emerge australia

Webinar 2

ME/CFS & long COVID: An evidence-based guide for General Practitioners

Optimal management of common symptoms and co-morbidities

Dr Mark Donohoe

John James Foundation

Proudly supported by the John James Foundation.

RACGP CPD Approved Activity

Acknowledgement of Country

Emerge Australia acknowledges Aboriginal and Torres Strait Islander people as the Traditional Custodians of the land on which we operate.

We pay our respect to the ongoing living cultures of Aboriginal peoples, and to Elders past and present and emerging.

Housekeeping

- 60 minutes for presentation
- 20 minutes for questions
- If you wish to put questions in the Q&A thread at any time, we will ask them during question time
- Webinars are recorded. Cameras and mics have been muted
- RACGP members will have their CPD uploaded within a week
- ME/CFS and long COVID aware GP directory

Speaker: Dr Mark Donohoe

Learning outcomes

1. Evaluate evidence from the patient, literature and clinical experience to develop management plans for ME/CFS or long COVID, including treating common symptoms and co-morbidities

Overview

- ME/CFS and long COVID are not a single disease
- NO magic bullet for cure
- Management means identifying symptoms and reducing disability
  - Small wins make a difference
- Research is emerging and often surprising
- Lots of claims, be aware and cautious
- ‘Normal range”……

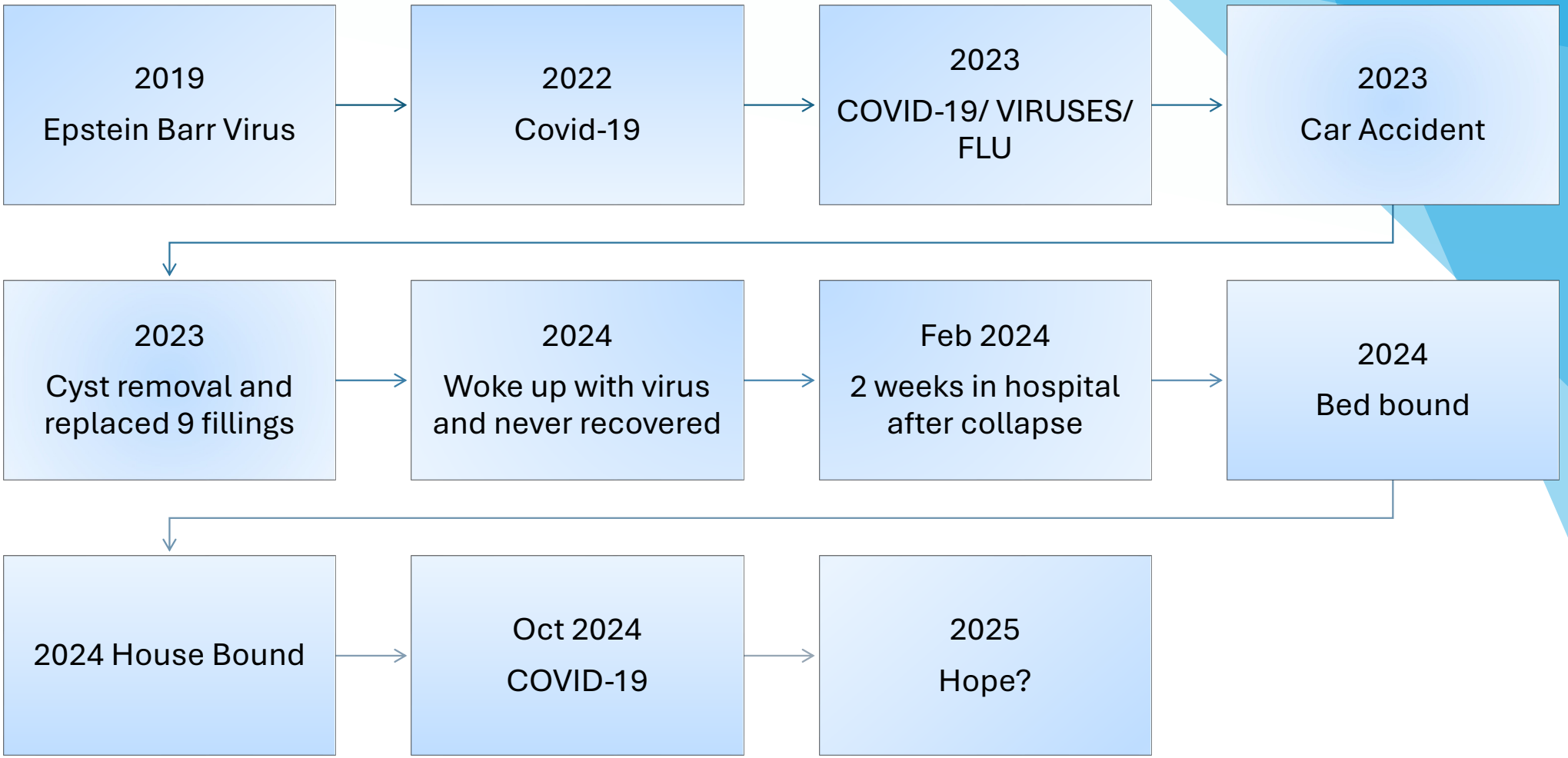
What is indicated?

What is likely to help?

What may help some?

What harms?

Timeline example



Early intervention – what does it mean?

Be aware of:

- Moving TOWARDS ME/CFS or long COVID
- Do NOT wait 12 weeks (long COVID) or 6 months (ME/CFS)
- Support rest & pacing
- Identify and treat co-infection & co-morbidities early
- Environment

2019

Epstein Barr Virus

From a work trip in Quanzhou, Fujian, China. Was very sick but pushed through with young kids and a busy business to run

2022

Covid-19

Family got it from a family holiday. I was the only one bedridden for 5 days

Knives in the throat and body aches. Took months to get back to pilates

May 2022

Anaemia - Ferritin IV

Became sensitive to chemicals and allergic to sulphites in wine

ME/CFS and long COVID

Symptomatic care

- Dysautonomia
- Fatigue
- Post-exertional malaise
- Movement
- Brain fog
- Pain
- Sensory Sensitivity
- Sleep
- GIT

Category care

- Persistent infection (SARS, EBV, other)
- Autoimmune
- Metabolic/mitochondrial
- Coagulopathy/micro clots
- MCAS

Dysautonomia

- Postural Orthostatic Tachycardia Syndrome (POTS) – has become a generic term for POTS/OI/OH/NMH
- Autonomic loss of function
- Presyncope, loss of general function
- Many proposed mechanisms, differ by individual
- Associated with hypermobility esp. in young

(Bryarly et al, 2019)

2019
Epstein Barr Virus

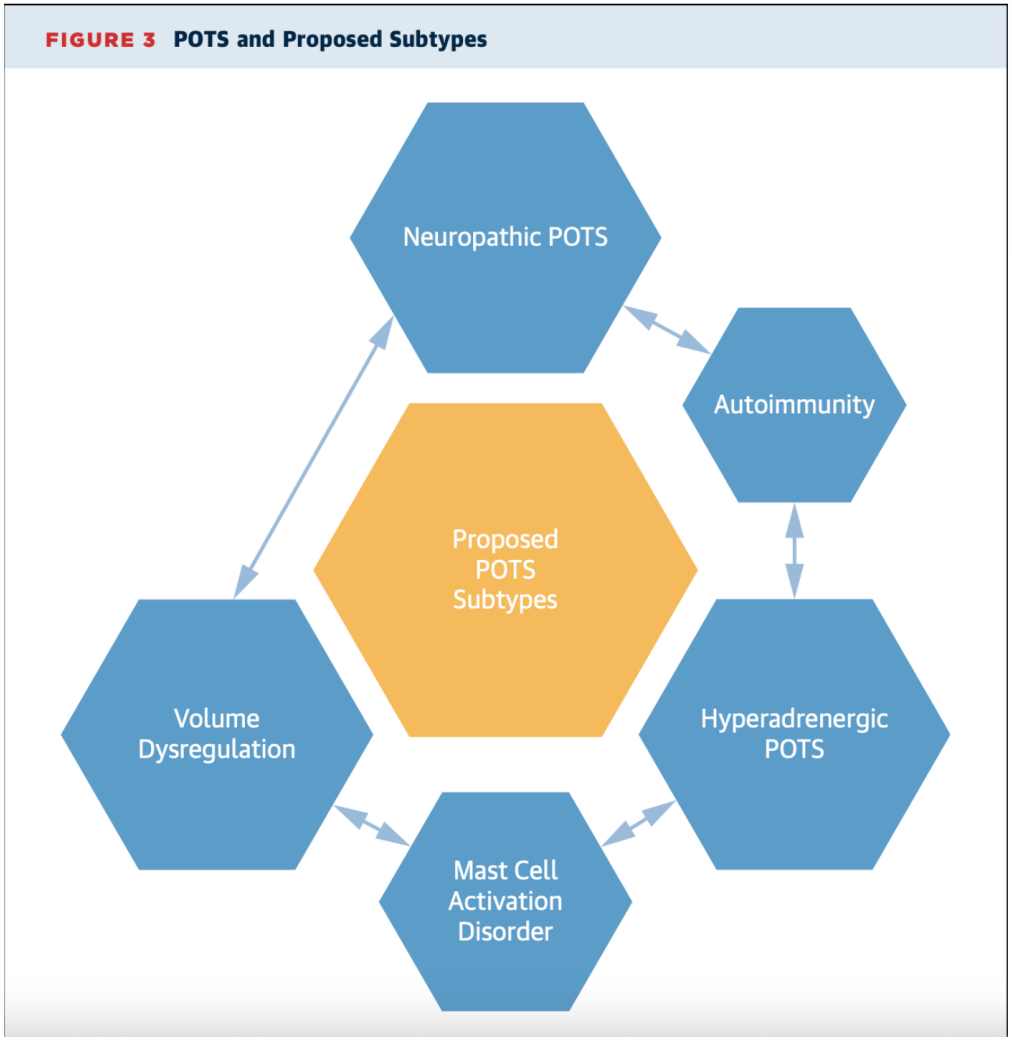
2022
Covid-19

2023
COVID-19/ VIRUSES/ FLU
So dizzy, can't exercise, memory problems, constipation, "weeing all the time"

Dependent acrocyanosis

(Wells & Tonkin, 2016)

POTS subdivisions

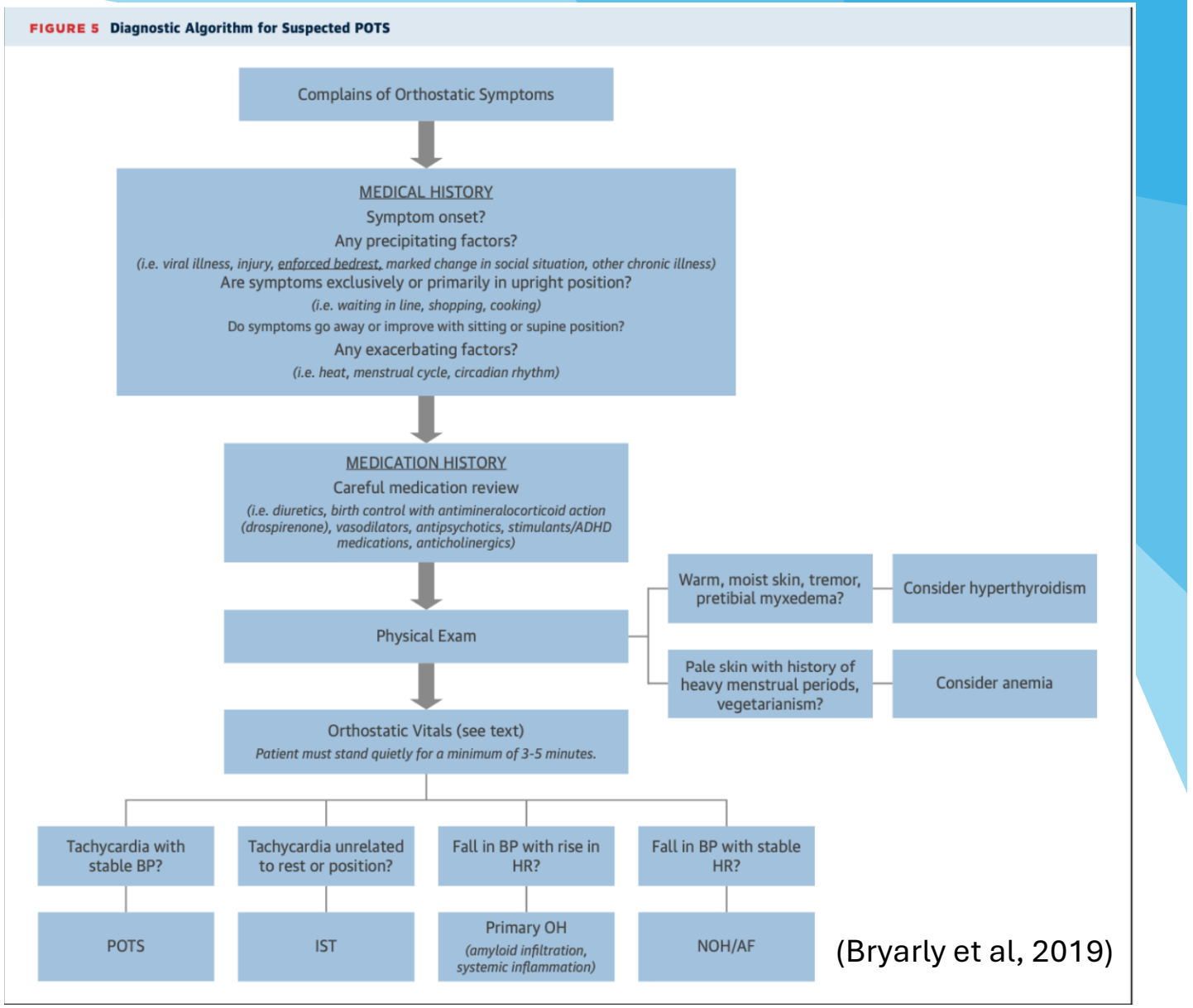


(Bryarly et al, 2019)

Diagnosis

- NASA lean test
- 24 hour monitors
- In office sit to stand

NASA lean test



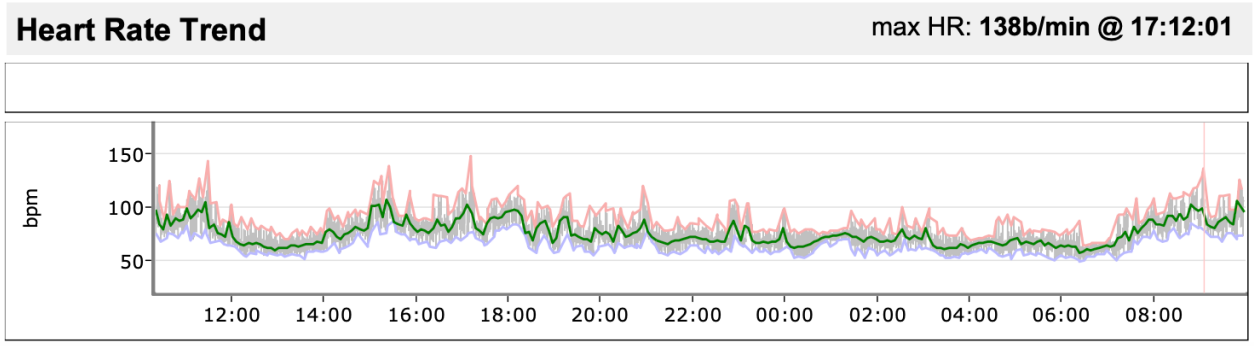
(Bryarly et al, 2019)

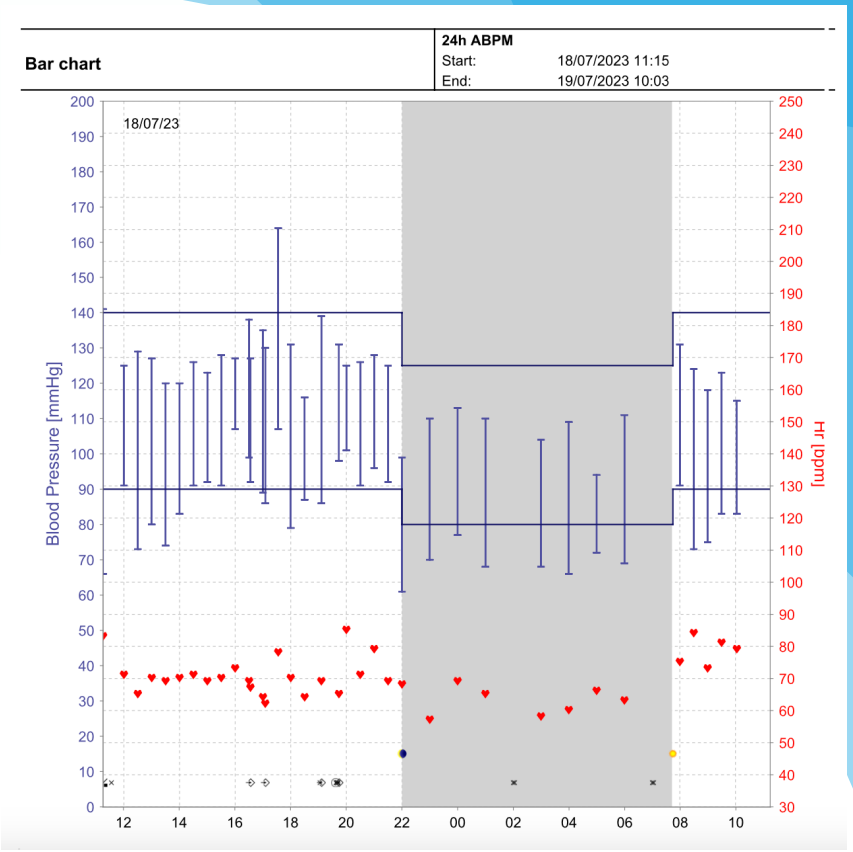
Looking at trends

INTERPRETATION

Sinus Rhythm at 54-138/75 bpm, (Min-Max/Average).

A Few (100-1000) ventricular ectopics. Rare (<100) atrial ectopics.
With atrial couplets/triplets. No significant pause (>1.8sec).
Symptoms were associated with SR and VEBs.





(With permission)

Management strategies

Foundations

- Non-drug approaches – 50% QoL improvement
- High dose electrolytes – at LEAST NaCl & H2O but consider K+ and Mg++
- High demand amino acids
  - serine, histidine, ornithine, glycine, aspartic acid and lysine sacrificed to preserve NaCl (Dunstan et al, 2023)
- Pacing activity
- Bio-feedback
- Autonomic rehabilitation

(Bryarly et al ,2019)

Pharmacological – True POTS

- Start with beta blockers unless contraindicated:
  - Propranolol 10 to 20 mg twice a day
  - Metoprolol 50 mg if propranolol not tolerated
- If beta blockers not tolerated (ARs are common):
  - Ivabradine at starting dose of 2.5 mg bd (short half-life)
  - Most are managed at:
  - 5 mg bd or tds, Max 7.5 mg tds
  - Taken on waking and after lunch, not before sleep

"I feel so much better knowing it's not in my head."

"On propranolol I feel less breathless, internal tremors are gone and I'm not 'anxious'"

Pharmacological – Volume depletion

- High thirst, excessive urination and/or sweat, nocturnal
  - Exclude DI, check aldosterone
- Fludrocortisone starting at 50 µg in mornings
  - Move on to 100µg or even 200 µg for symptom management
  - Check K+ as excreted
- IV saline infusions x 1-2 litres once or twice weekly or stat for acute episodes
- Desmopressin if polyuria and copeptin on 8 hr water restriction low
  - Start low (60 µg) and increase slowly, checking sodium regularly

(Bryarly et al, 2019; Snapper & Cheshier, 2022)

Pharmacological – Neurally Mediated Hypotension

- Midodrine starting at 2.5 mg bd (not before bed) increasing slowly
  - Beware of nocturnal hypertension
- Compression clothing works but is not popular (sport compression in popular!)
- Cold baths if tolerated
- Pyridostigmine if blotchy venous pooling of legs
  - Starting at 10 or 30 mg bd
  - Usual effective dose in 60 mg twice a day for adult

Dysautonomia summary

- Low hanging fruit with measurable outcomes
- Progression from lifestyle to medications slowly and reluctantly
- Revise after repeated NASA lean testing to minimise drug treatment
- Can mix and match ALL of the above with some care
- It’s not about getting the numbers right – it’s about function

Post-exertional malaise & movement

- PEM is an abnormal response to exertion & escalation of symptoms – often delayed
- Exertion = physical, cognitive, emotional, orthostatic, environmental……
- It DOES NOT respond to stimulant treatment!!!
    - Beware of the “everybody has ADHD” story

(Joseph et al 2023; Applemen et al, 2024)

Feb 2024

2 weeks in hospital after collapse

Passed out after shower

2 days in ED

Reacting to IV

Hospital kept testing HR lying and standing but didn’t mention the POTS.

Neuro mentioned ME/CFS but didn’t know anything about it

4 weeks bedridden then recovered enough to go on holiday

2024

Recovered enough for two weeks holiday doing 10k steps but then crashing

Berocca & B12 not helping

On return, woke up with virus and never recovered

Movement

- Avoid graded exercise therapy (GET)approach - harm identified recently on muscle biopsy and invasive CPET
- Maintain “energy envelope”
  - **Goal** is symptom stability NOT return to “being fit”
- Guided by severity of both fatigue, PEM and PEM duration
- Maintain movement and prevent excessive deconditioning – where possible
- Passive movement for those bedbound
- Can refer to PEM literate EP/Physio/OT

(NICE, 2021)

PEM – other options?

Aripiprazole usual indication schizophrenia 10mg – 30mg

Low dose aripiprazole?

- Off label but commonly used
- Compounded
  - Starting dose of 0.25 mg daily, increasing by 0.25 mg weekly
  - Maximum dose = 2 mg
  - Typical effective dose is between 0.75 and 1.25 mg
- About 50% success rate for PEM reduction across the board
- Worth having a PEM “Challenge” to assess benefit

(Crosby et al, 2021, TGA, 2024)

Fatigue – Low dose naltrexone (LDN)

- Naltrexone usual indication for alcohol dependence at 50mg dose
- **Low** dose naltrexone (LDN) is a foundation for ME/CFS
- Compounded
- Especially useful if pain/myalgia/arthralgia present (70% +)
- Multiple mechanisms of action proposed
- Dosage regimens are tricky and very individual
- Does not go well with opioid medications for pain

(Aicheson et al, 2023; Bateman et al, 2024; TGA, 2024)

Fatigue - LDN

- **Titration to find optimal dose**
  Week 1: 1 caps nightly = 1.5 mg
  Week 2: 2 caps nightly = 3 mg
  Week 3 and on: 3 caps nightly = 4.5mg
- **LDN "Gotchas"**
  1.5 mg too high for at least 1 in 5
- **Restart at 0.5 mg and escalate the same way**
  Sleep and dreaming can be disturbed
  Same dose may lose effect over time
  Can worsen PEM when it works and patient pushes too far
- **OTHERS**
  Coffee and stimulants work poorly
  Nicotine patches show some promise
  Some wild and sensible "autonomic reprogramming" programs

(Bateman Horne Center, 2024)

Where is our patient now?

Feb 2024

Never recovered after holiday

2024

Bed bound

Bed Bound with 20+ symptom. Shower once a week

Sometimes could get down stairs, crawl up sensitive to light & noise

Migraines, diarrhoea daily, Legs tingling & painful everyday

Completely paralysed during PEM crash, can't move arms or legs or drink water

Lasted 6 months till starting Low Dose Naltrexone

End 2024 Bed/house Bound

With pacing and LDN:

Bedbound two days a week

Rest after showers, eating

Friend over for an hour once a fortnight

Drs appointments = few days crash

Cognitive fatigue/brain fog

Causes:

- Low cellular energy = reduced function
- PEM
- Neuroinflammation
- Reduced cerebral perfusion

Contributors:

- Medications for other symptoms i.e. sleep, pain
- Chronic sleep dysfunction
- Secondary mental health issues
- Orthostatic intolerance – reduced cerebral blood flow

(Day et al, 2024; NAM, 2015)

Cognitive fatigue/brain fog

- Cognitive impairment (“brain fog”)
  - Brain and body usually together, but sometimes fatigue is all brain
  - Difference between fatigue and “brain fog”

- Slow information processing

- Difficulty with time time tested tasks

- Issues with short-term memory and concentration

- Task switching

- There can be a marked difference in cognitive performance between a rested and PEM state

(NICE, 2021)

Pharmacological - Cognitive fatigue/brain fog

Off label use of medications that may help but…

- Stimulants – significant risks for blunting perception of effort
- Modafanil 50 mg to 200 mg can provide good short term intermittent benefit – can disrupt sleep
- Mitochondrial support can often improve brain fog

- Ubiquinol, magnesium, alpha lipoic acid
- Methylene blue, others…

Cognitive Behavioural Therapy?

- CBT is not a primary treatment for ME/CFS
- Rates of premorbid psychological disorders in ME/CFS are the same as in any population with complex illness
- Refer as appropriate for associated mood disorders, anxiety, impact of chronic disease, sleep and pain management

Differentiating between ME/CFS and Depression:

- Motivation to exercise/partake in activities - high versus low

- Effect of exercise/activities – worse vs better

- Low sense of self worth/self esteem, anhedonia are not features of ME/CFS

- ME/CFS is not a functional neurological disorder

(Grach et al, 2023; NAM, 2015)

"I don't think your ME/CFS is caused by how you think, but it's really hard to deal with and sometimes it's good to get some help to manage the big changes in your life"

Pain

Common types and options for management:

- Managing the myalgias, arthralgias, headaches is a challenge
- Note the specific pain termed fibromyalgia
- When LDN works, it manages pain with minimal side effects
- Mind-body approaches are preferred
- Acupuncture and body work, touch therapies work well
- Access to these limited by finances or capacity to attend
- Be aware pain clinics do not usually understand PEM
- Compression or bracing with appropriate physiotherapist

Pharmacological -Pain

Common types and options for management:

- OTC

- Palmitoylethanolamide (PEA), magnesium, cannabis products

- Duloxetine, TCA’s

- LDN

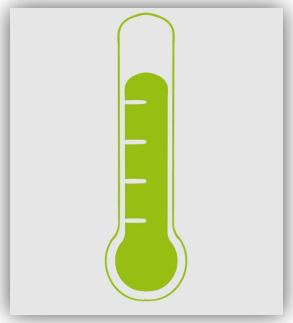
- Pregabalin, gabapentin – start LOW

Environmental load and sensory sensitivity

Scent and chemical

Environment

Temperature



Light

Interaction/sound

Environmental load and sensory sensitivity

- Telehealth
- Patients stay reclined in car and called when GP ready to see them
- Places to lie down and seating options
- Reduce fluorescent lighting
- Keep music volume low
- Use unscented cleaning products

"Do you have any sensory sensitivities?"

"Would you like me to turn the top lights off/close the blinds/adjust the temperature?"

"I'll talk to admin. Next time you can wait lying down in a spare room or your car, which is easier for you? "

"I will arrange with pathology to have them come to your home for blood tests"

Creating an ME/CFS friendly practice environment

Sleep

- **The specific sleep abnormalities**
  - Prolonged latency
  - Repeated night waking
  - **Waking unrefreshed no matter how long they sleep**
  - Often daytime sleep
- Primary sleep disorders (OSA, RLS etc) common, may exacerbate ME/CFS but are not the cause
  - Utilise existing pathways to screen for primary sleep disorders
- Altered circadian rhythm, made worse in PEM
- Sleep is REALLY hard to get right and so important as well – persist in helping

(NAM, 2015)

Sleep – non-medication first

- NOT primarily sleep “hygiene” issue but still address
  - Dark room, no gadgets, meal timing
- Relaxation and non-medication strategies
- Reduce all causes of sleep disruption i.e. pain, habits, room temp, PEM etc

Pharmacological - Sleep

Medications

- Melatonin
- Low dose TCA's
- Zolpiderm
- Alpha agonists
- OTC – drowsy antihistamines
- Benzodiazapines
- Modafanil for restoration of circadian rhythm?
- Atypical antipsychotics
- CBD

Supplements/herbs

- Magnesium
- B6 often added. Caution around multiple sources of B6
- Relaxation tea

Aim to treat the causes of the disturbance
Medication if necessary – consider half-life

Gastrointestinal

- Symptoms common
- Motility
- Microbiome
- COVID persistence in GUT
- Post-antibiotic issues
- SIBO

Categories – Mast Cell Activation Disorder (MCAS)

- Management rests on histamine management and esp. on gut
  - mast cell CD117 responses and restriction of triggering agents
- Some gut microbes are histamine-triggering
- Wide range of triggers
  - Medications, temperature, food, stress etc
- Managing triggers helps
- Wide range of symptoms across body systems

(Bryarly 2019; Sumantri & Rengganis, 2023)

Pharmacological - MCAS

Histamine blockers

- H1 - sedating and non-sedating - Ketotifen
- H2 - famotidine and nizatidine
- Quercetin

Mast cell stabilising

- Sodium cromoglycate 200 to 300 mg taken before meals

Mediator inhibition

- Monteleukast, aspirin

(Sumantri & Rengganis, 2023)

Categories

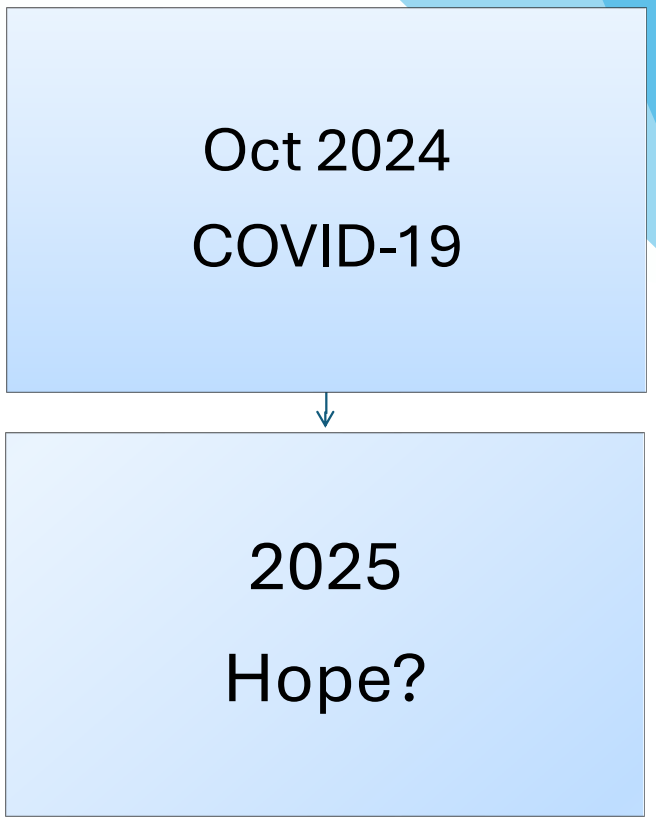
Persistent Infection	• Get the gut microbiome right with diet and probiotics • Antimicrobials for co-infection • Antiviral, antiparasitic, antifungal, antibacterial
Autoimmune	• Dietary management - gluten-free and milk-free trial, AI Diet Management of thyroiditis, esp Hashimotos use selenium 200 µg • Anti-inflammatories - Curcumin, omega 3s, NSAIDS
Metabolic/mitochondrial	• Manage pre-diabetes and metabolic syndrome • Consider mitochondrial support with ubiquinol 150 mg, B vitamin and magnesium, even methylene blue as trial of treatment • Caution over multiple sources of B6
Coagulopathy	• Dx is one of suspicion with d-dimer and fibrinogen markers • New imaging and testing (eg ophthalmology) • Anticoagulants may be indicated – specialist referral?- nattokinase, apixaban, etc

The weird and the wonderful...

- Nicotine patches (Leitzke, 2023)
- Ivermectin
- Metformin (Bramante et al, 2023)
- A wide range of peptides
- Be prepared for the “researchers”
- Methylcobalamin B12 high dose

Summary

- Make the diagnosis
- Provide education
- Give clear advice on avoidance of overexertion and teach pacing
- Patients want doctors to:
    1. validate their illness and acknowledge its impact
    2. provide ongoing support and monitor progress
- Goals:
    1. minimising or preventing PEM
    2. symptom relief
    3. improved quality of life



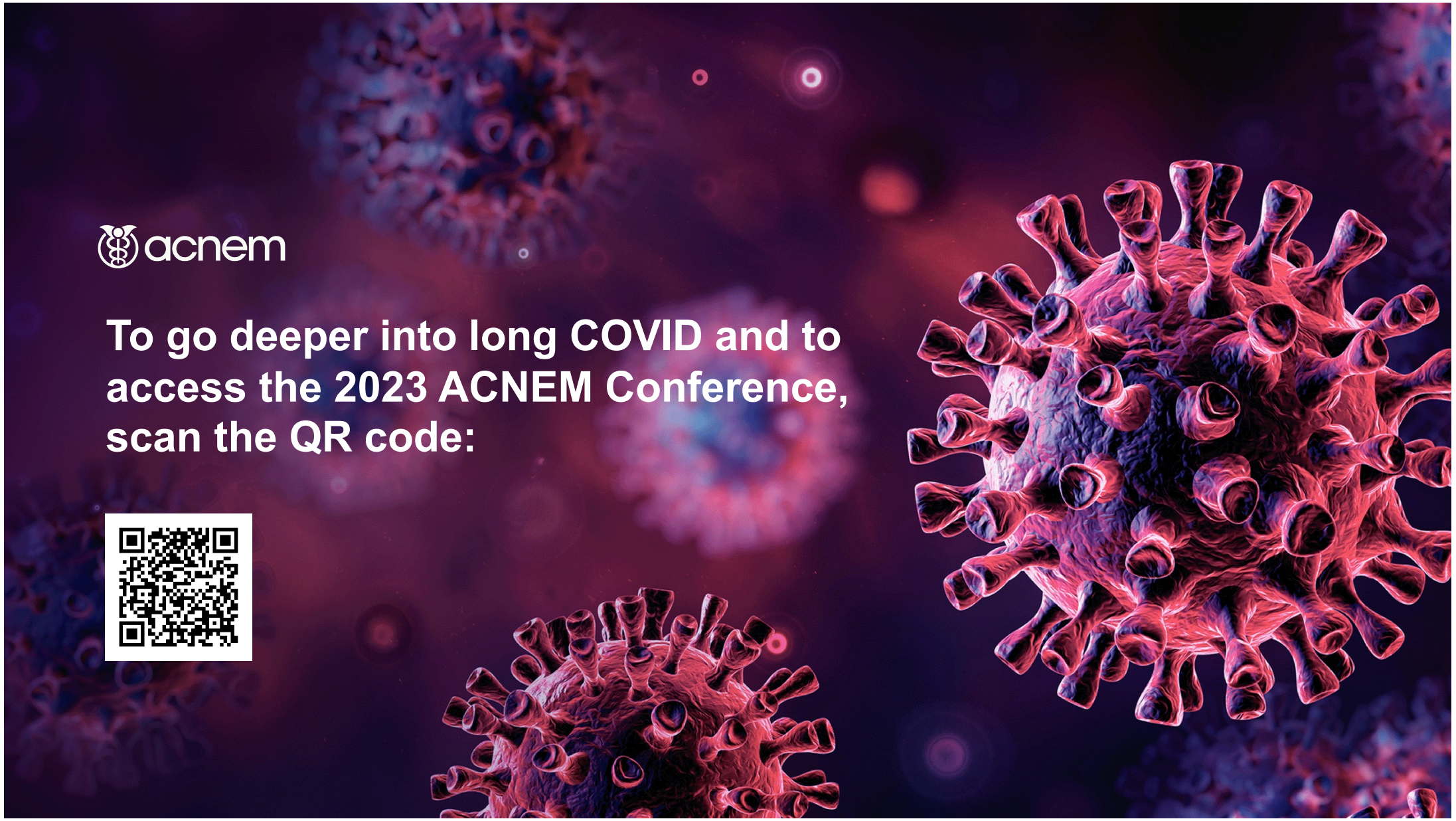
Additional resources

Emerge Australia can help your patients.

Emerge Australia offers a range of support through our patient support services.

We can help navigate topics that:

- Help in understanding the condition
- Explore social support options
- Help to prepare a strong DSP/NDIS application
- Support energy and activity management
- Aid in communicating healthcare requirements
- Connect people with their community
- Provide virtual community support services


acnem
To go deeper into long COVID and to access the 2023 ACNEM Conference, scan the QR code:

Resources

- Symptom severity and hierarchy chart:

https://emerge.org.au/wp-content/uploads/2023/04/symptomseverityhierarchyfromthinkgp.pdf

- NASA lean test:

https://emerge.org.au/wp-content/uploads/2023/04/nasa-lean-test-instructions.pdf

- Pacing fact sheet for patients:

https://emerge.org.au/wp-content/uploads/2023/11/Pacing-factsheet.pdf

- Energy management considerations for your practice:

https://emerge.org.au/wp-content/uploads/2024/06/MECFS-friendly-healthcare-practice-rebrand.pdf

References

Aitcheson, N., Lin, Z., & Tynan, K. (2023). Low-dose naltrexone in the treatment of fibromyalgia: A systematic review and narrative synthesis. *Australian journal of general practice*, *52*(4), 189–195. https://doi.org/10.31128/AJGP-09-22-6564

Appelman, B., Charlton, B.T., Goulding, R.P. *et al.* (2024). Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nat Commun* **15**(17) https://doi.org/10.1038/s41467-023-44432

Bateman, L. et al (2021). Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. Mayo Clinic Proceedings, Volume 96, Issue 11, 2861 – 2878. https://www.mayoclinicproceedings.org/action/showCitFormats?doi=10.1016%2Fj.mayocp.2021.07.004&pii=S0025-6196%2821%2900513-9

Bateman Horne Center. Low Dose Naltrexone (2024). https://batemanhornecenter.org/wp-content/uploads/2024/09/Low-Dose-Naltrexone-LDN-20240911.pdf

Baxter, H., Speight, N., & Weir, W. (2021). Life-Threatening Malnutrition in Very Severe ME/CFS. *Healthcare*, *9*(4), 459. https://doi.org/10.3390/healthcare9040459

Bramante et al. (2023). Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. T*he Lancet Infectious Diseases.* https://www.sciencedirect.com/science/article/pii/S1473309923002992?via%3Dihub

Bryarly, M, Phillips, L, Fu, Q. et al. (2019). Postural Orthostatic Tachycardia Syndrome: *JACC* Focus Seminar. *JACC*, 73 (10) 1207–1228.**https://doi.org/10.1016/j.jacc.2018.11.059**

Crosby, L.D., Kalanidhi, S., Bonilla, A. *et al.* (2021). Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole. *Journal of Translational Medicing,* **19**(50). https://doi.org/10.1186/s12967-021-02721-9

Davenport, T. E., Blitshteyn, S., Clague-Baker, N., Davies-Payne, D., Treisman, G. J., & Tyson, S. F. (2024). Long COVID Is Not a Functional Neurologic Disorder. *Journal of Personalized Medicine*, *14*(8), 799. https://doi.org/10.3390/jpm14080799

References

Davis, H.E., McCorkell, L., Vogel, J.M. *et al.* (2023). Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* **21**, 133–146 . https://doi.org/10.1038/s41579-022-00846-2

Day, H., Yellman, B., Hammer, S. et al. (2023). Cognitive impairment in post-acute sequelae COVID 19 and short term myalgic encephalomyelitis patients is mediated by orthostatic haemodynamic changes. Frontiers in Neuroscience. https://doi.org/10.3389/fnins.2023.1203514

Dunstan, R.H.(2023). High-demand amino acids could play an important role in supporting recover in medical practice. *ACNMEM*. https://www.acnem.org/wp-content/uploads/2024/06/acnem_Journal_DEC23_innovaate.pdf

Grach, S.L. et al. (2023). Diagnosis and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Mayo Clinic Proceedings*, Volume 98, Issue 10, 1544 – 1551. https://www.mayoclinicproceedings.org/article/S0025-6196(23)00402-0/fulltext

Day, H., Yellman, B., Hammer, S. et al. (2023). Cognitive impairment in post-acute sequelae COVID 19 and short term myalgic encephalomyelitis patients is mediated by orthostatic haemodynamic changes. *Frontiers in Neuroscience.* https://doi.org/10.3389/fnins.2023.1203514

Griffin, D.O. (2024). Postacute Sequelae of COVID (PASC or Long COVID): An Evidence-Based Approach. Open Forum Infectious Diseases. e (https://creativecommons.org/licenses/by/4.0/)

Joseph, P., et al. (2023). Exercise Pathophysiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Postacute Sequelae of SARS-CoV-2. *Chest*, 164(3), 717 – 726. https://journal.chestnet.org/article/S0012-3692(23)00502-0/fulltext

Leitzke M. (2023). Is the post-COVID-19 syndrome a severe impairment of acetylcholine-orchestrated neuromodulation that responds to nicotine administration?. *Bioelectronic medicine*, *9*(1), 2. https://doi.org/10.1186/s42234-023-00104-7

Montoya, J. G., Dowell, T. G., Mooney, A. E., Dimmock, M. E., & Chu, L. (2021). Caring for the Patient with Severe or Very Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Healthcare (Basel, Switzerland)*, *9*(10), 1331. https://doi.org/10.3390/healthcare9101331

National Academy of Medicine (NAM). (2015). Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. https://nap.nationalacademies.org/catalog/19012/beyond-myalgic-encephalomyelitischronic-fatigue-syndrome-redefining-an-illness

References

NICE. (2021). Myalgic encephalomyelitis/Chronic Fatigue Syndrome: diagnosis and management. LDN. https://www.nice.org.uk/guidance/ng206/chapter/Recommendations#managing-mecfs (Date accessed 12.11.2024).

Slater, M.A., et al. (2024). Fascia as a regulatory system in health and disease. Frontiers in Neurology. https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2024.1458385/full

Snapper, H., & Cheshire, W.P. (2022). Oral and intravenous hydration in the treatment of orthostatic hypotension and postural tachycardia syndrome. *Autonomic Neuroscience*. https://doi.org/10.1016/j.autneu.2022.102951

Sumantri, S., & Rengganis, I. (2023). Immunological dysfunction and mast cell activation syndrome in long COVID. *Asia Pacific allergy*, *13*(1), 50–53. https://doi.org/10.5415/apallergy.0000000000000022

Systrom, D. (2020). The exercise Response to pharmacologic cholinergic stimulation in myalgic Encephalomyelitis/chronic fatigue syndrome – detailed protocol. https://cdn.clinicaltrials.gov/large-docs/41/NCT03674541/Prot_SAP_000.pdf

Therapeutic Goods Administration. (2024). Naltrexone. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2024-PI-01545-1&d=20241201172310101

Therapeutic Goods Administration. (2024). Aripiprazole. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03820-3

Wells, R., & Tonkin, A. (2016). Clinical approach to autonomic dysfunction. *Internal Medicine Journal, 46(10), 1134-1139.* https://doi.org/10.1111/imj.13216