

Myalgic Encephalomyelitis

Evidence-Based Management

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What This Talk Covers

Defining the ME.
PENE as the organising principle.
What helps, pharmacologically and otherwise.
And what is ineffective or harmful.



This presentation does not constitute medical advice

and is for educational purposes only

Why ME, Not CFS

WHO has classified ME as a neurological disorder since 1969 (ICD-10 G93.3).

A fatigue model produces exercise prescriptions.

A neuroimmune model produces energy conservation.

Only one is safe.

Carruthers et al., J Intern Med 2011; WHO ICD-10 G93.3; NICE NG206, 2021

The International Consensus Criteria

01 **Criterion A is compulsory**

Post-exertional neuroimmune exhaustion. There is no six-month waiting period.

02 **Criteria B, C and D**

B: neurological impairments, one symptom from three of four categories.

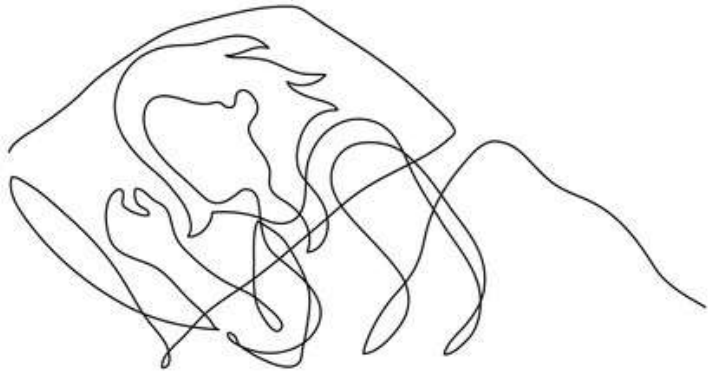
C: immune, GI and GU impairments, one from three of five.

D: energy production and ion transport, at least one.



Carruthers et al., J Intern Med 2011; International Consensus Primer, 2012

PENE: The Cardinal Feature



Fatigability

Marked, rapid physical and cognitive fatigability after exertion that may be minimal.

Exacerbation

The whole symptom profile set worsens

Recovery and Invisibility

Recovery usually exceeds 24 hours; relapses last days or weeks. The delay is why clinicians don’t see the crash.

Carruthers et al., J Intern Med 2011; Keller et al., J Transl Med 2024; Mancini et al., Front Physiol 2026

Severity

01 **Mild**

Significant reduction in activity

02 **Moderate**

Approximately 50% reduction in pre-illness activity.

03 **Severe**

Mostly housebound. Clinic-based reviews may begin to exclude this group

04 **Very Severe**

Mostly bedridden, need assistance with activities of daily living



International Consensus Primer, 2012; Institute of Medicine, 2015; Montoya et al., Healthcare 2021

Diagnosis and Investigation

01 Exertion History

What happens 24 to 72 hours after activityto assess for PENE.

02 Orthostatic Intolerance

Lying and standing blood pressure, or a 10-minute lean test.

03 Baseline Panel

FBC, inflammatory markers, electrolytes, renal and liver function, TFTs, glucose, coeliac serology, iron studies.

04 Additional testing if indicated

Autoimmune + infection serology, hormonal assays, sleep study, nutritional assessment.



NICE NG206, 2021; International Consensus Primer, 2012; US ME/CFS Clinician Coalition, 2021

Comorbidities to Seek

01 Orthostatic Intolerance

Present in most people with ME. The single most modifiable feature.

02 Mast Cell Activation

Flushing, dermographism, sensitivity to foods, odours and chemicals.

03 Non-Allergic Rhinitis

TRPV1 and TRPA1 sensory nerve overexpression.

04 Gut Dysfunction

Irritable bowel, small intestinal bacterial overgrowth, altered microbiome.

05 Other Common Overlaps

Fibromyalgia, migraine, sleep-disordered breathing, Hashimoto thyroiditis.



US ME/CFS Clinician Coalition. 2021: NICE NG206. 2021: Baroody et al.. J Allergy Clin Immunol Pract 2024

No Cure. A Great Deal of Care.

01 Prevent

Prevent post-exertional crashes. Repeated crashes may drive long-term deterioration.

02 Treat

Orthostatic intolerance, sleep, pain, gut symptoms, rhinitis, nutrition.

03 Accommodate

Preserve function, income, education and relationships.

04 Do No Harm

Several widely offered therapies make ME worse.

05 Frame Honestly

A serious chronic neuroimmune disease. Not coaching someone back to fitness.



International Consensus Primer, 2012; NICE NG206, 2021; US ME/CFS Clinician Coalition, 2021

Pacing and the Energy Envelope

01 Energy Envelope

The exertion a person can sustain without triggering PENE.

02 All Exertion Counts

Physical, cognitive, emotional, social.

03 Symptom-Contingent

Activity responds to the body, not to a schedule.

04 Aids Are Enabling

Shower chairs, wheelchairs, ear defenders, delivery, disability parking.

05 Pre-emptive Rest

Rest before the crash, not after it.

06 Permission

Doing less on a bad day is not failure.

NICE NG206, 2021; US ME/CFS Clinician Coalition, 2021; Sanal-Hayes et al., Fatigue 2024

Teaching Pacing in Practice

01 Set the Baseline Low

What is sustainable on a bad day, not a good one.

02 Diary With a Lag Column

Activity and symptoms, plus what happened 48 to 72 hours later.

03 Breaks and Rest

Short bouts with rest between. Lie down where there is orthostatic intolerance.

04 Heart Rate Ceiling

(220 minus age) x 0.60, set as an alarm on a smart watch.

05 The Evidence, Honestly

Sanal-Hayes 2024: no significant effect on function, pain or fatigue.

06 Why Recommend It Anyway

It is the only strategy consistent with PENE physiology, and it causes no harm.



International Consensus Primer, 2012; NICE NG206, 2021; US ME/CFS Clinician Coalition, 2021

Orthostatic Intolerance

Non-pharmacological management — present in most people with ME

Fluid and Salt

Increase fluid intake, and salt where blood pressure permits. Potassium and magnesium supplementation alongside.

Compression

Waist-high garments or an abdominal binder are recommended.

Posture and Medications

Knees above hips, head of bed elevated, counter-manoeuvres. Review medications.

US ME/CFS Clinician Coalition, 2021; Joseph et al., Chest 2022

Orthostatic Intolerance

Pharmacological management — all off-label in ME

Volume and Tone

Fludrocortisone 0.1–0.2 mg daily Midodrine 2.5–15 mg every 4 hours while upright

Rate Control

Propranolol 5–20 mg
Metoprolol XR 12.5–50 mg.
Ivabradine 2.5–7.5 mg bd

Pyridostigmine

30–60 mg q4–8h. Joseph & Systrom, Chest 2022: randomised, placebo-controlled, invasive CPET, n=45. Peak VO2 rose; placebo fell.

US ME/CFS Clinician Coalition, 2021; Joseph et al., Chest 2022

Sleep and Pain

Symptom-directed prescribing — all off-label

Sleep

Unrefreshing rather than absent.
Melatonin
Amitriptyline 5–25 mg
Doxepin 1–10 mg
Trazodone 12.5–100 mg
Mirtazapine 7.5-15mg

Pain

Low-dose naltrexone, duloxetine, gabapentinoids, paracetamol.
Avoid long-term opioids.

Caution

Standard sleep hygiene includes enforced daytime wakefulness and fixed rise times. In ME that is graded activity by another name. Adapt it.

US ME/CFS Clinician Coalition, 2021; NICE NG206, 2021; Sasso et al., Mol Med 2022

Low-Dose Naltrexone

Mechanism-targeted and still experimental

Mechanism

Opioid signalling inhibits TRPM3. Naltrexone antagonises that, potentially restoring channel and NK cell function. It also blocks HMGB1, TLR4 and NLRP3.

Evidence, Honestly

Polo 2019: 218 patients, 73.9% improved, but retrospective and uncontrolled.

Practical

Compounded, ~$150–200 to trial. 1.5–4.5 mg nocte, titrated up. Effect within 6–8 weeks.

Polo et al., Fatigue 2019; Bolton et al., BMJ Case Rep 2020; Cabanas et al., Front Immunol 2021; Sasso et al., Mol Med 2022; Gouda et al., Adv Ther 2026

Nutrition and the Microbiome

01 Malnutrition

Difficulty shopping, standing to cook, new intolerances, financial constraints.

02 CoQ10 With NADH

Randomised trials report improved fatigue, sleep and quality of life.

03 Quercetin and Ginseng

Quercetin: a placebo-controlled trial.
Ginseng: an open-label pilot only.

04 Probiotics

B. infantis 35624 reduced CRP, TNF-alpha and IL-6 in ME patients.

05 Synbiotic SIM01

Improved fatigue, memory and concentration in post-COVID condition.

06 Limitations

Small studies, mixed methods.
Adjuncts, not disease-modifying therapy.

Groeger et al., Gut Microbes 2013; Campagnolo et al., 2017; Castro-Marrero et al., Nutrients 2021; Rondanelli et al., 2023; Teitelbaum & Goudie, 2022; Lau et al., Lancet Infect Dis 2024

Severe and Very Severe ME

01 Home Visits

Attending clinic can cost weeks of function.

02 Nutrition Support

Oral first, but escalate if indicated before malnutrition is life-threatening.

03 Sensory Management

Ask about light, noise, touch, and fragrances, then mitigate.

04 Medication Dosing

A fraction of standard doses e.g. start naltrexone at 0.1 mg, not 4.5 mg.

05 Hospital Risk

Admission carries risk. Limit tests and encounters, protect the environment.

06 Safeguarding

Not a mental illness. Not anorexia. Carers are not neglecting them.



Montoya et al., Healthcare 2021; NICE NG206, 2021

Ineffective and Harmful Therapies

01 **NICE Guideline (NG206): do not offer**

Exercise as a cure.
Graded exercise therapy.
Programmes based on deconditioning theories.
The Lightning Process.

02 **Cognitive behavioural therapy**

Offer it as supportive care for the burden of chronic illness. Never as a cure, and never assuming abnormal illness beliefs cause ME.

Norwegian ME Association survey, 2012; Crawley et al., Arch Dis Child 2018; NICE NG206, 2021

The PACE Trial for GET

Why the evidence for graded exercise does not survive scrutiny

Outcome Switching

Recovery thresholds were changed after unblinding. Some participants met them before treatment began. Under the original protocol, ~4% recovered.

Design and Selection

Every trial unblinded with subjective outcomes. And ~90% of participants met criteria not requiring PEM, so most did not have ME.



White et al., Lancet 2011; Wilshire et al., BMC Psychol 2018; Larun et al., Cochrane 2024; BMJ 2025; Cooper & Papadopoulos, 2025

The Harm Data

What patients have reported, consistently, across two decades

Graded Exercise

Independent surveys: symptoms intensify in 54–74% of patients. Action for ME: 56% deteriorated, 28% improved.

Lightning Process

A Norwegian patient survey found 50% worsened and 25% deteriorated seriously. NICE reviewed surveys of over 15,000 respondents: harms outweighed benefits.

The Harms Are Predictable

If PENE means exertion beyond the envelope causes deterioration, incremental exertion is contraindicated.



Carruthers et al., J Intern Med 2011; Norwegian ME Association survey, 2012; NICE NG206, 2021

The Australian Problem

01 RACGP HANDI, April 2024

Still recommends incremental physical activity, citing PACE and Cochrane.

02 AGREE II: 2% vs 92%

HANDI scored 2% for rigour of development. NICE NG206 scored 92% on the same instrument.

03 AJGP, March 2026

Stallard, Praet, Gupta and Smith called for withdrawal. The CDC has already withdrawn its GET recommendation.

04 Until 2028, Follow NICE

NHMRC guidelines are in development. Publication expected late 2027, implementation 2028.



NICE NG206, 2021; Larun et al., Cochrane 2024; Stallard et al., Aust J Gen Pract 2026; NHMRC, 2026

Summary

DIAGNOSE

Obtain the exertion history.
Ask about the 24–72 hour lag.
Identify PENE early.

TREAT

Teach pacing first.
Identify and treat co-morbidities.
If prescribing off-label, start low, go slow.

DO NO HARM

Do not prescribe exercise as therapy.

