

Mestinon (pyridostigmine bromide) for aerobic capacity and nervous system improvements in POTS, OH, ME/CFS, Long Covid, FM and EDS

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Disclaimer:

The information in this leaflet is for informational purposes only. It does not substitute the need for professional medical advice or consultations with medical professionals. Always seek the advice of your doctor before starting a new medication or changing dosage.

Summary

- Mestinon (pyridostigmine bromide) is most often used to treat Myasthenia Gravis.
- It is used 'off-label' in Postural Tachycardia Syndrome (POTS), Orthostatic Hypotension, Myalgic Encephalomyelitis /Chronic Fatigue Syndrome (ME/CFS), long Covid related post-viral fatigue syndrome, Fibromyalgia (FM), and Ehlers-Danlos Syndrome (EDS) to improve aerobic capacity and balance the autonomic nervous system (ANS).
- Mestinon is an acetylcholinesterase inhibitor that prevents the acetylcholinesterase enzyme from breaking down a neurotransmitter called **acetylcholine**. Mestinon is also classified as a parasympathomimetic – a drug that enhances parasympathetic nervous system activity. Mestinon can also enhance the production of other neurotransmitters such as norepinephrine and dopamine.
- **Acetylcholine** is the chief neurotransmitter of the parasympathetic nervous or “rest and digest” system, (also called the cholinergic nervous system) and acts as a neuromodulator. It produces manifold effects including enhancing muscle contractions during exercise, dilating the blood vessels, slowing the heart rate, enhancing neuroplasticity, boosting motivation, increasing pleasurable feelings, helping arouse one to action, and enhancing productivity and task completion.
- For people with ME/CFS, initial dosage starts at 15mg and is slowly titrated upward to 60mg 3 times per day. It may take months to work and will not help everyone.
- It has a good safety profile but can cause several side effects.
- Case studies, and limited published research, report improvements particularly relating to fatigue, muscle strength and mental clarity.

The Open Medicine Foundation's LIFT trial is currently assessing Mestinon and low-dose naltrexone (LDN) – the two top medications from its treatment survey– both separately and in combination.

ME/CFS expert Clinicians, such as Dr Ric Arseneau, Clinical Professor, University of British Columbia, prescribe Mestinon for ME/CFS.

- Possible Mechanism:
By triggering the release of norepinephrine, Mestinon may be causing the veins to properly narrow, thus propelling blood back up to the heart and giving the muscles more blood. Retrospective studies suggest that pyridostigmine for ME/CFS can improve oxygen uptake, end-tidal carbon dioxide levels, and ventilatory efficiency.

Finding a way to boost the peripheral nervous system (PNS) by increasing acetylcholine levels could conceivably help with fatigue, gut, sleep, cognitive, stimuli hypersensitivity, and emotional lability issues.

Prescription Guidelines

Form

- 60mg Tablet
- 180mg Sustained Release (SR) – does not appear to be available in New Zealand

Dose guidelines

Source: Ric Arseneau, Clinical Professor, University of British Columbia

Starting dose:

- 15mg (1/4 tablet) in the morning. For those sensitive to medication consider 10mg. Take with food.

Adjusting the dose:

- Increase by 15 mg (¼ tablet) every few days
 - 15 mg (¼ tab) 3x a daily
 - 30 mg (½ tab) 3x a daily
 - 45 mg (¾ tab) 3x a daily
 - 60 mg (1 tab) 3x a daily
- The **target dose** is 60 mg 3x a daily
 - You may get benefit at a lower dose
 - Don't continue increasing if you get side effects
- Some patients may benefit from a higher dose, particularly those with POTS.
 - Switch from 60 mg 3x a day to 180 SR (sustained release) in the morning
 - Then you would add
 - Add 15 mg (¼ tab) 3x a daily
 - Increase by 15 mg (¼ tablet) at time every few days
 - If you get to 60 mg 3x a day you can switch to 180 mg SR in the evening (for a total dose of 180 mg SR twice a day)
- Few patients need more than this

Coming off the medication:

You will need to taper off.

Possible Side Effects

Patients rarely experience side effects, but the most common are:

- GI upset (e.g., upset stomach, nausea, vomiting)
- Diarrhea
- Abdominal pain
- Frequent urination
- Drooling
- Cold sweats
- Blurred vision / watery eyes
- Anxiety
- Muscle weakness

Contraindications – who shouldn't take it

- Asthma
- Heart disease
- Parkinson's
- Seizures
- Kidney disease
- Enlarged prostate

Research and clinical guidelines

- **Medication Handout – Mestinon (pyridostigmine)**
Ric Arseneau, MD FRCPC MA(Ed) MBA FACP CGP, Clinical Professor, The University of British Columbia
[https://www.dropbox.com/scl/fo/bcijh5x8xt3qqppklb2i/AHbFdXfdoYuvQ7mUs5gydW4?e=2&preview=Mestinon+\(pyridostigmine\).pdf&rlkey=ywp9ye2fmdoyox4lik28vrj2a&st=iyq9fjfh&dl=0](https://www.dropbox.com/scl/fo/bcijh5x8xt3qqppklb2i/AHbFdXfdoYuvQ7mUs5gydW4?e=2&preview=Mestinon+(pyridostigmine).pdf&rlkey=ywp9ye2fmdoyox4lik28vrj2a&st=iyq9fjfh&dl=0)
- **POTS Mestinon study: Acetylcholinesterase Inhibition Improves Tachycardia in Postural Tachycardia Syndrome**
Satish R Raj et al, 2005, Circulation
<https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.104.497594>
Conclusions: “Acute acetylcholinesterase inhibition significantly attenuated tachycardia in POTS. There was also an improvement in symptom burden with this promising therapy.”
Drug dosage: 30mg Pyridostigmine given orally.
- **Efficacy of a half dose of oral pyridostigmine in the treatment of chronic fatigue syndrome: three case reports**
Yasuo Kawamura et al, 2003, Pathophysiology
<https://pubmed.ncbi.nlm.nih.gov/14567934/>
Conclusions: These three cases generate the hypothesis that the fatigue in some patients with clinical CFS might be due to a combination of mild neuromuscular transmission defect combined with cholinergic dysautonomia. Support for this thesis derives from the improvement with cholinesterase inhibition.
Case 1: Oral pyridostigmine therapy (30 mg) resulted in marked improvement in symptoms.
Case 2: This patient responded dramatically to 10-mg pyridostigmine.

Case 3: Patient responded to 30-mg pyridostigmine with an improvement in her fatigue.

- **Neurovascular Dysregulation and Acute Exercise Intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome A Randomized, Placebo-Controlled Trial of Pyridostigmine**

Phillip Joseph et al, 2022, Chest Journal

[https://journal.chestnet.org/article/S0012-3692\(22\)00890-X/abstract](https://journal.chestnet.org/article/S0012-3692(22)00890-X/abstract)

See blog about this study in Other Information section below.

Interpretation: Pyridostigmine improves peak VO₂ in ME/CFS by increasing cardiac output and right ventricular filling pressures. Worsening peak exercise VO₂, cardiac output, and right atrial pressure following placebo may signal the onset of postexertional malaise. We suggest that treatable neurovascular dysregulation underlies acute exercise intolerance in ME/CFS.

- **Pyridostigmine in the treatment of postural orthostatic tachycardia: a single-center experience**

Khalil Kanjwal et al, 2011, PACE

<https://pubmed.ncbi.nlm.nih.gov/21410722/>

“The overall efficacy of pyridostigmine in our study was seen in 42% of total patients or 52% of patients who could tolerate taking the drug.”

Conclusion: The subgroup of POTS patients who can tolerate oral pyridostigmine may demonstrate improvement in their standing HR, standing diastolic blood pressure, and clinical symptoms of orthostatic intolerance.

- **POTS (Single patient study trailing treatments including pyridostigmine)**

Satish R. Raj, 2013, Circulation

<https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.112.144501>

“Pyridostigmine is a peripheral acetylcholinesterase inhibitor that can increase the levels of synaptic acetylcholine at both the autonomic ganglia and peripheral muscarinic parasympathetic receptors. Pyridostigmine 30 to 60 mg orally 3 times a day has been reported to result in long-term symptom improvement in ≈50% of POTS patients. Pyridostigmine can enhance bowel motility; thus, gastrointestinal adverse events are the most common reason for discontinuation of the drug.”

Conclusion: POTS is a disorder of the autonomic nervous system that can produce substantial disability among previously healthy people. Patients with POTS demonstrate an HR increase of ≥30 bpm within 10 minutes of standing (or higher in children), are often hyperadrenergic, and tend to have a low blood volume. Therapies targeting the hypovolemia and the excess sympathetic nervous system activation may help relieve symptoms.

- **Concise Review for Clinicians: Diagnosis and Management of ME/CFS**

Stephanie L. Grach et al, 2023, Mayo Clinical Proceedings

[https://www.mayoclinicproceedings.org/article/S0025-6196\(23\)00402-0/fulltext](https://www.mayoclinicproceedings.org/article/S0025-6196(23)00402-0/fulltext)

Table ‘Management considerations’ includes a recommendation for pyridostigmine for orthostatic intolerance.

“Regarding ME/CFS-specific therapies, studies suggest a benefit in particular from low-dose forms of medications such as pyridostigmine... for fatigue.”

Other Information

- **Pyridostigmine Bromide**
New Zealand Formulary, NZF v145-01 01 Jul 2024. https://nzf.org.nz/nzf_5713
- <https://www.medsafe.govt.nz/profs/datasheet/m/Mestinontab.pdf>
- <https://www.medsafe.govt.nz/consumers/cmi/m/mestinon.pdf>
- **Lifting ME/CFS: The OMF's Unique Two-Drug Clinical Trial to Begin Soon**
Cort Johnson, 2024, HealthRising blog
<https://www.healthrising.org/blog/2023/11/12/lift-open-medicine-foundation-chronic-fatigue-syndrome/>
- **The Life Improvement Trial (LIFT) announcement**
Open Medicine Foundation, Nov 2023 <https://www.omf.ngo/lift-trial/>

“The LIFT is a randomized, double-blind placebo trial that will investigate two particular drugs: Pyridostigmine (commonly known as Mestinon) and low-dose naltrexone (LDN) separately and together as a combination.”

“In a self-reported patient treatment survey, involving over 3,800 ME/CFS and Long COVID patients, these drugs showed significant benefits. Now, our LIFT trial seeks to scientifically validate these findings by testing the safety and efficacy of these treatments so that others may be able to benefit from these treatments as well.”

“The primary focus? To assess the effectiveness of these drugs in reducing symptoms like brain fog, fatigue, post-exertional malaise, and postural orthostatic tachycardia syndrome (POTS).”
- **Mestinon moves the needle on ME/CFS in unusual one-shot exercise study**
Cort Johnson, 2022, HealthRising blog
<https://www.healthrising.org/blog/2022/05/29/mestinon-chronic-fatigue-syndrome-exercise/>

Conclusion: The first exercise test resulted in increased energy consumption during the rest period, and reduced energy production (peak VO₂, cardiac output) during the second exercise test. All the patients also demonstrated “ventilatory inefficiency”; i.e. a potentially harmful reduction in CO₂ levels caused by hyperventilation.

The trial succeeded in demonstrating that blood vessel issues affecting the veins are impairing energy production in ME/CFS, and can be improved with a drug. While the effect size was not large (i.e. the improvements did not meet “clinical significance”), this unusual one-shot drug trial didn't appear to be designed to do that.

Instead, the study showed that the drug has the potential to move the needle biologically in people with ME/CFS; it turned off the “energy drain” seen during the rest period, and improved peak energy production and cardiac output during the second test. Conference reports suggest that long-term use of Mestinon may be able to actually increase aerobic capacity in ME/CFS.

Mestinon was never expected to be a cure-all drug. It may not be able to affect other problems such as the shunting of blood away from the muscles, mitochondrial problems, and hyperventilation that appear to be spread across the ME/CFS population. It may be most helpful in a large subset of the ME/CFS population who have problems constricting the veins in their legs, and thus have reduced blood flows to the heart and the reduction in energy production that goes along with that. (continued...)
- **A Mestinon Miracle: Vagus Nerve Stimulating Drug Helps Long Time ME/CFS Patient Exercise**

Cort Johnson, 2016, HealthRising blog

<https://www.healthrising.org/blog/2016/06/17/mestinon-chronic-fatigue-vagus-nerve-stimulation-exercise/>

Conclusion: The short history of Mestinon use in ME/CFS, FM and orthostatic intolerance has had mixed results. Mestinon did very well for our patient and in the three case reports from the Japanese. It's apparently one of the few drugs that can significantly impact fatigue and exercise in the right person. It can also help with sleep and autonomic functioning – as our case report of a patient indicated. It may also be able to impact mood. (continued...)

- **Mestinon for Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia, POTS, and Long COVID**

Cort Johnson, not dated, HealthRising Drug summary

<https://healthrising.org/treating-chronic-fatigue-syndrome/drugs/mestinon-for-chronic-fatigue-syndrome-me-cfs-fibromyalgia-pots-and-long-covid/>

“Many heart rate variability (HRV) studies indicate that the parasympathetic arm of the autonomic nervous system (PNS) has become inhibited and is no longer keeping the sympathetic nervous system (SNS) or “fight or flight” arm of the ANS in check in ME/CFS, fibromyalgia and POTS. Mestinon may also be able to increase growth hormone levels in these diseases.”

“David Systrom – the foremost proponent of pyridostigmine bromide in ME/CFS – believes that by triggering the release of norepinephrine, Mestinon is causing the veins to properly narrow, thus propelling blood back up to the heart and giving the muscles more blood. He notes that retrospective studies – studies done after the fact – suggest that pyridostigmine for ME/CFS can improve oxygen uptake, end-tidal carbon dioxide levels, and ventilatory efficiency.”

“Finding a way to boost the PNS by increasing acetylcholine levels could conceivably help with fatigue, gut, sleep, cognitive, stimuli hypersensitivity, and emotional lability issues.”

- **Dr David Systrom Discusses Mestinon Clinical Trial, Mitochondrial Dysfunction in ME/CFS, and More!** Video, 2022, 42 minutes

<https://youtu.be/6SBZAB7VnVE?si=wuA2l02d3Hec53DU>

- **Treatments Explored to Ease Post-Viral Symptoms of ME/CFS and Long COVID**

Miriam E. Tucker, Medscape, 2022

<https://www.medscape.com/viewarticle/978707?form=fpf>

See section ‘Pyridostigmine (Mestinon, Others)’

- **ME-pedia Webpage:**

Curated information from the ME/CFS community.

<https://me-pedia.org/wiki/Mestinon>