Supplementary Table S1: Clinical trials investigating treatments for chronic infections in ME/CFS.

Intervention (trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Ref
Rintatolimod (n/a)	OPT phase I (15)	1994 CDC	Illness severity (KPS 20-60)	400 mg/week for a variable period of time followed by 1200 mg/week 6 months	**PROMs** 1) Functional impairment (KPS) 2) Perceived cognitive performance (SCL-90-R) **Objective measures** 1) Exercise tolerance (treadmill) **Biological endpoints** 1) HHV-6 reactivation	**PROMs** 1) $p<0.01$ 2) $p<0.01$ **Objective measures** 1) $p<0.01$ **Biological endpoints** 1) $p<0.001$	[40]
Rintatolimod (n/a)	RCT (PA) phase II (Rintatolimod: 47, Placebo: 42)	1994 CDC	Illness severity (KPS 20-60), diagnosis >12 months	800 mg/week for 6 months	**PROMs** 1) Functional impairment (KPS) 2) Perceived cognitive performance (SCL-90-R) 3) Daily activity (ADL) 4) Psychiatric morbidity (DIS) **Objective measures** 1) Brain MRI 2) Exercise tolerance (treadmill) **Biological endpoints** 1) HHV-6 reactivation	**PROMs** 1) $p<0.05$ 2) $p<0.05$ 3) N.S. 4) N.S. **Objective measures** 1) N.S. 2) $p<0.001$ **Biological endpoints** 1) N.S.	[41]
Rintatolimod (NCT00215800)	RCT (PA) phase III (Rintatolimod: 93, Placebo: 101)	1994 CDC, 1988 CDC	KPS: 40-60, negative anti dsDNA, diagnosis >12 months	400 mg/week for 2 weeks, then 800 mg/week up to 40 weeks	**PROMs** 1) Functional impairment (KPS) 2) Daily activity (ADL) 3) Vitality (SF-36 subscale) 4) General health status (SF-36 subscale) **Objective measures** 1) Exercise tolerance (treadmill)*	**PROMs** 1) $p<0.01$ 2) N.S. 3) N.S. 4) $p<0.01$ **Objective measures** 1) $p<0.05$	[42]

VACV (n/a)	RCT (PA) (VACV: 14, Placebo: 13)	1994 CDC	Illness severity (EI≤5), elevated EBV serum IgM against VCA and/or EA detected	Group 1: VACV 4g/day for 6 months or placebo Group 2†: Cimetidine 500 mg twice per day or probenecid 500 mg twice per day plus VACV 4g/day	**PROMs** 1) Physical functional capacity (EI) **Biological endpoints** 1) EBV VCA IgM 2) EBV EA	**PROMs** 1) n/a **Biological endpoints** 1) n/a 2) n/a	[30]
VGCV (n/a)	OPT (12)	1994 CDC	Suspected viral onset	1800 mg/day for 3 weeks then 900 mg/day until 6 months	**Biological endpoints** 1) EBV VCA IgG and IgM antibodies 2) Antibodies against EBNA 3) Antibodies against EBV EA 4) HHV-6 IgG and IgM antibodies 5) HCMV IgG and IgM antibodies	**Biological endpoints** 1) *p*=0.008‡ 2) N.S.‡ 3) N.S.‡ 4) N.S.‡ 5) N.S.‡	[32]
VGCV (NCT00478465)	RCT (PA) (VGCV: 20, Placebo: 10)	1994 CDC	Suspected viral onset, elevated antibody titers against HHV-6 and EBV	1800 mg/day for 3 weeks and then 900 mg/day until 6 months	**PROMs** 1) Fatigue (MFI-20*) 2) Mental fatigue (MFI-20 subscale) 3) General fatigue, physical fatigue, reduced activity, reduced motivation (MFI-20 subscales) 4) Fatigue (FSS) 5) symptom severity (CDC-SI) 6) Physical functioning (self-report) 7) Cognitive functioning (self-report) 8) Sleep (SAQ) 9) Depression (HAM-D) **Objective measures** 1) Cognitive function (PASAT)	**PROMs** 1) N.S. 2) *p*=0.039 3) N.S. 4) *p*=0.006 5) N.S. 6) N.S. 7) *p*=0.025 8) N.S. 9) N.S. **Objective measures** 1) N.S.	[35]

	Biological endpoints	**Biological endpoints**
	1) Monocyte and neutrophil counts	1) $p<0.05$
	2) Cytokines	2) $p<0.05$
	3) EBV and HHV-6 IgG antibody titers	3) N.S.

Abbreviations:

1988 CDC: 1988 Centers for Disease Control and Prevention criteria for CFS by Holmes, 1994 CDC: 1994 CDC criteria for CFS by Fukuda, CDC-SI: CDC symptom inventory scores, DIS: diagnostic interview schedule, dsDNA: double-stranded deoxyribonucleic acid, EA: early antigens, EBV: Epstein Barr virus, EBNA: EBV nuclear antigens, EI: energy index, FSS: fatigue severity scale, HAM-D: Hamilton depression rating scale, HCMV: human cytomegalovirus, HHV-6: human herpesvirus-6, IgG: immunoglobulin G, IgM: immunoglobulin M, KPS: Karnofsky performance scale, MFI-20: 20-item multidimensional fatigue inventory, MRI: magnetic resonance imaging, n/a: not available, N.S.: not significant, OPT: open-label pilot study, PA: parallel arm, PASAT: paced auditory serial addition test, PROMs: patient-reported outcome measures, RCT: randomized placebo-controlled double-blinded clinical trial, SAQ: sleep assessment questionnaire, SCL-90-R: symptom checklist 90-R, VACV: valacyclovir, VGCV: valganciclovir, VCA: viral capsid antigen.

Trial codes:

NCT: ClinicalTrials.gov

Footnotes:

* Marks a primary outcome measure

† After 3 months of VCV, if the EI point score did not improve, participants from group 1 were switched to group 2.

‡ *P* values reported for “responders”

Supplementary Table S2: Clinical trials investigating treatments for immune disturbances in ME/CFS.

Intervention (trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Ref
Autoimmunity							
Cyclophosphamide (NCT02444091)	OPT phase II (40)	CCC	Disease duration >2 years	6 infusions (first infusion 600 mg/m^2 followed by 700 mg/m^2) at monthly intervals	**PROMs** 1) Fatigue*† 2) Functional level† 3) Vitality, social function, bodily pain (SF-36 subscales) 4) Fatigue (FSS) 5) Physical function (SF-36 subscale) 6) Physical activity (SF-36-PCS) **Objective measures** 1) Physical activity (number of steps)	**PROMs** 1) N.S. (3 months); p<0.001 (6, 9, 12, 15, 18 months)‡ 2) N.S. (3 months); p<0.01 (6 months); p<0.001 (9, 12, 15, 18 months) 3) n/a 4) n/a 5) p<0.001 (3, 6, 9, 12, 15, 18 months) 6) n/a **Objective measures** 1) p<0.01 (17-18 months), p<0.001 (7-9, 11-12 months)	[70]
Immunoadsorption(n/a)	POC (10)	CCC	Infection-triggered onset, severity (Bell scale of <50), elevated ß2 antibodies	5 cycles of immunoadsorption at days 1-3 and 6-7. After the 5th cycle patients received 25g IV IgG	**PROMs** 1) Symptom severity† 2) Fatigue and cognitive impairment (FACT-F) **Objective measures** 1) Muscle strength (pinch dynamometer) 2) Physical activity (steps/day) **Biological endpoints** 1) ß1 and ß2 IgG 2) M3/M4 receptor IgG 3) Total serum IgG 4) Tetanus IgG and PcP IgG 5) Endothelial function (PAT)	**PROMs** 1) n/a 2) p=0.038 (3 months), p=0.045 (6 months) **Objective measures** 1) N.S. 2) N.S. **Biological endpoints** 1) N.S. (3 months), p<0.05 (6 months) 2) N.S. 3) N.S. 4) N.S. 5) N.S.	[72]

Rituximab (NCT00848692)	RCT (PA) phase II (Rituximab: 15, Placebo: 15)	1994 CDC	-	Treatment: 2 infusions of 500 mg/m^2, 2 weeks apart Placebo: 2 infusions of equal volume of saline, 2 weeks apart	**PROMs** 1) Fatigue severity at 3 months post intervention*† 2) Fatigue severity† 3) Symptom severity† 4) Physical health (SF-36 subscale) 5) Physical function (SF-36 subscale) 6) Bodily pain (SF-36 subscale) 7) General health, social function, role emotional, mental health (SF-36 subscales) **Other** 1) Physician assessed fatigue severity	**PROMs** 1) N.S. 2) p=0.045 3) n/a 4) p=0.039 5) p=0.014 6) p=0.005 7) N.S. **Other** 1) p=0.021	[66]
Rituximab (NCT01156909)	OPT phase II (28)	1994 CDC CCC	-	2 infusions of 500 mg/m^2, 2 weeks apart Maintenance infusions at 3, 6, 10, and 15 months	**PROMs** 1) Fatigue severity† 2) Health related quality of life (SF-36)	**PROMs** 1) n/a§ 2) N.S. (3 months); p<0.01 (15 months); p<0.001 (6, 10, 20, 30, 36 months); p<0.0001 (24 months)	[67]
Rituximab (NCT02229942)	RCT (PA) (Rituximab: 77, Placebo: 74)	CCC	Disease duration 2-15 years (or ≥5 years if the disease was mild)	2 infusions of 500 mg/m^2 Rituximab, 2 weeks apart Maintenance infusions at 3, 6, 9, and 12 months	**PROMs** 1) Fatigue severity† 2) Health related quality of life (SF-36) 3) Fatigue severity (FSS) **Objective measures** 1) Physical activity (number of steps)	**PROMs** 1) N.S. 2) N.S. 3) N.S. **Objective measures** 1) N.S.	[68]
Immunodeficiency							
IVIG (n/a)	RCT (PA) (IVIG: 23, Placebo: 26)	1988 CDC	-	3 doses of IVIG (2g/kg/month) Placebo: 10% w/v maltose in equivalent volume	**PROMs** 1) Physical wellbeing (QAL) 2) Depression (Hamilton score) 3) Depression (Zung scale)	**PROMs** 1) p<0.01 2) p<0.01 3) n/a	[77]

					Biological endpoints 1) T cell analysis 2) DTH skin testing **Other** 1) Physician assessment of symptomatic and functional improvement	**Biological endpoints** 1) $p<0.01$ 2) $p<0.01$ **Other** 1) $p=0.03$	
IVIG (n/a)	RCT (PA) (IVIG: 14, Placebo: 14)	1988 CDC	-	6 doses of IVIG (1g/kg/month) Placebo: 1% albumin solution	**PROMs** 1) Symptom severity† 2) Physical and social functioning, health perceptions, and mental health (SF-36 subscales) **Biological endpoints** 1) IgG subclass	**PROMs** 1) N.S. 2) N.S. **Biological endpoints** 1) N.S.	[76]
IVIG (n/a)	RCT (PA) (0.5g/kg IVIG: 22, 1g/kg IVIG: 28, 2g/kg IVIG: 23, placebo: 26)	1992 NIH	-	3 doses of IVIG, participants randomly allocated to receive 0.5 g/kg/month, 1 g/kg/month or 2 g/kg/month) Placebo: 1% albumin solution	**PROMs** 1) Physical functioning (QAL) 2) Functional activity¶ 3) Mood (POMS) 4) Functional impairment (KPS) **Biological endpoints** 1) DTH skin testing 2) T cell analysis	**PROMs** 1) N.S. 2) N.S. 3) N.S. 4) N.S. **Biological endpoints** 1) N.S. 2) N.S.	[79]
Immunoglobulin G (n/a)	RCT (PA) (IVIG: 36, placebo: 34)	1994 CDC	Adolescents (11-18 years old)	3 doses (1 g/kg/month) Placebo: 10% w/v maltose solution with 1% albumin of equivalent volume for weight	**PROMs** 1) Anxiety (STAI) 2) Depression (BDI) 3) General health questionnaire **Biological endpoints** 1) DTH skin testing 2) IgG subclass **Other** 1) Functional improvement (physician	**PROMs** 1) $p=0.01$ 2) $p=0.002$ 3) $p<0.001$ **Biological endpoints** 1) N.S. 2) N.S. **Other** 1) $p<0.04$	[78]

	assessed)

Abbreviations:

1988 CDC: 1988 Centers for Disease Control and Prevention criteria for CFS by Holmes, 1992 NIH: 1992 NIH criteria for CFS by Schluederberg, 1994 CDC: 1994 CDC criteria for CFS by Fukuda, ß1: beta-1 adrenergic receptors, ß2: beta-2 adrenergic receptors, BDI: beck depression inventory, CCC: Canadian consensus criteria for ME/CFS by Carruthers, DTH: delayed-type hypersensitivity, FACT-F: 13 item questionnaire assessing fatigue, FSS: fatigue severity scale, IgG: immunoglobulin G, IV: intravenous, IVIG: intravenous immunoglobulin therapy, M3/M4: muscarinic M3 and M4 acetylcholine receptors, OPT: open-label pilot study, PA: parallel arm, PAT: pulse arterial tonometry, PcP: pneumococcal polysaccharide, POC: proof of concept, POMS: profile of mood states, PROMs: patient-reported outcome measures, QAL: quality of life scale, RCT: randomized placebo-controlled double-blinded clinical trial, SF-36: 36-item short form health survey, SF-36-PCS: SF-36 - physical component summary, STAI: state-trait anxiety inventory.

Trial codes:

NCT: ClinicalTrials.gov

Footnotes:

* Marks a primary outcome measure

† Assessment using unpublished questionnaires created by the authors

‡ *p* values reported for “responders”

§ *p* values not reported, but 64% of participants were said to have a “clinical response” based on fatigue severity scores

¶ Functional activity defined as the hours of self-reported non-sedentary activity per day

Supplementary Table S3: Clinical trials investigating treatments for metabolic disturbances in ME/CFS.

Intervention (Trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Reference
ALC + PLC (n/a)	OPT (ALC: 29, PLC: 30, ALC + PLC: 30)	1994 CDC	-	ALC group: 2 g/day PLC group: 2 g/day ALC+PLC group: 2g/day ALC and 2g/day PLC, 6 months	**PROMs** 1) Health impression (CGI) 2) Fatigue (MFI-20) 3) Pain (MPQ-DLV) **Objective measures** 1) Stroop test for attention concentration **Biological endpoints** 1) Free carnitine and carnitine esters	**PROMs** 1) ALC $p<0.0001$ PLC $p<0.0001$ ALC + PLC N.S. 2) ALC $p=0.015$ PLC N.S ALC + PLC N.S. 3) ALC $p=0.840$ PLC $p=0.380$ ALC + PLC $p=0.877$ **Objective measures** 1) ALC $p<0.0001$ PLC $p=0.011$ ALC + PLC $p=0.004$ **Biological endpoints** 1) ALC $p<0.05$ PLC $p<0.05$ ALC + PLC $p<0.05$	[97]
CoQ10 + NADH (NCT02063126)	RCT (PA) (CoQ10 + NADH: 39, Placebo: 34)	1994 CDC	-	CoQ10: 200mg/day NADH 20 mg/day 2 months	**PROMs** 1) Fatigue (FIS) 2) Pain (MPQ) 3) Sleep Quality (PSQI) **Biological endpoints** 1) Intracellular NAD+/NADH 2) CoQ10 levels 3) Lipid peroxidation 4) ATP production 5) Citrate synthase activity **Objective measures** 1) Max HR changes	**PROMs** 1) $p<0.05$ 2) N.S. 3) N.S. **Biological endpoints** 1) $p<0.001$ 2) $p<0.05$ 3) $p<0.05$ 4) $p<0.05$ 5) $p<0.05$ **Objective measures** 1) $p<0.05$	[105, 106]

					2) Exercise performance (VO_2, VCO_2) 3) Blood pressure (BP)	2) N.S. 3) N.S.	
CoQ10 + NADH (NCT03186027)	RCT (PA) (CoQ10 + NADH: 72, Placebo: 72)	1994 CDC	-	CoQ10: 200mg/day NADH 20mg/day 3 months	**PROMs** 1) Fatigue (FIS) 2) Sleep Quality (PSQI) 3) Health-related quality of life (SF-36)	**PROMs** 1) p=0.022 2) p=0.018 3) N.S.	[107]
CoQ10 + Se (NCT05128292)	OPT (30)	1994 CDC	-	CoQ10: 400 mg/day Se: 200 µg/day 2 months	**PROMs** 1) Fatigue (FIS) 2) Sleep Quality (PSQI) 3) Health-related quality of life (SF-36) **Biological endpoints** 1) Total antioxidant capacity 2) Lipid peroxidation 3) Inflammatory response (IL-1β, IL-6, IL-8, IL-10, TNF-α, and CRP) 4) Cardiovascular dysfunction (FGF-21 and NT-proBNP)	**PROMs** 1) p=0.021 2) N.S. 3) p=0.002 **Biological endpoints** 1) p<0.0001 2) p<0.0001 3) p<0.01 4) N.S.	[108]
D-ribose (n/a)	OPT (36)	1994 CDC (CFS) ACR (FMS)	CFS and/or FMS patients	D-ribose TID 5 g/day 3 weeks	**PROMs** 1) Energy level (DVAS) 2) Sleep (DVAS) 3) Mental clarity (DVAS) 4) Pain (DVAS) 5) Well-being (DVAS)	**PROMs†** 1) p<0.0001 2) p=0.0001 3) p=0.003 4) p=0.026 5) p<0.0001	[117]
D-ribose (NCT01108549)	OPT (226)	1994 CDC (CFS) ACR (FMS)	CFS and/or FMS patients	D-ribose TID 5 g/day 3 weeks	**PROMs** 1) Energy level (DVAS) 2) Sleep (DVAS)	**PROMs†** 1) p<0.0001 2) p<0.0001	[118]

					3) Mental clarity (DVAS) 4) Pain (DVAS) 5) Well-being (DVAS)	3) $p<0.0001$ 4) $p<0.0001$ 5) $p<0.0001$	
GAA (NCT02213679)	RCT (CO) (21)	1994 CDC	-	GAA: 2.4 g/day 3 months	**PROMs** 1) Fatigue (FIS) 2) Health-related quality of life (SF-36) **Objective measures** 1) Daily physical activity (actigraphy) 2) Muscular strength (maximum isometric strength) **Biological endpoints** 1) Serum creatine	**PROMs** 1) N.S. 2) N.S. **Objective measures** 1) $p<0.05$ 2) $p<0.05$ **Biological endpoints** 1) $p<0.01$	[91]
HRG80™ (n/a)	OPT (188)	1994 CDC	Severe illness	Capsules of 200 mg HRG80 or tablets of 100 mg HRG80 One or two tablets/day 1 month	**PROMs** 1) Composite score of energy, wellbeing and mental clarity (VAS)* 2) Energy (VAS) 3) Sleep (VAS) 4) Pain (VAS) 5) Wellbeing (VAS) 6) Mental clarity (VAS) 7) Stamina (VAS)	**PROMs** 1) $p<0.001$ 2) $p<0.001$ 3) $p<0.001$ 4) $p<0.001$ 5) $p<0.001$ 6) $p<0.001$ 7) $p<0.001$	[110]
KPAX002 (n/a)	POC (15)	1994 CDC	-	Methylphenidate: 5 mg BID the first 5 days, then scaled to 10 mg BID Mitochondria formula: 4 tablets BID 3 months	**PROMs** 1) Fatigue (CIS total)* 2) Concentration disturbance (CIS subscale) 3) Fatigue (VAS) 4) Concentration (VAS)	**PROMs** 1) $p<0.0001$ 2) $p<0.0001$ 3) $p<0.0001$ 4) $p<0.0001$	[119]

KPAX002 (NCT01966276)	RCT (PA) (KPAX002: 63, Placebo: 65)	1994 CDC	-	Methylphenidate: 5 mg TID the first 5 days, then scaled to 10 mg TID Mitochondria formula: 4 tablets TID 3 months	**PROMs** 1) Fatigue (CIS total)* 2) Fatigue (VAS) 3) Concentration disturbance (VAS)	**PROMs** 1) N.S. 2) N.S. 3) N.S.	[120]
L-carnitine and Amantadine (n/a)	RCT (CO) (28)	1994 CDC Australian Oxford	-	Two months of treatment with 1g TID L-carnitine or 100mg/day amantadine‡, 2 week washout period, two months in the opposite arm	**PROMs** 1) Fatigue (FSS) 2) Depression (BDI) 3) Psychiatric symptoms (SCL-90-R) 4) CFS impairment (CFS-II) 5) CFS severity (CFS-SI)	**PROMs§** 1) N.S. (4 weeks, 8 weeks) 2) $p<0.05$ (4 weeks, 8 weeks) 3) $p<0.05$ (4 weeks, 8 weeks) 4) $p<0.05$ (4 weeks, 8 weeks) 5) N.S. (4 weeks), $p<0.05$ (8 weeks)	[96]
NADH (n/a)	RCT (CO) (26)	1994 CDC	-	NADH 10 mg/day 1 month	**PROMs** 1) Symptom severity¶ **Biological endpoints** 1) Urinalysis (5-HIAA)	**PROMs** 1) $p<0.05$ **Biological endpoints** 1) $p<0.05$	[100]
NADH (n/a)	RCT (PA) (NADH: 36, Placebo: 41)	1994 CDC	-	NADH 20 mg/day 2 months	**PROMs** 1) Fatigue (VAS, FIS) 2) Functional impairment (KPS) 3) Mood (HAD) 4) Health related quality of life (SF-36) 5) Sleep (PSQI) **Objective measures** 1) Heart rate 2) SBP 3) DBP	**PROMs** 1) N.S. 2) N.S. 3) $p<0.05$ 4) N.S. 5) N.S. **Objective measures** 1) $p<0.05$ 2) N.S. 3) N.S.	[99]

Oxaloacetate (NCT04592354)	OPT (76)	1994 CDC	-	500 mg BID (n=23), 1,000 mg BID (n=29), 1,000 mg TID (n=24) 6 weeks	**PROMs** 1) Fatigue (CFQ)	**PROMs** 1) $p<0.005$	[98]
Ubiquinol-10 (n/a)	OPT (20)	1994 CDC	-	Ubiquinol-10: 150 mg/day 2 months	**PROMs** 1) Fatigue (CFQ) 2) Depression (CES-D) **Objective measures** 1) Arithmetic task (Uchida-Kraepelin Psychodiagnostic Test) 2) Sleep-wake cycle (Life Scope) 3) ANS function (APG) **Biological endpoints** 1) CoQ10 levels 2) Oxidation activity (d-ROMs test), 3) Antioxidant activity (BAP test)	**PROMs** 1) N.S. 2) $p<0.01$ **Objective measures** 1) $p<0.01$ 2) $p<0.01$ 3) N.S. **Biological endpoints** 1) $p<0.001$ 2) N.S. 3) N.S.	[104]
Ubiquinol-10 (n/a)	RCT (PA) (Ubiquinol-10: 14, Placebo: 17)	1994 CDC	-	Ubiquinol-10: 150 mg/day 3 months	**PROMs** 1) Fatigue (CFQ) 2) Depression (CES-D) **Objective measures** 1) Arithmetic task (Uchida-Kraepelin Psychodiagnostic Test) 2) Sleep-wake cycle (Life Scope) 3) Autonomic nervous function (APG) **Biological endpoints** 1) CoQ10 levels 2) Oxidation activity (d-ROMs test),	**PROMs** 1) N.S. 2) N.S. **Objective measures** 1) $p<0.05$ 2) N.S. 3) N.S. **Biological endpoints** 1) $p<0.001$ 2) N.S.	[104]

	3) Antioxidant activity (BAP test)	3) N.S.

Abbreviations:
1994 CDC: 1994 Centers for Disease Control and Prevention criteria for CFS by Fukuda, 5-HIAA: 5-hydroxyindoleacetic acid, ACR: American College of Rheumatology, ALC: acetyl L-carnitine, ANS: autonomic nervous system, APG: acceleration plethysmography, BAP: biological antioxidant potential, BDI: Beck depression inventory, BID: twice daily, BP: blood pressure, CES-D: Center for Epidemiologic Studies depression scale, CFS: chronic fatigue syndrome, CFS-II: chronic fatigue syndrome-impairment index, CFS-SI: chronic fatigue syndrome-severity index, CGI: clinical global impression of change, CIS: checklist individual strength, CoQ10: coenzyme Q10, CO: cross-over, CRP: C-reactive protein, DBP: diastolic blood pressure, DVAS: discrete visual analogue scale, DXA: dual X-ray absorptiometry, d-ROMs: reactive oxygen metabolite-derived compounds, FGF-21: fibroblast growth factor 21, FIS: fatigue impact scale, FMS: fibromyalgia syndrome, FSS: fatigue severity scale, GAA: guanidinoacetic acid, HADs: hospital anxiety and depression scale, HR: heart rate, HRG80™: hydroponically grown red ginseng, IL: interleukin, KPS: Karnofsky performance scale, n/a: not available, NAD+: oxidized form nicotinamide adenine dinucleotide, NADH: reduced form nicotinamide adenine dinucleotide, N.S.: not significant, NT-proBNP: amino-terminal pro-B type natriuretic peptide, MFI-20: 20-item multidimensional fatigue inventory, MPQ: McGill pain questionnaire, MPQ-DLV: McGill pain questionnaire-Dutch language version, OPT: open-label pilot study, PA: parallel arm, PLC: propionyl-L-carnitine, POC: proof of concept, PROMs: patient-reported outcome measures, PSQI: Pittsburgh sleep quality index, RCT: randomized placebo-controlled double-blinded clinical trial, SBP: systolic blood pressure, SCL-90-R: symptom checklist 90-R, Se: selenium, SF-12: 12-item short form survey, SF-36: 36-item short form health survey, SPPB: short physical performance battery, TID: three times a day, TNF-α: tumor necrosis factor-alpha, VAS: visual analogue scale, VCO_2: pulmonary carbon dioxide output, VO_2: pulmonary oxygen update.
Trial codes:
NCT: ClinicalTrials.gov
Footnotes:
* Marks primary outcome measure
† *p* values reported grouped FMS only, CFS only and FMS + CFS patients together
‡ 13 of 28 enrolled patients stopped taking amantadine due to side effects
§ *p* values only given for L-carnitine treatment
¶ Assessment using unpublished questionnaires created by the authors

Supplementary Table S4: Clinical trials investigating treatments for gastrointestinal disturbances in ME/CFS.

Intervention (Trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Reference
Antibiotic (ACTRN12615000457549)	OPT (22)	CCC	Stool *Streptococcus* count > 10^5 CFU/g	400 mg Erythromycin, BID for 6 days	**PROMs** 1) Sleep (Day and sleep diary) 2) Mood (POMS-SF) 3) Symptom severity (SSH) **Objective measures** 1) Sleep (actigraphy) **Biological endpoints** 1) Stool *Streptococcus* count, *Enterococcus* count, *Lactobacillus* count, *Enterococcus %, Lactobacillus* %, *Bifidobacterium %* 2) Stool *Bifidobacterium* count 3) Stool *Streptococcus* % 4) Stool *Bifidobacterium %*	**PROMs** 1) p=0.020 2) N.S. 3) N.S **Objective measures** 1) N.S. **Biological endpoints** 1) N.S. 2) p=0.006 3) p=0.030 4) p=0.004	[143]
FMT (NCT04158427)	RCT (PA) (FMT: 5, Placebo: 6)	IoM	-	Bowel preparation using polyethylene glycol, followed by FMT of 30 g of fecal transplant from a universal donor (treatment) or the same patient (placebo) *via* colonoscopy	**PROMs** 1) Fatigue (VAS, MFIS) 2) Health related quality of life (15D, EQ-5D-3L)	**PROMs** 1) N.S. 2) N.S.	[160]
Leaky gut diet (n/a)	OPT (41)	1994 CDC	Increased IgM and/or IgA in response to LPS as confirmed in previous study (Maes *et al*. 2007)	Leaky gut diet, supplemented with L-carnitine, CoQ10, taurine and lipoic acid in case of carnitine and/or CoQ10 shortage, or curcumine and quercetine in case of systemic or intracellular inflammation. Details of leaky gut diet and dosage of supplements not stated.	**PROMs** 1) Symptom severity (FFS) **Biological endpoints** 1) Serum IgM against bacteria 2) Serum IgA against bacteria	**PROMs** 1) p<0.0001 **Biological endpoints** 1) $p \leq 0.020^{\dagger}$ 2) N.S.	[136]
Probiotic (n/a)	RCT (PA) (Probiotic: 19, Placebo: 16)	CCC	Not bedridden	Probiotic (8 x 10^9 CFU of *Lactobacillus casei* Shirota), TID for 8 weeks	**PROMs** 1) Depression (BDI) 2) Anxiety (BAI)	**PROMs** 1) N.S. 2) p<0.05	[149]

Probiotic (n/a)	OPT (15)	1994 CDC	-	200 ml probiotic yogurt (10^8 CFU/ml of *Lactobacillus* F19, *Lactobacillus acidophilus* NCFB 1748, *Bifidobacterium lactis* Bb12), BID 30 days	**PROMs** 1) Symptoms (VAS, SF-12)	**PROMs** 1) N.S.	[151]
Probiotic (n/a)	RCT (PA) (Probiotic:28, Placebo: 20)‡	1994 CDC	No GI disorders	Probiotic (1 x 10^{10} CFU of *Bifidobacterium infantis* 35264), once per day for 8 weeks	**Biological endpoints** 1) Inflammation (plasma IL-6) 2) Inflammation (plasma TNF-α, CRP)	**Biological endpoints** 1) N.S. 2) $p<0.05$	[150]
Probiotic (n/a)	OPT (9)	1994 CDC	-	Week 1: Two cups of Enterelle (*Enterococcus faecium* UBEF-41, *Saccharomyces cerevisiae* spp. *boulardii, Lactobacillus acidophilus* LA 14) Week 2: Two cups of Bifiselle (*Bifidobacterium longum, B. breve, B. bifidum, B. infantis*) Rotanelle (*B. longum* AR81) Week 3: Two cups of Ramnoselle (*L. rhamnosus GG*, *L. acidophilus*) BID and two cups of Enterelle per day Week 4 - 8: Two cups of Citogenex (*L. casei*, *B. lactis*) and two cups of Rotanelle per day	**PROMs** 1) Physical health (SF-36) 2) Mental health (SF-36) 3) Fatigue (CFQ) 4) Depression (BDI-I) 5) Depression (BDI-II) **Biological endpoints** 1) Immunology (serum IgM) 2) Immunology (urinary free cortisol, plasma ROMs, serum IgG, serum IgA, ESR, DHEA-S, faecal calprotectin, serum CRP)	**PROMs** 1) N.S. 2) N.S. 3) N.S 4) N.S. 5) N.S. **Biological endpoints** 1) $p<0.05$ (IgM increased) 2) N.S.	[153]
Probiotic (ACTRN12614001077651)	OPT (44)	CCC	Stool *Streptococcus* count > 3 x 10^5 CFU/g and > 5% of total anaerobic microorganisms	Week 1: baseline measurements Week 2: 400 mg erythromycin BID Week 3: 2 capsules of Pro4-50 (2.5 x 10^{10} CFU *Lactobacillus rhamnosus*, 1.5 x 10^{15} CFU *Bifidobacterium lactis,* 5 x 10^6 CFU *B. breve,* 5 x 10^6 CFU *B. longum*), per day Week 4: 400 mg erythromycin BID	**PROMs** 1) Mood (POMS-SF)* 2) Mood (DASS-21) 3) Sleep efficiency (sleep diary) 4) Sleep (PSQI global score) 5) Sleep SOL, WASO (sleep diary) 6) Fatigue (MFI-20 subscale) 7) Brain fog (MTFQ subscale) 8) Total symptoms (SSH) **Objective measures**	**PROMs** 1) N.S. 2) N.S. 3) $p=0.035$ 4) $p=0.027$ 5) N.S. 6) N.S. 7) N.S. 8) $p=0.001$ **Objective measures**	[152]

	Week 5: 2 capsules of Pro4-50, once per day	1) Sleep efficiency (actigraphy)* 2) Sustained visual attention (RVP-A')* 3) Sleep WASO (actigraphy) 4) Sleep SOL, restlessness/sleep fragmentation index (actigraphy) 5) Processing speed 6) Story memory 7) Cognitive flexibility 8) Verbal fluency 9) Word memory, spatial working memory, visual learning, planning) **Biological endpoints** 1) Stool *Streptococcus* count 2) Stool *Bifidobacteria* and *Lactobacillus* count 3) D-lactate (urinary D-lactate:L-lactate ratio)	1) N.S. 2) $p<0.001$ 3) $p=0.007$ 4) N.S. 5) $p=0.004$ 6) $p=0.002$ 7) $p=0.001$ 8) $p=0.014$ 9) N.S. **Biological endpoints** 1) $p=0.003$ 2) N.S. 3) N.S.

Abbreviations:

15D: 15-dimension instrument for measuring health related quality of life, 1994 CDC: 1994 Centers for Disease Control and Prevention criteria for CFS by Fukuda, BAI: Beck anxiety inventory, BDI: Beck depression inventory, BDI-I: BDI version 1, BDI-II: BDI version 2, BID: twice daily, CCC: Canadian consensus criteria for ME/CFS by Carruthers, CFQ: Chalder fatigue questionnaire, CFU: colony-forming units, CRP: C-reactive protein, DASS-21: depression, anxiety and stress scale-21, DHEA-S: dehydroepiandrosterone sulfate, DSM: diagnostic and statistical manual of mental disorders, EQ-5D-3L: 3-level version of the EQ-5D developed by the EuroQol group, ESR: erythrocyte sedimentation rate; ESS: Epworth sleepiness scale; FFS: FibroFatigue scale, FMT: fecal microbe transplant, GI: gastrointestinal, HRQOL: health-related quality of life, IgA: immunoglobulin A, IgM, immunoglobulin M, IL-6: Interleukin-6; IoM: Institute of Medicine criteria, LPS: lipopolysaccharide, MAPI: multivariable apnoea prediction index; MFI-20: 20-item multidimensional fatigue inventory, MFIS: modified fatigue impact scale, MTFQ: multiple fatigue types questionnaire, n/a: not available, NCT: ClinicalTrials.gov study identifier, N.S.: not significant, OPT: open-label pilot study, PA: parallel-arm, POMS-SF: profile of mood states - short form, PROMS: patient-reported outcome measures, PSQI: Pittsburgh sleep quality index, RCT: randomized placebo-controlled double-blinded clinical trial, ROMs: reactive oxygen metabolite; RVP-A': rapid visual processing-A', SF-12: 12-item short form survey, SF-36: 36-item short form health survey, SOL: sleep onset latency, SSH: symptom severity and severity hierarchy chart, TID, three times a day, TNF-α: tumor necrosis factor-alpha, TST: total sleep time; VAS: visual analogue scale, WASO: wake after sleep onset.

Trial codes:

ACTRN: Australian and New Zealand Clinical Trial Registry, NCT: ClinicalTrials.gov

Foot notes:

* Marks a primary outcome measure

† Antibodies against *Hafnia alvei*, *Pseudomonas aeruginosa*, *Morganella morganii*, *Pseudomonas putida*, *Citrobacter koseri* and *Klebsiella pneumoniae*, were measured ($p = 0.005$, $p = 0.01$, $p = 0.004$, $p = 0.001$, $p = 0.001$ and $p = 0.02$, respectively)

‡ Apart from a ME/CFS cohort, study included cohorts of ulcerative colitis patients, psoriasis patients, and healthy controls

Supplementary Table S5: Clinical trials investigating treatments for neurological disturbances in ME/CFS.

Intervention (Trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Reference
Duloxetine (NCT00375973)	RCT (PA) (Duloxetine: 30, Placebo: 30)	1994 CDC	Severity (MFI-20 general fatigue subscale of ≥13)	Duloxetine 60-120mg/day or placebo for 12 weeks	**PROMs** 1) General fatigue*, physical fatigue, reduced activity, reduced motivation (MFI-20 subscales) 2) mental fatigue (MFI-20 subscale) 3) Pain severity (BPI) 4) Pain interference (BPI) 5) Anxiety and depression (HADS) 6) Symptoms (CDC-SI) 7) Health related quality of life (SF-36) 8) Improvement (PGI-I) 9) Severity (CGI subscale)	**PROMs** 1) N.S. 2) p=0.01 3) p=0.05 4) p=0.03 5) N.S. 6) N.S. 7) N.S. 8) N.S. 9) p=0.02	[180]
Fluoxetine (n/a)	RCT (PA) (Fluoxetine, depressed: 21, Fluoxetine, non-depressed: 24, Placebo, non-depressed: 28, Placebo depressed: 23)	Oxford	Depressed patients (BDI score of ≥16) Non-depressed patients (BDI score of ≤10)	20 mg/day Fluoxetine or placebo, for 8 weeks	**PROMs** 1) Subjective fatigue (CIS subscale and daily observed fatigue score)†* 2) Depression (BDI and SCL-90)†* 3) Symptoms (SIP)* 4) Physical Activity (CIS subscale and daily observed activity score)†* 5) Sleep (CIS subscale and daily observed sleep score)†* 6) Cognitive function (CIS subscale and SIP, daily observed memory and concentration score)† 7) Social interactions (SIP subscale)* 8) Self efficacy expectations (MHLC subscale and self observation list)†*	**PROMs** 1) N.S. 2) N.S. 3) N.S. 4) N.S. 5) N.S. 6) N.S. 7) N.S. 8) n/a	[177]

					Objective measures 1) Physical activity (Actometer) †* 2) Cognitive function (complex reaction-time test)*	**Objective measures** 1) N.S. 2) N.S.	
Fluoxetine and GET (n/a)	RCT (PA) (Fluoxetine and GET: 33, Placebo drug and GET: 34, Fluoxetine and placebo GET: 35, Placebo drug and placebo GET: 34)	Oxford	-	20 mg/day Fluoxetine or placebo, over six months. Treatment GET involved physiotherapist appointments at weeks 0, 1, 2, 4, 8, 12, 20 and 26 where they received a prescribed exercise program with a physiotherapist receiving instructions to undertake their preferred aerobic activity for 20 minutes ≥3 times a week, with activity intensity increasing when there was a consistent HR reduction of 10 bpm post exercise and reduced perceived exertion. Placebo GET involved participants attending physiotherapist appointments during which they discussed 7-day activity diaries but were not offered specific exercise guidance.	**PROMs** 1) Fatigue (CFQ)* 2) Health related quality of life (SF-36) 3) Anxiety and depression (HADS) **Objective measures** 1) Muscle strength (HGS) 2) Functional work capacity‡ (ergometer)	**PROMs**§ 1) N.S. 2) N.S. 3) p=0.04 (week 12), N.S. (week 26) **Objective measures**§ 1) n/a 2) N.S.	[178]
Fludrocortisone (n/a)	RCT (PA) (Fludrocortisone: 38, Placebo: 46)	1994 CDC	Neurally mediated hypotension (tilt table test) Mild/moderate (≥65 on GWS)	Fludrocortisone acetate, titrated to 0.1 mg/day or placebo for 9 weeks	**PROMs** 1) Wellness (GWS) 2) Health related quality of life (SF-36) 3) Depression (BDI) 4) Mental Fatigue (WMFI) 5) Mood (POMS-SF) 6) Activity (DASI) **Objective measures** 1) Tilt table testing	**PROMs** 1) N.S. 2) N.S. 3) N.S. 4) N.S. 5) N.S. 6) N.S. **Objective measures** 1) N.S.	[202]
Fludrocortisone (n/a)	RCT (CO) (20)	1994 CDC 1988 CDC	-	6 weeks treatment with 0.1mg/day¶ fludrocortisone or placebo, 6 weeks washout period, 6 weeks in the opposite arm.	**PROMs** 1) Fatigue (VAS)* 2) Unrefreshing sleep (VAS)* 3) Muscle pains (VAS)*	**PROMs##** 1) N.S. 2) N.S. 3) N.S.	[203]

					4) Inability to concentrate (VAS)*	4) N.S.	
					5) Headaches (VAS)*	5) N.S.	
					6) Forgetfulness (VAS)*	6) N.S.	
					7) Confusion (VAS)*	7) N.S.	
					8) Joint pains (VAS)*	8) N.S.	
					9) Painful lymph nodes (VAS)*	9) N.S.	
					10) Sore throat (VAS)*	10) N.S.	
					11) Light headedness (VAS)*	11) N.S.	
					12) Depression (VAS)*	12) N.S.	
					13) Distance before exhausted#*	13) N.S.	
					14) Health related quality of life (SF-36)*	14) N.S.	
					15) Mood status (PANAS)	15) N.S.	
					Objective measures	**Objective measures##**	
					1) Cognitive processing speed (Hicks paradigm reaction time test)	1) N.S.	
					2) Treadmill (time to exhaustion)	2) N.S.	
Ginkgo and Cistanche (GkoCist) (NCT02807649)	RCT (PA) (Placebo: 64, Low dose: 62, High dose: 64)	1994 CDC	-	High dose (Ginkgo at 180mg/day and Cistanche at 450mg/day), low dose (Ginko at 120mg/day and Cistanche at 300mg/day), or placebo for 60 days.	**PROMs**	**PROMS**	[195]
					1) Physical fatigue (CFQ)	1) $p<0.0001$	
					2) Mental fatigue (CFQ)	2) $p<0.0001$	
					3) Physical health (WHOQOL subscale)	3) $p=0.0024$	
					4) Psychological health (WHOQOL subscale)	4) N.S.	
					5) Social relationships (WHOQOL subscale)	5) N.S.	
					6) Living environment (WHOQOL subscale)	6) N.S.	
					7) Sexual Life (SLQ)	7) $p<0.0001$	
					Biological endpoints	**Biological endpoints**	
					1) Blood ammonia	1) $p=0.01$	
					2) Blood lactic acid	2) $p=0.005$	
					3) Liver and Kidney Function	3) N.S.	

Low-dose phenelzine (n/a)	RCT (PA) (Phenelzine: 9, Placebo: 9)	1994 CDC	-	Phase 1: all participants took one placebo pill per day for 2 weeks. Phase 2: active treatment group received alternating days of 15mg phenelzine pill and placebo pill for 2 weeks. Phase 3: active treatment group received 15mg/day phenelzine for 2 weeks. Placebo group took one placebo pill per day.	**PROMs** 1) Functional Status (FSQ) 2) Mood (POMS-SF) 3) Depression (CES-D) 4) Illness Severity (ISS) 5) Fatigue (FSS) 6) Symptoms (Sx)	**PROMS** 1) N.S. 2) N.S. 3) N.S. 4) N.S. 5) N.S. 6) N.S.	[175]
LDX (NCT01071044)	RCT (PA) (LDX: 15, Placebo: 11)	1994 CDC	Patients with executive impairment (measured using BRIEF-A)	30 mg/day LDX for 2 weeks, 50 mg/day LDX for 2 weeks, 70 mg/day LDX for 2 weeks (dose escalation in the absence of adverse events)	**PROMs** 1) Executive Function (BRIEF-A) 2) Fatigue (FSS) 3) Anxiety (HAM-A) 4) Pain (MPQ) 5) Fibromyalgia (FIQ) 6) ADHD (ADHDRS) 7) Severity (CGI subscale)	**PROMS** 1) p=0.005 2) p=0.008 3) N.S. 4) p = 0.046 5) N.S. 6) p=0.038 7) p = 0.022	[184]
MELATOZINC (NCT03000777)	RCT (PA) (Melatonin: 28, Placebo: 32)	1994 CDC	-	1mg Melatonin + 10 mg Zinc, 1 hour before sleep for 16 weeks	**PROMs** 1) Fatigue (FIS) 2) Anxiety and Depression (HADS) 3) Sleep Quality (PSQI) 4) Dysautonomia (COMPASS31) 5) Health related quality of life (SF-36) **Biological endpoints** 1) 6-sulfatoxymelatonin 2) Zinc	**PROMS** 1) p<0.05 2) N.S. 3) N.S. 4) N.S. 5) N.S. **Biological endpoints** 1) p<0.0001 2) N.S.	[191]
S-citalopram (n/a)	OPT (16)	1994 CDC	Co-morbid MDD	10-20 mg of S-citalopram daily for up to 12 weeks	**PROMs** 1) Fatigue (CFQ, FIS) 2) PEM (CFS-SR) 3) Sore throat (CFS-SR) 4) Tender lymph nodes (CFS-SR) 5) muscle pain (CFS-SR) 6) Joint pain (CFS-SR) 7) Headache (CFS-SR) 8) Sleep (CFS-SR) 9) Cognitive function (CFS-SR) 10) CFS severity (CGI subscale)	**PROMS** 1) p<0.0005 2) p=0.001 3) p=0.005 4) N.S. 5) p=0.001 6) p=0.025 7) p<0.0005 8) p<0.0005 9) p<0.0005 10) p<0.0005	[176]

	11) CFS improvement (CGI subscale)	11) $p<0.0005$
	12) Depression (HAM-D, BDI)	12) $p<0.0005$
	13) MDD severity (CGI subscale)	13) $p=0.001$
	14) MDD improvement (CGI subscale)	14) $p<0.0005$

Abbreviations:

1988 CDC: 1988 Centers for Disease Control and Prevention criteria for CFS by Holmes, 1994 CDC: 1994 CDC criteria for CFS by Fukuda, ADHDRS: attention deficit hyperactivity disorder rating scale, BAI: Beck anxiety inventory, BDI: Beck depression inventory, BP: blood pressure, BPI: brief pain inventory, BPM: beats per minute, BRIEF-A: behavior rating inventory of executive function-adult, CDC-SI: CDC symptom inventory scores, CES-D: Centers for Epidemiological Studies depression scale, CFQ: Chalder fatigue questionnaire, CFS-SR: CFS symptom rating, CGI: clinical global impressions, CO: cross-over, COMPASS31: composite autonomic symptom score 31-items questionnaire, CIS: checklist of individual strength, DASI: Duke activity status index, FIS: fatigue impact scale, FIQ: fibromyalgia impact questionnaire, FSQ: functional status questionnaire, FSS: fatigue severity scale, GET: graded exercise therapy, GWS: global wellness scale, HADS: hospital anxiety and depression scale, HAM-A: Hamilton anxiety rating scale, HAM-D: Hamilton depression rating scale, HGS: hand grip strength, HR: heart rate, ISS: illness severity scale, LDX: Lisdexamfetamine Dimesylate, MDD: major depressive disorder, MFI-20: 20-item multidimensional fatigue inventory, MHLC: multidimension health locus of control, MPQ: McGill pain questionnaire, n/a: not available, N.S. not significant, OPT: open-label pilot study, PA: parallel-arm, PANAS: positive and negative effect scale, PGI-I: patient global impression of improvement, POMS-SF: profile of mood states - short form, PROMs: patient-reported outcome measures, PSQI: Pittsburgh sleep quality index, RCT: randomized placebo-controlled double-blinded clinical trial, SF-36: 36-item short form health survey, SIP: sickness impact profile, SLQ: sexual life quality questionnaire, Sx: 16-question Symptom Checklist, UGWS: unidimensional global wellness scale, VAS: visual analogue scale, WHOQOL: World Health Organization quality of life questionnaire, WMFI: Wood mental fatigue inventory.

Trial codes:

NCT: ClinicalTrials.gov

Footnotes:

* Marks a primary outcome measure

† Total combined score from more than one measure to assess a domain

‡ Function work capacity defined as the amount of oxygen consumed in the last minute of exercise per kg of body weight

§ *p* values for fluoxetine treatment reported

¶ The dose of fludrocortisone was double if participants reported no improvement at week 2.

Distance walked before exhaustion was ascertained using a 5-point rating scale: 1 point – 1 block, 2 points – 1-3 blocks, 3 points – 3 to 8 blocks, 4 points – 1 to 3 miles, 5 points – 3 miles or more.

Comparisons are between the active vs placebo phases of the study

Supplementary Table S6: Clinical trials investigating treatments for neuroendocrine disturbances in ME/CFS.

Intervention (Trial code)	Study design (Cohort size)	Diagnostic criteria	Patient subgroup	Treatment regime	Outcome measures	Outcome significance	Reference
CT38 (NCT03613129)	OPT (17)	1994 CDC, CCC and IoM	-	Subcutaneous infusion of CT38, with doses at: 0.20 µg/kg/hour, for 3 hours for 2 days 0.03 µg/kg/hour, for 3.5 hours for 3 days 0.06 µg/kg/hour, for 3.5 hours for 3 days 0.01 µg/kg/hour, for 3.5 hours for 3 days	**PROMs** 1) Symptoms (TDSS) 2) Physical Health (SF-36-PCS) 3) Mental Health (SF-36-MCS)	**PROMs** 1) p=0.011 2) p=0.005 3) N.S.	[235]
DHEA (n/a)	OPT (23)	1988 CDC	Suboptimal serum levels of DHEA-sulphate (<2.0µg/mL)	25 mg/day DHEA for 6 months†	**PROMs** 1) Functional disability (MHAQII) 2) Pain‡ 3) Fatigue‡ 4) Satisfaction with activity level‡ 5) Coping with the illness‡ 6) Feelings of helplessness‡ 7) Depression‡ 8) Anxiety‡ 9) Thinking‡ 10) Memory‡ 11) Sexual problems‡ **Biological endpoints** 1) Free testosterone 2) Total cholesterol 3) LDL 4) HDL	**PROMs** 1) n/a 2) p=0.035 3) p=0.009 4) p=0.033 5) N.S. 6) p=0.015 7) N.S. 8) p<0.01 9) p<0.01 10) p<0.05 11) N.S. **Biological endpoints** 1) p=0.001 2) N.S. 3) N.S. 4) p=0.016	[228]
GH (n/a)	RCT (PA) (GH: 10, Placebo: 10)	1994 CDC	Nocturnal peak of <10 µg/L of GH	6.7 µg/kg GH per day for 12 weeks. Following treatment period, the 17 patients remaining were given the above concentration of GH for 9 months	**PROMs** 1) Quality of Life (NHP, QoL-AGHDA) **Objective measures** 1) Weight 2) Muscle Strength 3) Skinfold Thickness 4) Fat-free mass 5) Total body water 6) Fat mass 7) BMI	**PROMs** 1) N.S. **Objective measures** 1) N.S. 2) N.S. 3) N.S. 4) p=0.006 5) p=0.003 6) N.S. 7) N.S.	[229]

					Biological endpoints 1) Hormone levels (IGF-I) 2) Hormone levels (Thyrotrophin, tri-iodo thyronine, thyroxine, prolactin, cortisol, follicle-stimulating hormone, lutenizing hormone, testosterone) 3) Serum Lipoprotein(a) 4) Amino acids (Tyrosine, valine, tryptophane, phenylalanine, isoleucine and leucine)	**Biological endpoints** 1) $p<0.001$ 2) N.S. 3) $p=0.003$ 4) $p<0.005$	
Low-dose hydrocortisone (n/a)	RCT (PA) (Hydrocortisone: 35, Placebo: 35)	1994 CDC	-	16 mg/m^2/day hydrocortisone per day, 20-30mg at 8AM and 5 mg at 2PM for 12 weeks	**PROMs** 1) Wellness (SI-GHS) 2) Mood (POMS) 3) Symptoms (SCL-90R) 4) Sickness (SIP) 5) Depression (BDI) 6) Activity (AS-10) **Biological endpoints** 1) Resting and cosyntropin-stimulated cortisol levels	**PROMs** 1) $p<0.01$ 2) N.S. 3) N.S. 4) N.S. 5) N.S. 6) N.S. **Biological endpoints** 1) $p<0.01$	[225]
Low-dose hydrocortisone (n/a)	RCT (CO) (Hydrocortisone: 16, Placebo: 16)	1994 CDC		5 – 10 mg hydrocortisone, once per day for 28 weeks	**PROMs** 1) Fatigue (FS-11) 2) Disability (WSAS) 3) Health related quality of life (SF-36) 4) Psychological symptoms (GHQ) **Biological endpoints** 1) 24h urinary free cortisol 2) Insulin stress test	**PROMs** 1) $p=0.04$ 2) $p=0.006$ 3) N.S. 4) $p=0.003$ **Biological endpoints** 1) N.S. 2) $p=0.52$	[226]

Abbreviations:

1988 CDC: 1988 Centers for Disease Control and Prevention criteria for CFS by Holmes, 1994 CDC: 1994 CDC criteria for CFS by Fukuda, ACTH: adrenocorticotropic hormone, AS-10: 10-point activity scale, BDI: Beck depression inventory, BMI: body mass index, CCC: Canadian consensus criteria for ME/CFS by Carruthers, CGI-21: clinical global impression scale-21, CO: cross-over, DHEA: dehydroepiandrosterone, FS-11: 11-item fatigue scale, GH: growth hormone, GHQ: general health questionnaire, hCRH: human corticotropin-related hormone, HDL: high density lipoprotein, IGF-I: insulin-like growth factor-I, IoM: Institute of Medicine, LDL: low density lipoprotein, MHAQII: modified health assessment questionnaire version 2, NCT: ClinicalTrials.gov study identifier, NHP: Nottingham health profile, n/a: not available, N.S.: not significant, OPT: open-label pilot study, POMS: profile of mood states, PROMS: patient-reported outcome measures, QoL-AGHDA: quality of life assessment in GH-deficient adults, RCT: randomized placebo-controlled double-blinded clinical trial, SCL-90R: Symptom Checklist-90-R, SF-36: 36-item short form health survey, SF-36-MCS: SF-36 – mental component summary, SF-36-PCS: SF-36 – physical component summary, SI-GHS: single item global health scale, SIP: sickness impact profile, TDSS: total daily symptom scores, WSAS: work and social adjustment scale.

Trial codes:
NCT: ClinicalTrials.gov
Footnotes:
† Dosage of DHEA increased by increments of 25mg/day to a maximum of 100mg/day in participants whose DHEA-sulphate levels remained <2 µg/mL or no clinical response
‡ Assessment tool not reported