11.5); n=34; Symptom checklist-90-R positive symptom total scale not reported, High=Top is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear

- Actual outcome for adults; severity mixed or unclear: Hamilton Depression rating Scale at 12 weeks; Group 1: mean -0.8 (SD 3.8); n=32, Group 2: mean 0.1 (SD 2.9); n=33; Hamilton Depression Rating Scale 0-52 Top=High is poor outcome

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 3, Reason: unclear; Group 2 Number missing: 2, Reason: unclear

Protocol outcome 2: Adverse events at longest follow up available

- Actual outcome for adults; severity mixed or unclear: Any adverse reaction at 12 weeks; Group 1: 31/35, Group 2: 27/35;

Adverse reactions included fatigue, depressed mood, difficulty with concentration, increased appetite, weight gain and more. Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 0, Reason: 0; Group 2 Number missing: 0, Reason: 0 Protocol outcome 3: Activity levels at longest follow up available - Actual outcome for adults; severity mixed or unclear: Activity scale at 12 weeks; Group 1: mean 0.3 (SD 1.1); n=34, Group 2: mean 0.7 (SD 1.4); n=34; Activity scale unclear Top=High is good outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: hydrocortisone group had better status generally; Group 1 Number missing: 1, Reason: unclear; Group 2 Number missing: 1, Reason: unclear Protocol outcome 4: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Wellness scale at 12 weeks; Group 1: mean 6.3 (SD 11.7); n=30, Group 2: mean 1.7 (SD 8.8); n=35; Wellness scale 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Wellness score 38.8/37.6; Group 1 Number missing: 5, Reason: no pre-treatment scores; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile at 12 weeks; Group 1: mean -2.5 (SD 6.4); n=33, Group 2: mean -2.2 (SD 6.8); n=34; Sickness Impact Profile not reported, Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: SIP 18.7/17.9; Group 1 Number missing: 2, Reason: unclear; Group 2 Number missing: 1, Reason: unclear	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Montoya 2018[52]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=135)
Countries and setting	Conducted in USA; Setting: Conducted at 4 sites in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-59; met CDC 1994 criteria; complained of alertness and concentration difficulties; otherwise in good health based on medical history and screening; willing not to use any nutritional, herbal, or caffeine/pseudoephedrine containing compounds
Exclusion criteria	Pregnancy; active substance abuse; major depression; active medical conditions for which methylphenidate hydrochloride is contraindicated; daily anxiolytics; daily use of >1 antidepressant; use of MAOs, CNS stimulants and narcotic opioids; abnormal laboratory test values; ECG abnormalities
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age: Drug/placebo: 42.8/42.3 years. Gender (M:F): 36:92. Ethnicity: Drug/placebo: white 90%/91%; Asian 3%/0; African American 2%/8%; Other 5%/2%
Further population details	-
Extra comments	Drug/placebo: duration of CFS symptoms >=10 years 48%/46%; mean CIS total score 112.2/112.4
Indirectness of population	Serious population indirectness: 1994 CDC criteria used; PEM not a compulsory feature

Interventions	(n=67) Intervention 1: sympathomimetic/central antihypertensive drugs - methylphenidate. 5mg methylphenidate daily for week 1 and 10mg twice daily for weeks 2 to 12. Mitochondrial modulator (nutritional supplement) given as 4 tablets twice daily. The combination of these two agents is called KPAX002. KPAX002 is comprised of a low dosage of methylphenidate hydrochloride, combined with nutrients believed to modulate mitochondrial function. Duration 12 weeks. Concurrent medication/care: Taken with breakfast and lunch. Indirectness: No indirectness (n=65) Intervention 2: placebo. Placebo version of KPAX002 treatment. Unclear if this meant both placebo versions of methylphenidate and mitochondrial modulator, or just the former. Likely to be both. . Duration 12 weeks. Concurrent medication/care: Taken with breakfast and lunch. Indirectness: No indirectness
Funding	Funding not stated (No conflicts of interest statement made)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: METHYLPHENIDATE (RITALIN) (KPAX002) versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Checklist Individual Strength (CIS) total score at 12 weeks; Group 1: mean -16.9 (SD 23.52); n=63, Group 2: mean -13.8 (SD 22.15); n=65; Checklist Individual Strength scale 20-140, High=Top is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Change values analysed so any unreported baseline discrepancies may not create sig bias; Group 1 Number missing: 4, Reason: did not meet ITT criteria of at least 1 complete treatment; Group 2 Number missing: 3, Reason: did not meet ITT criteria of at least 1 complete treatment

Protocol outcome 2: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: AEs leading to discontinuation at 12 weeks; Group 1: 8/63, Group 2: 3/65
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Change values analysed so any unreported baseline discrepancies may not create sig bias; Group 1 Number missing: 4, Reason: did not meet ITT criteria of at least 1 complete treatment; Group 2 Number missing: 3, Reason: did not meet ITT criteria of at least 1 complete treatment
- Actual outcome for adults; severity mixed or unclear: Serious AEs (pyelonephritis) at 12 weeks; Group 1: 1/63, Group 2: 0/65
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Change values analysed so any unreported baseline discrepancies may not create sig bias; Group 1 Number

missing: 4, Reason: did not meet ITT criteria of at least 1 complete treatment; Group 2 Number missing: 3, Reason: did not meet ITT criteria of at least 1 complete treatment	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Morriss 2002[56]**
Study type	RCT (Patient randomised; Crossover: 2 weeks)
Number of studies (number of participants)	1 (n=10)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient clinic for CFS at a general hospital in UK
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 Fukuda
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CFS diagnosed by Fukuda criteria; no non-CFS diagnoses accounting for symptoms
Exclusion criteria	ICD-10 Depressive episode; psychotropic medication, oral contraceptives, steroids, thyroxine, bromocriptine or anti-hypertensive medication in previous 15 days; age <18 years or above 60 years; BMI <15, >30; migraine; pregnancy or breast feeding.

Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 46(7.6). Gender (M:F): 1:1. Ethnicity: unclear
Further population details	-
Extra comments	BMI 24.8; NART IQ 118.4; Total fatigue 31.7; Cognitive failures questionnaire total score 57.8; HADS depression 5.5; HADS anxiety 5.5; somatosensory amplification 27.5; duration of CFS 75mo
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=10) Intervention 1: sympathomimetic/central antihypertensive drugs - clonidine. Clonidine IV infusion 2.5 micrpog/kg in 10ml normal saline over 5 minutes. Duration One-off treatment. Concurrent medication/care: Heparinised cannula used for infusion. Cross-over and randomised order for clonidine/placebo with washout of 2 weeks. Indirectness: No indirectness (n=10) Intervention 2: placebo. IV infusion of 10ml normal saline over 5 mins. Duration One-off treatment. Concurrent medication/care: Heparinised cannula used for IV. Cross-over and randomised order for clonidine/placebo with washout of 2 weeks. Indirectness: No indirectness
Funding	Academic or government funding (MRC)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO

Protocol outcome 1: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Stockings of Cambridge - minimum moves at 30 minutes; Group 1: mean 9 (SD 2.18); n=9, Group 2: mean 10.22 (SD 2.39); n=9.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Stockings of Cambridge - initial thinking time (s) at 30 minutes; Group 1: mean 7.99 (SD 4.34); n=9, Group 2: mean 9.27 (SD 4.13); n=9

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Stockings of Cambridge - subsequent thinking time (s) at 30 minutes; Group 1: mean 1.38 (SD 2.46); n=9, Group 2: mean 1.89 (SD 3.07); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Rapid Visual Information Processing - reaction time (s) at 30 minutes; Group 1: mean 5 (SD 1.52); n=9, Group 2: mean 5.15 (SD 1.22); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Intradimensional (IDS) set sift/extradimensional (EDS) set shift: IDS errors at 30 minutes; Group 1: mean 0.44 (SD 0.73); n=9, Group 2: mean 0.22 (SD 0.44); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Intradimensional (IDS) set sift/extradimensional (EDS) set shift: EDS errors at 30 minutes; Group 1: mean 1.78 (SD 1.56); n=9, Group 2: mean 4.44 (SD 6.64); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Spatial working memory: between-search errors at 30 minutes; Group 1: mean 7.09 (SD 4.21); n=9, Group 2: mean 9.26 (SD 6.82); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: Spatial working memory: strategy score at 30 minutes; Group 1: mean 31.56 (SD 5.96); n=9, Group 2: mean 31.78 (SD 6.38); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.
- Actual outcome for adults; severity mixed or unclear: pattern recognition - number correct at 30 minutes; Group 1: mean 22.3 (SD 1.3); n=9, Group 2: mean 21.4 (SD 2.2); n=9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome:

No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used. - Actual outcome for adults; severity mixed or unclear: spatial recognition - number correct at 30 minutes; Group 1: mean 15.2 (SD 2.9); n=9, Group 2: mean 15.3 (SD 2.1); n=9 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used. - Actual outcome for adults; severity mixed or unclear: spatial span - length at 30 minutes; Group 1: mean 6.4 (SD 1.26); n=9, Group 2: mean 6.1 (SD 1.2); n=9 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used. - Actual outcome for adults; severity mixed or unclear: Delayed matching to sample 2-s delay at 30 minutes; Group 1: mean 6.56 (SD 1.69); n=9, Group 2: mean 7.78 (SD 1.39); n=9 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used. - Actual outcome for adults; severity mixed or unclear: Paired associate learning - sets completed at 30 minutes; Group 1: mean 8.89 (SD 0.33); n=9, Group 2: mean 8.89 (SD 0.33); n=9 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.; Group 2 Number missing: 1, Reason: Patient placed on exclusion medication by GP between the tests. Only received placebo but data for both arms not used.	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Olson 2003[61]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=20)
Countries and setting	Conducted in Australia; Setting: Newcastle Sleep Disorders Centre, Australia
Line of therapy	Not applicable
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fukuda
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Fukuda criteria; normal results for overnight sleep study; mean daytime latency of >7 minutes;
Exclusion criteria	history of alcohol or other substance abuse; history of epilepsy; history of MI; current hypertension; cardiac arrhythmias; angina pectoris; coeliac disease; psychiatric disorders other than depression; use of anti-depressant drugs
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range: 17-72. Gender (M:F): 7:13. Ethnicity: unclear
Further population details	-
Extra comments	Dexa/placebo; length of illness 7.1yrs/5.6yrs; mean sleep latency 12.9mins/13mins; member of patient support group 10%/0%; employed 80%/80%; age 32.1/39.7
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=10) Intervention 1: Amphetamines - dexamphetamine. Dexamphetamine 5mg twice daily for first week. Dose increased to 10mg twice daily if indicated at start of 2nd week. Increment repeated if appropriate at start of 3rd week. This dose continued for a further 4 weeks. Duration 6 weeks. Concurrent medication/care: None. Indirectness: No indirectness

	(n=10) Intervention 2: placebo. Identical doses and strategies for increase as study drug. Duration 6 weeks. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Sigma Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DEXAMPHETAMINE versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 Physical composite at 6 weeks; Group 1: mean 6.9 (SD 13.97); n=10, Group 2: mean 5.2 (SD 10.76); n=10; SF36 physical composite 0-100, High=Top is good outcome; Comments: sds estimated from 95% CIs given for each group in the paper
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 Mental composite at 6 weeks; Group 1: mean 4.2 (SD 11.46); n=10, Group 2: mean 3.9 (SD 12.86); n=10; SF36 mental composite 0-100, High=Top is good outcome; Comments: sds estimated 95% CIs given for each group in the paper
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 6 weeks; Group 1: mean -1.45 (SD 1.09); n=10, Group 2: mean -0.03 (SD 1.11); n=10; Fatigue Severity Scale scale not reported, High=Top is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: sleep latency at 6 weeks; Group 1: mean 13 Time taken to fall asleep when light turned off (mins) (SD 5.45); n=10, Group 2: mean 11.8 Time taken to fall asleep when light turned off (mins) (SD 3.77); n=10; Comments: sds estimated from 95% CIs given for each group in the paper. Final values used as groups very similar at baseline.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: AEs - anorexia at 6 weeks; Group 1: 5/10, Group 2: 1/10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Pardini 2011[63]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy; Setting: Single centre through referrals from clinicians and through self-referrals
Line of therapy	Not applicable
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fukuda
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Fukuda criteria; routine laboratory tests within normal ranges; no neurological or psychiatric conditions
Exclusion criteria	None reported
Recruitment/selection of patients	consecutive

Age, gender and ethnicity	Age - Mean (SD): 31.9 (1.8). Gender (M:F): 18:22. Ethnicity: unclear
Further population details	-
Extra comments	Baseline details: Amisulpride/fluoxetine: FSS 50.5/52.4; VAS pain 59.9/55.9; HADS A 5.3/5.3; HADs D 4.9/5.1; SF-12 41.3/41.7; CGI-S 4.9/4.6; mean disease duration 2.5 years/2.9 years
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM is not a compulsory feature
Interventions	(n=20) Intervention 1: Antipsychotics. Amisulpride (a substituted benzamide) is an atypical antipsychotic. 25 mb bid. Duration 12 weeks. Concurrent medication/care: None. Indirectness: No indirectness (n=20) Intervention 2: antidepressants - selective serotonin reuptake inhibitors. Fluoxetine 20 mg uid. Duration 12 weeks. Concurrent medication/care: None. Indirectness: No indirectness
Funding	No funding (No conflicts of interest statement)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANTIPSYCHOTICS versus SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF-12 at 12 weeks; Group 1: mean 53.2 (SD 4.8); n=20, Group 2: mean 37.6 (SD 4.9); n=20; SF12 0-100 Top=High is good outcome; Comments: Baseline values very similar (41.3/41.7) slightly favouring fluoxetine, so this does not create bias explaining final follow up result in favour of amisulpride
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue Severity Scale at 12 weeks; Group 1: mean 36.3 (SD 8.6); n=20, Group 2: mean 48.9 (SD 4.9); n=20; Fatigue severity scale 9-63 Top=High is poor outcome; Comments: Slight difference at baseline (50.5/52.4) but not enough to explain result at follow up
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: HADS - anxiety at 12 weeks; Group 1: mean 4.5 (SD 1); n=20, Group 2: mean 4.9 (SD 1); n=20; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: groups same at baseline (5.3/5.3) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for adults; severity mixed or unclear: HADS - depression at 12 weeks; Group 1: mean 4.3 (SD 0.9); n=20, Group 2: mean 4.2 (SD 1); n=20; Hospital anxiety and depression scale 0-21 Top=High is poor outcome; Comments: Similar baseline values (4.9/5.1) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Pain at longest follow up available - Actual outcome for adults; severity mixed or unclear: VAS pain at 12 weeks; Group 1: mean 40.5 (SD 13.1); n=20, Group 2: mean 53.1 (SD 8.3); n=20; Visual analogue scale 0-100 Top=High is poor outcome; Comments: Different at baseline, but favouring fluoxetine at baseline (59.9/55.9) so the baseline difference did not create bias towards the observed 12 week effect in favour of amisulpride. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: FIBSER - global burden at 12 weeks; Group 1: mean 0.8 (SD 0.7); n=20, Group 2: mean 0.6 (SD 0.8); n=20; Frequency, Intensity, and Burden of Side Effects Rating Scale not reported Top=High is poor outcome; Comments: Measures overall burden of AEs Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Clinical Global Impression Severity (CGI-S) at 12 weeks; Group 1: mean 2.9 (SD 0.6); n=20, Group 2: mean 4.2 (SD 1.1); n=20; Clinical global impression severity 1-7 Top=High is poor outcome; Comments: Amilsupride worse at baseline (4.9/4.6) so baseline discrepancy does not explain benefit for amisulpride at follow up. Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	Peterson 1990[65]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: All treatments were administered in individual rooms in the Drug Evaluation Unit, Hennepin County Medical Center.
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients were diagnosed according to the CFS diagnostic criteria of Holmes 1988
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable:
Inclusion criteria	A diagnosis of CFS was established after thorough medical, psychometric, and psychiatric evaluations did not establish another explanation for chronic fatigue, and after the other criteria for a case definition of CFS were met (Holmes 1988).
Exclusion criteria	The psychometric assessment was performed, consisted of three standardized questionnaires (Beck Depression Inventory, Zung Self-Rating Anxiety Scale, and Symptom Checklist-90). Seventeen patients scored within the normal range on all three tests; 13 patients had abnormal scores on one or more psychometric tests, all of whom were interviewed by a psychiatric co-investigator (CS) who found no evidence of underlying psychopathology as an explanation of chronic fatigue.
Recruitment/selection of patients	Patients were recruited from a CFS Research Program established at Hennepin County Medical Center, Minneapolis, Minnesota, in July 1988.
Age, gender and ethnicity	Age - Mean (SD): 40.8 (11.2). Gender (M:F): 22 females, 8 males. Ethnicity: Not stated.

Further population details	-
Extra comments	Duration of illness in years, mean (SD): 3.8 (2.2)
Indirectness of population	Serious indirectness: Holmes 1988 criteria used; PEM is not a compulsory feature
Interventions	(n=15) Intervention 1: immunomodulatory drugs - IV immunoglobulin G. Patients were scheduled to receive a total of six infusions of IV IgG (1 g/kg body weight, Gammagard ®, Hyland Division, Baxter Healthcare Corp., Glendale, California). The IV IgG solution was prepared according to the package insert; each millilitre of solution contained 50 mg of IgG. The fusions were initiated at a rate of 0.5 mL/kg/hour and increased as per the IV IgG package insert to a maximum of 4 mL/kg/hour. All treatments were administered in individual rooms in the Drug Evaluation Unit, Hennepin County Medical Center. Treatments were given at intervals of 30 +/- 3 days. The first infusion was administered on Study Day 0 and the sixth infusion on Study Day 150. Duration Once per month for six months (6 infusions). Concurrent medication/care: During the course of the study, patients were permitted to take vitamins, nonsteroidal anti-inflammatory agents, decongestants, antihistamines, oral contraceptives, antibiotics, and other medications as prescribed by their primary physicians. Indirectness: No indirectness (n=15) Intervention 2: placebo. Participants in the placebo group received the same course of IV but IgG was replaced with an exactly correlating volume of a 1% albumin solution as placebo. The albumin solution was made using albumin USP 25% (Buminate, Baxter Healthcare Corp.) dissolved in normal saline; the resulting solution contained 10 mg/mL of albumin. Duration Once per month for six months (6 infusions). Concurrent medication/care: During the course of the study, patients were permitted to take vitamins, nonsteroidal anti-inflammatory agents, decongestants, antihistamines, oral contraceptives, antibiotics, and other medications as prescribed by their primary physicians. Indirectness: No indirectness
Funding	Study funded by industry (This work was supported in part by a grant from Baxter Healthcare Corp., Glendale, California. Dr. Lurie is a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IMMUNOGLOBULIN G versus PLACEBO

Protocol outcome 1: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Physical functioning on the Medical Outcome Study Short Form at 150 days (final treatment day); Group 1: mean

56 (SD 23.2); n=14, Group 2: mean 51.8 (SD 22.2); n=14; Medical Outcome Study Short Form 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): IV IgG 63.1 (25.9), Placebo 66.1 (21.0) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Serious adverse event; Group 2 Number missing: 1, Reason: Serious adverse event Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Mental health on the Medical Outcome Study Short Form at 150 days (final treatment day); Group 1: mean 58.3 (SD 17.4); n=14, Group 2: mean 62.9 (SD 13.3); n=14; Medical Outcome Study Short Form 0-100 Top=High is good outcome; Comments: Baselines, mean (SD): IV IgG 63.7 (17.1), Placebo 59.7 (13.4) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Serious adverse event; Group 2 Number missing: 1, Reason: Serious adverse event Protocol outcome 3: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: Major adverse events at 150 days (final treatment day); Group 1: 3/15, Group 2: 3/15; Comments: Nature of adverse events unclear. One participant in each group dropped out of the study as a result of their major adverse experience. Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Peterson 1998[64]**
Study type	RCT (Patient randomised; Crossover: 6 weeks)
Number of studies (number of particants)	1 (n=25)
Countries and setting	Conducted in USA; Setting: Patients on registries of a research programme in Minneapolis, or a CFS clinic

Line of therapy	Not applicable
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Holmes and Fukuda criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of CFS
Exclusion criteria	Fatigue severity during the preceding month of <5 on a 0-10 VAS; taking fludrocortisone or another medication that could confound interpretation of the results
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 39.7 (10.9). Gender (M:F): Define. Ethnicity: White: 100%
Further population details	-
Extra comments	Mean treatment duration 7 years; acute infectious onset 88%; Fatigue VAS 7.4; SF36 Physical 43.2;
Indirectness of population	Serious indirectness: Holmes 1988 and 1994 CDC criteria used; PEM is not a compulsory feature
Interventions	(n=25) Intervention 1: oral corticosteroids - fludrocortisone/hydrocortisone/other. Initial dose of fludrocortisone acetate was 0.1mg via 1 tablet orally. Dose doubled if no AEs reported after 2 weeks of treatment. Duration 6 weeks. Concurrent medication/care: Patients told not to make any dietary changes (including salt intake) during study. Cross-over study: patients randomised to order of drug/placebo with 6 week washout period. Indirectness: No indirectness (n=25) Intervention 2: placebo. identical tablets taken at same dosing regimen as study drug. Duration 6 weeks. Concurrent medication/care: Patients told not to make any dietary changes (including salt intake) during study. Cross-over study: patients randomised to order of drug/placebo with 6 week washout period. . Indirectness: No indirectness

Funding	Academic or government funding (Minnesota CFS association, Institute for Research and Education of Health System Minnesota, Minneapolis Medical Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUDROCORTISONE/HYDROCORTISONE/OTHER versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
-Actual outcome for adults; severity mixed or unclear: SF-36 general well-being at 6 weeks; Group 1: mean 32.1 (SD 12.4); n=20, Group 2: mean 35.8 (SD 15.9); n=20; SF36 general well-being 0-100, High=Top is good outcome; Comments: 32.9/35.6 at baseline
Risk of bis: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Baseline details: No clinically important difference in outcome at baseline; Group Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
-Actual outcome for adults; severity mixed or unclear: SF-36 social at 6 weeks; Group 1: mean 40.1 (SD 20.4); n=20, Group 2: mean 38.2 (SD 21.4); n=20; SF36 social 0-100, High=Top is good outcome; Comments: 33.6/38.2 at baseline
Risk of bis: All domain – High, Selection – Low, Blinding – Low, Incomplete outcome data – High, Outcome reporting – Low, Measurement – Low, Crossover – Low; Indirectness of outcome: No indirectness; Baseline details: No clinically important difference in outcome at baseline; Group Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 emotional well-being at 6 weeks; Group 1: mean 72.6 (SD 13.9); n=20, Group 2: mean 68.8 (SD 15.4); n=20; SF36 emotional well-being 0-100, High=Top is good outcome; Comments: 73.9/73.9 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: same for outcome at baseline; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 emotional role limitation at 6 weeks; Group 1: mean 87.8 (SD 22.8); n=20, Group 2: mean 87.8 (SD 25.4); n=20; SF36 emotional role 0-100, High=Top is good outcome; Comments: 84.2/91.2 baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 physical at 6 weeks; Group 1: mean 49.7 (SD 20.4); n=20, Group 2: mean 42.1 (SD 21.4); n=20; SF36 physical 0-100, High=Top is good outcome; Comments: 43.2/43.7 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 role physical at 6 weeks; Group 1: mean 13.2 (SD 19.3); n=20, Group 2: mean 25 (SD 34.4); n=20; SF36 role physical 0-100, High= Top is good outcome; Comments: 23.7/15.8 at baseline

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 energy or fatigue at 6 weeks; Group 1: mean 20.3 (SD 14.5); n=20, Group 2: mean 18.2 (SD 16.2); n=20; SF36 energy or fatigue 0-100, High=Top is good outcome; Comments: 19/14.7 baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: SF-36 pain at 6 weeks; Group 1: mean 49.9 (SD 25.2); n=20, Group 2: mean 50.5 (SD 22.1); n=20; SF36 pain 0-100, High=Top is good outcome; Comments: 46.1/49.2 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue VAS at 6 weeks; Group 1: mean 7.5 (SD 1.2); n=20, Group 2: mean 7.5 (SD 2.2); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 7.4/7.1 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: inability to concentrate VAS at 6 weeks; Group 1: mean 5.2 (SD 2.5); n=20, Group 2: mean 5.8 (SD 2.6); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 6.1/6.1 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: same for outcome at baseline; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: forgetfulness VAS at 6 weeks; Group 1: mean 4.7 (SD 2.7); n=20, Group 2: mean 5.6 (SD 2.3); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 5.9/6.2 at baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to

affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: confusion VAS at 6 weeks; Group 1: mean 4.3 (SD 2.7); n=20, Group 2: mean 4.4 (SD 2.4); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 5.1/5.4 at baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: reaction time (s) at 6 weeks; Group 1: mean 0.35 (SD 0.07); n=20, Group 2: mean 0.36 (SD 0.08); n=20; Comments: 0.35/0.37 at baseline
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Positive and negative effect scale (PANAS) positive affect at 6 weeks; Group 1: mean 22.7 (SD 8.3); n=20, Group 2: mean 21.7 (SD 6.7); n=20; PANAS 10-50; High=Top is good outcome; Comments: 22.9/22.7 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: same for outcome at baseline; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 5: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: muscle pain VAS at 6 weeks; Group 1: mean 5.8 (SD 3.1); n=20, Group 2: mean 5.9 (SD 2.4); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 6.1/5.9 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome
- Actual outcome for adults; severity mixed or unclear: joint pains VAS at 6 weeks; Group 1: mean 4.8 (SD 3.8); n=20, Group 2: mean 5.1 (SD 2.9); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 5.1/4.3 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 6: Sleep quality at longest follow up available

- Actual outcome for adults; severity mixed or unclear: Unrefreshing sleep VAS at 6 weeks; Group 1: mean 7.7 (SD 2); n=20, Group 2: mean 8.2 (SD 1.8); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 8.2/7.1 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 7: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: adverse events causing withdrawal from study at 6 weeks; Group 1: 0/20, Group 2: 2/20; Comments: racing pulse and severe headache
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: same for outcome at baseline; Group 1 Number missing: 5, Reason: withdrawal due to worsening of symptoms, family problems, rest unclear; Group 2 Number missing: 5, Reason: ovarian surgery unrelated to treatment, rest unclear
- Actual outcome for adults; severity mixed or unclear: adverse events at 6 weeks; Group 1: 4/20, Group 2: 4/20; Comments: fludrocortisone arm: chest tightness/severe headache, severe headache, others unclear (6 events, some patients experienced multiple events); placebo arm: racing pulse, severe headache, others unclear 5 events, some patients experienced multiple events).
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: same for outcome at baseline; Group 1 Number missing: 5, Reason: withdrawal due to worsening of symptoms, family problems, rest unclear; Group 2 Number missing: 5, Reason: ovarian surgery unrelated to treatment, rest unclear
Protocol outcome 8: Activity level at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Distance until exhausted at 6 weeks; Group 1: mean 2.7 (SD 1); n=20, Group 2: mean 2.7 (SD 1.3); n=20; Distance before exhausted 1-5; High=Top is good outcome; Comments:2.5/2.5 at baseline; 1=1 block, 2=1 to 3 blocks, 3=3 to 8 blocks, 4=1 to 3 miles, 5=3 miles or more
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: No difference in outcome at baseline; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 9: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Treadmill time (mins) at 6 weeks; Group 1: mean 22.8 (SD 9.2); n=20, Group 2: mean 20.2 (SD 11.5); n=20; Comments: 19.3/20 at baseline
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome

Protocol outcome 10: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: headaches VAS at 6 weeks; Group 1: mean 6 (SD 2.6); n=20, Group 2: mean 6 (SD 2.4); n=20; Visual analogue

scale 0-10; High=Top is poor outcome; Comments: 6/6.2 at baseline Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). Favours drug so overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome - Actual outcome for adults; severity mixed or unclear: painful lymph nodes VAS at 6 weeks; Group 1: mean 3.5 (SD 3.3); n=20, Group 2: mean 3.7 (SD 3.5); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 4/3.9 at baseline Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome - Actual outcome for adults; severity mixed or unclear: sore throat VAS at 6 weeks; Group 1: mean 3.1 (SD 2.1); n=20, Group 2: mean 3.3 (SD 3); n=20; Visual analogue scale 0-10; High=Top is poor outcome; Comments: 3.2/3 at baseline Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: There were differences for the outcome at baseline, and the final outcome values not adjusted (p values for adjusted analysis though). But favours placebo so not overestimating treatment effect; Group 1 Number missing: 3, Reason: 3 withdrawn due to worsening symptoms - likely to affect outcome; Group 2 Number missing: 1, Reason: ovarian surgery - unlikely related to outcome	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Physical functioning at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Care needs at longest follow up available; Impact on families and carers at longest follow up available

Study	**Randall 2005[68]**
Study type	RCT (Patient randomised; Crossover: 2 weeks; half-life is 15 hours, so will have dropped by a factor of 2 to the power 22 so to < 1/4,200,000 of the starting dose; therefore appropriate in terms of the drug in system)
Number of studies (number of participants)	1 (n=14)
Countries and setting	Conducted in United Kingdom; Setting: unclear
Line of therapy	Not applicable

Duration of study	Intervention time: 20 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fukuda
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Fukuda criteria for CFS; age 18-70; restless legs syndrome rating scale <10; MMSE >=26; surgically sterile, 2 years post-menopausal, non-pregnant, non-lactating, using a method of birth control.
Exclusion criteria	Any clinical condition explaining chronic fatigue; current major depressive disorder; LV hypertrophy; symptomatic mitral valve prolapse; hypertension (sbp >160 mmHg); and disorder interfering with drug absorption, distribution, metabolism or excretion; history of alcohol/drug abuse; sight, hearing or movement problems; colour blindness; >8 cups of coffee per day; familiarity with the cognitive tests used in study;
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 41.2(3.3). Gender (M:F): 7:7. Ethnicity: unclear
Further population details	-
Extra comments	MMSE 29.2; Epworth sleepiness 9.1; MSLT mean sleep latency 16.4min; HADS A 5.1; HADS D 5.1; CGI-S 4.1; illness duration 5.4yrs; caffeine 3.3 cups/day; alcohol 4.1 units per week; sbp 120.6; dbp 78; pulse 72.2; RR 16.6; weight 75.7kg; temperature 36.6C.
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=14) Intervention 1: modafinil. 200mg modafinil; dose increased slowly at 3 day intervals starting at 100mg until required dose reached. Duration 20 days. Concurrent medication/care: Patients used a medication diary. Indirectness: No indirectness

	(n=14) Intervention 2: modafinil. 400mg. Dose increased from stating dose of 100mg at 3 day intervals as tolerated. Duration 20 days. Concurrent medication/care: medication diary given. Indirectness: No indirectness (n=14) Intervention 3: placebo. Identical doses of placebo. Duration 20 days. Concurrent medication/care: Medication diary used. Indirectness: No indirectness
Funding	Study funded by industry (Cephalon UK - unrestricted grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MODAFINIL versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 vitality at 20 days; Group 1: mean 29.6 (SD 26.55); n=14, Group 2: mean 26.1 (SD 23.94); n=14; SF36 vitality 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 vitality at 20 days; Group 1: mean 21.4 (SD 20.57); n=14, Group 2: mean 26.1 (SD 23.94); n=14; SF36 vitality 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 Physical Function at 20 days; Group 1: mean 55.4 (SD 29.12); n=14, Group 2: mean 53.6 (SD 27.3); n=14; SF36 physical function 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 Physical Function at 20 days; Group 1: mean 48.6 (SD 29.55); n=14, Group 2: mean 53.6 (SD 27.3); n=14; SF36 physical function 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia,

nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 Physical role limitation at 20 days; Group 1: mean 10.7 (SD 27.3); n=14, SF36 physical role 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 Physical role limitation at 20 days; Group 1: mean 19.2 (SD 32.16); n=14, Group 2: mean 21.4 (SD 32.16); n=14; SF36 physical role 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 emotional role limitation at 20 days; Group 1: mean 66.1 (SD 47.5); n=14, Group 2: mean 95.2 (SD 11.97); n=14; SF36 emotional role 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 emotional role limitation at 20 days; Group 1: mean 85.7 (SD 31.4); n=14, Group 2: mean 95.2 (SD 11.97); n=14; SF36 emotional role 0-100, High=Top is good outcome; Comments: 400mg modafinil

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 mental health at 20 days; Group 1: mean 68 (SD 21.7); n=14, Group 2: mean 74.9 (SD 12.34); n=14; SF36 mental health 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 mental health at 20 days; Group 1: mean 69.2 (SD 19.07); n=14, Group 2: mean 74.9 (SD 12.34); n=14; SF36 mental health 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0

- Actual outcome for adults; severity mixed or unclear: SF36 pain at 20 days; Group 1: mean 59.5 (SD 32.91); n=14, Group 2: mean 57.2 (SD 30.67); n=14; SF36 pain 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 pain at 20 days; Group 1: mean 50 (SD 32.16); n=14, Group 2: mean 57.2 (SD 30.67); n=14; SF36 pain 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 social at 20 days; Group 1: mean 43.7 (SD 26.57); n=14, Group 2: mean 43.7 (SD 30.68); n=14; SF36 social 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 social at 20 days; Group 1: mean 38.9 (SD 32.16); n=14, Group 2: mean 43.7 (SD 30.68); n=14; SF36 social 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 general health at 20 days; Group 1: mean 50.1 (SD 23.57); n=14, Group 2: mean 49.2 (SD 21.7); n=14; SF36 general health 0-100, High=Top is good outcome; Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: SF36 general health at 20 days; Group 1: mean 47.5 (SD 19.83); n=14, Group 2: mean 49.2 (SD 21.7); n=14; SF36 general health 0-100, High=Top is good outcome; Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Chalder's physical fatigue at 20 days; Group 1: mean 12.6 (SD 7.1); n=14, Group 2: mean 13.6 (SD 7.85); n=14; Chalder's physical fatigue 0-21, High=Top is poor outcome. Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Chalder's physical fatigue at 20 days; Group 1: mean 14.1 (SD 4.49); n=14, Group 2: mean 13.6 (SD 7.85); n=14; Chalder's physical fatigue 0-21, High=Top is poor outcome. Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Chalder's mental fatigue at 20 days; Group 1: mean 7.2 (SD 3.74); n=14, Group 2: mean 7.4 (SD 2.99); n=14; Chalder's mental fatigue 0-21, High=Top is poor outcome. Comments: 200mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Chalder's mental fatigue at 20 days; Group 1: mean 8.4 (SD 2.24); n=14, Group 2: mean 7.4 (SD 2.99); n=14; Chalder's mental fatigue 0-21, High=Top is poor outcome. Comments: 400mg modafinil. A more appropriate paired analysis [ie MD(SE)] not available. However the current analysis will be conservative in that it will tend to underestimate the precision. sds calculated from SE in paper
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: adverse effects including headaches, light headedness, disturbed balance, palpitations, insomnia, nausea, increased tendency to cry and constipation (patient 1); headaches, heavy legs and lethargy (patient 2); headaches (patient 3).; Group 2 Number missing: 0

Protocol outcome 3: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Any adverse events at 20 days; Group 1: 9/14, Group 2: 8/14; Comments: 200mg modafinil
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Any adverse events at 20 days; Group 1: 12/14, Group 2: 8/14; Comments: 400mg modafinil
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Mortality at longest follow up available; Cognitive function at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up; Psychological status at longest follow up available; Physical function at longest follow up available; Pain at longest follow up available

Study	**RituxME trial: Fluge 2019[23]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=152)
Countries and setting	Conducted in Norway; Setting: 4 university hospitals and 1 general hospital in Norway
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Canadian consensus criteria; patients where the workup uncovers other pathology as a possible cause of symptoms were excluded
Stratum	adults; severity mixed or unclear: aged 18 to 65 years; ME/CFS according to Canadian consensus criteria; mild or mild/moderate 40%, moderate 30%, moderate/severe and severe 30%; patients with very severe ME/CFS (WHO function class IV), who were totally bedridden and in need of care were excluded
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Patients with ME/CFS according to Canadian criteria of 2003; disease duration: 2-15 years; for patients with mild ME/CFS disease duration must be a minimum of 5 years; severity: mild, mild/moderate, moderate, moderate/severe and severe ME/CFS; age: 18-65 years; signed informed consent

Exclusion criteria	Patients with fatigue, who do not comply with the diagnostic Canadian criteria for ME/CFS or disease duration < 24 months or > 15 years; patients where the workup uncovers other pathology as a possible cause of symptoms; patients with very severe ME/CFS (WHO function class IV), who are totally bedridden and in need of care; pregnancy or breast feeding; previous cancer (except basal cell carcinoma of the skin or cervix dysplasia); previous long-term systemic treatment with immunosuppressive agents (Imurel, Sandimmun, Cellcept), except steroid treatments for e.g. obstructive lung disease or other autoimmune diseases like ulcerative colitis; serious endogenous (primary) depression; lack of ability to complete the study including follow-up; known serious multi-allergy, clinically assessed with an elevated risk of allergic reactions during rituximab infusion; reduced kidney function (creatinine > 1.5 x reference area); reduced liver function (bilirubin > 1.5 x reference area, or transaminase > 1.5 x reference area); known HIV-positivity, previous hepatitis B or hepatitis C, or reason to suspect other ongoing and clinically relevant infection; known immunodeficiency disorders with an elevated risk involved in therapeutic B lymphocyte depletion, e.g. hypogammaglobulinemia
Recruitment/selection of patients	referrals from physicians or direct requests from patients or their relatives to be evaluated for future clinical trials
Age, gender and ethnicity	Age - Mean (SD): Rituximab 37.8 (11.4), Placebo 35.5 (11.2) years. Gender (M:F): 27/124. Ethnicity: not reported
Further population details	-
Extra comments	NA
Indirectness of population	No indirectness: NA
Interventions	(n=77) Intervention 1: immunomodulatory drugs - rituximab. Induction treatment with 2 infusions, 2 weeks apart, of rituximab (MabThera, Roche), 500 mg/m2 of body surface area (maximum of 1000 mg). In the maintenance phase, patients received a 500-mg fixed dose of rituximab at 3, 6, 9, and 12 months. Duration 12 months. Concurrent medication/care: One hour before infusions, all patients received premedication with1g of oral acetaminophen, 10 mg of cetirizine, and 8mg of dexamethasone. Indirectness: No indirectness; Indirectness comment: NA Comments: NA (n=75) Intervention 2: placebo. Induction treatment with 2 infusions, 2 weeks apart, of 500 mg/m2 of body surface area (maximum of 1000 mg) saline with added human albumin (Flexbumin [Baxalta] or Albunorm [Octapharma]), 0.4 mg/mL, to ensure no visible difference from the active comparator. In the maintenance phase, patients received a 500-mg fixed dose of saline with human albumin at 3, 6, 9, and 12 months. Duration 12 months. Concurrent medication/care: One hour before infusions, all patients received premedication with1gof oral acetaminophen, 10 mg

	of cetirizine, and 8mg of dexamethasone. Indirectness: No indirectness; Indirectness comment: NA Comments: NA
Funding	Academic and government funding (The Norwegian Research Council, Norwegian Regional Health Trusts, Kavli Trust, MEandYou Foundation, and Norwegian ME Association.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RITUXIMAB versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue severity scale at 18 months ; MD; -0.07 (95%CI -3.21 to 3.08) (p value: 0.68) NA Fatigue severity scale 9-63 Top=High is poor outcome, Comments: Baseline values: Rituximab 59.1 (6.7), placebo 59.88 (3.3);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew
- Actual outcome for adults; severity mixed or unclear: Fatigue score (NRS) at 16-20 months ; MD; -0.06 (95%CI -0.51 to 0.39) (p value : 0.79) NA Fatigue NRS 0-10 Top=High is poor outcome, Comments: Baseline values: rituximab 3, placebo 3;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical functioning at 24 months ; MD; 1.24 (95%CI -7.38 to 9.86) (p value : 0.68) NA SF36 physical functioning 0-100 Top=High is good outcome, Comments: Baseline values: Rituximab 35.24 (21.9), placebo 32.45 (19.1);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew
- Actual outcome for adults; severity mixed or unclear: Function level % at 16-20 months ; MD; -0.68 (95%CI -5.9 to 4.54) (p value: 0.31) NA function percentage 0-100 Top=High is good outcome, Comments: Baseline values: rituximab 20.14 (11.5), placebo 18.37 (8.8);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew

Protocol outcome 3: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Adverse events with possible or probable relation to intervention at 24 months ; Group 1: 26/77, Group 2: 12/74
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew - Actual outcome for adults; severity mixed or unclear: Serious adverse events with possible or probable relation to intervention at 24 months ; Group 1: 8/77, Group 2: 0/74; Comments: 4 admissions in 2 patients were due to febrile neutropenia, 2 admissions in 1 patient were due to dizziness and nausea, and 1 admission in 1 patient was due to headache and gastroenteritis. Two patients had infusion-related reactions, 1 of whom was also admitted for tests because of noncardiac chest pain. One patient was admitted for examination for involuntary movements, and another for a transient facial paresis. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew - Actual outcome for adults; severity mixed or unclear: Suspected unexpected serious adverse reaction at 24 months ; Group 1: 2/77, Group 2: 1/74; Comments: 1 metrorrhagia with hysterectomy and 1 suspected but unconfirmed coronary disease in the rituximab group, 1 transient paresis in left extremities in the placebo group Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew Protocol outcome 4: Activity levels at longest follow up available - Actual outcome for adults; severity mixed or unclear: Mean steps per 24 hours at 17-21 months ; MD; -127 (95%CI -1004 to 749) (p value : 0.58) number of steps , Comments: Baseline values: rituximab 3297 (2047), placebo 3233 (2099); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: patient withdrawal; Group 2 Number missing: 2, Reason: 1 patient excluded, did not receive intervention (withdrew consent), 1 patient withdrew
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Roerink 2017[70]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Netherlands; Setting: Outpatient department, referred from regional hospitals, CFS treatment centers and a Dutch patient advocacy foundation.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CDC criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	female patients with CFS fulfilling CDC criteria; 18-59 years; maximum fatigue duration of 10 years or recent progression of symptoms; minimum score of 40 on fatigue severity scale of CIS; SIP score of at least 700.
Exclusion criteria	Females who are pregnant or nursing, intend to get pregnant during the study, use or have used psychotropic medication in the past month, received a live vaccine during the last 4 weeks, had substance abuse in the past 3 months, have had symptoms more than 10 years, are taking any medication except oral contraceptives and/or paracetamol, have current engagement in CFS research, do not have the ability to understand the nature and the extent of the trial and the procedure required, have psychiatric conditions (major depression, psychosis, eating disorders, anxiety disorders, bipolar disease and post-traumatic stress disorder).
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Median: anakinra 30, placebo 32. Gender (M:F): No male patients. Ethnicity: unclear
Further population details	-
Extra comments	anakinra/placebo: illness duration 44/39 months; BMI 25/25; CIS fatigue 52/51; SIP 1647/1706; SF36 social functioning 33/39; SF36 physical function 48/56; SCL-90 152/148; VAS max pain 7/7; mean cdc symptoms 7/6

Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=25) Intervention 1: pro-inflammatory cytokine antagonists - Anakinra. Anakinra (Interleukin-1 receptor antagonist) 100mg subcutaneously per day. Duration 4 weeks. Concurrent medication/care: Each participant provided with a box containing 28 syringes and supplies of drug. Patients instructed by physician on how to administer. Daily alarm used to assist compliance, along with adherence monitoring. Indirectness: No indirectness (n=25) Intervention 2: placebo. Identical placebo given in identical doses intramuscularly. Duration 4 weeks. Concurrent medication/care: Each participant provided with a box containing 28 syringes and supplies of drug. Patients instructed by physician on how to administer. Daily alarm used to assist compliance, along with adherence monitoring. Indirectness: No indirectness
Funding	Academic or government funding (Interleukin Foundation. Drugs provided by Swedish Orphan Biovitrium)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANAKINRA versus PLACEBO

Protocol outcome 1: Mortality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: death at 24 weeks; Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: CIS fatigue at 24 weeks; MD; 1.3 (95%CI -5.3 to 8); Checklist individual strength fatigue 8-56, High=Top is poor outcome; Comments: Based on ANCOVA, adjusting for baseline;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF36 physical function at 24 weeks; MD; -4 (95%CI -15.1 to 7.1, SF36 physical function 0-100, High=Top is good outcome. Comments: Based on ANCOVA, adjusting for baseline;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Symptom Checklist 90 at 24 weeks; MD; 3 (95%CI -8.6 to 14.6); Symptom checklist 90 scale 90-450, High=Top is poor outcome; Comments: Based on ANCOVA, adjusting for baseline;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: VAS maximum pain score at 24 weeks; MD; 0.34 (95%CI -1.1 to 1.7); visual analogue scale 0-10, High=Top is poor outcome; Comments: Based on ANCOVA, adjusting for baseline;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: adverse events at 24 weeks; Group 1: 24/25, Group 2: 14/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for adults; severity mixed or unclear: withdrawal due to adverse events at 24 weeks; Group 1: 1/25, Group 2: 0/25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: Sickness Impact profile at 24 weeks; MD; 91.2 (95%CI -275.8 to 458.1); Sickness impact profile 0-5799, High=Top is poor outcome; Comments: Based on ANCOVA, adjusting for baseline;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Baseline details: Though some baseline discrepancies all outcomes adjusted for baseline; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Cognitive function at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Rowe 2001[77]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: Two tertiary referral centres in the USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 11 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-50; CDC 1994 criteria
Exclusion criteria	History of conditions/drugs that could be exacerbated by fludrocortisone or tilt table testing; previous fludrocortisone use at doses > 106 mg/day; enrolment in another CFS study; psychiatric conditions requiring therapy; alcohol or substance abuse
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 36.2 to 37.3. Gender (M:F): 33:66. Ethnicity: White 98%; no other information provided

Further population details	-
Extra comments	FCA/placebo: age >30 76%/82%; currently working 56%/53%; on disability 20%/8%; duration of CFS 6.9y/6y; at least moderate severity of illness (score of >65 on global wellness scale)
Indirectness of population	Very serious indirectness: All participants had neurally-mediated hypotension and 1994 CDC criteria used; PEM not a compulsory feature.
Interventions	(n=50) Intervention 1: oral corticosteroids - fludrocortisone/hydrocortisone/other. Fludrocortisone starting at a dose of 0.025 mg/day (1 capsule) for a week, then 0.05 mg/day (2 capsules) for the following week, and eventually increased to 0.1 mg/day (4 capsules) for remaining 7 weeks. Duration 9 weeks. Concurrent medication/care: Patients advised to drink at least 2L of fluid per day and to keep normal NaCl intake to their usual levels. Both groups also had KCl tablets 10mEq/day for duration of treatment. If AEs emerged, doses were reduced to previously tolerated levels. Indirectness: No indirectness (n=50) Intervention 2: placebo. identical capsules containing methylcellulose only given exactly as the study drug in the same dose increments. Duration 9 weeks. Concurrent medication/care: Patients advised to drink at least 2L of fluid per day and to keep normal NaCl intake to their usual levels. Both groups also had KCl tablets 10mEq/day for duration of treatment. If AEs emerged, doses were reduced to previously tolerated level. Indirectness: No indirectness
Funding	Academic or government funding (National institute of Allergy and Infectious Diseases; NIH; CFIDAA Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUDROCORTISONE/HYDROCORTISONE/OTHER versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Wood Mental Fatigue Inventory at 11 weeks; Group 1: mean 14.1 (SD 10.9); n=38, Group 2: mean 13.3 (SD 9.6); n=45; Wood mental fatigue inventory 0-36; High=poor outcome; Comments: 16.3/18.3 at baseline, which supports placebo as better
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5
- Actual outcome for adults; severity mixed or unclear: POMS vigour subscale at 11 weeks; Group 1: mean 8.8 (SD 6.1); n=38, Group 2: mean 8.6 (SD 6.7); n=45; POMS

vigour subscale 0-32, High=Top is good outcome; Comments: 7.9/6.7 at baseline - favours study drug and thus explains follow up result
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5
- Actual outcome for adults; severity mixed or unclear: POMS fatigue subscale at 11 weeks; Group 1: mean 16.2 (SD 7.3); n=38, Group 2: mean 16.4 (SD 7.9); n=45; POMS fatigue subscale 0-28, High=Top is poor outcome; Comments: 19.6/21.3 - favours study drug at baseline so explains follow up result
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: SF 36 Physical function at 11 weeks; Group 1: mean 58.9 (SD 21.9); n=38, Group 2: mean 51.4 (SD 27.8); n=45; SF36 physical function 0-100, High=Top is good outcome; Comments: 54.8/45.1 at baseline so favours study drug which explains follow up result
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Beck Depression Inventory at 11 weeks; Group 1: mean 10.4 (SD 7.2); n=38, Group 2: mean 10.8 (SD 6.8); n=45; Beck depression inventory 0-63, High=Top is poor outcome; Comments: Baseline 14.7/15, so baseline discrepancy explains follow up result
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5
- Actual outcome for adults; severity mixed or unclear: SF 36 mental health at 11 weeks; Group 1: mean 68.6 (SD 19.1); n=38, Group 2: mean 69.8 (SD 16.3); n=45; SF36 mental health 0-100, High=Top is good outcome. Comments: 63.7/66.3 - favours placebo so this may explain follow up result favouring placebo
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcome 4: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: adverse effects at 11 weeks; Group 1: 23/38, Group 2: 32/45; Comments: 61% of drug patients and 71% of

placebo patients had at least 1 adverse effect. Denominators not stated so assumed it is the denominators given for efficacy outcomes.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcome 5: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Duke activity Status Index at 11 weeks; Group 1: mean 9.2 (SD 10.6); n=38, Group 2: mean 6.7 (SD 7.3); n=45; Duke activity status index 0-58.2, High=Top is good outcome. Comments: 7.8/5 at baseline - favours study drug and this explains follow up result
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcome 6: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: Wellness Score at 11 weeks; Group 1: mean 3.8 (SD 11.5); n=38, Group 2: mean 2.7 (SD 10); n=45; Wellness score scale not reported, High=Top is good outcome; Comments: 46.8/40.7 at baseline – favours study drug
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 12, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 12; Group 2 Number missing: 5, Reason: list of reasons given but these include some of those where data were available so not able to report reasons for these specific 5

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Snorrason 1996[79]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=49)

Countries and setting	Conducted in Iceland; Setting: Outpatient clinics of the National University Hospital of Iceland and a rheumatological
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 weeks
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Not using a recognised consensus-based set of criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CFS, defined as symptoms of fatigue for >50% of time and lasting >6 months, major sleep disturbances and myalgia; minor psychiatric symptoms allowed
Exclusion criteria	Medical conditions known to produce symptoms of fatigue; major psychiatric diagnosis
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 43.44 to 44.46. Gender (M:F): 7:42. Ethnicity: unclear
Further population details	-
Extra comments	Galnathamine/placebo: duration of illness 13.68/11.79 years
Indirectness of population	Serious indirectness: Downgraded for unclear CFS criteria.
Interventions	(n=25) Intervention 1: Galantamine hydrobromide. 10mg 3x daily, reached by a schedule of escalating dosage. Duration 8 weeks. Concurrent medication/care: Optional cross-over design added to parallel group RCT design - patients could cross-over after 2 weeks if failed to improve or had symptoms worsening. Indirectness: No indirectness (n=24) Intervention 2: placebo. placebo 3 x daily. Duration 8 weeks. Concurrent medication/care: Optional cross-over design added to parallel group RCT design - patients could cross-over after 2 weeks if failed to improve or had

	symptoms worsening. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GALANTAMINE HYDROBROMIDE versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue VAS at 2 weeks; Group 1: mean 7.25 (SD 2.1); n=25, Group 2: mean 7.11 (SD 1.35); n=24; Fatigue visual analogue scale range not reported, High=Top is poor outcome; Comments:7.72/7.41 at baseline
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: memory VAS at 2 weeks; Group 1: mean 5.63 (SD 3.16); n=25, Group 2: mean 4.72 (SD 2.46); n=24; Memory visual analogue scale, High=Top is Comments: baseline 4.86/5.22
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Myalgia VAS at 2 weeks; Group 1: mean 7.52 (SD 1.97); n=25, Group 2: mean 7.99 (SD 1.26); n=24; Myalgia visual analogue scale, High=Top is poor outcome; Comments: 8.57/8.56 at baseline
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Sleep quality at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Sleep disturbance VAS at 2 weeks; Group 1: mean 7 (SD 2.35); n=25, Group 2: mean 6.66 (SD 2.49); n=24; Sleep disturbance visual analogue scale, High=Top is poor outcome; Comments: baseline 7.52/7.77 - goes against follow up scores
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: AEs dizziness VAS at 2 weeks; Group 1: mean 4.26 (SD 2.77); n=25, Group 2: mean 3.54 (SD 3.12); n=24; Comments: 3.95/2.95 at baseline

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Return to school or work at longest follow up available - Actual outcome for adults; severity mixed or unclear: Work capacity/satisfaction on VAS at 2 weeks; Group 1: mean 4.92 (SD 2.15); n=25, Group 2: mean 5.09 (SD 1.67); n=24; Work capacity/satisfaction visual analogue scale, High=Top is good outcome; Comments: baseline 4.81/5.25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Psychological status at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Steinberg 1996[84]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in USA; Setting: patients recruited from a patient CFS registry in USA
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Holmes criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable

Inclusion criteria	CFS defined by Holmes criteria
Exclusion criteria	None
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 36.2(11.4). Gender (M:F): 7:23. Ethnicity: unclear
Further population details	-
Extra comments	Atopic history 73.3%; immediate skin test reactivity 53.3%
Indirectness of population	Serious indirectness: Holmes 1988 criteria used; PEM not a compulsory feature
Interventions	(n=15) Intervention 1: Antihistamines - terfenadine. 60mg terfenadine twice daily. Duration 2 months. Concurrent medication/care: Permitted to take oral contraceptives, antibiotics, vitamins, aspirin, NSAIDS, beta adrenergic agonists; not permitted to take antihistamines, decongestants, tricyclic antidepressants or ENT anti-inflammatory agents. Indirectness: No indirectness (n=15) Intervention 2: placebo. placebo twice daily. Duration 2 months. Concurrent medication/care: Permitted to take oral contraceptives, antibiotics, vitamins, aspirin, NSAIDS, beta adrenergic agonists; not permitted to take antihistamines, decongestants, tricyclic antidepressants or ENT antiinflammatory agents. Indirectness: No indirectness
Funding	Study funded by industry (Marion Merrell Dow Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TERFENADINE versus PLACEBO

Protocol outcome 1: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: modified Medical Outcome Study Short Form - physical functioning at 2 months; Group 1: mean 63.1 (SD 17.52); n=14, Group 2: mean 69.66 (SD 18.09); n=14; Medical Outcome Study Short Form - physical functioning 0-100, High=Top is good outcome; Comments: 60.32/64.53 at baseline, favouring placebo - this may explain follow up results
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 1, Reason: perception of no improvement; Group 2 Number missing: 1, Reason: perception of no improvement Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: modified Medical Outcome Study Short Form - mental health at 2 months; Group 1: mean 63.89 (SD 21.36); n=14, Group 2: mean 74.62 (SD 15.31); n=14; Medical Outcome Study Short Form - mental health 0-100, High =Top is good outcome; Comments: 64.29/77.18 at baseline - explains follow up result Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: see results section; Group 1 Number missing: 1, Reason: perception of no improvement; Group 2 Number missing: 1, Reason: perception of no improvement	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Straus 1988[86]**
Study type	RCT (Patient randomised; Crossover: 37 days)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in USA; Setting: National Institutes of Health
Line of therapy	Not applicable
Duration of study	Intervention time: 37 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Holmes CDC criteria

Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CFS by Holmes CDC criteria; no other medical diagnosis explaining symptoms; titres of antibodies to diffuse or restricted early antigens of Epstein barr virus of >=1:40 or to lack antibodies to EBNA <1:2)
Exclusion criteria	None reported
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 34.1(7.5). Gender (M:F): 8:19. Ethnicity: unclear
Further population details	-
Extra comments	Duration of illness 6.8yrs; years of education 14.9yrs; vocationally disabled 12/27; working part time 10/27; single or divorced 14/27; with children 7/27
Indirectness of population	Serious indirectness: Holmes 1988 criteria used; PEM not a compulsory feature
Interventions	(n=27) Intervention 1: antiviral drugs - acyclovir. IV acyclovir (500mg per square metre) infused over a period of 60 minutes in 150ml of saline every 8 hrs for 7 days of hospitalisation. Vigorous oral hydration encouraged. Then discharged to take 800mg acyclovir tablets for 30 days. Duration 37 days. Concurrent medication/care: Cross-over - order of acyclovir/placebo randomised. Indirectness: No indirectness (n=27) Intervention 2: placebo. IV placebo (500mg per square metre) infused over a period of 60 minutes in 150ml of saline every 8 hrs for 7 days of hospitalisation. Vigorous oral hydration encouraged. Then discharged to take 800mg placebo tablets for 30 days. Duration 37 days. Concurrent medication/care: Cross-over - order of acyclovir/placebo randomised. Indirectness: No indirectness
Funding	Study funded by industry (Burroughs Wellcome)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACYCLOVIR versus PLACEBO

Protocol outcome 1: Psychological status at longest follow up available
- Actual outcome for young people; severity mixed or unclear: POMS anxiety at 37 days; MD; 2.92 (95%CI 0.6334 to 5.2066); Profile of mood states anxiety 0-36, High=Top is poor outcome; Comments: paired analysis.;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0
- Actual outcome for young people; severity mixed or unclear: POMS depression at 37 days; MD; 3.97 (95%CI 0.6946 to 7.2454); Profile of mood states depression 0-60, High=Top is poor outcome; Comments: Paired analysis;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0
- Actual outcome for young people; severity mixed or unclear: POMS anger at 37 days; MD; 2.30 (95%CI -0.1308 to 4.7308); Profile of mood states anger 0-48, High=Top is poor outcome; Comments: paired analysis;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0
- Actual outcome for young people; severity mixed or unclear: POMS vigour at 37 days; MD; -2.05 (95%CI -4.6456 to 0.5456); Profile of mood states vigour 0-32, High=Top is good outcome; Comments: paired analysis;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0
- Actual outcome for young people; severity mixed or unclear: POMS fatigue at 37 days; MD; 1.26 (95%CI -1.006 to 3.526); Profile of mood states fatigue 0-28, High=Top is poor outcome; Comments: paired analysis;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0
- Actual outcome for young people; severity mixed or unclear: POMS confusion at 37 days; MD; 1.83 (95%CI 0.5734 to 3.0866); Profile of mood states confusion 0-28, High=Top is poor outcome; Comments: paired analysis;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0

Protocol outcome 2: Adverse events at longest follow up available - Actual outcome for young people; severity mixed or unclear: AEs - reversible renal failure at 37 days; Group 1: 3/27, Group 2: 0/27 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Activity levels at longest follow up available - Actual outcome for young people; severity mixed or unclear: rest (hrs/day) at 37 days; MD; -0.05 (95%CI -0.8328 to 0.7328, Comments: paired analysis); Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this would have greatly affected the mean POMs and wellness scores; Group 2 Number missing: 0 Protocol outcome 4: Symptom scales at longest available follow up - Actual outcome for young people; severity mixed or unclear: Wellness score at 37 days; MD; -1.08 (95%CI -7.2806 to 5.1206); Wellness scale not reported; Comments: paired analysis; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: renal failure - had they been included this may have affected the mean POMs and wellness scores; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Strayer 2012[88]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=234)
Countries and setting	Conducted in USA; Setting:

Line of therapy	Not applicable
Duration of study	Intervention + follow up: Stage I (extracted here) 42 weeks. Stage II (placebo group crossover) 24 weeks.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients were diagnosed with CFS according to CDC diagnosis criteria (Holmes 1988)
Stratum	adults; severity mixed or unclear: Patients were stratified according to treadmill duration (≥9 minutes vs >9 minutes) then randomised.
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	1. A diagnosis of CFS, as defined by the Center for Disease Control (1988 CDC case definition) ≥12 months; 2. Age range: ≥18 years old, ≤60 years old; 3. Males or non-pregnant, non-lactating females: Females must be of non-child-bearing potential (either post-menopausal for two years or surgically sterile, including tubal ligation) or using an effective means of contraception (birth control pills, intrauterine device, diaphragm). Females who are less than two years post-menopausal, those with tubal ligations, and those using contraception must have a negative serum pregnancy test within the two weeks prior to the first study medication infusion. Females of child-bearing potential agree to use an effective means of contraception from four weeks prior to the baseline pregnancy test until four weeks after the last study medication infusion. 4. A reduced quality of life as determined by a documented KPS of 40 to 60 on three occasions, each at least 14 days apart, during the twelve weeks immediately preceding the start of study drug infusions. The KPS must be rounded in increments of ten. 5. Ability to walk (minimum of 20 seconds) on the moving treadmill (grade=0%; belt speed=1 mph) on a minimum of two occasions during the twelve weeks immediately preceding study entry. 6. Laboratory documentation (baseline or historical following onset of CFS) of a negative antinuclear antibody or a negative anti-ds DNA, a negative rheumatoid factor, and an erythrocyte sedimentation rate. 7. Laboratory documentation that the patient is euthyroid (patients on thyroid replacement therapy must be on a stable dose during the eight week washout period) based on thyroid profile (T4, T3, TSH, T3 uptake and Free T4 index) performed during baseline. 8. Ability to provide written informed consent indicating awareness of the investigational nature of this study.

Exclusion criteria	1. Inability to return to the investigator's site for scheduled infusions and evaluations during Stages 1 and 2 of the study. 2. Chronic or intercurrent acute medical disorder or disease making implementation or interpretation of the protocol or results difficult or unsafe. 3. Pregnant or lactating females. 4. Treatment with any of the following therapies within the eight weeks immediately preceding the start of study baseline or during baseline: systemic glucocorticoids (ie, hydrocortisone, prednisone, etc.) or mineralocorticoids (ie, fludrocortisone [Florinef], etc.), interferons, interleukin-2, systemic antivirals, gamma globulin, or investigational drugs and experimental agents not yet approved for use in the United States. The patient was to give written consent prior to discontinuation of any drugs listed under this criterion. 5. Prior participation in a study of Poly I:C12U. 6. Medical necessity, as determined by the patient's private doctor or the principal investigator, to continue aspirin (ASA) or non-steroidal anti-inflammatory (NSAID) drugs for 20 consecutive days or for more than 10% of the study duration (i.e., 28 total days for Stage 1 and 17 total days for Stage 2). 7. Ability to exercise over 18 minutes during any of the baseline ET procedures. 8. Evidence or history of any exclusion criteria for the ET testinga. Previous documented evidence of myocardial infarction or recent significant change in the resting electrocardiogram (ECG) suggesting infarction or other acute cardiac events.b. Current symptoms of coronary insufficiency (i.e., angina pectoris and/or ST segment depression on ECG).c. Evidence of uncontrolled atrial or frequent or complex ventricular ectopy, or myocardial conduction defect which would increase the risk of syncope (for example, second degree or higher A-V block).d. History of congestive heart failure, suspected or known dissecting aneurysm, recent systemic or pulmonary embolus, severe valvular heart disease, ventricular aneurysm, active or suspected myocarditis or pericarditis, thrombophlebitis or intracardiac thrombi, or acute infection.e. Evidence of moderate or severe obstructive pulmonary disease.f. Resting diastolic blood pressure >115 mm Hg or resting systolic blood pressure >200 mm Hg.g. Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, or myxedema).h. Concurrent use of any beta blockers and/or bronchodilators which cannot remain at a stable dosage level during the eight- (8-) week washout period and continuing during baseline and Stages 1 and 2. 9. History of alcohol or other substance abuse within two (2) years before the onset of the chronic fatigue and/or at any time afterward. 10. History of suicidal ideation or a suicide attempt within two (2) years of baseline. 11. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa.
Recruitment/selection of patients	353 patients initially signed consents. 46 failed to meet entry criteria and 67 decided to withdraw from the study prior to completing baseline procedures. 240 patients were randomized.

Age, gender and ethnicity	Age - Mean (SD): Rintatolimod group 43.4 (9.2), placebo group 43.5 (10.1). Gender (M:F): 170 females, 64 males. Ethnicity: Not stated.
Further population details	-
Extra comments	Duration of CFS symptoms, mean (SD) years: rintatolimod group 9.6 (5.36), placebo group 9.7 (6.08)
Indirectness of population	Serious indirectness: Holmes 1988 criteria used; PEM is not a compulsory feature
Interventions	(n=117) Intervention 1: immunomodulatory drugs - rintatolimod (Ampligen). Patients initially received a 200 mg IV dose of rintatolimod twice weekly for two weeks. Following this, a 400 mg dose of rintatolimod was administered twice weekly for 40 weeks. Duration 42 weeks. Concurrent medication/care: Not stated.. Indirectness: No indirectness (n=117) Intervention 2: placebo. Patients initially received a 200 mg IV dose of placebo (physiological saline) twice weekly for two weeks. Following this, a 400 mg dose of saline placebo was administered twice weekly for 40 weeks. . Duration 42 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Study funded by industry (This study was funded, designed, and analyzed by Hemispherx Biopharma with oversight by the Food & Drug Administration (FDA) including statistical analysis. Following completion of FDA audits, the decision to publish was made.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RINTATOLIMOD (AMPLIGEN) versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults - severe: Vitality score (SF36) at 42 weeks; Group 1: mean 10, Group 2: mean 10
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Over 10% participants missing overall. Insufficient variance data reported for analysis; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.; Group 2 Number missing: 9, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults - severe: Karnofsky Performance Score (KPS) at 42 weeks; Group 1: mean 55, Group 2: mean 50

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Over 10% participants missing overall. Insufficient variance data for analysis; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.; Group 2 Number missing: 9, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.
- Actual outcome for adults - severe: Activities of Daily Living (ADL) at 42 weeks; Group 1: mean 72.4, Group 2: mean 69.4
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Over 10% participants missing overall. Insufficient variance data for analysis; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.; Group 2 Number missing: 9, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.

Protocol outcome 3: Adverse events at longest follow up available
- Actual outcome for adults - severe: Serious Adverse Events possibly or probably treatment-related at 42 weeks; Group 1: 1/117, Group 2: 2/117; Comments: Rintatolimod group: suicide attempt; placebo group: difficulty breathing/chest tightness, epilepsia partialis continua/seizures. There were 15 SAEs in rintatolimod group including non-treatment related: cerebral aneurysm, depression, anxiety, suicidal thoughts, upper respiratory tract infection, headache, suicide attempt, abscess, abdominal pain (x2), pulmonary embolism, uterine fibroids, cerebrovascular accident, parasthesia, abdominal pain with gastric distention. There were 7 SAEs in placebo group including non-treatment related: abdominal pain, difficulty breathing with chest tightness, accidental injury, epilepsia partialis continua, cholelithiasis, anxiety, depression
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Over 10% participants missing overall.; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Exercise performance measure at longest follow up available
- Actual outcome for adults - severe: Treadmill exercise duration in seconds at 42 weeks; Group 1: mean 672 (SD 314.1); n=100, Group 2: mean 616 (SD 286.7); n=108; Comments: Baselines, mean (SD): Rintatolimod 576 (257.5) Placebo 588 (234.4)
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Over 10% participants missing overall.; Indirectness of outcome: No indirectness ; Group 1 Number missing: 17, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.; Group 2 Number missing: 9, Reason: Dropout due to: CFS symptoms, lack of efficacy, adverse events, other medical reasons and other non-medical reasons.

Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	Sulheim 2014[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120 CFS patients (excluding 68 healthy controls))
Countries and setting	Conducted in Norway; Setting: The Department of Paediatrics at Oslo University Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 8 weeks + 22 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients were diagnosed with CFS according to NICE diagnostic criteria for CFS in children/adolescents.
Stratum	young people; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	In agreement with clinical guidelines, the study applied a broad case definition requiring 3 months of unexplained disabling, chronic/relapsing fatigue of new onset. The study did not require that patients meet any other accompanying symptom criteria.
Exclusion criteria	Referring units were required to confirm that the patient did not have any medical or psychiatric disorder that might explain the fatigue and that they had experienced no concurrent demanding life event.
Recruitment/selection of patients	All 20 hospital paediatric departments in Norway, as well as primary care paediatricians and general practitioners, were invited to refer patients with CFS aged 12 to 18 years consecutively to the Department of Paediatrics at Oslo University Hospital, a national referral center in Norway for young patients with CFS.
Age, gender and ethnicity	Age - Mean (SD): 15.4. Gender (M:F): 34 males, 86 females. Ethnicity: Scandinavian: 118 (98%) Non-Scandinavian: 2 (1.7%)
Further population details	

Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: sympathomimetic/central antihypertensive drugs - clonidine. Tablets containing 25µg of clonidine hydrochloride (Catapresan; Boehringer Ingelheim) were enclosed in orange opaque, demolition-resistant lactose capsules (Apoteket Produktion and Laboratorier). Clonidine lowers blood pressure dose dependently, possibly increasing the risk of adverse effects in patients with CFS who already experience orthostatic intolerance. Therefore, clonidine dosages were chosen to yield plasma concentrations within the lower range of what is considered clinically effective. Based on a previous pilot study, the following algorithm was used: (1) Patient weight greater than 35 kg: 2 capsules twice daily for 8 weeks (ie, clonidine, 50 µg twice daily, in the intervention group); and (2) Patient weight less than 35kg: 1 capsule twice daily for 8 weeks (ie, clonidine, 25 µg twice daily, in the intervention group). Therapy was initiated 1 week after the baseline investigational program. One-half of the dose was given during the first 3 days to minimize introductory adverse effects. After 8 weeks of the full dose, the dose was halved for 1 additional week to avoid rebound effects, after which treatment was discontinued. At therapy initiation, each patient was supplied with a defined number of capsules. The residual number at week 8 was counted, and an index of adherence was calculated. Clonidineplasma concentration was measured at weeks 3 and 8. Duration 8 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=60) Intervention 2: placebo. Empty capsules were used as placebo comparators. Duration 8 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Other (This study was funded by Health South–East Hospital Trust, the University of Oslo,Oslo and Akershus University College of Applied Sciences, the Norwegian Competence Network of Paediatric Pharmacotherapy, Simon Fougner Hartmann's Family Foundation, and Eckbo's Family Foundation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONIDINE versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Chalder Fatigue Questionnaire (CFQ) total sum score at 30 weeks; MD; 0.5 (95%CI -14.7 to 15.7); Chalder Fatigue Questionnaire scale not reported, High=Top is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason:

Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Fatigue Disability Index (FDI) total sum score at 30 weeks; Mean; 0.2 (95%CI -13.3 to 13.6); Fatigue Disability Index scale not reported, High=Top is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 3: Cognitive function at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Digit span backward test total at 30 weeks; Mean; -0.5 (95%CI -1.2 to 0.1);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for young people; severity mixed or unclear: BPI average pain score at 30 weeks; Mean; 0.4 (95%CI -0.4 to 1.1); Brief pain inventory 0-10, High=Top is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 5: Sleep quality at longest follow up available
- Actual outcome for young people; severity mixed or unclear: KSQ insomnia score at 30 weeks; Mean; 0.1 (95%CI -0.3 to 0.4); Karolinska sleep questionnaire insomnia scale not reported, High=Top is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 6: Adverse events at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Adverse effects, self-reported at 9 weeks; Group 1: 43/57, Group 2: 33/51; Comments: Events are total number of participants who experience one or more of the following adverse effects: drowsiness, dry mouth, unwellness, constipation, sleepiness, loose stool, rash,

itching, sadness, headache, breast development in men, dry nasal mucus membranes, hallucinations, confusion, nightmares, "tingling" in extremities, pain in the extremities, dizziness when rising, blurred vision, dry eyes, oedema in the extremities, and 'other'.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Some adverse effects are poorly defined, e.g. "unwellness" and "other"; Baseline details: Unclear - most reported baseline characteristic tables compare CFS patients and healthy controls at baseline, rather than between groups. Groups were stratified according to duration of CFS (>18< months) before randomisation.; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 7: Activity levels at longest follow up available
- Actual outcome for young people; severity mixed or unclear: Steps per day measured by accelerometer at 30 weeks; Mean; 119 (95%CI -796 to 1035);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcome 8: Symptom scales at longest available follow up
- Actual outcome for young people; severity mixed or unclear: CFS symptom inventory hypersensitivity score at 30 weeks; Mean; -0.03 (95%CI -0.4 to 0.3); CFS symptom inventory hypersensitivity score scale not reported, High=Top is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: 5 dropouts reported, but unclear which 3 dropouts were not interviewed regarding adverse effects. Reasons for dropout: 2 headache, 1 syncope, 1 declined to take capsules, 1 declined participation.; Group 2 Number missing: 9, Reason: Reasons for dropout: 5 declined participation, 1 declined to take capsules, 1 suspected suicidality, 1 abdominal discomfort, 1 incurrent illness.

Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Psychological status at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**The 2010[93]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=67)
Countries and setting	Conducted in Netherlands; Setting: Patients referred to CFS specialist clinic at a University Hospital
Line of therapy	Not applicable
Duration of study	Intervention time: 10 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 1994 CDC
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CDC 1994 criteria; scoring above clinical cut-off on the CIS fatigue sub-scale and SIP 8
Exclusion criteria	Current psychiatric morbidity; pregnancy/lactating; lactose intolerance; psychotropic drug use; experimental medications
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 34.7 to 35.8. Gender (M:F): 20:47. Ethnicity: unclear
Further population details	-
Extra comments	Ondansetron/placebo: CIS fatigue 49.4/50; SIP 8 1375/1359; CDC symptoms 7.4/6.8
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=33) Intervention 1: 5-HT3 receptor antagonists - Ondansetron. Ondansetron (8 mg tablets). 16mg per day in 2 doses. Duration 10 weeks. Concurrent medication/care: None. Indirectness: No indirectness (n=34) Intervention 2: placebo. identical placebo - 2 tablets taken per day. Duration 10 weeks. Concurrent

	medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (GlaxoSmithKline)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ONDANSETRON versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: CIS fatigue at 12 weeks; Group 1: mean 44 (SD 11.1); n=33, Group 2: mean 45.4 (SD 11.5); n=34; Checklist individual strength fatigue subscale 8-56, High=Top is poor outcome; Comments: 49.4/50 at baseline - so may partially explain follow up direction of effect. ANCOVA (adjusting for baseline) p=0.73, which concurs with this.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See results section for values at baseline. Because of small numbers, random mixing probably inadequate to allow good baseline comparability, despite good methodology in other respects; Group 1 Number missing: 2 (but imputed so included in analysis), Reason: increased feeling of malaise; Group 2 Number missing:

Protocol outcome 2: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Complaints of constipation at 12 weeks; Group 1: 3/33, Group 2: 1/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See results section for values at baseline. Because of small numbers, random mixing probably inadequate to allow good baseline comparability, despite good methodology in other respects; Group 1 Number missing: 2 (but imputed so included in analysis), Reason: increased feeling of malaise; Group 2 Number missing:
- Actual outcome for adults; severity mixed or unclear: Increased feeling of malaise at 12 weeks; Group 1: 2/33, Group 2: 0/34
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See results section for values at baseline. Because of small numbers, random mixing probably inadequate to allow good baseline comparability, despite good methodology in other respects; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Activity levels at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Actometer (objective accelerometer-based method of measuring activity) at 12 weeks; Group 1: mean 55 (SD 15.5); n=33, Group 2: mean 60.6 (SD 17.9); n=34; Comments: 54.1/58.4 at baseline - so explains follow up result. ANCOVA p=0.9
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: See results section for values at baseline. Because of small numbers, random mixing probably inadequate to allow good baseline comparability, despite good methodology in other respects; Group 1 Number missing: 2 (but imputed so included in analysis), Reason: increased feeling of malaise; Group 2 Number missing:

Protocol outcome 4: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Sickness Impact Profile (SIP) 8 at 12 weeks; Group 1: mean 1063 (SD 525.5); n=33, Group 2: mean 1172 (SD 694.6); n=34; Sickness Impact Profile (SIP) 8 0-5799, High=Top is poor outcome; Comments: 1375/1359 at baseline - so does not explain follow up benefit for ondansetron. ANCOVA p =0.3, however Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See results section for values at baseline. Because of small numbers, random mixing probably inadequate to allow good baseline comparability, despite good methodology in other respects; Group 1 Number missing: 2 (but imputed so included in analysis), Reason: increased feeling of malaise; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	**Vercoulen 1996[97]**
Study type	Systematic Review
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Netherlands; Setting: Randomly selected from CFS database to outpatient clinic of a university hospital in netherlands.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 14 weeks (6 weeks treatment + 8 weeks follow up)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: London (Sharpe) criteria
Stratum	adults; severity mixed or unclear

Subgroup analysis within study	Not applicable
Inclusion criteria	London criteria for CFS; fatigue > 1year; CIS fatigue score 35 or more; Depressed patients had to have BDI of 16 or more; non-depressed patients BDI of 10 or less
Exclusion criteria	Any alternative illness that could explain symptoms; psychiatric diagnosis besides major depressive disorder in depressed patients; any psychiatric disorder in non-depressed patients; pregnancy or lactation; lack of contraception in women of childbearing age; previous exposure to fluoxetine in a trial; previous lack of response to fluoxetine; recent trial participation; any prescribed medications except incidental analgesics that could not be stopped; current psychotherapy
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 37.8 to 29.9. Gender (M:F): 23:73. Ethnicity: unclear
Further population details	-
Extra comments	Median (range) duration of CFS: 5.5 (1-30); Married/cohabiting: 68/96; Currently working 17/96. Paper stratified to depressed and non-depressed patients. However the results relevant to this review have been given in a form that covers both strata.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature
Interventions	(n=54) Intervention 1: antidepressants - selective serotonin reuptake inhibitors. Fluoxetine 20mg once daily. Duration 8 weeks. Concurrent medication/care: None. Indirectness: No indirectness (n=53) Intervention 2: placebo. Placebo given once daily. Duration 8 weeks. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Eli Lilly, Netherlands)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS versus PLACEBO	

Protocol outcome 1: Fatigue at longest follow up available - Actual outcome for adults; severity mixed or unclear: CIS fatigue at 8 weeks; MD -0.164 (95% CI -0.64 - 0.31); Checklist individual strength fatigue subscale 8-56, High=Top is poor outcome; Fluoxetine change from baseline - placebo change from baseline; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Beck depression inventory at 8 weeks; MD -0.186 (95% CI -0.35 - -0.02); Beck depression inventory 0-63, High=Top is poor outcome; Fluoxetine change from baseline - placebo change from baseline; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events Protocol outcome 3: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: adverse events - tremor at 14 weeks; Group 1: 18/45, Group 2: 13/51; Placebo results reported as 30 (26%) in paper, which must be a typo, as 30/51 would be 60%, which seems unlikely in the placebo group. Therefore the 26% has been taken as the more likely figure, which yields a numerator of 13. But the possibility of an error here should be realised; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events - Actual outcome for adults; severity mixed or unclear: adverse events - perspiration at 14 weeks; Group 1: 30/45, Group 2: 20/51; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events Protocol outcome 4: Symptom scales at longest follow up available - Actual outcome for adults; severity mixed or unclear: worsening of symptoms at 14 weeks; Group 1: 7/45, Group 2: 12/51; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events - Actual outcome for adults; severity mixed or unclear: improvement in symptoms at 14 weeks; Group 1: 8/45, Group 2: 5/51; Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: adverse events; Group 2 Number missing: 2, Reason: adverse events	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	Vollmer-conna 1997[99]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=99)
Countries and setting	Conducted in Australia; Setting: 2 collaborating centres in Australia - 1 in Sydney and 1 in Australia
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Inadequate method of assessment/diagnosis: Criteria not part of the group of criteria recognised by our review as 'consensus based' - Schluederberg criteria
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of CFS based on medical history, a through physical examination, and laboratory assessment.
Exclusion criteria	Pregnancy; on NASAIDs, steroids, immunomodulatory agents, choline esterase inhibitors; previously received immunologic therapy; recent history of asthma
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Range of means: 38-41. Gender (M:F): 24:75. Ethnicity: not reported
Further population details	-
Extra comments	ImG low/ImG med/ImG high/placebo: disease duration (yrs) 6/7/5/7; Immune cells CD4+ (billions/L)0.99/0.98/0.77/0.96; CD8+ (billions/L) 0.65/0.55/0.52/0.57; DTH response 14/9/13/11; Karnovsky score

	73/70/67/71; QAL score 477/522/481/396; POMS depression 16.8/11.3/18.6/15.9; POMS confusion 9.4/5.7/9.6/9.3; POMS fatigue 20.1/17.7/16/21.3; POMS energy -13/-9.3/-7.3/-16; non sedentary activity (h/day) 5/5/5/5
Indirectness of population	Serious indirectness: unclear criteria used. Schluederberg 1992 publication was not included in the diagnostic criteria review as it presented a review of the CDC 1988 criteria rather than an original set of criteria.
Interventions	(n=22) Intervention 1: immunomodulatory drugs - IV immunoglobulin G. IV immunoglobulin 0.5 g/kg. Immunoglobulin was Intragram. 3 infusions each lasting 24 hours at monthly intervals. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=28) Intervention 2: immunomodulatory drugs - IV immunoglobulin G. IV immunoglobulin 1 g/kg. Immunoglobulin was Intragram. 3 infusions each lasting 24 hours at monthly intervals. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=23) Intervention 3: immunomodulatory drugs - IV immunoglobulin G. IV immunoglobulin 2g/kg. Immunoglobulin was Intragram. 3 infusions each lasting 24 hours at monthly intervals. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness (n=26) Intervention 4: placebo. Identical placebo solution given IV. 3 infusions each lasting 24 hours at monthly intervals. Duration 3 months. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Commonwealth Serum laboratories Also CFS society of NSW)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IMMUNOGLOBULIN G versus PLACEBO

Protocol outcome 1: Quality of life at longest follow up available
- Actual outcome for adults; severity mixed or unclear: QAL, POMS depression, POMS confusion, POMS fatigue, POMS energy at 6 months; All these outcomes : no data provided.
QAL: NS between-group effect (p>0.13) for the 3 different Ig doses versus placebo
POMS energy: NS between-group effect (p>0.75) for the 3 different Ig doses versus placebo
Other POMS outcomes (depression, confusion, fatigue): NS
Hours in non-sedentary activity: NS

Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Physical functioning at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Karnofsky scale at 6 months; Median (IQR)
Low dose 0.5 g Ig 80 (70-80) placebo 77.5 (70-80) [NS]
Baseline discrepancy: 77.5/70 which partially explains result;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for adults; severity mixed or unclear: Karnofsky scale at 6 months; Median (IQR)
Medium dose 1 g Ig 80 (70-80) placebo 77.5 (70-80) [NS]
Baseline discrepancy: 70/70 ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for adults; severity mixed or unclear: Karnofsky scale at at 6 months; Median (IQR)
Low dose 2 g Ig 75 (70-80) placebo 77.5 (70-80) [NS]
Baseline discrepancy: 70/70 ;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Adverse events (high dose) at 3 months; Group 1: 18/23, Group 2: 23/26; Comments: Constitutional symptoms including headaches, worsened fatigue, malaise, and concentration impairment, typically developing 12 to 24 hours after the completion of an infusion and persisting up to 10 days.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Adverse events (medium dose) at 3 months; Group 1: 20/28, Group 2: 23/26; Comments: Constitutional symptoms including headaches, worsened fatigue, malaise, and concentration impairment, typically developing 12 to 24 hours after the completion of an infusion and persisting up to 10 days.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for adults; severity mixed or unclear: Adverse events (low dose) at 3 months; Group 1: 18/22, Group 2: 23/26; Comments: Constitutional symptoms including headaches, worsened fatigue, malaise, and concentration impairment, typically developing 12 to 24 hours after the completion of an infusion and persisting up to 10 days.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality at longest follow up available; Fatigue at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Wearden 1998[103]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=136)
Countries and setting	Conducted in United Kingdom; Setting: UK-based hospital.
Line of therapy	Not applicable
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: All participants met the 'Oxford' CFS diagnosis criteria (Sharpe et al 1991).
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	All subjects met operationalised 'Oxford' research criteria (Sharpe et al, 1991) for CFS: (a) a principal complaint of fatigue of at least six months' duration, exacerbated by physical activity (and usually mental activity); (b) impairment in three out of four areas of activity (activities of daily living, occupational, social or leisure activities); (c) no medical cause of fatigue.

Exclusion criteria	Subjects with schizophrenia, bipolar disorder, eating disorder, alcohol or illicit drug misuse, those with current suicidal ideation, a history of ischaemic heart disease or an inability to read and write English were excluded. Pre-menopausal women were required to take precautions against pregnancy during the trial. Subjects taking anti-depressant medication were required to stop and undergo at least a two week washout period before entering the trial. Antidepressants were not withdrawn (and patients were excluded from the trial) if patients were judged to have any significant suicidal risk.
Recruitment/selection of patients	Patients over 18 years of age were recruited from consecutive referrals to a university department of medicine out-patient clinic drawing from across north-west England and north Wales between June 1993 and March 1995.
Age, gender and ethnicity	Age - Mean (SD): 38.7 (10.8) years. Gender (M:F): 97 female, 39 male. Ethnicity: Not stated.
Further population details	-
Extra comments	Four armed trial, including exercise comparison: (1) exercise and fluoxetine, n=33; (2) exercise and placebo drug, n=34; (3) exercise placebo and fluoxetine, n=35; (4) exercise placebo and placebo drug, n=34.
Indirectness of population	Serious indirectness: Oxford criteria used; PEM is not a compulsory feature
Interventions	(n=35) Intervention 1: antidepressants - selective serotonin reuptake inhibitors. Fluoxetine at a fixed daily dose of 20 mg. Plus exercise placebo. Duration 6 months. Concurrent medication/care: The fluoxetine treatment was accompanied by a placebo exercise programme in which a participant activity diaries were reviewed by a physiotherapist. The same was done in the placebo drug group. Subjects were not offered any specific advice on how much exercise they should be taking, but were told to do what they could when they felt capable and to rest when they felt they needed to. Indirectness: No indirectness (n=34) Intervention 2: placebo. Placebo drug and placebo exercise. The placebo to fluoxetine was a capsule of similar taste and appearance, taken daily. Participants in the placebo drug group also received the same exercise placebo as the fluoxetine group. Duration 6 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=34) Intervention 3: Graded exercise programme. Subjects were instructed to carry out their preferred aerobic activity (usually walking/jogging, swimming or cycling), for 20 minutes, at least three times per week. The intensity of the activity was initially set at a level which utilised oxygen at approximately 75% of the subject's tested functional

	maximum. Subjects monitored their prescribed exercise programmes on a chart along with pre- and post-exercise heart rates and perceived exertion. Exercise intensity was increased when there was a consistent recorded reduction of 10 beats per minute in post-exercise heart rate for one week and two points on the perceived exertion scale (about three times in six months in an adherent patient). Subjects adhered to the exercise programme if their charts showed that they had performed the required activity, at the required intensity, at least three times per week. Plus placebo drug. Duration 6 months. Concurrent medication/care: Participants in this group also received placebo drug of a capsule of similar taste and appearance to fluoxetine, taken daily. Indirectness: No indirectness (n=33) Intervention 4: Fluoxetine and graded exercise programme, combined intervention. Fluoxetine at a fixed daily dose of 20 mg. Graded exercise intervention: Subjects were instructed to carry out their preferred aerobic activity (usually walking/jogging, swimming or cycling), for 20 minutes, at least three times per week. The intensity of the activity was initially set at a level which utilised oxygen at approximately 75% of the subject's tested functional maximum. Subjects monitored their prescribed exercise programmes on a chart along with pre- and post-exercise heart rates and perceived exertion. Exercise intensity was increased when there was a consistent recorded reduction of 10 beats per minute in post-exercise heart rate for one week and two points on the perceived exertion scale (about three times in six months in an adherent patient). Subjects adhered to the exercise programme if their charts showed that they had performed the required activity, at the required intensity, at least three times per week. Plus placebo drug. Duration 6 months. Concurrent medication/care: Participants in this group received both exercise intervention and fluoxetine. Other background treatment not stated. Indirectness: No indirectness
Funding	Other (The study was funded by a grant from the Linbury Trust.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs plac. Fatigue on the 14-item Chalder fatigue scale at 26 weeks; Group 1: mean -3 (SD 8.15); n=35, Group 2: mean -2.7 (SD 7.77); n=34; Chalder fatigue scale not reported, High=Top is poor outcome; Comments: SDs calculated from reported CI 95% ranges
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs plac. Depression on the Hospital Anxiety and Depression Scale (HADS) depression subscale at 26 weeks; Group 1: mean -1.7 (SD 3.78); n=35, Group 2: mean -1.3 (SD 2.87); n=34; HADS depression 0-21, High=Top is poor outcome; Comments: SDs calculated from reported CI 95% ranges
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 3: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs plac. Functional work capacity (VO2 max, mL O2 per kg per minute; change score) at 26 weeks; Group 1: mean 1 mL O2 kg-1 min-1 (SD 5.8222); n=35, Group 2: mean -0.1 mL O2 kg-1 min-1 (SD 4.8722); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS versus GRADED EXERCISE PROGRAMME

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs exer. Fatigue on the 14-item Chalder fatigue scale at 26 weeks; Group 1: mean -3 (SD 8.15); n=35, Group 2: mean -5.7 (SD 10.9); n=34; Chalder fatigue scale not reported, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs exer. Depression on the Hospital Anxiety and Depression Scale (HADS) depression subscale at 26 weeks; Group 1: mean -1.7 (SD 4.01); n=35, Group 2: mean -1.2 (SD 3.49); n=34; HADS depression 0-21, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 3: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs exer. Functional work capacity (VO2 max, mL O2 per kg per minute; change score) at 26 weeks; Group 1: mean 1 mL O2 kg-1 min-1 (SD 5.8222); n=35, Group 2: mean 2.8 mL O2 kg-1 min-1 (SD 5.732); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS versus SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND GRADED EXERCISE PROGRAMME COMBINED

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs combo. Fatigue on the 14-item Chalder fatigue scale at 26 weeks; Group 1: mean -3 (SD 8.15); n=35, Group 2: mean -6 (SD 10.43); n=33; Chalder fatigue scale not reported, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs combo. Depression on the Hospital Anxiety and Depression Scale (HADS) depression subscale at 26 weeks; Group 1: mean -1.7 (SD 4.01); n=35, Group 2: mean -2 (SD 3.67); n=34; HADS depression 0-21, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 3: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Flu vs combo. Functional work capacity (VO2 max, mL O2 per kg per minute; change score) at 26 weeks; Group 1: mean 1 mL O2 kg-1 min-1 (SD 5.8222); n=35, Group 2: mean 2 mL O2 kg-1 min-1 (SD 4.2303); n=33
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND GRADED EXERCISE PROGRAMME COMBINED versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Combo vs plac. Fatigue on the 14-item Chalder fatigue scale at 26 weeks; Group 1: mean -6 (SD 10.43); n=33, Group 2: mean -2.7 (SD 7.77); n=34; Chalder fatigue scale not reported, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 2: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Combo vs plac. Depression on the Hospital Anxiety and Depression Scale (HADS) depression subscale at 26 weeks; Group 1: mean -2 (SD 3.67); n=33, Group 2: mean -1.3 (SD 2.87); n=34; HADS depression 0-21, High=Top is poor outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

Protocol outcome 3: Exercise performance measure at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Combo vs plac. Functional work capacity (VO2 max, mL O2 per kg per minute; change score) at 26 weeks; Group 1: mean 2 mL O2 kg-1 min-1 (SD 4.2303); n=33, Group 2: mean -0.1 mL O2 kg-1 min-1 (SD 4.8722); n=34
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND GRADED EXERCISE PROGRAMME COMBINED versus GRADED EXERCISE PROGRAMME

Protocol 1: Fatigue at longest follow up available - Actual outcome for adults; severity mixed or unclear: Combo vs exer. Fatigue on the 14-item Chalder fatigue scale at 26 weeks; Group 1: mean -6 (SD 10.43); n=33, Group 2: mean -5.7 (SD 10.9); n=34; Chalder fatigue scale not reported, High=Top is poor outcome; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5 Protocol outcome 2: Psychological status at longest follow up available - Actual outcome for adults; severity mixed or unclear: Combo vs exer. Depression on the Hospital Anxiety and Depression Scale (HADS) depression subscale at 26 weeks; Group 1: mean -2 (SD 3.67); n=33, Group 2: mean -1.2 (SD 3.49); n=34; HADS depression 0-21, High=Top is poor outcome; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5 Protocol outcome 3: Exercise performance measure at longest follow up available - Actual outcome for adults; severity mixed or unclear: Combo vs exer. Functional work capacity (VO2 max, mL O2 per kg per minute; change score) at 26 weeks; Group 1: mean 2 mL O2 kg-1 min-1 (SD 4.2303); n=33, Group 2: mean 2.8 mL O2 kg-1 min-1 (SD 5.732); n=34 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Pain at longest follow up available; Sleep quality at longest follow up available; Adverse events at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available ; Symptom scales at longest available follow up

Study	**Young 2013[107]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)

Countries and setting	Conducted in USA; Setting: Suburban research and treatment centre in USA
Line of therapy	Not applicable
Duration of study	Intervention time: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Fukuda
Stratum	adults; severity mixed or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	CFS as diagnosed by Fukuda criteria, plus medical history, clinical interview, brief clinical examination and responses to CF checklist; aged 18-60; Global executive composite score that was 1.5 sds above standardised population mean; able to swallow medication; ability to communicate; capacity to fully comply with procedures and restrictions.
Exclusion criteria	Psychostimulant in past 6 months; positive test for pregnancy; not using accepted forms of contraception during the study; breastfeeding; severe comorbid psychiatric diagnoses; history of psychosis; pervasive medical disorders, severe Axis II disorders; severe substance dependence; chronic/acute medical condition that could be affected by study medication: hypothyroidism, hypertension; fibromyalgia therapy; weight <30 kg or >120kg
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 41 (21-59). Gender (M:F): 1:25. Ethnicity: unclear
Further population details	-
Extra comments	Aged 21-59 with CFS and cognitive complaints
Indirectness of population	Serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature
Interventions	(n=15) Intervention 1: Amphetamines - Lisdexamphetamine. Lisdexamfetamine given as a flexible morning dose (progressing from 30, through 50, and then to 70 mg/day) provided no serious AEs occurred. Duration 6 weeks. Concurrent medication/care: None. Indirectness: No indirectness

	(n=15) Intervention 2: placebo. Identical placebo given in same incremental doses. Duration 6 weeks. Concurrent medication/care: None. Indirectness: No indirectness
Funding	Study funded by industry (Shire)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CISDEXAMPHETAMINE versus PLACEBO

Protocol outcome 1: Fatigue at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Fatigue severity Scale at 6 weeks; Group 1: mean 20.92 'mean improvement' (SD 14.71); n=13, Group 2: mean 5 'mean improvement' (SD 11.73); n=11; Fatigue severity scale 9-63, High=Top is poor outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high.

Protocol outcome 2: Cognitive function at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Behaviour rating Inventory of Executive Function (BRIEF): Global executive composite at 6 weeks; Group 1: mean 21.38 (SD 15.85); n=13, Group 2: mean 3.36 (SD 7.26); n=11; Behaviour rating Inventory of Executive Function scale not reported, High=Top is poor outcome; Comments: results reported are 'improvements'
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high.

Protocol outcome 3: Psychological status at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Hamilton anxiety scale at 6 weeks; Group 1: mean 11.31 'mean improvement' - any positive value represents an improvement (SD 9.74); n=13, Group 2: mean 6.18 'mean improvement' - any positive value represents an improvement (SD 8.28); n=11
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high.

Protocol outcome 4: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: McGill pain questionnaire at 6 weeks; Group 1: mean 10.38 'mean improvement' (SD 8.84); n=13, Group 2: mean 2.54 'mean improvement' (SD 9.53); n=11
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

	Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high. Protocol outcome 5: Adverse events at longest follow up available - Actual outcome for adults; severity mixed or unclear: Adverse events: headache at 6 weeks; Group 1: 2/15, Group 2: 1/11 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high. - Actual outcome for adults; severity mixed or unclear: Adverse events: dry mouth at 6 weeks; Group 1: 1/15, Group 2: 0/11 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high. - Actual outcome for adults; severity mixed or unclear: Adverse events: insomnia at 6 weeks; Group 1: 1/15, Group 2: 0/11 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high. - Actual outcome for adults; severity mixed or unclear: Discontinuation due to adverse events at 6 weeks; Group 1: 2/15, Group 2: 0/11; Comments: Adverse events: insomnia at visit 3, anxiety at visit 5 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high. Protocol outcome 6: Symptom scales at longest available follow up - Actual outcome for adults; severity mixed or unclear: Clinical Global Improvement - severity at 6 weeks; Group 1: mean 1.92 'mean improvement' (SD 1.5); n=13, Group 2: mean 0.64 'mean improvement' (SD 0.92); n=11 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Due to adverse events; Group 2 Number missing: 4, Reason: These were screen failures and so exclusion not related to outcome. Therefore not counted. Thus differential between groups is 13.33%, which is high.
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Physical functioning at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available

Study	Zachrisson 2002[109]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Sweden; Setting: The study was conducted in a special unit at a single hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 32 weeks (24 weeks intervention + final follow-up at 32 weeks)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants met 1994 CDC criteria for CFS diagnosis (as well as ACR criteria for FM). Investigations prior to study entry included physical examination, vital signs and blood parameters.
Stratum	adults; severity mixed or unclear: Age 18-65 years; severity mixed or unclear (according to global assessment of illness severity measured at baseline 17% were moderately ill, 70% markedly ill, 12% severely ill, 1% most extremely ill)
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Female; age 18-6 years; met both ACR criteria for fibromyalgia and 1994 CDC criteria for CFS; functional impairment related to these syndromes as documented by ≥6 months of full- or part-time sick leave. Prescribed medications allowed to continue, as long as they were in a steady state.
Exclusion criteria	Pathological values of significance recorded from laboratory results; signs or symptoms of ongoing severe psychiatric or other somatic disorder (patients with a history of depressed mood and earlier treatment with antidepressants were included if the history did not include melancholia or psychotic features; autoimmune or rheumatological disorders.
Recruitment/selection of patients	Consecutive patients referred from primary care centres to special unit at a hospital in Sweden
Age, gender and ethnicity	Age - Mean (range): staph toxoid 49 (26-65); placebo 47 (20-63). Gender (M:F): 0-100. Ethnicity: Not reported

Further population details	-
Extra comments	Staph toxoid/placebo, mean (range): Duration of symptoms (years) 11 (1-40) / 12 (1-36); BMI 27 (18-41) / 26 (18-41). % participants reporting the following features of illness: 47% low grade fevers, 57% sore throat, 87% prone to infections, 63% onset related to regional pain later becoming generalised, 16% onset related to acute infection, 15% onset related to pregnancy/delivery, 6% onset directly related to generalised pain - reported to be no significant differences between groups.
Indirectness of population	Very serious indirectness: 1994 CDC criteria used; PEM not a compulsory feature and all participants also met diagnostic criteria for fibromyalgia.
Interventions	(n=50) Intervention 1: staphylococcus vaccine. Staphylococcus toxoid preparation, Staphypan Berna (SB). Composed of undefined extracts of 2 strains of staphylococci (S. aureus and S. epidermidis), and a preservative compound thiomersal. Injection given subcutaneously in gluteal region by nurse. Drug administered in increasing doses of 0.1ml, 0.2ml, 0.3ml, 0.4ml, 0.6ml, 0.8ml, 0.9ml, and 1.0ml weekly, followed by booster doses of 1.0ml every 4 weeks with final dose given week 24. Drug kept in 1ml ampoules and packed in boxes marked with patient numbers. Both active substance and placebo caused slight local pain and reaction after injection. . Duration 24 weeks. Concurrent medication/care: Patients were allowed to continue with prescribed medication during the study, as long as they were in a steady state. Concomitant medications (reported for study population as a whole): 79% on antidepressants (low doses tricyclics or SSRIs), 42% on hypnotics, 21% on benzodiazepines, 19% on medication for GI problems.. Indirectness: No indirectness; Indirectness comment: NA (n=50) Intervention 2: placebo. Sterile water. Injection given subcutaneously in gluteal region by nurse. Administered in increasing doses of 0.1ml, 0.2ml, 0.3ml, 0.4ml, 0.6ml, 0.8ml, 0.9ml, and 1.0ml weekly, followed by booster doses of 1.0ml every 4 weeks with final dose given week 24. Drug kept in 1ml ampoules and packed in boxes marked with patient numbers. Similar in colour to active treatment. Both active substance and placebo caused slight local pain and reaction after injection. Duration 24 weeks. Concurrent medication/care: Patients were allowed to continue with prescribed medication during the study, as long as they were in a steady state. Concomitant medications (reported for study population as a whole): 79% on antidepressants (low doses tricyclics or SSRIs), 42% on hypnotics, 21% on benzodiazepines, 19% on medication for GI problems. Indirectness: No indirectness; Indirectness comment: NA
Funding	Equipment / drugs provided by industry (The study drug was provided by SSVI, Berne)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STAPHYLOCOCCUS VACCINE versus PLACEBO

Protocol outcome 1: Pain at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Visual analogue scale of pain at 32 weeks; Group 1: mean 5.9 (SD 2.2); n=49, Group 2: mean 6.2 (SD 1.95); n=49; Visual analogue of pain Unclear Top=High is poor outcome; Comments: Baseline scores, mean (SD): staph toxoid 6.2 (1.69); placebo 6.2 (1.71).
Paper reports line used was 100mm long. Range likely to be 0-10 (cm) instead of 0-100 (mm) based on values reported.
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - missing data (n=4 in each group) supplemented by carrying forward last rated scoring.; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender (all patients female), duration of symptoms, BMI. Baseline scores comparable. ; Blinding details: Patient reported outcome; Group 1 Number missing: 1, Reason: n=1 dropped out prior to any assessments (bereavement).; Group 2 Number missing: 1, Reason: n=1 dropped out prior to any assessments (diagnosed with hypertension which required treatment)

Protocol outcome 2: Adverse events at longest follow up available
- Actual outcome for adults; severity mixed or unclear: Most frequent adverse events at 26 weeks; Group 1: 28/50, Group 2: 26/50; Comments: Breakdown of common AEs (staph toxoid/placebo): Headaches 12/3; infections 5/11; skin disorders 4/5; GI problems 2/2; nausea/vomiting 3/1; depression 1/2; cardiovascular problems, palpitations 1/2. AEs were listed irrespective of causal relationship with study drug.
Does not include local reaction at site of injection (100% of participants experienced this, but severity was not rated to preserve blinding)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender (all patients female), duration of symptoms, BMI, baseline scores for other outcomes. ; Blinding details: Nurses who assessed outcomes were different to nurses who administered treatment; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for adults; severity mixed or unclear: Clinical global assessment of side effects at 26 weeks; Mean; Patient rated measure of side effects 1-4 Top=High is poor outcome, Comments: Scale: 1=no side effects, 2=do not significantly interfere with functioning), 3=significantly interfere with functioning, 4=outweigh therapeutic benefit)
Number of patients who experienced side effects: staph toxoid (n=50) 13 (26%); placebo (n=50) 7 (14%)
Number of patients who gave each rating on the scale, staph toxoid (n=50)/placebo (n=50): 1, 37/43; 2, 5/2; 3, 2/0; 4, 6/5 ;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender (all patients female), duration of symptoms, BMI, baseline scores for other outcomes. ; Blinding details: Patient reported outcome; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Symptom scales at longest available follow up
- Actual outcome for adults; severity mixed or unclear: Clinical global impression of change at 32 weeks; Group 1: mean 3.7 (SD 1.51); n=49, Group 2: mean 4.4 (SD 1.08); n=49; Clinical global impression of change 1-7 Top=High is poor outcome; Comments: Measured at end of study only

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - missing data (n=4 in each group) supplemented by carrying forward last rated scoring. Patients who discontinued before week 26 or were not evaluated for other reasons received the worst score on the clinical global impression of change scale (as only measure at end of study); Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender (all patients female), duration of symptoms, BMI.; Blinding details: Observer reported outcome; Group 1 Number missing: 1, Reason: n=1 dropped out prior to any assessments (bereavement).; Group 2 Number missing: 1, Reason: n=1 dropped out prior to any assessments (diagnosed with hypertension which required treatment) - Actual outcome for adults; severity mixed or unclear: Clinical global impression of severity at 32 weeks; Group 1: mean 4.5 (SD 0.52); n=49, Group 2: mean 4.8 (SD 0.62); n=49; Clinical global impression of severity 1-7 Top=High is poor outcome; Comments: Baseline scores, mean (SD): staph toxoid 5.0 (0.63); placebo 5.0 (0.54) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Missing data - missing data (n=4 in each group) supplemented by carrying forward last rated scoring.; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Comparable for age, gender (all patients female), duration of symptoms, BMI. Baseline scores comparable. ; Blinding details: Observer reported outcome; Group 1 Number missing: 1, Reason: n=1 dropped out prior to any assessments (bereavement).; Group 2 Number missing: 1, Reason: n=1 dropped out prior to any assessments (diagnosed with hypertension which required treatment)	
Protocol outcomes not reported by the study	Quality of life at longest follow up available; Mortality at longest follow up available; Fatigue at longest follow up available; Physical functioning at longest follow up available; Cognitive function at longest follow up available; Psychological status at longest follow up available; Sleep quality at longest follow up available; Activity levels at longest follow up available; Return to school or work at longest follow up available; Exercise performance measure at longest follow up available; Care needs at longest follow up available ; Impact on families and carers at longest follow up available