Chronic Fatigue Syndrome | Myalgic Encephalomyelitis – Neurobiology | Diagnosis | Management

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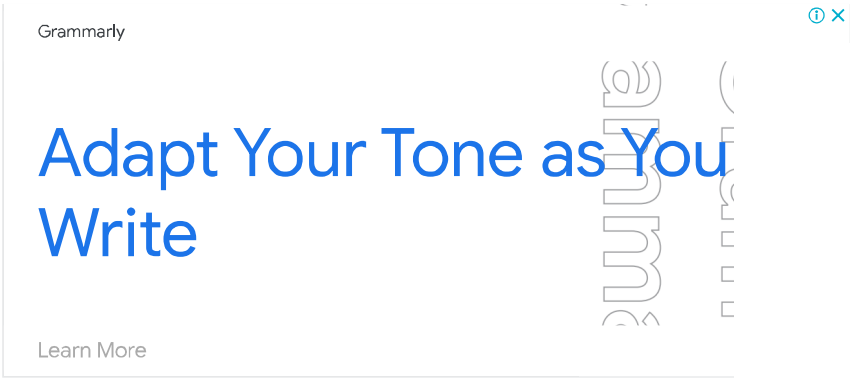
Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) is a disabling and complex clinical condition characterised by unexplained and persistent post-exertional fatigue along with cognitive, immunological, endocrinological and autonomic dysfunction.

There is an overlap between Long Covid and CFS / ME symptomatology.



There have been several consensus research and clinical definitions to describe CFS; e.g. Fukuda, Holmes, International Consensus Criteria (ICC), Oxford, Canadian Consensus Criteria (CCC), Australian, Ramsay and Systemic Exertion Intolerance Disease (SEID).

Researchers have extensively used the Fukuda CFS case definition for the past two decades. [Fukuda et al., 1994]

One of the limitations of the Fukuda criteria is that some individuals who meet the criteria do not have core symptoms of the illness, such as post-exertional malaise, unrefreshing sleep, or memory/concentration problems. Its use is also prone to misdiagnosis or overdiagnosis.

On the other hand, the Canadian ME/CFS criteria identify a smaller subset of patients with more severe functional impairment and post-exertional malaise symptoms. [Carruthers et al., 2003], [Jason et al., 2014]

EPIDEMIOLOGY OF CFS / ME

- Prevalence : 0.004% to 2.54%. The differences in prevalence may be due to the various consensus criteria used in the diagnosis.
- The annual incidence of CFS is 370/100,000, and the prevalence is 740/100,000 individuals in a study in Scotland. [Lawrie et al., 1997]
- It occurs in all ages
- No specific ethnic preponderance
- Women to male ratio = 2:1
- 70% of chronic fatigue syndrome patients are middle-aged women.
- The median duration of the illness is approximately seven years with a variable prognosis.
- Cancer and cardiovascular abnormalities are the most common causes of death in individuals with ME and CFS.

Recovery: [Cairns & Hotopf, 2005]

- 5% of patients recover completely
- 40% of patients improve during follow up.
- 8-30% return to work.
- 5-20% report worsening of symptoms.

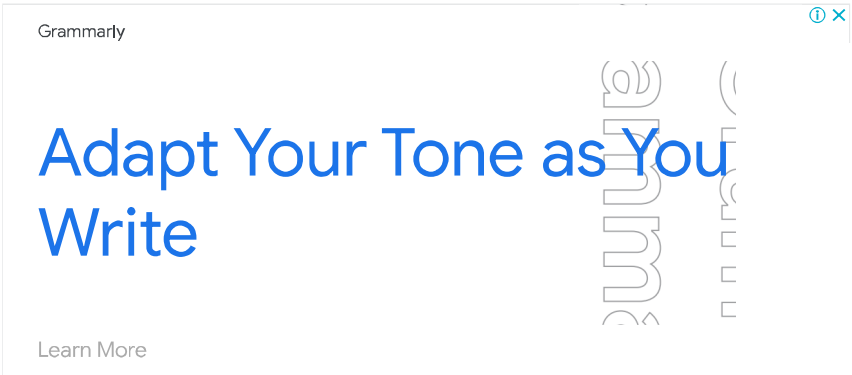
Economic costs:

- Estimated between 18-24 billion USD in the US. In Australia, the healthcare-related expenditure and associated income loss for ME/CFS were estimated at $14.5 billion. [Close et al., 2020]

HISTORY OF CHRONIC FATIGUE SYNDROME (CFS) / MYALGIC ENCEPHALOMYELITIS (ME)

In 1934, a series of outbreaks of a previously unknown illness were recorded worldwide, which was initially confused with poliomyelitis but was eventually differentiated and became known as "*epidemic neuromyasthenia*". [Parish, 1978]

Another outbreak occurred in Akureyri, Iceland, in 1946; the disease came to be called "*Akureyri Disease*", or Icelandic disease, through much of the 1940s and 1950s.



In 1955, a similar outbreak in Royal Free hospital in London with 55 nurses, doctors, assistants, and other health personnel hospitalised with a series of symptoms after an upper airway infection before the onset of disease.

This condition was also associated with gastrointestinal ulceration, acute vertigo, sore throat, severe headache, nuchal pain, pain in the limbs, extreme lassitude, and paraesthesia. [BMJ, 1957]

The term *"benign myalgic encephalomyelitis"* was chosen for the outbreak.

The World Health Organisation recognised ME in 1969.

In 1970, two psychiatrists in the United Kingdom reviewed the reports of 15 outbreaks of benign myalgic encephalomyelitis and concluded that these outbreaks: [McEvedy et al., 1970]

> *Were psychosocial phenomena caused by one of two mechanisms, either mass hysteria on the part of the patients or altered medical perception of the community.*

This was reinforced by the European Psychiatric Society, who proposed myalgic encephalomyelitis was a psychosocial phenomenon caused by mass hysteria.

The above findings were refuted by Dr Melvin Ramsay, who then proposed the first diagnostic criteria for CFS. [Ramsay, 1988]

In 1987, the Centers for Disease Control and Prevention (CDC) convened a working group to reach a consensus on the clinical features of the illness. The first definition of CFS was published in 1988.

In 1994 Fukuda proposed a clinical and investigative protocol to be created in a comprehensive and integrated approach to study ME.

DIAGNOSTIC CRITERIA FOR CHRONIC FATIGUE SYNDROME (CFS) / MYALGIC ENCEPHALOMYELITIS (ME)

A recent review of case definitions highlighted the complexity and confusion around diagnosis, affecting prevalence rates depending on the diagnostic criteria used. [Lim & Son 2020]

The review focused on commonly used 8 case definitions: Ramsay, International Consensus Criteria (ICC), Holmes, Australian, Oxford, Fukuda, Canadian Consensus Criteria (CCC), Revised Canadian Consensus Criteria and Systemic Exertion Intolerance Disease (SEID).

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The 8 definitions have 30 symptoms in the inclusion criteria that can be subcategorized into five groups: 9 neurologic, 6 neurocognitive, 2 neuroendocrine, 5 autonomic, and 7 immunologic symptoms.

- The ICC, CCC, Holmes, and Fukuda need 4 to 8 symptoms to meet the criteria
- The ME (Ramsay, ICC) and ME/CFS (CCC) involve all five subcategories
- CFS definitions (Holmes, Australian, Oxford, and Fukuda) cover mainly the neurologic and neurocognitive symptoms.

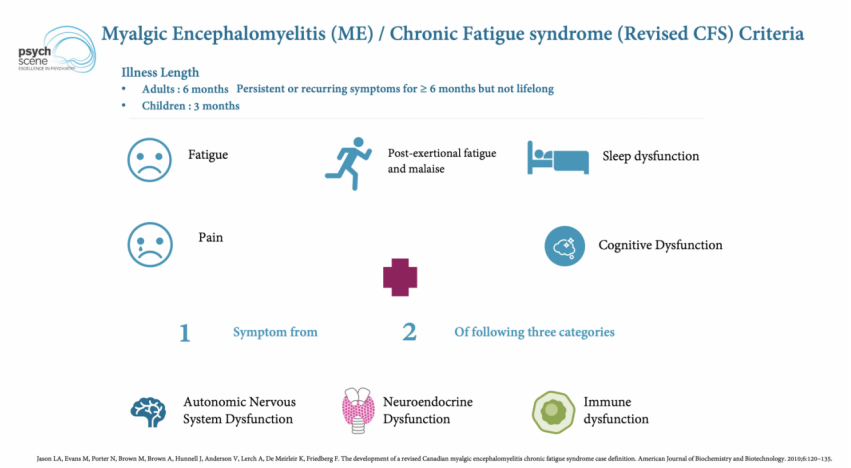
Exclusion criteria:

- CFS, ME/CFS, and SEID definitions recognised depression and anxiety as possible symptoms or comorbidities of the illness
- ME (Ramsay, ICC) criteria considered those symptoms as exclusions

In 2010, Jason and colleagues revised the CCC and provided explicit rules for applying this case definition, including a questionnaire for assessing symptoms. The Revised CCC was intended to better operationalize the CCC. [Jason et al, 2010]

The CCC requires only the presence of a symptom to count toward a diagnosis, whereas the Revised CCC specifies that minimum levels of frequency and severity be present for a symptom to count toward a diagnosis. Fewer patients meet the criteria for ME/CFS under the Revised CCC than do so under the CCC or the Fukuda definition.

This article will focus on the Revised Canadian Consensus Criteria, mainly due to its better specificity and inclusion of other organic conditions in the diagnosis. It also can differentiate between chronic fatigue syndrome and depression as a cause of fatigue. [Bested & Marshall, 2015]



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The Revised Canadian Consensus Criteria

1. Fatigue.
2. Post-exertional fatigue and malaise.
3. Sleep dysfunction.
4. Pain.
5. Cognitive dysfunction.

At least one symptom from two of the three following categories:

- Autonomic nervous system dysfunction
- Neuroendocrine dysfunction
- Immune dysfunction

NEUROBIOLOGY | PATHOPHYSIOLOGY OF CFS / ME

Genetics: [Albright et al., 2011]

- Female gender is a predisposing factor.
- Increased relative risk among first-degree relatives (2.70), second-degree relatives (2.35), and third-degree relatives (1.93).
- Higher concordance in monozygotic twins (55%) compared to dizygotic twins(19%).
- 21 SNP's were significantly associated with ME/CFS compared with depressed to normal groups. [Shimosako & Kerr, 2014]

2. Infections: [Bested & Marshall, 2015]

- Approximately 50–80% of patients with ME/CFS start suddenly with a flu-like illness.
- CFS / ME occur in 11% of people with severe infections: Epstein Barr Virus, non-EBV associated glandular fever, Ross River Virus, Giardia Lamblia, Parvovirus, B19 and Q fever.
- Prodromal infections include sinusitis, bronchitis, gastroenteritis, flu-like illness or parasites, e.g. Giardiasis.

3. Trauma:

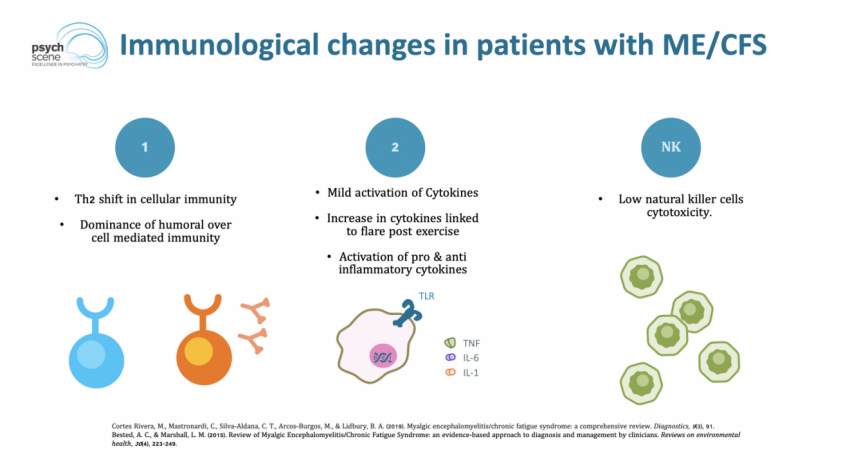
- Around 50% of patients with CFS report at least one type of childhood trauma. [Tomas et al., 2013]
- Trauma is linked to HPA axis dysfunction and may explain the link between childhood trauma and CFS.

Read more about the impact of stress on the HPA axis.

Read more about the Neurobiology of PTSD.

- Chronic stress or trauma is associated with hypocortisolism, a biological marker of developmental risk for CFS rather than a correlate of the disorder itself.
- CFS may thus be conceptualised as a disorder of adaptation promoted by early environmental insults with a subsequent failure to compensate for these insults via HPA axis dysfunction (negative feedback, unopposed NE release via hypocortisolism).

4. Systemic Inflammation / Immunological Changes:



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An imbalance between TH1 and TH2 immunity.

- T helper cells play an important role as part of the body's immune system.
- TH1 is responsible for cellular immunity with TH2 cells in humoral immunity (Antibody-mediated).
- There is a TH2 shift in cellular immunity with greater dominance of humoral immunity, resulting in antibodies that may be linked to new allergies, medication or multiple chemical sensitivity.

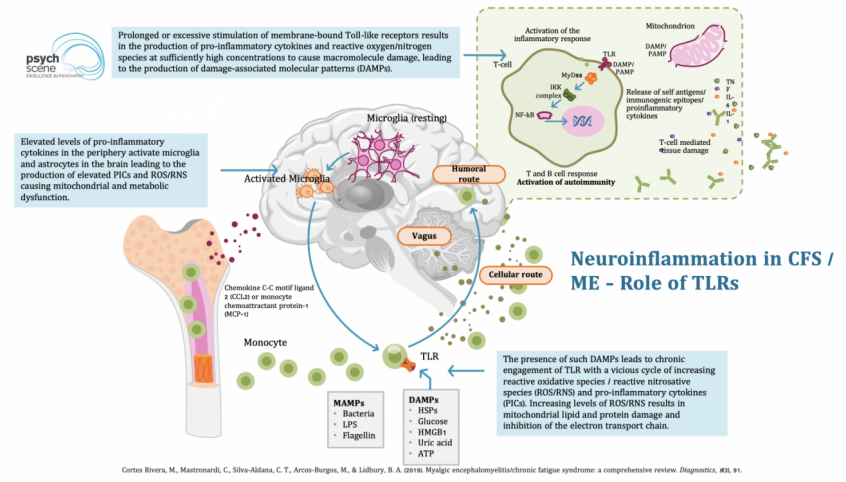
Low natural killer cells cytotoxicity.

- NK cells are part of the innate immune system and provide surveillance against tumour cells and infections.
- Patients with ME/CFS have poorly functioning NK cells.
- The poor NK function correlates with the severity of the illness and disturbs cognitive function.

Activation of cytokines:

- Increased cytokines post-exercise.
- Fatigue severity significantly correlated with inflammation
- Elevated adipokine levels
- Prominent activation and pro and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks.
- Increased bacterial translocation sustained by the leaky gut theory of increased IgA levels against lipopolysaccharides (LPS) of Gram-negative bacteria

5. Neuroinflammation:



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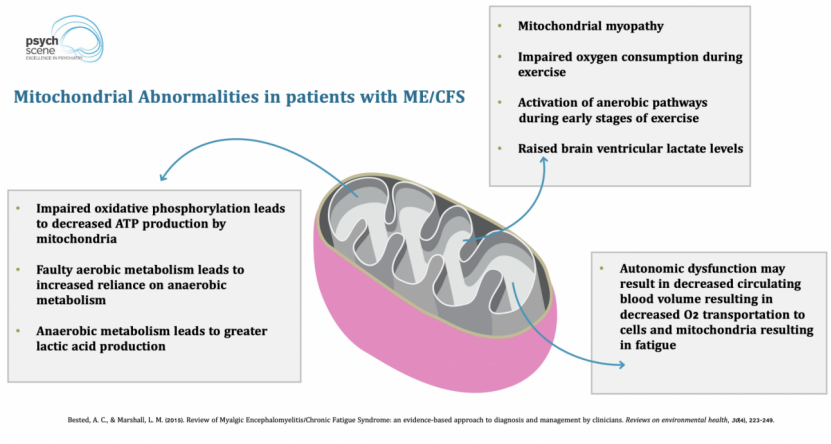
- Prolonged or excessive stimulation of membrane-bound Toll-like receptors (TLR) results in the production of pro-inflammatory cytokines and reactive oxygen/nitrogen species (ROS / RNS) at sufficiently high concentrations to cause macromolecule damage leading to the production of damage-associated molecular patterns (DAMPs).
- Such DAMPs lead to chronic engagement of TLR with a vicious cycle of increasing reactive oxidative species / reactive nitrosative species (ROS/RNS) and pro-inflammatory cytokines (PICs). Increasing ROS/RNS results in mitochondrial lipid and protein damage and inhibition of the electron transport chain.
- Elevated pro-inflammatory cytokines in the periphery activate microglia and astrocytes in the brain, leading to elevated PICs and ROS/RNS, causing mitochondrial and metabolic dysfunction.
- Glial activation due to systemic inflammation may be one of the causes of chronic pain in patients with ME/CFS involving pathological processes of allodynia and hyperalgesia via the impact of bidirectional neural glial signalling.

Learn more about neuroinflammation in this video – Neuroinflammation Simplified.

6. Autoimmune Activation:

- B cell impairment resulting in the possibility of increased autoantibody production.
- Associated with autoimmune disorders such as hyperthyroidism, Sjogren's disease
- Presence of Antinuclear antibodies, Rheumatoid factor and thyroid antibodies.
- Antibodies also found to viruses, Epstein Barr Virus, Cytomegalovirus, Human Herpes Virus, Parvovirus, etc.

7. Mitochondrial Abnormalities:



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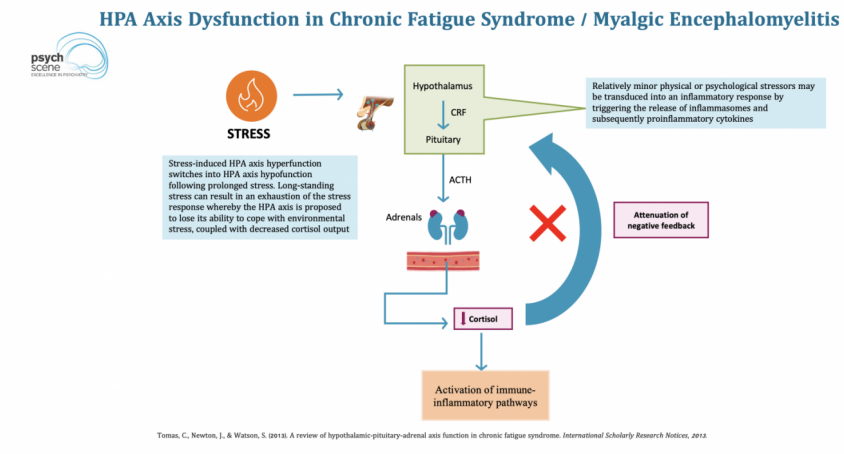
- Mitochondrial myopathy
- Impaired oxygen consumption during exercise
- Activation of anaerobic metabolic pathways in the early stages of exercise and raised brain ventricular lactate levels.
- In some patients with ME/CFS, mitochondria may be functioning normally but with low mitochondrial ATP (due to the brain's autonomic dysfunction), resulting in decreased circulating blood volume and decreased transportation of oxygen to the cells resulting in fatigue.

8. HPA Axis dysfunction



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- Enhanced corticosteroid-induced negative feedback
- Basal hypocortisolism
- Attenuated diurnal variation
- Blunted DHEA response to ACTH injection.
- It has been hypothesised that the HPA axis dysfunctions in ME/CFS are similar to dysfunctions in prolonged critical illness. [Stanculescu et al., 2021]

9. Neuroendocrine Dysregulation:

- Low Insulin Growth Factor (IGF), also known as somatomedin levels
- Exaggerated growth hormone response to pyridostigmine.
- Increased prolactin response to buspirone could reflect changes in dopamine function via buspirone's effect on postsynaptic 5HT1A receptors.
- Disturbance of fluid metabolism, evidenced by low baseline levels of arginine vasopressin and aldosterone in patients compared to controls.
- Raised neuropeptide Y correlated with the severity of symptoms and is proposed as a biomarker to distinguish subsets of CFS. [Fletcher et al., 2010]
- ME/CFS patients had similar TSH levels as controls, but lower Free T3, Total T4, and Total T3, which the authors suggest resembles N*on-thyroidal Illness Syndrome* (NTIS), also called *euthyroid sick syndrome* or *low T3 syndrome*; a feature that also occurs in critically ill patients in ICU. [Stanculescu et al., 2021]

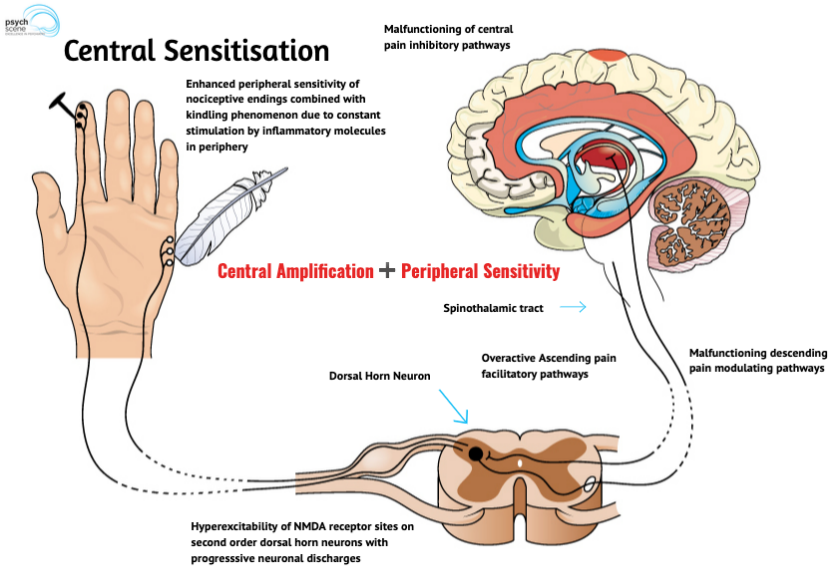
10. An imbalance between aerobic and anaerobic metabolism :

- May explain post-exertional malaise and fatigue.
- The aerobic oxidative system is a primary source of energy during physical activities lasting longer than 90 seconds. However, due to the disturbed aerobic metabolism in individuals with CFS, the anaerobic metabolism pathways take precedence, resulting in less energy, lactic acid production, and a disturbance of ATP/ADP metabolic cycling.

11. Central Neuronal Sensitisation:

- Central sensitisation is characteristic of neuropathic pain, manifested as an exaggerated response to noxious stimuli, reduced threshold for pain and spread sensitivity around the innervation territory of the injured nerve.
- Constant stimulation of inflammatory molecules affects peripheral sensitivity to further non-noxious stimuli.

- Sensitised neurons may continue to fire after the initial stimulation has ceased in a phenomenon known as kindling. Thus, an insidious peripheral, central neurogenic sensitisation loop takes place resulting in the maintenance of symptoms.



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12. EEG changes:

- EEG shows widespread cortical hypoactivation, demonstrated by increased delta and decreased beta frequency bands which explain cognitive dysfunction.
- Peak alpha frequency, a measure of cognitive vigilance, is reduced in 58% of the cortex in CFS patients than controls and is negatively correlated to fatigue. It is also linked to the clinical symptom of brain fog. [Bested and Marshall, 2015], [Zinn et al., 2018]

13. Sleep dysfunction:

- Decreased sleep efficiency.
- Decreased total sleep time.
- Reduced time spent in deep restorative delta wave sleep.
- Multiple arousals with alpha wave intrusions during sleep.
- 20% of patients with ME/CFS may have a primary sleep disorder.

14. Autonomic dysfunction:

- Heart rate variability is abnormal in patients with ME/CFS.
- Benign cardiac rhythm disturbances, non-specific T-wave changes, repetitive oscillating T-wave inversions, and flat T-waves media were identified.
- Low blood volume related to orthostatic symptoms.
- Ehlers-Danlos Syndrome and joint hypermobility are higher in ME/CFS patients, associated with orthostatic tolerance.

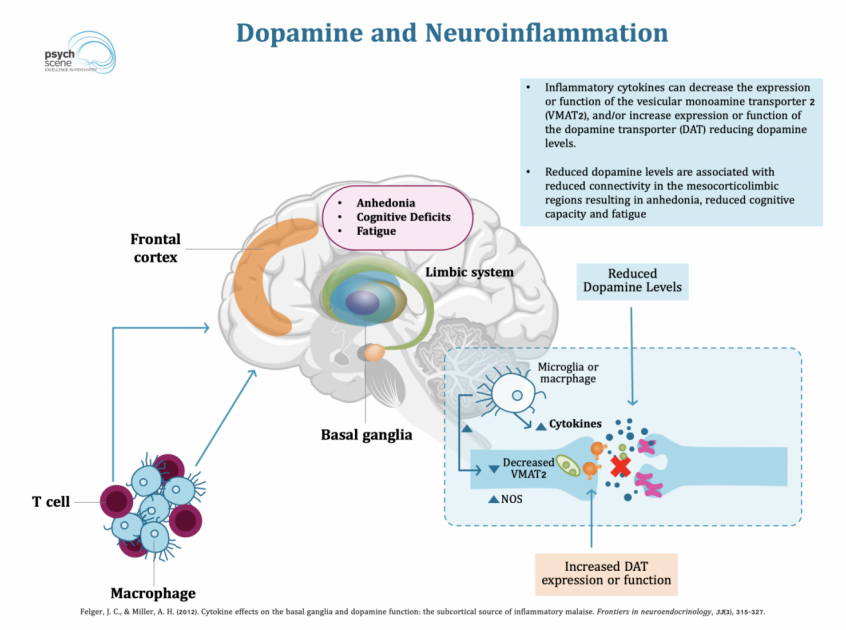
15. Alterations in serotonin transmission:

- The 5HT1A receptor activation is a critical contributor to central fatigue. [Kavanagh et al., 2019]
- Central fatigue correlates with increased levels of 5HT and its metabolites in the CNS.

16. Alterations in dopamine metabolism:

- Inflammatory cytokines can decrease the expression or function of the vesicular monoamine transporter 2 (VMAT2) and/or increase the expression or function of the dopamine transporter (DAT), reducing dopamine levels. [Felger & Miller, 2012]
- In individuals with higher baseline CRP levels, Bupropion plus SSRI was more effective than SSRI alone. [Towards personalising depression treatment]
- Dopamine plays an important role in cognition, motivation and hedonic capacity.

- According to the dopamine imbalance hypothesis, fatigue is also associated with reduced connectivity between the regions innervated with dopamine, i.e. the mesocorticolimbic pathways, possibly due to reduced dopamine levels. This connectivity is improved after administration of dopaminergic medication (methylphenidate and bromocriptine) and treat fatigue. [Dobryakova et al., 2015]
- According to the hypothesis, fatigue might occur when there is too much or too little dopamine. i.e. an inverted U shaped curve. [We covered a similar effect on cognition was covered in the diagnosis and management of ADHD with too much dopamine impairing cognition and too little associated with symptoms of ADHD]



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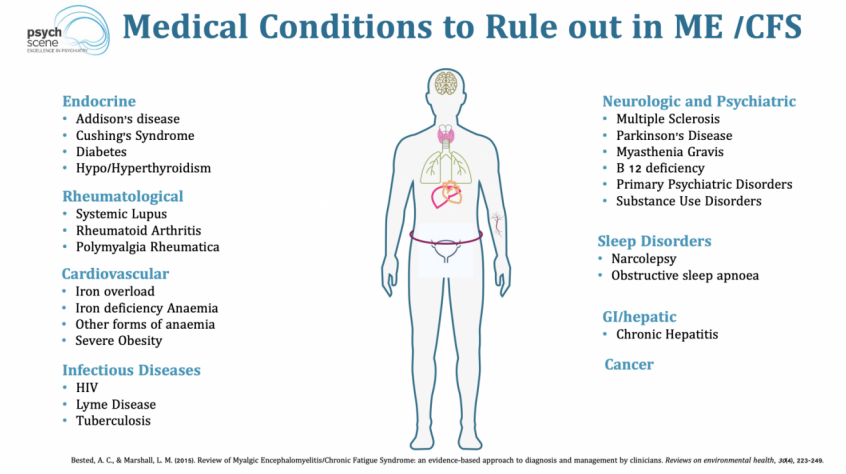
CLINICAL EVALUATION OF CHRONIC FATIGUE SYNDROME / MYALGIC ENCEPHALOMYELITIS

There are three key steps in the evaluation of CFS /ME

1. Ruling out organic causes
2. Treating comorbid conditions
3. Diagnosis of CFS based on consensus criteria

1. Ruling out organic causes:

Fatigue, sleep disturbance, cognitive disturbance and pain may be caused by several medical conditions outlined in the table below.



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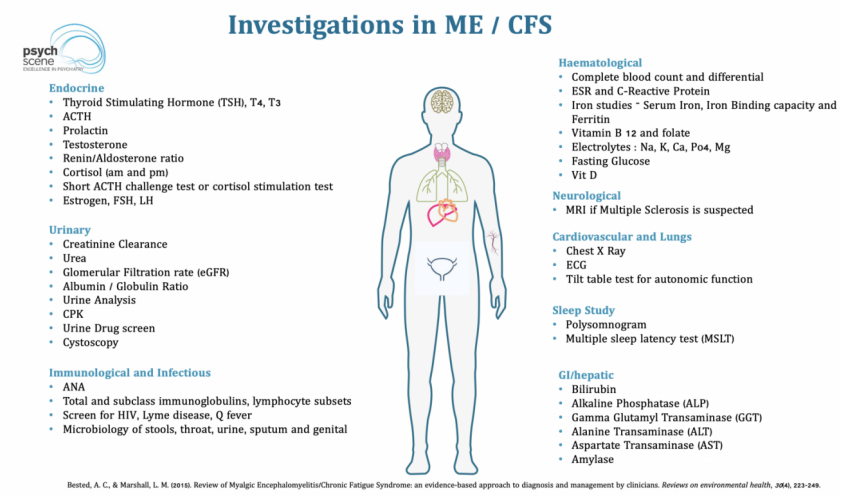
There is no blood test or specific biomarker to rule out ME or CFS. However, the following tests may assist in diagnosing organic conditions that may have a cumulative effect on chronic fatigue syndrome.



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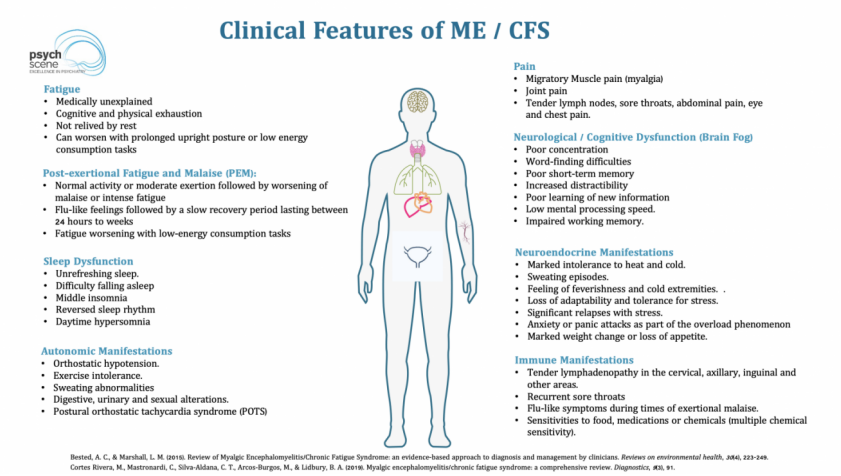
2. Assessing Comorbid Conditions:

- Fibromyalgia.
- Multiple chemical sensitivities.
- Orthostatic intolerance.
- Irritable bowel syndrome.
- Irritable bladder syndrome.
- Interstitial cystitis.
- Sicca Syndrome.
- Temporomandibular Joint Syndrome.
- Migraine headache.
- Allergies.
- Thyroiditis.
- Raynaud's phenomenon.
- Prolapsed mitral valve.

3. Diagnosis of Chronic Fatigue Syndrome – Clinical Diagnostic Canadian Consensus Criteria:



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The following are clinical features with their descriptions

Fatigue:

- Cognitive and physical exhaustion.
- Weakness and heaviness.
- General malaise.
- Lightheadedness.
- Sleepiness.
- Wired fatigue.
- CFS may reduce activity level by 50% or more, and some patients may be completely bedridden.

Post-exertional Fatigue and Malaise (PEM):

This particular criterion differentiates patients from fatigue due to depression. Depression patients feel better after exertion as exercise or physical activity acts as an antidepressant.

- PEM refers to severe physical or mental/cognitive post-exertional fatigue.
- Patients describe a *brain fog* which includes poor concentration, word-finding difficulties and poor short-term memory.
- Flu-like feelings followed by a slow recovery period that lasts between 24 hours to weeks.
- Fatigue can worsen with low-energy consumption tasks and is not relieved by rest.

Cardiopulmonary exercise test (CPET):

CPET provides an objective assessment of PET.

A 2-day CPET procedure can provide evidence of the pathophysiology across multiple systems that may not be apparent at rest by assessing the integrated response to exercise through a comprehensive evaluation of the pulmonary, cardiovascular, haematopoietic, neuropsychological and musculoskeletal systems. [Stevens et al., 2018]

- The first CPET is used to measure VO2 peak and provoke PEM.
- The second CPET measures the impact of PEM on the Ventilatory threshold (VT).

A meta-analysis showed a significant alteration of workload at VT, especially on the 2nd day of CPET in ME/CFS patients providing support of a link between PEM symptom and alterations in metabolism and mitochondrial ATP production in ME/CFS. [Lim et al, 2020]

Sleep Dysfunction

- Unrefreshing sleep.
- Difficulty falling asleep.
- Middle insomnia (multiple interruptions when trying to sleep).
- Reversed sleep rhythm.
- Daytime hypersomnia.
- 20% of patients may have sleep apnoea, upper airway resistance syndrome, restless leg syndrome or other sleep disorders.

Read more on neurobiology, diagnosis and management of insomnia

Pain:

- Migratory Muscle pain (myalgia). Some patients may meet the criteria for fibromyalgia.
- Joint pain
- Less common are tender lymph nodes, sore throats, abdominal pain, eye and chest pain.

Neurological/Cognitive Dysfunction:

Cognitive dysfunction is closely associated with fatigue

Subjective complaints by patients:

Patients describe the cognitive changes as *brain fog*.

- Problems remembering
- Difficulty expressing thoughts
- Difficulty paying attention
- Slowness of thought

- Absent-mindedness
- Difficulty understanding.

Cognitive findings include:

- Low mental processing speed.
- Impaired working memory.
- Poor learning of new information.
- Difficulty with word retrieval.
- Increased distractibility.
- Decreased concentration and attention span.
- Inability to multi-task.

Other cognitive and neurological difficulties may include:

- Ataxia.
- Muscle weakness.
- Fasciculations.
- Overload phenomenon where patients may be hypersensitive to sensory stimulation including bright lights, noise, odours and temperature extremes. This overload can lead to a *'crash'* due to mental exhaustion.

Autonomic Manifestations:

- Orthostatic hypotension.
- Exercise intolerance.
- Sweating abnormalities.
- Digestive, urinary and sexual alterations.
- Postural orthostatic tachycardia syndrome (POTS)

Neuroendocrine Manifestations:

- Loss of thermostatic stability with marked intolerance to heat and cold.
- Sweating episodes.
- Feeling of feverishness and cold extremities.
- Worsening in symptoms during changes of the weather.
- Loss of adaptability and tolerance for stress.
- Significant relapses with stress.
- Anxiety or panic attacks as part of the overload phenomenon, with recovery being slower than normal.
- Marked weight change or loss of appetite.

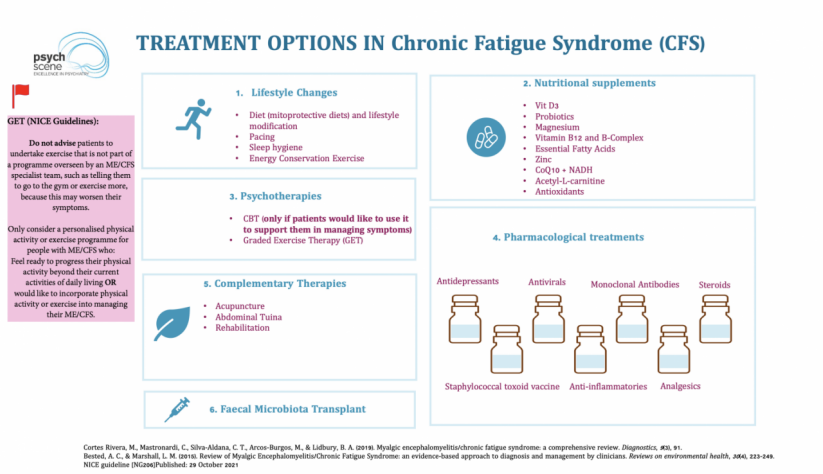
Immune Manifestations:

- Tender lymphadenopathy in the cervical, axillary, inguinal and other areas.
- Recurrent sore throats with non-exudative pharyngitis and bilateral crimson crescents visible in the soft palate's anterior pillars (palatoglossal arches).
- Erythema may extend into the uvula.
- Flu-like symptoms during times of exertional malaise.
- Sensitivities to food, medications or chemicals (multiple chemical sensitivity).

MANAGEMENT OF CHRONIC FATIGUE SYNDROME (CFS)

Aims of treatment

1. Improvement in symptoms, function and quality of life.
2. Prevention of worsening symptoms.
3. Help patients cope with the emotional impact and grief resulting from the development of a complex, debilitating illness.
4. Prevention of the development of depression and potential suicide by managing physical and psychological symptoms.
5. Prevention of new, environmentally associated worsening such as multiple chemical sensitivity.



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NON-PHARMACOLOGICAL MANAGEMENT OF CFS / ME

Energy conservation exercise:

- An exercise programme to be tailored to the individual patient.

Graded exercise therapy (GET):

- As patients with depression were included in the Oxford studies, the studies erroneously concluded that CFS patients improved with GET.
- **GET is contra-indicated and can be harmful to patients with ME/CFS using the CCC criteria.** [Bested and Marshall, 2015]
- In a more recent study of a multidisciplinary intervention, which combined group CBT and GET with pharmacological treatment, at 12 months after completion, GET was slightly inferior to usual medical care alone, had not improved fatigue or health-related quality of life, and resulted in worse physical function and bodily pain scores. [Nunez et al., 2011]
- The recent NICE guidelines also outline that graded exposure therapy should not be offered. [NICE guidelines]

Do not advise people with ME/CFS to undertake exercise that is not part of a programme overseen by an ME/CFS specialist team, such as telling them to go to the gym or exercise more, because this may worsen their symptoms.

*Only consider a personalised physical activity or exercise programme for people with ME/CFS who feel ready to progress their physical activity beyond their current activities of daily living **or** would like to incorporate physical activity or exercise into managing their ME/CFS.*

Tell people about the risks and benefits of physical activity and exercise programmes. Explain that some people with ME/CFS have found that they can make their symptoms worse, for some people it makes no difference and others find them helpful.

If a physical activity or exercise programme is offered, it should be overseen by a physiotherapist in an ME/CFS specialist team.

Pacing:

Pacing has consistently been shown to be the most effective, safe, acceptable and preferred form of activity management for CFS/ME. It should therefore be a key component of any illness management programme.[ME Association, 2015]

- Learning to pace by taking breaks or rest between activities.
- Enhancing awareness of the body's needs.
- Encouraging staying within the energy envelope or physical boundary.
- Using an activity log and recording the daily routines.
- Breaking tasks into multiple steps.

Sleep Hygiene:

- Establishing a sleep-wake routine to retrain the circadian rhythm.
- Pace activities during the day to avoid aggravating symptoms that interfere with sleep.
- Avoid watching TV or computer devices before bed to stimulate Melatonin production.
- Blue light blocking glasses may help.
- Reduce or eliminate caffeine-containing beverages.
- Meditate, relax and wind down before bedtime for 20 minutes to an hour to reduce sympathetic tone and increase relaxation.
- Darken the bedroom with blackout curtains or use a sleep mask to produce Melatonin.
- In the morning, exposure to bright, natural light or a seasonal affective disorder light is helpful.

Read more on sleep hygiene: stimulus control and sleep restriction methods.

Cognitive dysfunction.

- No specific medications.
- Pace activities that use mental energy, using a diary or a memory book.
- Promote habits to simplify life.

Psychological therapies

- While earlier trials (the 1990s and 2000s) of CBT in CFS showed benefits, more recent CBT trials have failed to show consistent benefits in patients with CFS/ME. [Kim et al., 2020]
- Cognitive therapy may be an effective treatment for adolescents with CFS/ME. Adolescents with CFS who received internet based CBT reported improvement in fatigue, physical function and school attendance.[Nijhof et al., 2012]
- According to the recent NICE guidance, it should only be offered to support people who live with ME/CFS to manage their symptoms, improve their functioning and reduce the distress associated with having a chronic illness. [NICE guidelines]

The PACE trial (Pacing, graded activity, and cognitive behaviour therapy), which was a large scale 5 year trial of treatment for CFS from 2005 to 2010, funded by the UK Government at the cost of £5 million, found that both CBT and GET, when given appropriately as supplements to specialist medical care, are more effective in improving both fatigue and physical functioning in people with CFS, than are Adaptive pacing therapy (APT) and Specialist medical care (SMC) alone. [White et al., 2011]

The PACE trial was criticised for methodological flaws. [Wilshire et al., 2017]

The **ME association patient survey** concluded: [ME Association, 2015]

- GET should be withdrawn with immediate effect as a primary intervention for everyone with ME/CFS.
- CBT in its current delivered form should not be recommended as a primary intervention for people with ME/CFS.
- Our results indicate that GET should form no part of any activity management advice employed in the delivery of CBT, as this also led to a negative impact on outcomes.

- Pacing was consistently shown to be the most effective, safe, acceptable and preferred form of activity management for people with ME/CFS.

PHARMACOLOGICAL MANAGEMENT OF CFS / ME

A systematic review of the pharmacological management of ME/CFS identified 20 drug therapies from 26 studied, and 18 applied the Fukuda criteria as the primary tool for inclusion criteria. [Collatz et al., 2016]

11 medications were shown to be either slightly, mildly or moderately effective in the respective study groups. 6 out of 11 of them had significant results in the fatigue outcome. No medications showing a significant effect to be considered a gold standard in the pharmacological treatment of ME/CFS. Since there are multiple mechanisms, several pharmacological therapies may be used to treat ME/CFS.

A 2020 systematic review showed eight interventions with statistical significance: [Kim et al., 2020].

Pharmacological:

1. Staphypan Berna
2. Rintatolimod [Poly(I):poly(C_{12}U]
3. CoQ_{10} + NADH

Non-pharmacological therapies:

- Cognitive-behaviour-therapy-related treatments
- Graded-exercise-related therapies
- Rehabilitation
- Acupuncture
- Abdominal tuina. Tuina is a form of manipulative therapy often used in conjunction with acupuncture, moxibustion, fire-cupping, t'ai chi, and qigong carried out in China. Abdominal Tuina (AT) is a combination of Tuina and abdominal examination.

However, there was no effective intervention with coherence and reproducibility. [Kim et al., 2020].

Overview of pharmacological treatments studied in CFS [Castro-Marrero et al., 2017]

Dextroamphetamine and Methylphenidate

- A stimulant that induces the release of dopamine and noradrenaline.
- ADHD and CFS may be comorbid, especially in females, and stimulants may be effective (Read more about ADHD in females). There may be common pathophysiological mechanisms underpinning ADHD, CFS and possibly fibromyalgia. [Young, 2013]
- Dexamphetamine was effective in a small RCT. Larger trials are needed. [Olson et al., 2003]
- Methylphenidate at a dose of 2 x 10 mg/day was significantly better than placebo in relieving fatigue and concentration disturbances in a minority of chronic fatigue syndrome patients. [Blockmans et al, 2006].
- Useful in POTS. (see later)

Nefazodone:

- SSRI and potent serotonin antagonist (5HT2A and 5HT2C). Weak SNDRI (Serotonin-noradrenaline-dopamine reuptake inhibitor).
- Nefazodone may improve mood, fatigue and sleep disturbances.

Antidepressants:

- TCAs are useful in managing pain and sleep
- CFS/ME patients usually respond to much lower doses of tricyclics than those used to treat people with depression
- SSRIs/ SNRI (Duloxetine) may be helpful for CFS/ME subjects who experience significant chronic neuropathic pain, fibromyalgia, anxiety/depression and other mood disorders.

- Mirtazapine in an RCT was beneficial for fatigue and global clinical impression in the group receiving CBT first followed by mirtazapine, not in a group that started on mirtazapine followed by CBT. [Stubhaug et al., 2008]

Low Dose Naltrexone:

- Naltrexone at low dose may work as an immune modulator.
- Naltrexone blocks the activation of Toll Like Receptor -4 (TLR-4) and therefore, inhibits microglia activation. [Weitzer D, 2020].
- The Transient Receptor Potential Melastatin 3 (TRPM3) which is a nociceptor channel has significant opioid receptors.
- The TRPM3 channel is implicated in calcium (Ca 2+) -dependent Natural Killer (NK) cell immune functions which play a role in the pathophysiology of CFS / ME. [Cabanas et al, 2021].
- Naltrexone by acting as a mu-opioid receptor antagonist negates opioid inhibitory function on TRPM3. Restoration of TRPM3 ion channel activity re-establishes appropriate Ca2+ signalling and NK cells' activation and effector functions.
- Most recommended doses are between 3.0–5 mg/day.
- Benefits at a higher dose ceiling of 12 mg has been reported. [Bolton et al, 2020].

Rintatolimod [Mitchell, 2016]

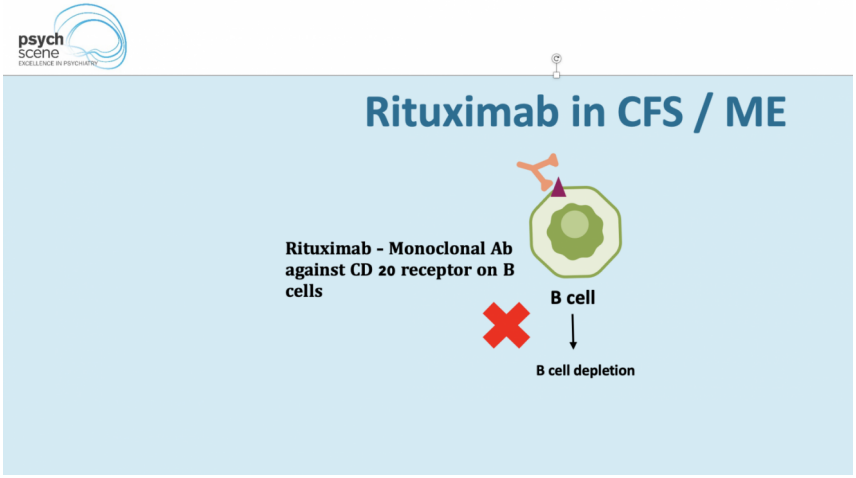
- Mismatched, double-stranded RNA molecule with immunomodulatory and antiviral properties.
- TLR3 agonist without helicase activation prevents the activation of inflammatory cytokines.
- Inducer of interferon and TNF activity
- Shown benefit in open-label trials.

Vagancicolovir:

- Nucleotide analogue inhibitor which inhibits viral replication during DNA multiplication (for DNA- and retroviruses) or RNA multiplication (for RNA viruses)
- Valganciclovir treatment, independent of the baseline antibody titers, was associated with self-rated improvement in physical and cognitive functioning for CFS patients who had positive HHV-6 and/or EBV serologies. Longer valganciclovir treatment correlated with an improved response. [Watt et al., 2012]

Monoclonal antibodies: Rituximab

- Decreased activity and number of B cells by inhibiting DC20, thus reducing inflammation.
- While open-label studies demonstrated symptom alleviation and improved quality of life, an RCT showed B-cell depletion using several infusions of rituximab over 12 months was not associated with clinical improvement in patients with ME/CFS. [Fluge et al., 2019]
- Side effects include neutropenia and increases in severe infection.



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Interferons and Immunoglobulins:

- No clear evidence.

Hormones:

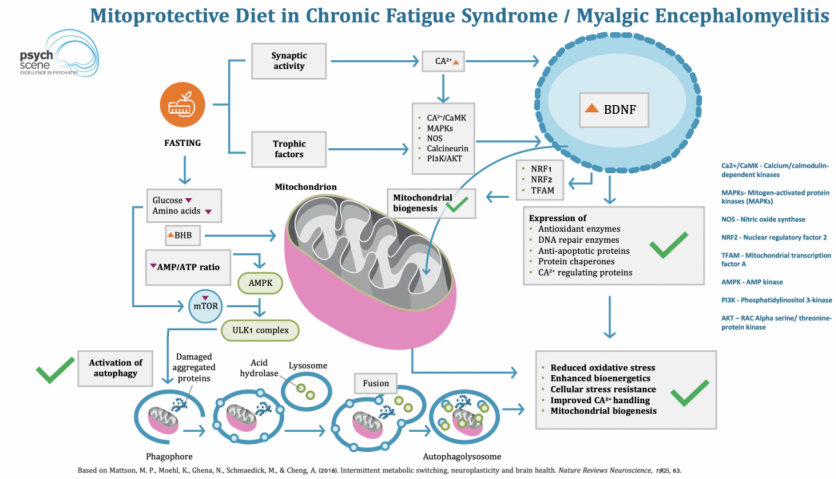
- Hydrocortisone, Fludrocortisone and hydrocortisone plus fludrocortisone.
- Results are inconclusive
- Adrenal suppression, mood disorders, weight gain comorbidities and side effects.

Staphylococcal toxoid vaccine (Staphypan Berna)

- Repeated administration of the Staphypan Berna vaccine in patients with fibromyalgia/chronic fatigue syndrome causes a serological response to several staphylococcal antigens, particularly to certain extracellular toxins and enzymes, which is related to the clinical outcome of treatment. [Zachrisson et al., 2004]

Dietary interventions

- Mitoprotective diets: caloric restriction, fasting diets and ketogenic diets (high fat, carbohydrate-deficient diet). [Cortes Rivera et al., 2019]



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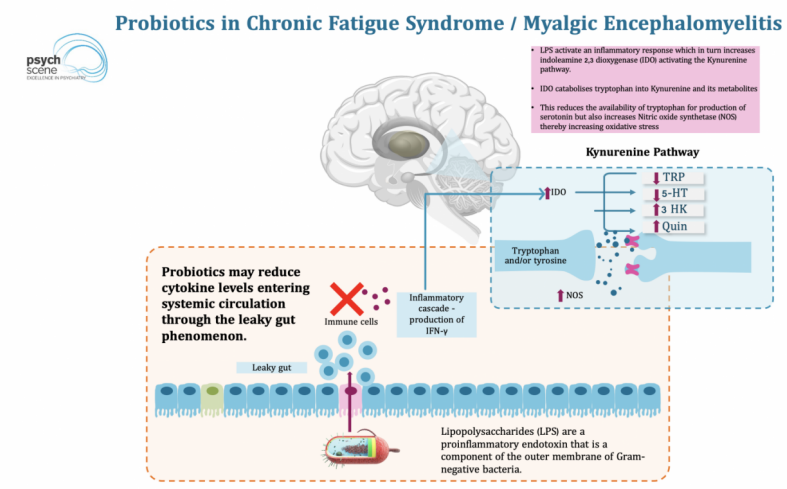
- Fasting results in a metabolic switch to ketosis, which produces ketones such as Beta-hydroxybutyrate (BHB), which can also upregulate the expression of brain-derived neurotrophic factor (BDNF) and may thereby promote mitochondrial biogenesis, synaptic plasticity and cellular stress resistance.

Whilst there has been some benefit in some patients, they are not beneficial for all patients and may not contribute to the complete recovery of the disease due to other mechanisms involved.

Probiotic interventions

- Reducing cytokine level entering the systemic circulation by the leaky gut phenomenon.



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- Patients with ME/CFS may have symptoms of frequency, dysuria and bladder pain. Low-grade bacterial infection should be ruled out.
- Patients with viral, bacterial or parasitic infections (e.g. herpes viruses, enteroviruses, Borrelia burgdorferi, mycoplasma, Giardia lamblia) may benefit from long-term antibiotics, anti-parasitic or antiviral therapy. [Bansal et al., 2012]
- If intestinal dysbiosis is present, L-glutamine or butyrate or using evidence-based probiotics may relieve symptoms. [Maes & Leunis, 2008]
- The administration of Lactobacillus casei strain Shirota in CFS patients over 8 weeks reduced anxiety scores. Likewise, this probiotic changed the faecal composition following 8 weeks of treatment. Additionally, the treatment with Bifidobacterium infantis 35624 in CFS patients reduced inflammatory biomarkers during the same period. The evidence about the usefulness of probiotics in CFS and FMS patients remains limited. [Roman et al., 2018]

Faecal Microbiota Transplantation.

- The gut-brain axis is postulated in the pathophysiology of many psychiatric disorders.
- With evidence that a *'leaky gut'* may be linked to CFS /ME, FMT may act as a possible treatment option.
- Response rates of as high as 70% have been reported, with benefits maintained for 15-20 years in uncontrolled studies. [Smits et al., 2013]

Matching medications to clinical symptoms:

Cognitive disability and reduced functional status:

- Moclobemide
- Lisdexamfetamine dimethylate.

Fatigue and post-exertional malaise

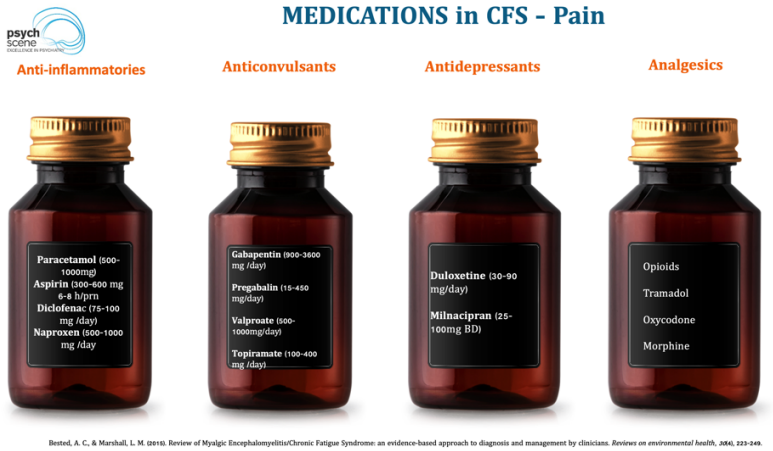
- A low dose of hydrocortisone 5 to 10 mg daily found short term improvement in fatigue but with a relapse once the drug was discontinued.
- High dose hydrocortisone may have an unfavourable risk-benefit ratio.

Orthostatic Intolerance & Postural Tachycardia Syndrome (POTS)

- Changing positions slowly from lying to sitting and then standing
- Increasing salt and electrolyte intake with fluids to increase blood volume can reduce postural hypotension and tachycardia symptoms.
- Fludrocortisone 0.1–0.2 mg/day or Midodrine 10 mg up to four times daily
- Low dose Atenolol (25-50 mg) or Propranolol (10-20 mg) may be used to treat tachycardia or palpitations from postural hypotension.
- Medications for POTS target the following mechanisms (Reduction of heart rate / peripheral vasoconstriction/ sympatholysis / blood volume expansion) [Miller & Raj, 2018]
- Methylphenidate (10 mg 3 times daily) can improve symptoms of fatigue and pre-syncope in patients with refractory POTS.

- In POTS, patient-reported successful treatments for brain fog include stimulant medications (amphetamine-based and modafinil), salt tablets, and vitamin B12 injections. [Ross et al., 2013]
- A recent placebo-controlled trial found that modafinil increased orthostatic BP but did not significantly worsen standing HR or acute orthostatic symptoms in POTS patients. In addition, there are case studies of favourable responses to modafinil 100-200 mg. [Kpaeyeh et al., 2014]

Pain and inflammation:



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- NSAIDs, ibuprofen and naproxen relieve frequent or severe joint inflammation, headaches and fevers.
- Tricyclic antidepressants (amitriptyline, doxepin, nortriptyline, desipramine) for sleep and pain
- TCAs may provide an anti-anxiety effect and improve locomotor activity.

Anxiety / Depression –

- SSRIs help with anxiety and depression, other mood disorders, and the patient's chronic neuropathic pain.

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COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Nutritional supplements may improve physical and mental fatigue in individuals with specific nutritional deficiencies.

Acetyl-L-carnitine

- Facilitates movement of acetyl coenzyme A into the mitochondria providing antioxidant, neuromodulatory, and neuroprotective effects.
- May benefit both cognitive status and physical function

Essential Fatty Acids:

- Erythrocyte omega-3 index (5.75%) and n-3 PUFA levels are low in individuals with CFS/ME.
- Low EPA + DHA levels may be a risk factor for poor cardiovascular health and pro-inflammatory status in CFS/ME. [Castro-Marrero et al., 2018]
- High doses of evening primrose oil containing γ-linolenic acid (GLA) and fish oil concentrate containing eicosapentaenoic acid (EPA) and DHA showed benefits for fatigue, myalgia, dizziness, poor concentration and depression in patients with post-viral fatigue syndrome; a subset of CFS.

Magnesium:

- Magnesium supplementation may be beneficial in patients with a deficiency

Vitamin B12:

- Frequent injections of highly concentrated methylcobalamin combined with an individual daily high dose of oral folic acid may be safe and effective for fatigue and other CFS/ME symptoms. [Regland et al., 2015]

Antioxidants

- Antioxidants (including α-lipoic acid, vitamin E or C) are a group of vitamins, minerals, and enzymes that help protect cells from oxidative stress damage and improve mitochondrial function.
- Treatment with a multivitamin and mineral supplement could be a safe and easy way to improve CFS/ME symptoms and quality of life in CFS/ME. [Maric et al., 2014]

Coenzyme Q_{10} plus NADH and mitochondrial dysfunction

- As mitochondrial dysfunction is linked to CFS, resulting in decreased ATP production, CoQ_{10} and NADH, which increase cellular ATP production via mitochondrial oxidative phosphorylation, their supplementation could help improve fatigue and other symptoms in CFS/ME.

CONCLUSION

The management of ME/CFS continues to remain a challenge in medical and psychiatric practice. There are many pathophysiological mechanisms involved, which requires a targeted strategy targeting multiple mechanisms.

Due to the unclear aetiology, diagnostic uncertainty and resultant heterogeneity, there are no established recommendations in clinical practice or guidelines.

In practice, pharmacological and non-pharmacological treatments are used in the treatment of ME/CFS. More research is required to understand the pathophysiology and, therefore, allow the development of more effective treatments to improve the quality of life for patients with ME/CFS.

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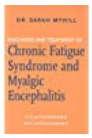

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References

The Chronic Fatigue Syndrome: A Comprehensive Approach To Its Definition And Study

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic And Treatment Protocols

Examining Case Definition Criteria For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis

A Population-Based Incidence Study Of Chronic Fatigue

A Systematic Review Describing The Prognosis Of Chronic Fatigue Syndrome

The Economic Impacts Of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome In An Australian Cohort

Early Outbreaks Of 'Epidemic Neuromyasthenia

An Outbreak Of Encephalomyelitis In The Royal Free Hospital Group, London, In 1955

Concept Of Benign Myalgic Encephalomyelitis

The Definitive Description Of ME (Ramsay)

Review Of Case Definitions For Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

The Development Of A Revised Canadian Myalgic Encephalomyelitis Chronic Fatigue Syndrome Case Definition.

Review Of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: An Evidence-Based Approach To Diagnosis And Management By Clinicians

Evidence For A Heritable Predisposition To Chronic Fatigue Syndrome

Use Of Single-Nucleotide Polymorphisms (SNPs) To Distinguish Gene Expression Subtypes Of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)

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The Dopamine Imbalance Hypothesis Of Fatigue In Multiple Sclerosis And Other Neurological Disorders

Cardiopulmonary Exercise Test Methodology For Assessing Exertion Intolerance In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

The Prospects Of The Two-Day Cardiopulmonary Exercise Test (CPET) In ME/CFS Patients: A Meta-Analysis.

Health-Related Quality Of Life In Patients With Chronic Fatigue Syndrome: Group Cognitive Behavioural Therapy And Graded Exercise Versus Usual Treatment. A Randomised Controlled Trial With 1 Year Of Follow-Up

Results And In-Depth Analysis Of The 2012 ME Association Patient Survey Examining The Acceptability, Efficacy And Safety Of Cognitive Behavioural Therapy, Graded

Exercise Therapy And Pacing, As Interventions Used As Management Strategies For ME/CFS

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Chronic Fatigue Syndrome: Naltrexone As An Alternative Treatment.

Potential Therapeutic Benefit Of Low Dose Naltrexone In Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Role Of Transient Receptor Potential Melastatin 3 Ion Channels In Pathophysiology And Treatment.

Low-Dose Naltrexone As A Treatment For Chronic Fatigue Syndrome.

Efficacy Of Rintatolimod In The Treatment Of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)

Response To Valganciclovir In Chronic Fatigue Syndrome Patients With Human Herpesvirus 6 And Epstein–Barr Virus IgG Antibody Titers

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Normalization Of Leaky Gut In Chronic Fatigue Syndrome (CFS) Is Accompanied By A Clinical Improvement: Effects Of Age, Duration Of Illness And The Translocation Of LPS From Gram-Negative Bacteria

Are Probiotic Treatments Useful On Fibromyalgia Syndrome Or Chronic Fatigue Syndrome Patients? A Systematic Review

Therapeutic Potential Of Fecal Microbiota Transplantation

Pharmacotherapy For Postural Tachycardia Syndrome. Auton Neurosci. 2018

What Is Brain Fog? An Evaluation Of The Symptom In Postural Tachycardia Syndrome.

Hemodynamic Profiles And Tolerability Of Modafinil In The Treatment Of Postural Tachycardia Syndrome: A Randomized, Placebo-Controlled Trial.

Low Omega-3 Index And Polyunsaturated Fatty Acid Status In Patients With Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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