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Chronic fatigue syndrome

The right clinical information, right where it's needed

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Summary

- Chronic fatigue syndrome (CFS) is characterised by a sudden or gradual onset of persistent disabling fatigue, post-exertional malaise (PEM, exertional exhaustion), unrefreshing sleep, cognitive and autonomic dysfunction, myalgia, arthralgia, headache, and sore throat and lymph nodes, with symptoms lasting at least 6 months.

- Exertional exhaustion is the critical aspect that distinguishes myalgic encephalomyelitis/CFS from other nociceptive, interoceptive, and fatiguing illnesses.

- The lack of energy may be caused by autoimmune and metabolomic dysfunction that reduces mitochondrial ATP production.

- The primary goals of management are to provide a supportive healthcare environment with a team of occupational, physio, and other appropriate therapists who will manage symptoms and improve functional capacity.

- The chronic but fluctuating disabilities require substantial lifestyle changes to plan each day's activities carefully, conserve energy resources for the most important tasks, schedule rest periods to avoid individuals overtaxing themselves, and to improve the quality of sleep.

- Medications are not curative. Pharmacotherapy is indicated to treat pain, migraine, sleep disturbance, and comorbid conditions such as irritable bowel syndrome, anxiety, or depression.

Definition

Definitions of chronic fatigue syndrome (CFS) have evolved from a focus on fatigue and impairment as described in the Centers for Disease Control criteria (CDC),[1] to post-exertional malaise (PEM)/exertional exhaustion in myalgic encephalomyelitis (ME)/CFS as defined by the Canadian Consensus Criteria,[2] [3] and systemic exertion intolerance disease (SEID) introduced by the US Institute of Medicine.[4] [5] These 3 definitions have compatible criteria that focus on PEM, disability, sleep, pain, and cognition.[6] [7]

Exertional exhaustion is the critical aspect that distinguishes ME/CFS from other nociceptive, interoceptive, and fatiguing illnesses. This means people with CFS must make significant lifestyle changes to conserve their physical resources and mental concentration to stay competent in normal occupational, educational, and social settings. They are often limited to a few hours per day of productive endeavours, with the remainder of the time spent resting with slow and partial recovery from the disorganised thoughts, total body pain, malaise, and other features of their chronic fatigue state. Consideration of 'fatigue' as mental or physical tiredness is too simplistic to encompass the scope of impairment in CFS, and belies the inadequacy of the vocabulary of fatigue. There is a strong bias to the vocabulary of acute viral illness, such as influenza and poliomyelitis, because these were considered historical precedents of CFS.

CFS is characterised by a sudden or gradual onset of persistent disabling fatigue, post-exertional malaise (PEM, exertional exhaustion), unrefreshing sleep, cognitive and autonomic dysfunction, myalgia, arthralgia, headaches, and sore throat and lymph nodes, with symptoms lasting at least 6 months.[8] PEM is the hallmark of CFS. The fatigue is not related to other medical conditions, and symptoms do not improve with sleep or rest.

Myalgic encephalomyelitis (ME) is more strictly defined than CFS. ME is defined by: disabling fatigue; post-exertional malaise; sleep, pain, cognitive and autonomic dysfunction; and chemical irritant sensitivity.[6] [7]

Systemic exertion intolerance disease (SEID) was defined by the US Institute of Medicine (IOM). Diagnosis of SEID requires disabling fatigue, PEM, unrefreshing sleep, and cognitive and autonomic dysfunction that is persisting, moderate or severe, and present at least 50% of the time in order to denote the unique symptom spectrum.[4]

It is inappropriate to use the 1991 Oxford criteria of fatigue as an alternative for CFS because the Oxford criteria are based on 'mild fatigue', do not require PEM, and allow inclusion of chronic idiopathic fatigue, depression, and other fatiguing conditions.[9] Up to 30.5% of the population have chronic fatigue[10] and would meet Oxford criteria for study inclusion. Studies that used the Oxford criteria are not representative of the more severe and restricted definitions of CFS that the CDC, Canadian Consensus, or SEID criteria define. Exercise and cognitive behavioural therapy studies that used the Oxford criteria for study inclusion are biased and misleading because people with true CFS are underrepresented, with excessive recruitment of people with chronic idiopathic fatigue and depression who are known to respond well to these modalities.[11]

Metabolomics dysfunction[12] [13] and beneficial effects of rituximab provide new insights into the pathophysiological mechanisms of CFS. These studies of biological dysfunction suggest that CFS does not overlap with chronic idiopathic fatigue or depression.

Epidemiology

The prevalence of chronic fatigue syndrome (CFS) varies according to the population studied, the survey methodology, and the criteria used to establish the diagnosis.[25] Prevalence estimates for adults in the US range between 0.007% and 2.8% in the community,[26] [27] [28] and up to 3% in primary care.[29] Similarly, rates of CFS range between 0.11% and 2.6% in the UK.[30] [31] The overall estimated minimal yearly incidence was 0.015%. A meta-analysis found significant variability in prevalence rates for CFS/myalgic encephalomyelitis (ME) when using self-reported (3.28%) and clinically assessed (0.76%) methods.[32] The prevalence of CFS among adolescents was between 0.003% and 0.5%.[33] [34] There is little information about the prevalence in children. In Australia prevalence rates were estimated at 5.5 per 100,000 in children under 10 years of age, and 48 per 100,000 in 10 to 19 year olds.[35] CFS was 2 to 3 times more prevalent among women than among men,[36] with peak ages of onset during adolescence and between 30 and 50 years.[26] [37] Community surveys carried out in the US have found that English-speaking white Americans had a lower risk of CFS than Latino, African-American, or Native American people.[26] [27] [38] One study carried out in England found a prevalence of CFS among people of Pakistani ancestry of 3.5% (odds ratio 4.1; 95% confidence interval 1.6 to 10.4), compared with 0.8% in white people.[39] Factor analysis suggests ME, as defined by the Canadian consensus criteria, represents 40% to 60% of people with CFS defined by the 1994 US Centers for Disease Control and Prevention 'Fukuda' criteria.[1] [40]

Aetiology

Although viral and bacterial infections (e.g., Epstein-Barr virus, *Mycoplasma pneumonia*), and immunological (e.g., IgG subclass deficiencies), neuroendocrine, genetic, gastrointestinal, and psychological factors have been investigated as initiating triggers, the aetiology of chronic fatigue syndrome (CFS) remains unknown.[29] [41] However, evidence is accumulating that suggests an inflammatory component to CFS.[40] Randomised placebo-controlled studies have shown rituximab, an anti-CD20 monoclonal antibody that causes B-cell ablation, induced remission in approximately 50% of patients with CFS, with symptoms recurring after stopping rituximab treatment.[42] [43] These findings suggest the presence of an autoreactive disease in a subset of patients with CFS.[44] Immunological dysfunction is also suggested by the association of CFS with specific HLA haplotypes,[45] and natural killer cell dysfunction.[46] An exciting new development has been demonstration of abnormal metabolomics patterns in peripheral blood in CFS.[12] [13]

These studies provide a new starting point for investigating whether this is a sporadic disease, or if there are inherited risk factors that may indicate a genetic predisposition. However, as mitochondrial dysfunction and metabolomics imbalance are found in many illnesses, it will be critical to define the sensitivity and specificity of patterns in CFS compared with other diseases in its differential diagnosis.

Pathophysiology

The introduction of new technologies has implicated dysfunctional metabolomics, autoreactive, and neuroimmune mechanisms as potential pathophysiological mechanisms in chronic fatigue syndrome (CFS).

Historically, 2 schools of thought for the pathophysiological mechanisms of CFS have existed: viral infection followed by a chronic post-viral fatigue state, such as the Royal Free Hospital and Incline Village, Nevada, cohorts illustrated;[47] [48] and epidemic neurasthenia.[49] [50] Case series going back to the 1920s are limited in their details of past outbreaks, long-term follow-up of disabilities, the medical knowledge and the inability to make molecular diagnoses at the time of writing, and the absence that still persists of biomarkers

and other objective diagnostic tools. Some clusters of cases among young nurses in poliomyelitis hospitals have been retrospectively interpreted as epidemic hysteria.[51] Early studies were inconsistent and often produced non-reproducible findings, mainly due to small sample sizes, and lack of standardisation among studies. The perception of an epidemic was sometimes explained by the presence of a doctor who knew about CFS and identified it at the usual local background rate compared with another community that lacked a physician knowledgeable in CFS and, therefore, did not diagnose any cases.

Onset has been reported to be sudden and consistent with an infectious disease (72% of one case series) but definite evidence of acute microbial infection is infrequent (7%). Non-infectious events, such as motor vehicle accidents or surgery (11%), as well as no apparent precipitating event (17%), have been reported. Immunisation is not a significant precipitant.[52] Epstein-Barr virus and enterovirus are the two most common infectious triggers of CFS/ME. However, it has not been possible to identify chronic active viral or prion infections in the vast majority of patients with CFS.[53]

Extensions of rodent stress studies suggested altered hypothalamic-pituitary-adrenal (HPA) axis, serotonin, and dopamine function.[54] [55] [56] HPA axis dysregulation may be due to behavioural changes in sleep, and prolonged physical inactivity.[57]

Excessive or burned out stress responses have been applied to CFS. An alternative approach to stress is to examine mechanisms of threat assessment, and the strong negative emotion and innate self-preservation defensive responses of arousal, freezing, fight or flight, tonic immobility, collapsed immobility, and quiescent immobility.[58] Recognition of a potential threat triggers arousal with activation of hypothalamus, sympathetic and somatomotor systems. Sympathetic efferents vasoconstrict salivary gland vessels leading to a dry mouth; an increase in proximal laryngeal muscle tone, causing a high-pitched voice; tachycardia; tachypnoea; and increased tone to skeletal and smooth muscles. Imminent danger provokes action as either fight or flight. The amygdala and limbic forebrain activate areas of the lateral periaqueductal grey matter (LPAG) to cause laryngeal muscle contraction with low pitched guttural sounds, activation of premotor regions in the pons and medulla to activate motor networks, and basal ganglia, cerebellum, and cortical loops to execute the plan of response. Vagal parasympathetic tone to the heart is reduced. Non-opioid projections from the LPAG to the dorsal horn block ascending pain signals. There is decreased activation of ventromedial prefrontal cortex, rostral anterior cingulate, thalamus, and occipital cortex.

An alternative to fight or flight is the freeze response, which involves focused awareness, muscle rigidity, and immobility. This is caused by activation of the ventrolateral periaqueductal grey matter (VLPAG) that acts as a brake on LPAG functions and so blocks the muscle activity of the fight or flight response. Muscle tone and respiratory rate are high. Vagal activation is modulated by withdrawal of nucleus ambiguous respiration-related vagal efferents and activation of non-respiration-related vagal efferents from the vagal dorsal motor nucleus that cause a sudden deceleration of heart rate (fear bradycardia) despite the augmented sympathetic tone. Escalation of the threat leads to amygdala-mediated inhibition of the VLPAG and initiation of an immediate, active fight or flight response. Freezing in humans is a transient state of hypervigilance with steady posture (reduced body sway) and bradycardia, or highly blunted sympathetic tachycardia. Tonic immobility is an ancient defence mechanism that is used if freeze, fight or flight fail, and death may be imminent. The extreme afferent sensory overload of struggling in the grasp of a predator activates deep somatic and vagal visceral afferents that deactivate the amygdala and LPAG leading to unopposed VLPAG activity. Increased muscle tone and 'waxy rigidity' may be due to VLPAG activation of ventral medulla, ventral spinal motor neurons, or basal ganglia circuits. Activation of the periaqueductal grey matter and rostral ventromedial medulla lead to descending opioid analgesia. The sympathetic system is shut down leading to unopposed parasympathetic bradycardia and slow, shallow respiratory rate. Defence

programmes of the enteric nervous system lead to defecation. Derealisation and depersonalisation may occur, particularly if dissociative posttraumatic stress disorder (PTSD) is present. The medial prefrontal, rostral, and dorsal anterior cingulate, and right anterior insula of the brain's salience network are activated, which may contribute to vivid memories of the tonic immobility event. Rape-induced paralysis or immobility when under fire in battle are examples of tonic immobility. Faint, or collapsed immobility ('playing possum') is a more extreme form of VLPAG activation with sudden bradycardia or asystole, with compromised brain stem blood flow leading to flaccidity and complete loss of consciousness (syncope). Quiescent immobility is another variant of VLPAG-mediated immobility that occurs after escape from the threat, but with cessation of spontaneous activity, absence of startle responses and vocalisations, hypotension, and bradycardia.

Neuroimaging studies suggest decreased brain blood flow in temporal, parietal, frontal, and subcortical areas,[59] with differential prefrontal and temporal activation during cognitively demanding tasks in people with CFS relative to controls.[60] Reduced grey matter volume in the dorsolateral prefrontal cortex may be more related to pain than fatigue symptoms.[61] Basal ganglia activation is reduced in those with CFS.[62] Functional connectivity between the anterior and posterior cingulate cortex correlated with Chalder Fatigue scores.[63] In adolescent patients with CFS, fatigue was correlated with decreased salience network connectivity, while pain correlated with increased functional connectivity between the left middle insula and caudate.[64] Autonomic dysfunction in CFS has been correlated with reduced volumes of brainstem vasomotor nuclei,[65] the midbrain reticular formation, and the hypothalamus, as well as in limbic nuclei involved in stress responses.[66] Prefrontal myelination[67] and inferior fronto-occipital fasciculus white matter were altered in CFS.[68] Microglial activation in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons suggests neuroinflammation in CFS.[69]

'Small heart syndrome' with small left ventricular size and low cardiac output has been proposed to lead to poor physical stamina and chronic fatiguing status.[70] [71]

The gut microbiome has a reduced diversity in people with CFS, based on comparisons of 16 ribosomal RNA sequences.[72] In addition, gut microbes have an increased propensity to translocation into the circulation after exercise in CFS.[73] Therefore, new approaches are needed to evaluate microbes that do not share sufficient sequence homology with standard bacterial, archaebacterial, and fungal 16S rRNA.

Gene polymorphisms in TNF alpha, IL1b, IL4, IL6, INF-gamma, and glucocorticoid receptor (NR3C1) are shared by CFS, cancer, and other disease-related fatigue states.[74] Evidence showing consistent patterns of immunological abnormalities with B cells, T cells, natural killer cells, and cytokine levels in CFS are beginning to emerge.[42] [43] [75] [76] [77] [78] Natural killer cell dysfunction in CFS/ME has been interpreted as a risk factor for chronic viral infection, but again no microbes have been identified.[46] [77] [79] [80] [81] Alterations in cytokine expression in blood,[82] cerebrospinal fluid,[76] [83] and peripheral leukocyte populations,[84] as well as alterations in micro RNA expression,[85] epigenomic methylation patterns,[86] and systems biology modelling,[78] provide evidence to support the role of inflammatory processes in the pathophysiology of CFS/ME. Acute stressors have powerful effects on adrenal hormone secretion (cortisol, epinephrine [adrenaline]) that modulate gene expression in lymphocytes, natural killer cells, and other populations of peripheral blood leukocytes.[87] Some of these alterations may be characteristic of CFS immune status. Mast cell activation syndrome results in fatigue, gastroesophageal reflux, as well as dermatographism with elevated heparin, prostaglandin D2, histamine, and chromogranin A.[88] [89] Flow cytometric and cytokine assessments were unhelpful.

Ehlers-Danlos syndrome (hypermobile type) has been associated with fatigue, sleep disorders, chronic pain, deconditioning, cardiovascular autonomic dysfunction, bowel and bladder dysfunction, psychological issues, and nutritional deficiencies that can mimic CFS.[90] For example, submaximal exercise is a stressor

in CFS that induces distinct patterns of change in mRNAs for nociceptive sensor proteins, ion channels, and adrenergic and other receptors in peripheral blood leukocytes of the majority (71%) of patients with CFS, but not in controls or patients with depression, prostate cancer, multiple sclerosis, or fibromyalgia.[91] [92] [93] [94] [95] Submaximal exercise may also identify a second CFS phenotype (29%) with suppressed adrenergic receptor alpha 2A mRNA and no elevations of any other mRNA after exercise; this minority of people had greater orthostatic intolerance compared with the majority (who had elevated mRNA) after exercise. Exercise-induced mRNA changes were not found in depression.

Metabolomics dysfunction has been demonstrated in 20 metabolic pathways in CFS,[12] [13] [96] and leads to significant reduction in some amino acids in CFS compared with control patients. The lack of energy in CFS may be caused by autoimmune and metabolomic dysfunction that reduces mitochondrial ATP production.[97] Amino acids follow 3 routes to fuel the tricarboxylic acid (TCA, Krebs) cycle in mitochondria. People with CFS had lower levels of category II amino acids that are converted to acetyl-CoA (isoleucine, leucine, lysine, phenylalanine, tryptophan, and tyrosine), and category III amino acids that are converted to TCA cycle intermediates (methionine, valine, histidine, glutamine, glutamate, proline, asparagine, and aspartate). By contrast, category I amino acids that are converted to pyruvate via pyruvate kinase were not different (alanine, cysteine, glycine, serine, and threonine). People with CFS had increased expression of mRNA for proteins that inhibit pyruvate kinase, namely pyruvate dehydrogenase kinase 1, 2, and 4 (PDK1, PDK2, PDK4), and sirtuin 4 (SIRT4).[12] Inhibition of pyruvate kinase means people with CFS cannot efficiently burn category I amino acids for energy production. Instead, category II and III amino acids are consumed as fuel, but because they are converted into TCA cycle intermediates, they generate less ATP. The result is reduced overall efficiency of oxidative phosphorylation and reduced ATP production. Each pyruvate kinase inhibitor has its own pattern of expression throughout the body; this may explain the wide range of functional deficiencies, such as the anaerobic threshold at low exercise workloads, that many people with ME/CFS experience.[98] [99] [100]

Although these findings indicate that significant advances have been made in identifying inflammatory, autoreactive, and metabolomics mechanisms in the pathophysiology of CFS/ME, these correlations do not indicate causation. There is no consensus on objective biomarkers as diagnostic features, or the characterisation of CFS phenotypes. These studies need to be replicated, and their findings confirmed in larger studies. The sensitivity and specificity of cytokines, neuromediators, leukocyte numbers and their functions (e.g., natural killer cells), and magnetic resonance imaging in patients with CFS have not yet been established compared with healthy controls; neither has CFS been definitively differentiated from fibromyalgia, chronic idiopathic fatigue, cancer-related fatigue, Gulf War illness, and other diseases in the differential diagnosis of CFS-like fatiguing, nociceptive, interoceptive, and cognitive dysfunction syndromes. Until these potential biomarkers have been clinically verified, the pathophysiology of CFS will remain unclear, and diagnosis will be based entirely on self-reported symptoms and functional impairments.

Excess mortality due to cardiovascular causes is indicated by a younger age of death in CFS (median = 58.8 years) compared with the overall US population (median = 77.7 years).[101] Causes for this large difference may include misdiagnosis of coxsackie enteroviral myocarditis and congestive heart failure as CFS, excessive stress responses leading to bradycardia or asyncope,[58] [102] [103] or other unknown cardiac risk factors.

Classification

US Institute of Medicine (IOM) 2015 proposed diagnostic criteria for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME)[4]

The IOM revised the clinical diagnostic criteria for CFS/ME in 2015 following a comprehensive analysis of the literature and expert consultation. Systemic exertion intolerance disease (SEID) has been proposed by the IOM as an alternative term for CFS/ME to emphasise that dysfunction involves the entire body. A significant improvement over the nominal (present vs. absent) scoring systems was to set standards for the severity (moderate, substantial, or severe intensity) and frequency (present at least half of the time) of symptoms.

A diagnosis of CFS/ME (SEID) is made if patients have the following 3 symptoms:

- Substantial reduction/impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months, is accompanied by fatigue that is often profound, is of new or definite onset, is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
- Post-exertional malaise (PEM)
- Unrefreshing sleep.

Patients are also required to have at least 1 of the following symptoms:

- Cognitive impairment
- Orthostatic intolerance.

Symptoms must be present at least half of the time and have moderate, substantial, or severe intensity.

Pain symptoms and systemic hyperalgesia were not included in the IOM criteria due to insufficient published data in people with CFS.

Canadian Consensus Criteria for myalgic encephalomyelitis (ME/CFS)[2] [3]

These criteria define persistent or recurring chronic fatigue as lasting for over 6 months, but not a lifetime. Impairment includes substantial reductions in occupational, educational, social, and personal activities compared with before the fatigue started. Classic ME/CFS symptoms are listed below and persist or recur during the prior 6 months of illness. Symptoms may predate the reported onset of fatigue.

- Post-exertional malaise, fatigue, or exhaustion. The activity or exertion causing problems may be relatively mild, such as walking up a flight of stairs, using a computer, or reading a book. It does not have to be strenuous exercise. There must be a loss of physical stamina, loss of mental stamina, rapid or sudden muscle fatigue, cognitive fatigue, post-exertional malaise and/or fatigue, and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 2 to 24 hours or longer.
- Unrefreshing sleep is present with problems of sleep quantity (e.g., inability to fall asleep, early awakening, or prolonged sleep), and rhythm disturbance (e.g., day/night reversal or frequent naps).
- Pain (or discomfort) that is widespread and migratory in nature, and manifests as achy and sore muscles. Myofascial pain, arthralgia, and stiffness in more than one joint but erythema, oedema, or other signs of inflammation are absent. Visceral pain includes non-cardiac chest pain (e.g., costochondritis, oesophageal spasm), epigastric, periumbilical, pelvic, or other abdominal pain. Headaches are more frequent and severe than prior to onset of the fatigue. Migraine is common, with localisation behind the eyes or in the back of the head, and with associated severe photophobia,

phonophobia, nausea, or emesis that are exacerbated by usual daily activities; avoidance behaviours include lying in a dark, quiet room.

Two or more neurological/cognitive manifestations are required:

- Impaired short-term memory (self-reported, or observed difficulty recalling information or events).
- Difficulty maintaining focused attention. Disturbed concentration may impair ability to remain on task or to screen out extraneous/excessive stimuli.
- Loss of visual depth perception.[14]
- Difficulty finding the right word.
- Frequently forget what wanted to say.
- Absent-mindedness.
- Slowness of thought.
- Difficulty recalling information.
- Need to focus on one thing at a time.
- Trouble expressing thought.
- Difficulty comprehending information.
- Frequent loss of train of thought.
- Sensitivity to bright lights or noise.
- Muscle weakness/muscle twitches.

At least one symptom from two of the following 3 categories:

- Orthostatic and visceral manifestations: complaints of dizziness or fainting; feeling unsteady when standing up; disturbed balance; palpitations with or without cardiac arrhythmias. Positive tilt table test for postural orthostatic tachycardia or neurally mediated hypotension. Shortness of breath, nausea, irritable bowel syndrome, or bladder pain.
- Thermal instability and appetite: recurrent feelings of feverishness and cold extremities; sweating episodes; intolerance of extremes of heat and cold; and documentation of subnormal body temperature. There may be marked changes in weight and/or appetite.
- Interoceptive manifestations: recurrent flu-like symptoms, repeated feverishness and sweats, non-exudative sore or scratchy throat, lymph nodes tender to palpitation with minimal or no swelling, and chemical irritant sensitivities to food, odours, or chemicals (non-allergic rhinopathy).

Exclusionary conditions:

- Medical: any active medical condition that may explain chronic fatigue, may be an exclusion. Such conditions include: untreated hypothyroidism; untreated sleep apnoea; narcolepsy; malignancies; unresolved hepatitis; multiple sclerosis; rheumatic autoimmune diseases; HIV/AIDS; severe obesity developing after the onset of ME/CFS (BMI greater than 40); coeliac disease; and Lyme disease.
- Psychiatric: conditions that are active or were treated in the past 5 years that may explain chronic fatigue. Such conditions include: schizophrenia and other psychotic disorders; bipolar disorder; active alcohol or substance abuse for the past 6 months (successfully treated substance abuse should not be considered exclusionary); active anorexia nervosa or bulimia nervosa; and depressive disorders with melancholic or psychotic features.

1994 US Centers for Disease Control and Prevention (CDC) case definition for chronic fatigue syndrome (CFS)

A diagnosis of CFS is made if the patient meets the established CDC diagnostic criteria.[1] If a patient does not meet the criteria, he or she may be diagnosed with idiopathic chronic fatigue. The reason for failing to meet diagnostic criteria for CFS should be specified.

The 1994 CDC diagnostic criteria for CFS include the following:[1]

Clinically evaluated, unexplained, persistent or relapsing fatigue must have been present for at least 6 months. The fatigue is not the result of ongoing physical exertion and resting, sleeping, and downgrading activity is non-restorative. The fatigue causes significant impairment in personal, social, and/or occupational domains and represents a substantial reduction in premorbid levels of activity and functional capacity.
The weakness of these criteria is the nominal scale of symptoms being present or absent without suitable gradations to define significant levels of impairment.

The concurrent presence of at least 4 of the following symptoms over a 6-month period:

- Impaired short-term memory
- Sore throat
- Tender lymph nodes/glands
- Muscular pain
- Joint pain in multiple areas
- New-onset headaches
- Unrefreshing sleep
- Post-exertional fatigue/malaise lasting more than 24 hours.

Oxford criteria for fatigue[9]

The Oxford criteria define CFS when mild to severe symptoms of fatigue, sleep disturbance, and myalgia are present.[9] No weight was given to the presence or absence of other complaints. Few medical conditions were articulated as exclusionary illnesses. Instead, the criteria recommended that other medical conditions were prospectively listed in study publications. Depression, anxiety, and chronic idiopathic fatigue (CIF) were permitted by the Oxford criteria.

Chronic idiopathic fatigue

Chronic idiopathic fatigue (CIF) is a diagnosis of exclusion when fatigue exists without sufficient other findings to designate CFS or other medical illnesses. Up to 30.5% of the population have chronic fatigue[10] and would meet the Oxford criteria for study inclusion.

Case history

Case history #1

A 40-year-old female physician and marathon runner develops a sudden-onset flu-like illness that does not resolve over a period of several weeks. Symptoms progress with persistent daytime fatigue, arthralgia without joint swelling or redness, sleep fragmentation, memory problems, new-onset migraine, and difficulties sustaining minor levels of physical activity. Activities that were previously well tolerated, such as walking to the shops, now induce body heaviness, difficulty with cognition, and sensation of instability. Tasks require far greater effort to complete, and are followed by an incapacitating reduction in working memory, total body pain, and listlessness. Her electronic medical record system at work has become incomprehensible, which has reduced her ability to see patients, and caused her manager to suspend her from work because of unproductivity. Resting between tasks, naps, and overnight sleep are unrefreshing and do not resolve symptoms. Sadness and frustration are an anticipated reaction to the abrupt chronic decline in health and stamina, and family and former peers have shown disbelief. Doctors have told her it's all in her head. Repeated physical examinations and routine laboratory studies over the last 6 months have been within normal limits. Hypothyroidism, Lyme disease, and infection with Epstein-Barr virus have been excluded.

Other presentations

Chronic fatigue syndrome (CFS) can present with multiple co-occurring problems, such as chronic pain, fibromyalgia, exertion-induced cognitive dysfunction ('brain fog'), migraine, anxiety, depression, irritable bowel syndrome (IBS), autonomic instability, and medication intolerance. Evaluation of comorbid conditions may complicate and extend the diagnostic process.

A small subset of patients with CFS-like symptoms may have chronic unresolved Epstein-Barr virus (EBV), cytomegalovirus (CMV), Q fever, or enterovirus (e.g., coxsackievirus) infection, or other locally endemic infectious diseases that can only be diagnosed at tertiary centres depending upon local referral patterns. Tender, palpable, posterior cervical triangle lymphadenopathy and fevers >39°C (>102.2°F) may be found in this minority. Sudden-onset, post-infectious cases may follow Epstein-Barr virus in adolescents and many microbial diseases in adults; it is not clear whether these represent a distinct pathophysiological phenotype compared with slower-onset CFS.

A further subset may have undiagnosed IgG subclass deficiencies. Autoimmune thyroiditis, family history of autoimmunity, and the outcomes of recent rituximab clinical trials suggest an autoimmune diathesis.

Among adolescents, CFS/ME is the most common cause of prolonged medical leave from school.[15] Adolescent CFS is associated with enhanced sympathetic nervous activity, low-grade systemic inflammation, and attenuated hypothalamus-pituitary-adrenal axis function.[16] In addition to fatigue, children and adolescents with CFS present with headaches, sleep disturbance, cognitive difficulties, and large activity reduction.[16] [17] Stomach ache and rash are more common than in adults. Younger age was associated with a more equal gender balance and sore throats but fewer cognitive symptoms. Adolescents were more likely to have headaches and comorbid depression. By comparison, adults experienced greater levels of anxiety, tender lymph nodes, palpitations, dizziness, general malaise, and pain.[18] Additional features are decline in academic performance, disruption of daily routines, loss of friends, dropping out of extracurricular activities such as sports, and irritability in response to their disease.

Families with CFS in several generations are known, but have not been systematically tested for genetic transmission, maternal transmission of mitochondria, penetrance in males and females, or in large enough numbers to generate useful genome-wide association studies. Studies in identical twins suggest 32% heritability.

One quarter of veterans deployed to the 1990 to 1991 Persian Gulf War, and 15% who were not deployed, developed a symptom complex that overlaps with CFS.[19] [20] However, Gulf War illness (GWI) is limited to the cohort who had exposures to military events from 1990 to 1991.[21] The Kansas Gulf War illness criteria[22] require 3 elements from the following 7 categories (numbers in parentheses are the odds ratios for the presence of each symptom in deployed veterans compared with non-deployed veterans who were in the US military from 1990 to 1991):

Fatigue/sleep problems: feeling unwell after exercise or exertion (4.28); fatigue (4.10); moderate or multiple fatigue symptoms (3.32); problems falling or staying asleep (2.98); not feeling rested after sleep (2.69).

Pain symptoms: pain in muscles (4.57); body pain, hurting all over (3.93); moderate or multiple pain symptoms (3.57); pain in joints (3.27).

Neurological/cognitive/mood symptoms: night sweats (5.33); feeling irritable or having angry outbursts (5.18); problems remembering recent information (4.92); symptomatic response to chemicals, odours (4.62); difficulty concentrating (4.60); trouble finding words when speaking (4.20); moderate or multiple neurological symptoms (3.94); low tolerance for heat or cold (3.67); feeling dizzy, lightheaded, or faint (3.35); feeling down or depressed (2.99); headaches (2.96); eyes very sensitive to light (2.62); blurred or double vision (2.49); numbness or tingling in extremities (2.33); tremors or shaking (1.95).

Gastrointestinal symptoms: nausea or upset stomach (4.25); abdominal pain or cramping (4.23); moderate or multiple gastrointestinal symptoms (3.63); diarrhoea (3.38).

Respiratory symptoms: difficulty breathing or catching breath (4.09); moderate or multiple respiratory symptoms (3.37); wheezing in the chest (2.51); persistent cough when don't have cold (2.20).

Skin symptoms: rashes (5.73); moderate or multiple skin symptoms (4.09).

Other symptoms: mouth sores (6.63); unusual hair loss (5.79); ringing in ears (4.06); self or partner has burning sensation after sex (3.75); hearing loss (3.34); sore or swollen glands in neck (2.94); sinus congestion (2.64); sore throat (2.39); problems with teeth or gums (2.04).

The overlap of symptoms with CFS is so striking that the US Department of Veterans Affairs uses CFS criteria to assess disability in GWI veterans. Fibromyalgia has generally been considered a different entity from post-viral CFS. The 1990 American College of Rheumatology criteria for the classification of fibromyalgia required widespread pain and the physical sign of tenderness to thumb pressure at 18 traditional tender points.[23] These criteria were revised in 2010 to remove the sign of systemic hyperalgesia and replace it with symptoms of fatigue, waking unrefreshed, cognitive dysfunction, and somatic complaints.[24] Many patients with CFS also meet these criteria, which leads to confusion about the proper diagnosis. There is a critical need to find objective ways to define these illnesses and distinguish their pathophysiological mechanisms, or to show that they are different presentations of a common underlying pathology.

Step-by-step diagnostic approach

Chronic fatigue syndrome (CFS):

- Is a chronic disabling disease of reduced productivity (chronic fatigue)
- Has a characteristic temporal pattern where minimal physical, cognitive, or emotional effort (an event in usual daily life) triggers immediate or delayed onset of significant, prolonged physical, cognitive, nociceptive, and interoceptive impairments (post-exertional malaise [PEM])
- The person with PEM does not return to normal capabilities after sleep because sleep patterns are disrupted and unrefreshing
- The level of impairment must be moderate to severe and present more than 50% of the time
- Additional features include orthostatic intolerance.

Diagnosis is based on:

- The positive, inclusive, requirements of prolonged functional impairment (fatigue), the significant reduction in functional capacity following physical, cognitive, emotional, or other exertion (PEM), and associated features of pain, interoceptive dysfunction, and orthostatic intolerance;
- Development of a problem list to facilitate the process of clinical evaluation; and
- Appropriate exclusion of other medical and psychiatric conditions in the differential diagnosis of chronic fatiguing, interoceptive, nociceptive, and cognitive illnesses.

Background: post-exertional malaise/fatigue (PEM)

PEM is the most characteristic feature of CFS/myalgic encephalomyelitis (ME). The Canadian Consensus Criteria ('Carruthers') provide the most discriminating case definition for CFS.[2] [3] They state that fatigue must be persistent or recurring over the past 6 months, but not lifelong. There must also be 'substantial reductions in previous levels of occupational, educational, social and personal activities compared to before the fatigue'. Post-exertional malaise, fatigue, or exhaustion is defined by analogy: 'The activity or exertion causing problems may be relatively mild such as walking up a flight of stairs, using a computer, or reading a book. It does not have to be strenuous exercise. There must be a loss of physical stamina, loss of mental stamina, rapid/sudden muscle fatigue, cognitive fatigue, post-exertional malaise and/or fatigue, and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. The recovery is slow, often taking 2 to 24 hours or longer.'

The case presentation can change over time as symptoms wax and wane and are transiently replaced by other complaints. The 6-month duration of symptoms is part of the criteria, but the diagnosis may be made in less than 6 months when the characteristic set of symptoms is present and alternative diagnoses have been excluded. This is particularly important because prompt diagnosis and reasonable limitation of activities may improve prognosis, particularly in adolescents. Because fatigue and pain are common complaints with broad differential diagnoses, periodic re-evaluation is of value to identify other medical conditions with similar symptoms to CFS/ME. A study involving a UK-based tertiary referral clinic found that 19% of people initially referred for CFS evaluation had other chronic medical diseases, 8% had primary sleep disorders, 6% had psychological or psychiatric illnesses, and 2% had cardiovascular disease.[136]

Fatigue refers to the cognitive and physical state of weariness with an inability to plan and execute usual tasks. Greater cognitive and physical effort is required to complete even routine daily tasks. In patients with idiopathic fatigue, the physical and cognitive exhaustion can be overcome by cessation of

physical, cognitive, emotional, or other activities combined with restful sleep. However, this is not the case in patients with CFS, as unrefreshing sleep is a characteristic finding. Chronic pain and hyperalgesia affecting muscles, joints, subcutaneous tissues, mucosal surfaces, and any other location innervated by somatic and sympathetic sensory neurons are common presenting symptoms in CFS.

Fatigue is a complex and multidimensional construct that has been defined as a feeling that interferes with usual functioning, a sense of diminished energy, and an increased need to rest, as well as physical or mental weariness resulting from exertion.[137] Maintenance of resting metabolic rate (energy required to maintain life at rest) accounts for 60% to 70% of all energy consumed by an individual over 24 hours. 'Fatigability' may represent an increase in this basal rate, addition of other energy demands, such as chronic inflammation, or limitations to the ability to generate the required energy levels. Greater fatigability may determine functional status by setting a lower activity limit aimed at maintaining the feeling of fatigue within a tolerable range. In this way, fatigue becomes a major determinant of sedentary behaviour. Interventions that target fatigue by increasing energy availability may reduce sedentary behaviour and disability.

The Central Fatigue Hypothesis[138] posits that exercise increases serotonin production in the brain, which in turn augments lethargy and loss of drive, resulting in reduced motor unit recruitment and, ultimately, poorer physical and mental efficiency. Exercise is a consistent component of fatigue reduction programmes, but these are rarely aimed at increasing specific daily activities or reducing individual barriers to physical activity. Patients with osteoarthritis who received activity strategy training to reduce fatigue burden in their homes experienced less pain and fatigue, and were more physically active than patients who participated in group exercise and received general health education.[139] People with sleep disturbances felt their condition improved with exercise, increased daily activity, bright-light therapy, and cognitive behaviour therapy;[140] [141] however, this suite of interventions has not been tested in CFS. Drug therapy has focused on inducing sleep rather than improving daytime function.

Fatigue may be viewed as a static sensation, perception, or emotion unrelated to activity level as in chronic idiopathic fatigue (CIF),[9] or a dynamic process of emotional and behavioural change induced by cognitive or physical effort (exertional exhaustion).[1] [2] [3] The Brighton Collaboration Fatigue Working Group considered fatigue to be a pervasive 'perception of a lack of energy, or a feeling of tiredness that affects mental and physical activity, which differs from sleepiness or lack of motivation'.[142] Under normal circumstances, excessive cognitive and/or physical effort leads to a sensation of tiredness that leads to cessation of effort; this fatigue is readily reversed after refreshing sleep. Fatigue can be considered pathological when it: occurs on a frequent or daily basis (e.g., more than 50% of the time); interferes with the ability to perform usual life activities; has a delayed onset after exertion (exertional exhaustion); induces characteristics of an acute illness, such as influenza, other viral prodrome, or autoimmune flare but without the ensuing infection or inflammatory tissue injury (post-exertional malaise); and leads to pervasive debility in working memory, task planning and execution, physical capacity, and a devalued sense of the potential rewards that may accrue from continued cognitive or physical efforts.[143]

There may be a general reduction in afferent signal filtering or protective neural barrier functions so that nociceptive, interoceptive, somatosensory, and autonomic afferent inputs lead to perceptions of heightened threat to personal wellbeing. Dysregulated sensory afferent perception at the level of the anterior insula may contribute to the photophobia and phonosensitivity as in migraine; vestibular dysregulation of orthostatic imbalance; chemosensitivity to inhalants; irritation of pharyngeal (sore throat), gastroesophageal (gastroesophageal reflux, non-cardiac chest pain), and intestinal (irritable bowel syndrome [IBS]) mucosal surfaces; mechanicosensitive stretch receptor activation in musculotendinous

junctions, myofascial, and joint capsules (myalgia, arthralgia, sensitivity to deep pressure with systemic hyperalgesia); and chemosensitive and mechanosensitive nociceptors throughout mucosal (e.g., dyspnoea) and fascial surfaces (e.g., tenderness of lymph nodes). If these sensory inputs are perceived as threats at the level of the amygdala, they may induce inappropriate and exaggerated protective physiological sympathetic and hypothalamic stress or fear responses.[58] [102] [103] Autonomic 'freeze, fight, fright, faint' stressor responses may contribute to peripheral manifestations including palpitations, sweating, orthostasis, vasodilation with sense of cutaneous warmth followed by heat loss and chilling, and urgency for defecation and urination. Many of these magnified or disinhibited perceptual experiences have been incorporated into CFS/ME criteria.[1] [2] [3]

The diagnosis of CFS is based on the characteristic, self-reported patient history of substantial disabling fatigue with PEM. Fatigue, which may be profound, must be of new or definite onset (i.e., not lifelong), persist for 6 or more months, and lead to a substantial reduction or impairment in the ability to engage in occupational, educational, social, or personal activities compared with pre-illness levels. The fatigue and associated symptoms are not due to ongoing excessive exertion, and are not alleviated by rest. PEM refers to the fatigue and cognitive dysfunction that may develop immediately following exertion of any sort or, more characteristically, after a delay of up to 24 hours. PEM does not respond to rest, and may last several days or longer.

Substantial fatigue and PEM have formed the basis of several criteria for CFS/ME. For example, the 1994 US Centers for Disease Control and Prevention (CDC) 'Fukuda' criteria requires substantial fatigue for 6 months plus 4 of the following 8 ancillary criteria:[1]

- PEM
- Sleep disturbances
- Problems with memory or concentration
- New onset of headaches after the fatigue
- Myalgia
- Arthralgia
- Sore throat
- Sore lymph nodes.

PEM with delayed onset of symptoms is an important aspect of CFS/ME.[144] Diagnosis in children should be considered after 3 months of unexplained fatigue and other symptoms, because prompt diagnosis and training in wellness, coping skills, and strategies for more efficient daily living offer a beneficial prognosis.[145] Treatment in children should focus on supportive symptom alleviation, physical function through tolerated levels of exercise, continued social development by participation in school and other activities, and emotional wellbeing within a well-adjusted family setting.[146]

A growing appreciation of the importance of PEM as a unique feature of CFS/ME led to the 2003 Canadian working case definition of CFS/ME, which clustered fatigue, PEM, sleep disturbance, and pain.[3] In addition, the Canadian Consensus Criteria requires at least 2 of the following self-reported neurological/cognitive symptoms:

- Impaired memory
- Difficulty concentrating
- Absentmindedness
- Loss of depth perception
- Photosensitivity

- Muscle weakness or twitching.

It also requires at least 1 symptom from 2 of the following 3 categories:

- Autonomic manifestations, including dizziness, neurally mediated hypotension, postural orthostatic tachycardia, palpitations, unsteadiness, disturbed balance, dyspnoea, bladder dysfunction, or IBS
- Neuroendocrine manifestations, including sensations of feverishness, heat and/or cold intolerance, excessive sweating, or abnormal appetite
- Immune manifestations, including recurrent flu-like symptoms, non-exudative sore or scratchy throat, repeated fevers and sweats, lymph nodes tender to palpitation but with minimal or no swelling, and new sensitivities to food, odours, or chemicals.

Features of pain were expanded to include cephalgia/headache, abdominal pain, myalgia, arthralgia, myofascial pain, and atypical chest pain.

The 2011 International Consensus Criteria for CFS/ME aimed to streamline the definitions by clustering a number of symptoms (e.g., PEM, fatigue, unrefreshing sleep) into categories of post-exertional neuroimmune exhaustion, neurological impairment, immunological impairment, and energy production/transport impairment. [International consensus criteria: Myalgic encephalomyelitis] [2] However, these categories are not justified by common underlying pathogenic mechanisms. For example, feverishness, flushing chills, and sweating have been interpreted as separate manifestations of infections. Using the principle of Occam's Razor, a more straightforward explanation is sudden onset of widespread cutaneous vasodilation with flow of red, hot, oxygenated blood to the upper epidermal plexus where it provides the appearance of flushing, the sensation of warmth by stimulation of non-myelinated temperature-sensitive cutaneous nerve endings, and radiant loss of heat. Sympathetic system activation leads to adrenergic tachycardia, and (cholinergic) sweating with water evaporation of water from the epidermal surface, and convective loss of heat. The perception of loss of heat is registered by cool-sensitive cutaneous unmyelinated nerve endings sensitivity to cool temperature and, when combined with the return of ambient temperature blood to the central circulation, leads to the sensation of a chill. Further sympathetic responses of piloerection (goosebumps) and vasoconstriction lead to pallor. The need to rewarm the core induces shivering and heat retention behaviours, such as pulling on additional clothes, crawling into bed, and using heating pads. There is no need to postulate a viral infection based on this autonomic cycle.

In 2015, the US Institute of Medicine (IOM) reviewed the evidence for CFS/ME and proposed the term 'systemic exertion intolerance disease' (SEID), which emphasises the 3 primary symptoms of the disease: sustained fatigue, PEM, and unrefreshing sleep. [US Institute of Medicine: CFS/ME criteria] [4] Symptoms should persist for at least 6 months and must be moderate to severe intensity during at least half of this time. Either cognitive impairment or orthostatic intolerance must also be present according to the IOM criteria, but pain symptoms are not required.

Background: cognitive impairment

Cognitive impairment can be triggered by excessive effort of any kind. It may manifest as 'brain fog', 'confusion', and/or inability to focus or concentrate on usual activities, find the right word, or do arithmetic. Working memory, the very-short-term resource needed to perform tasks effectively, accounts for the loss of train-of-thought. Working memory is impaired more than short-term or long-term episodic memory. Memory impairment is not permanent or progressive as in mild cognitive impairment or Alzheimer's disease.

Task-relevant details enter the salience network of conscious perception via the anterior insula and its communications with the dorsal anterior cingulate cortex to set appropriate goals for the task at hand. Dorsolateral frontal and inferior lateral parietal cortical regions of the executive control network store information that may be relevant to task completion in a working memory registry, and maintain attention to the task.

Normal thresholds in the dorsal horn of the spinal cord and brainstem block afferent information about extraneous cutaneous and somatic sensation, nociception, interoception from visceral organs, and distracting light, sound, smell, and other sensory stimuli not related to the task at hand. However, if these thresholds are reduced, then lower levels of afferent stimuli may breach these barriers, reach the level of conscious perception, and distract the salience and executive control networks away from the task. This disruption can lead to activation of the default mode network and intrusion into the task completion network. Activation of default modes in the ventromedial prefrontal and medial parietal cortex leads to internal autobiographical memory recall and analysis, and mind wandering.

Background: orthostatic intolerance

Orthostatic intolerance is a component of the systemic exertion intolerance disease (SEID) criteria.[4] Orthostatic intolerance is the presence of dizziness, lightheadedness, nausea, spatial disorientation, visual changes, or malaise, which are specifically linked to assuming or maintaining an upright posture. Symptoms abate once supine.[147] It may limit activities such as standing in line or shopping. Postural changes in vital signs may not be found despite standing for 1 or 2 minutes, and may require 10 minutes to become measurable.

The differential diagnosis of orthostatic intolerance includes initial orthostatic intolerance. It is defined by lightheadedness lasting less than 30 seconds after standing, with a transient drop in beat-to-beat blood pressure of more than 20 mm Hg systolic and 10 mm Hg diastolic blood pressure. This is due to rapid redistribution of blood to the pelvis and lower limbs, with a lag in sympathetic activation and muscular (mechanical) blood return to the central circulation. Sustained hypotension within the first 3 minutes of standing may be due to neurogenic causes with systemic sympathetic failure of adrenergic vasoconstriction and parasympathetic dysfunction, or to non-adrenergic hypovolaemia and vasodilator drugs.

Postural orthostatic tachycardia syndrome (POTS) is defined by chronic orthostatic symptoms plus postural tachycardia of ≥30 beats per minute (≥40 beat per minute in adolescents) that occurs within 10 minutes of standing and in the absence of hypotension. POTS may be neuropathic with loss of regional vasoconstriction that is insufficient to cause systemic hypotension, and with reduced vagal activity that allows sinus tachycardia to occur. Hyperadrenergic POTS is driven by increased sympathetic acceleration of the atrial sinus node. Autoantibodies to adrenergic beta 1, beta 2, and alpha 1a receptors may account for differences in symptom profiles in some people with POTS.[148]

Postural vasovagal syndrome leads to loss of consciousness and falling. It has a sudden onset after standing and is caused by hypotension and reduced cerebral perfusion. Spontaneous recovery to the normal conscious state occurs after lying down. Cardiac output is reduced due to dilation of vascular beds from loss of systemic or splanchnic-hepatic adrenergic vasoconstriction or splanchnic venodilation. Acute baroreflex dysfunction may contribute. Prolonged Valsalva maneuvers with strong parasympathetic slowing of sinus rhythm, reduced preload and cardiac output may cause bradycardia with transient loss of consciousness.

Most patients with orthostatic intolerance have exercise deconditioning (90%) with reduced oxygen uptake at maximum effort during cardiopulmonary exercise testing (VO2max <85% of predicted by maximum).[147] [149] This is especially the case in chronically bedridden and inactive people,[149] although caution is required if post-exertional malaise is provoked. CFS represents a special case because maximal exercise on 2 days leads to a significant 10% to 15% decrease in VO2max that is not seen in other diseases.[98] [99] [100]

Unlike orthostatic intolerance, POTS is not more prevalent in CFS than the general population for either adolescents (18.2% vs. 17.4%, respectively), or adults (5.7% vs. 6.9%, respectively).[150] The sole defining feature of POTS that distinguishes it from other forms of orthostatic intolerance is symptomatic postural tachycardia of ≥30 beats per minute after being upright for 5 minutes.[151] People with POTS and positive heads-up tilt table test results include sporadic and familial cases.[152] Families with POTS show vertical transmission including male-to-male, dominant expression with incomplete penetrance, and a 2.5:1 female:male ratio.[148] [153] Autoantibodies in POTS would be consistent with other reports of autoreactivity in CFS.[148]

Orthostatic intolerance without postural tachycardia includes structural vestibular damage with vertigo and unsteadiness; vestibular migraine, vestibular paroxysmia, Meniere's disease, and functional dizziness (persistent postural perceptual dizziness without other findings).[154] Vertiginous episodes induce anxiety with increased attention to head and body position, proprioception, and motion with bilateral contraction of leg muscles.

Diagnostic criteria and differential diagnosis

The more selective and evidence-based case designation criteria from the CDC, the Canadian working group, and the IOM are preferred to the older Oxford criteria[9] and the UK National Institute of Health and Care Excellence (NICE) criteria.[155] This is in part due to the inclusion of mental dysfunction and overlap with psychiatric disease in the Oxford criteria and NICE criteria.[156]

A limitation of CFS studies using the Oxford criteria is that patients with affective disorders and milder fatigue may be recruited, which can bias outcomes in favour of cognitive behavioural therapy and graded exercise.[157] [158] As a result, studies using the Oxford criteria[157] [158] [159] [160] should be referred to as fatigue studies because they do not require moderate to severe fatigue and post-exertional malaise that the more rigorous CDC and Canadian definitions of CFS mandate. This is a major problem because conclusions based on people with mild fatigue cannot be extrapolated to the much more severe CFS cases. Conversely, biomarkers, metabolomics, autoreactive, and other CFS pathologies defined using the more rigorous CFS criteria cannot be generalised to milder fatigue in chronic idiopathic fatigue or as defined by the Oxford criteria. It is inappropriate to apply any treatments defined using the Oxford criteria to the more severe entities of CFS and SEID.[4] This is strongly supported by the National Institutes of Health (NIH) Pathways to Prevention working group that recommended the retirement of the Oxford criteria because it may impair progress and cause harm.[161]

The diagnostic process for CFS is complicated by several factors. Significant functional impairments are predominantly based on self-reported symptoms, which can be measured using a rating scale, such as the functional capacity scale (score ranges from 0 [no energy with severe symptoms] to 10 [no symptoms]) proposed by the International Association for CFS/ME. [International Association for CFS/ME: Functional capacity scale] [4]

Fatigue is a common symptom reported by patients, and it may be related to multiple disorders. There are presently no reliable or specific biological causes, biomarkers, objective findings, or laboratory anomalies

that are indicative of CFS. Chronic idiopathic fatigue does not have the ancillary symptoms of CFS/ME, such as post-exertional malaise.

Overlapping conditions, such as fibromyalgia and major depressive disorder, are common and may predate, coincide with, or follow the onset of CFS.[162] Depression is characterised by anhedonia, agitation or retardation of motion, feelings of guilt and worthlessness, and recurrent thoughts of death, which do not characterise patients with CFS. Only fatigue, cognition, and insomnia symptoms overlap with CFS, unless all CFS physical manifestations are considered to be somatisation. Physical symptoms shared by functional somatic syndromes, such as migraine and IBS, are common but not specific to CFS. A multidisciplinary team may be required, with referral to appropriate specialists as part of the diagnostic exclusionary process.

Successful therapy begins with a trustful relationship with the patient, and may proceed with mindfulness, biofeedback, measured breathing with prolonged exhalation, eye movement desensitisation and reprocessing, grounding interventions to interrupt immobility, cognitive behavioural therapies, and occasionally clonazepine, clonidine, propranolol, serotonin reuptake inhibitors, or dual serotonin and norepinephrine (noradrenaline) reuptake inhibitors as adjuncts for anxiety. These threat analysis and defence responses are not typical of CFS. Their presence helps identify alternative conditions in the differential diagnosis such as PTSD, phobias, agitated depression and other states. When present, they provide insights into individual coping strategies and offer opportunities for recognising perceived threats in daily life and abrogating their effects.

Co-occurring conditions and medications may also further complicate and prolong assessment and management strategies. Medical exclusions for CFS include the following:[144]

- Organ failure (e.g., emphysema, cirrhosis, cardiac failure, chronic renal failure)
- Chronic infections (e.g., HIV/AIDS, hepatitis B or C)
- Rheumatic and chronic inflammatory diseases (e.g., SLE, Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis)
- Major neurological diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurological deficits)
- Diseases requiring systemic treatment (e.g., organ or bone marrow transplantation, systemic chemotherapy, radiation of brain, thorax, abdomen, or pelvis)
- Major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency)
- Primary sleep disorders (e.g., narcolepsy).

Sleep apnoea may be a co-existing but independent finding that should be treated to see whether the fatigue and unrefreshing sleep improve. Conditions found at examination that exclude CFS include adverse effects of medications, chronic sleep deprivation or poor sleep hygiene, untreated hypothyroidism, untreated or unstable diabetes mellitus, and body mass index greater than 40.

Psychiatric exclusions include lifetime diagnoses of bipolar affective disorders, schizophrenia, delusional disorders, dementia, organic brain disorders, and alcohol or substance abuse within 2 years before onset of the fatiguing illness. Major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia that have resolved for more than 5 years before the onset of the current chronically fatiguing illness should not be considered exclusionary.

Physical examination may be normal. Autonomic intolerance, such as orthostatic hypotension and postural orthostatic tachycardia, may be present but it is unlikely to be detected by lying and standing

vital signs. Tenderness to palpation may indicate fibromyalgia according to the 1990 American College of Rheumatology criteria.[23] Dysregulated visual accommodation, swaying on standing during Romberg testing, altered physical appearance of the pharyngeal mucosa, and frontal release signs have not been well documented for CFS diagnosis.

Physicians are cautioned against using extensive and costly evaluative and diagnostic procedures given the absence of known biological underpinnings of CFS and the lack of verified biomarkers.

Key historical factors

Prior to the onset of significantly impairing chronic fatigue, patients typically report normal levels of physical fitness, activity, and energy. However, fatigue may have existed in a gradual or relapsing-remitting pattern before becoming chronic. It is not clear whether sudden onset of severe fatigue in <30 days versus a pattern of more chronic gradual worsening represents distinct syndromes with different aetiologies, such microbial infections, or acute onset of autoimmune disease, as opposed to more chronic development of dysfunctional pathologies. Some patients report historical patterns of overactivity and underactivity prior to disease onset. In some cases, documented viral infections or stressful events may predate the onset of chronic fatigue.

Patients may complain of increased sensitivity to astringent chemicals and odours (e.g., house cleaning fluids, bleach, cigarette smoke, gasoline), waxing and waning of flu-like symptoms (e.g., malaise, myalgia, feverishness), nausea, intolerance of ambient hot or cold temperatures, and dizziness. Although clinical symptoms and presentation may mimic viral infections or other known medical conditions, a review of the clinical history may not reveal any biological cause for the fatigue. History should address other conditions that are implicated by each patient's individualised differential diagnosis.

- Post-exertional malaise (PEM). The key historical feature is to document post-exertional malaise. Delayed onset of dysfunction is typical in CFS. People with CFS have often reduced their levels of exertion to avoid this severe trigger of exacerbations. It is useful to ask about their usual daily activities that do not induce PEM, and find some mild exertional activities that may cause a short period of several hours of fatigue that responds to rest. These may be as intensive as cognitive exertion at work, time spent in meetings, computer tasks, walking the dog, or shopping. Then more demanding tasks such as going out with friends, mowing the lawn, or housework can be addressed for their propensity to induce immediate or delayed-onset fatigue that may last hours to overnight or several days. Patients may actively avoid this level of activity unless they have no other options.

  A diary of usual levels of fatigue and pain can be kept to establish their typical level of fatigue, and to show the increases in fatigue severity that follow the exertional activity. This tool can help teach patients to organise their time to marshal their energy reserves, enabling them to complete essential tasks before immediate fatigue symptoms, or before the point that is likely to induce a delayed exacerbation.
- Fatigue. The vocabulary of fatigue is poorly developed in the English language. Seeking alternative words that distinguish the intense sensation of overwhelming tiredness from sleepiness; descriptions of typical scenarios of dysfunction in daily life; exploring the coincidence of weariness with total body pain, heaviness, or joint stiffness; and identifying features associated with the onset of disorganised or ruminating thought processes that prohibit efficient task planning (brain fog) are all ways to discriminate CFS from other fatiguing states. Establishing the time course of symptom progression after an emotional, physical, cognitive, or social stressor is important for establishing triggers of immediate and delayed functional deficits that may otherwise not appear to be logically

connected (e.g., physical activity leading to cognitive dysfunction). Clinicians may learn from their CFS patients' experiences to become more adept at identifying CFS and its many presentations.

- Chronic pain. Chronic pain in muscles and joints affecting the total body but without swelling or acute inflammation is a central tenet of CFS, but has traditionally been considered as fibromyalgia. The 2010, 2011, and 2016[163] recommendations for fibromyalgia evaluate the widespread distribution of pain in anatomical sites, but now add severity scores for fatigue, sleep, cognitive and somatic complaints to diagnose fibromyalgia with 'fibrofog'. These modifications have removed the physical sign of thumb pressure causing pain as an assessment of systemic hyperalgesia and replaced it with several key elements of CFS diagnostic criteria. This increases the overlap between CFS and fibromyalgia without offering any objective or semi-objective criteria to distinguish the pathological disease states. Analysis of the 2010 criteria generates clusters of pain-predominant and fatigue-predominant patients who may correspond to potential fibromyalgia and CFS subgroups.[164] [165] Because the fibromyalgia criteria do not investigate PEM, the finding of exertional exhaustion may become more valuable for distinguishing CFS.
- Headache. New-onset headaches must be distinguished from a return of perimenstrual migraine or post-concussion/post-mild traumatic brain injury headaches. The severity of migraine in CFS is often underappreciated, particularly by physicians who do not endorse the concept of CFS as a legitimate disease. Migraines may occur several days per week to per month and isolate the patient from family and work. The light and sound sensitivity can be moderate during interictal periods between migraines but lead to sound avoidance, extensive use of sunglasses, and closed curtains during the daytime. Sensory sensitivities become more overwhelming during migraines and lead to avoidance behaviours. Treatment with triptans or topiramate can greatly enhance capacity to work and enjoy family activities.
- Sleep alteration. Sleep alterations are almost universal in CFS, but are difficult to distinguish from the poor sleep hygiene of the general population. Insomnia may be accompanied by rumination about tasks not completed. Sleep interruption is common, and should be distinguished from overactive bladder and other other medical interruptions during sleep. Prolonged sleep until noon, frequent napping during the day or falling asleep after returning from work or social events are common. Sleep apnoea may occur with the usual risk factors, such as obesity, but the addition of continuous positive airway pressure therapy (CPAP) or oral appliances to aid breathing are unlikely to reverse the overall CFS symptom profile. In patients with posttraumatic stress disorder (PTSD) after Gulf War illness, CPAP face masks may precipitate traumatic memories and nightmares of the 1990 to 1991 war.
- Cognitive dysfunction. Cognitive dysfunction follows a pattern of disrupted working memory, executive control, fragmented salience network function, and default mode network intrusion. Task completion requires intact sensing and assessment of task-relevant details from the environment, including proprioceptive and vestibular afferent information about body position and movement.

  Returning to the task at hand requires reestablishing salience and executive control functions, and switching off the default mode of the internally directed distractor task in a process that may be similar to rebooting a computer. Recycling through this process is inefficient and tiring, and may contribute to the cognitive dysfunction of brain fog. Discussing the mental effort that is required to complete a task can be an effective way to document these alterations of working memory, concentration, and cognitive dysfunction, and to provide insight for both the physician and patient with CFS that can lead to recognition of these alterations and development of cognitive training to reduce their impact.

- Orthostasis. Orthostatic intolerance is a feature of the systemic exertion intolerance disease (SEID) criteria. Symptoms include dizziness, lightheadedness, unsteadiness, impaired balance, vertigo, or fear of falling that last for more than 30 seconds after standing up. If autonomic dysfunction is present, then postural hypotension with a decrease of systolic blood pressure of greater than 20 mmHg, or POTS with an increase in heart rate to greater than 30 beats per minute or to above 120 beats per minute may occur.

Key physical examination factors

There are no typical objective findings from physical examination of a patient with CFS. However, signs of visual dysfunction in CFS/ME are under investigation.[166] Patients may present with a variety of signs and symptoms not specific to CFS, such as a low-grade fever, resting and orthostatic tachycardia, orthostatic hypotension, lightheadedness or imbalance when standing up but without changes in vital signs, tender non-enlarged lymph nodes, abdominal tenderness below the xiphisternum and inferolateral to the umbilicus (gastritis and IBS, Chia's sign), joint hypermobility/laxity, and muscle and joint hyperalgesia ('tender points').

Tenderness to palpation may indicate fibromyalgia according to the 1990 American College of Rheumatology criteria.[23] The presence of allodynia may support a diagnosis of chronic widespread pain.

Autonomic intolerance such as orthostatic hypotension and postural orthostatic tachycardia may be present, but are unlikely to be detected by lying and standing vital signs. Postural orthostatic tachycardia syndrome (POTS) is diagnosed by an incremental increase in heart rate of ≥30 beats per minute (≥40 beats per minute in adolescents) between 5 minutes of recumbent rest, and 5 minutes of standing.

Dysregulated visual accommodation, swaying on standing during Romberg testing, altered physical appearance of the pharyngeal mucosa, and frontal release signs have not been well documented for CFS diagnosis. Signs that are not typical of CFS/ME, such as palpable lymphadenopathy and high fever require further investigation to exclude other medical conditions.

Key laboratory tests

The standard battery of laboratory testing is typically normal in patients with CFS. Extensive laboratory or imaging studies are not indicated. The NIH has recommended the following panel of tests for patients presenting with persistent, debilitating fatigue lasting at least 6 months:[167]

- FBC with WBC differential
- HIV test
- ESR
- C-reactive protein (CRP)
- Urea, creatinine, and electrolytes
- Blood glucose
- Calcium, phosphorus
- TSH
- Alkaline phosphatase, aspartate and alanine aminotransferases (AST/ALT)
- Total protein, albumin, and globulin.

A serum ferritin test may be valuable for the evaluation of borderline anaemia that may exacerbate the effects of decreased circulating volume and dysautonomia leading to orthostatic imbalance. Other

laboratory tests may include antibody tests for gluten sensitivities/coeliac disease, antinuclear antibody (ANA) test, and rheumatoid factor. The panel should be ordered to establish a baseline when first establishing care with a patient. ANA has been frequently stated to be positive in CFS, so it is prudent to determine whether there is a high titre (suggestive of SLE) or low titre. Rheumatoid factor has not been as well defined in prospective fashion.

More extensive or repeat laboratory testing is not recommended due to lack of sensitivity or specificity of laboratory studies in diagnosing CFS. The panel should be used to exclude, identify, or treat other clinical conditions contributing to fatigue (e.g., hypothyroidism). Extensive serological testing for: hepatitis B or C, Epstein Barr, cytomegalovirus and other herpes viruses, and *Borrelia burgdorferi* and other Lyme disease; related organisms have not been effective at identifying cohorts with treatable infections. Drug seeking behaviours and evidence of illicit or prescription drug abuse can be identified by blood or urine drug testing. A history of chronic recurrent purulent sinusitis and bronchitis may warrant testing for hypogammaglobulinaemia. Haemoglobin A1c is useful to assess comorbid type 2 diabetes mellitus with fatigue, neuropathy, or autonomic dysfunction that may appear similar to CFS.

Risk factors

Strong

female sex

- The condition is approximately 2 to 3 times more common among women than men.[36]

autoimmunity

- A prospective randomised double-blind placebo-controlled study of rituximab in chronic fatigue syndrome (CFS) found B-cell mediated autoimmunity in up to 60% of people with CFS.[42] [43] [104] Rituximab responders may have personal or family histories of autoreactive disease. Additional clinical trials and new biomarkers are required to fully establish the role of autoimmune mechanisms in CFS.

Weak

positive family history of CFS

- Rates of chronic fatigue syndrome (CFS) are higher among first-degree relatives.[105] A study of female twin pairs found concordance rates of 38% and 11% among monozygotic and dizygotic pairs, respectively.[106]
- Conclusions regarding heritability in CFS are limited given that no population-based familial or twin studies have been conducted.

genetic factors

- Twin studies suggest premorbid emotional distress may be mediated by genetic factors to increase risk for chronic fatigue illnesses.[107]
- Gene polymorphisms may be present in serotonin transporter, glucocorticoid, and mineralocorticoid receptors, and other systems in chronic fatigue syndrome (CFS).[108] Glutamate-receptor, ionotropic, kinase 2 (GRIK2) and neuronal PAS domain protein 2 (NPAS2) were identified by both single-nucleotide polymorphism (SNP) and peripheral blood mononuclear cell gene expression analyses in a genome-wide association study of 40 patients with CFS and 40 non-fatigued control patients.[109] In another genome-wide association study involving 42 patients with CFS and 38 control patients, 430

SNPs in non-coding and 12 SNPs in coding regions of the genome were identified.[110] However, reproducibility of these findings from independent studies has been poor.

- A study involving 193 CFS/ME cases and 196 age- and gender-matched controls has found some mitochondrial DNA haplogroup-specific SNPs associated with certain neurological, inflammatory, and/or gastrointestinal symptoms, but no single gene alteration was associated with susceptibility to CFS/ME.[111]

gut microbiome

- Stool-sample microbiomes have shown higher relative abundance of Bacteroidetes and lower abundance of Firmicutes and Actinobacteria in patients with CFS compared with healthy controls.[73] Maximal exercise increased stool Firmicutes/Bacilli abundances in patients with CFS, and altered the ability of gut bacteria to cross the intestinal barrier and enter the peripheral circulation. Changes in gut permeability after exertion may be relevant to CFS pathophysiology.[112]

infections

- Epstein-Barr virus (EBV) infection (infectious mononucleosis) evolves into chronic fatigue syndrome (CFS) in 13% of adolescents after 6 months.[113] The rate drops to around 4% at 24 months indicating a high rate of remission in adolescents.
- Enteroviral gastritis has been proposed as a cause of CFS but has not been independently confirmed.[114] [115] [116]
- CFS/myalgic encephalomyelitis (ME) has been reported sporadically after cases of Q fever, parvovirus, and other infections.[117] [118] [119] CFS may also follow acute Lyme disease. The entity of chronic Lyme disease and its symptomatic overlap with CFS requires more mechanistic and pathological data for comment.
- An uncontrolled case series of 741 people with CFS/ME reported a 15% positive response rate to various combinations of antivirals plus intravenous immunoglobulin.[120] Such reports demonstrate the need for randomised double-blind placebo-controlled studies of rationally selected patients with CFS/ME and therapies with identification of putative agents to better understand the association between infection and CFS. However, antiviral medications have not been successful in treating the broad spectrum of CFS.[121] [122] [123]
- To date, there is no consistent evidence to support any viral or other infectious agent in the majority of CFS/ME cases.[29] [41]

psychological factors

- Psychological factors, personality traits, and past history of physical or sexual abuse have not been definitively associated with chronic fatigue syndrome (CFS). Childhood trauma,[124] personality traits such as 'action-proneness' and emotional instability,[107] [125] and historical patterns of persistent overactivity and underactivity may confer risk for CFS in adulthood.[126] [127] [128] Depression severity is associated with disability.[129]
- The relationship of depression with CFS must be tempered by the high rate of psychopathology in the general population. In one US-based study carried out in Georgia, mood disorders (18%), post-traumatic stress disorder (PTSD; 6.6%), and generalised anxiety disorder (GAD; 5.8%) were associated with fatigue, lower education, female sex, and Hispanic ethnicity.[130]
- In one UK-based study, suicide-specific mortality was found to be significantly increased in patients with CFS compared with the general population (standardised mortality ratio 6.85, 95% confidence interval: 2.22 to 15.98; P = 0.002). This indicates the need for physician awareness and compassion in the care of these patients.[131]

ancestry

- Community surveys found that English-speaking white Americans had a lower risk of chronic fatigue syndrome (CFS) than Latino, African-American, or Native American people.[26] [27] In England the prevalence of CFS among people of Pakistani ancestry has been found to be 3.5% (odds ratio 4.1; 95% confidence interval 1.6 to 10.4), while its prevalence is 0.8% in white people.[39]

joint hypermobility/laxity

- Joint hypermobility is associated with fatigue in children,[132] chronic fatigue syndrome (CFS; 21%),[133] anxiety, postural orthostatic tachycardia syndrome (POTS), irritable bowel syndrome (IBS), other functional somatic syndromes, and brainstem alterations on magnetic resonance imaging.[134] However, impaired range of motion in the spine and limbs have also been reported in adolescents with CFS.[135]

History & examination factors

Key diagnostic factors

persistent disabling fatigue (common)

- Not alleviated by sleep, rest, or activity restriction. The pattern of fatigue may be persistent or relapsing and remitting, and may be present for over 6 months in adults.
- Fatigue may show mild remissions but without a return to the usual, previous state of health and activity. Fatigue must be moderate to severe and persist for more than 50% of the time.[4]

post-exertional malaise/fatigue (PEM), exertional exhaustion (common)

- Minor levels of physical and/or mental exertion are poorly tolerated. Low levels of physical or cognitive activity or emotional stressors lead to exacerbations of fatigue, pain, and cognitive dysfunction. Such exacerbations may have immediate onset or be delayed by several hours, and they may persist for hours, overnight, or several days despite rest and reduced activity. Exertional exhaustion is the characteristic finding in CFS.
- PEM is a required symptom for the US Institute of Medicine (IOM) definition of systemic exertion intolerance disease (SEID),[4] and for the Canadian working group definition of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME).[2]

short-term memory and/or concentration impairment (common)

- Disruption of short-term memory, particularly very-short-term working memory, is common, whereas long-term memory disruption is uncommon.
- Attention or concentration difficulties, word-finding difficulties, and slowness of information processing may also be apparent.
- Indicates dysfunction of the brain's working memory system, which is the very-short-term resource needed for doing tasks quickly. Working memory is impaired more than short-term or long-term memory. Memory impairment is not permanent or progressive as found in mild cognitive impairment or Alzheimer's disease.

sore throat (common)

- Episodic discomfort that may be associated with flu-like complaints and tender lymph nodes.

generalised arthralgia without inflammation (common)

- Widespread joint pain may be compounded by physical deconditioning secondary to excessive resting.
- There are typically no signs of joint inflammation.
- Joint laxity, which can be the cause of diffuse joint pain, exists in around 21% of patients with chronic fatigue syndrome (CFS).[133]

headache/migraine with onset after the fatigue (common)

- New-onset headaches or significant change in headache locus or severity.
- Comorbid migraine and tension headaches are common, but are often not treated.

unrefreshing sleep (common)

- Sleep disruption may be characterised by hyposomnia, hypersomnia, or fragmented sleep.
- Sleep disruption compounded by behavioural changes to sleep cycle (e.g., increased resting and sleeping during normal waking hours).
- Poor sleep hygiene with reversal of sleep and wake cycles may occur.

orthostatic intolerance (common)

- Dizziness, lightheadedness, spatial disorientation, or malaise after standing up from a recumbent or resting position.[4] [147]
- May limit activities such as standing in a queue or shopping. Postural changes in vital signs may not be found despite standing for 1 or 2 minutes.

diffuse muscular, tendon, fascial, and other pain (common)

- Widespread muscular pain may be compounded by physical deconditioning secondary to excessive resting.
- The definition of systemic exertion intolerance disease (SEID) by the Institute of Medicine (IOM) does not include pain due to lack of evidence from the published literature. However, pain may be more common than reported in the literature.

tender lymph nodes/glands (uncommon)

- Tender axillary, cervical, and/or subauricular nodes.
- Discrete, palpable lymph nodes suggest infectious, neoplastic, or other diagnoses.

Other diagnostic factors

age of onset (adolescence and 30 to 50 years) (common)

- Peak ages of onset are in adolescence and between 30 and 50 years.[26] [37]

flu-like symptoms (malaise, myalgia, feverishness) (common)

- Frequent waxing and waning of flu-like symptoms, including malaise, myalgia, and feverishness.

dizziness/lightheadedness (common)

- Dizziness at rest and during exertion. Dizziness or lightheadedness when standing up that may seem like motion sickness.

anxiety, affective disorder, atypical depression (common)

- Around 40% of chronic fatigue syndrome (CFS) patients have clinical depression and/or anxiety, which is similar to many other chronic medical illnesses.[162] Anxiety, depressed affect, and maladaptive coping skills may predate or co-occur with CFS.

- Other stigmata of depression, such as anhedonia, psychomotor agitation or retardation, feelings of worthlessness, excessive or inappropriate guilt, and recurrent thoughts of death and suicide, are not typical of CFS but instead indicate comorbid depressive disorder. Thoughts of suicide should be openly addressed, and all patients at risk for suicide immediately referred to the local emergency department or another appropriate resource centre.

sensations of altered temperature (common)

- Symptoms such as intolerance of ambient hot or cold temperatures, feverishness, sweating, chills, or the need to wear extra clothing compared with others may occur.

exertion-induced cognitive dysfunction (affecting working memory, not persistent) (common)

- Exertion-induced cognitive dysfunction affecting working memory. As it is not persistent, the cognitive dysfunction differs from that which occurs with neurodegenerative diseases.

irritant sensitivities (uncommon)

- Patients with chronic fatigue syndrome (CFS) commonly become more sensitive to astringent chemicals and odours, such as house cleaning fluids, bleach, cigarette smoke, and gasoline. Airway symptoms may be akin to multiple chemical sensitivity disorder. Nasal congestion and rhinorrhoea may be due to non-allergic rhinopathy with hyperactive cholinergic reflexes, which may be responsive to anticholinergic nasal sprays such as ipratropium or tiotropium bromide. Rates of positive allergy skin tests and ranges of IgE levels appear to be similar for patients with CFS and those without CFS.[168]

feverishness (uncommon)

- The sensation of 'feverishness' is common, but chronic low-grade fever or fluctuating fever and subnormal temperatures are not present in chronic fatigue syndrome.

Diagnostic tests

1st test to order

Test	Result
FBC with WBC differential • Ordered as a baseline investigation to exclude active infection. • Not diagnostic. • Repeat only as clinically indicated.	**normal**
ESR • Ordered as a baseline investigation to exclude inflammatory process. • Not diagnostic. • Repeat only as clinically indicated.	**normal to low**
CRP • Ordered at baseline to exclude inflammatory processes. • Not diagnostic. • Repeat only as clinically indicated.	**normal**

Test	Result
comprehensive metabolic panel • Ordered as a baseline investigation to exclude renal or liver dysfunction, acute infection, or malignancy. • Includes serum electrolytes, urea/creatinine, calcium, phosphorus, aspartate transaminase (AST)/alanine transaminase (ALT), total protein, albumin, globulin. • Fasting blood sugar assesses for diabetes. • Correction of abnormalities, if found, should be undertaken and symptoms assessed with follow-up. • Repeat only as clinically indicated.	**normal**
TSH • Ordered as a baseline investigation to exclude hypothyroidism. • Correction of abnormalities, if found, should be undertaken and symptoms assessed with follow-up. • Repeat only as clinically indicated.	**normal**
antinuclear antibody (ANA), rheumatoid factor • Ordered at baseline to exclude inflammatory markers for connective tissue diseases. ANA has been frequently stated to be positive in chronic fatigue syndrome, so it is prudent to determine whether there is a high titre suggestive of systemic lupus erythematosus, or a low titre. Rheumatoid factor has not been as well defined in prospective fashion. • Not diagnostic. • Repeat only as clinically indicated.	**negative**
HIV antibody test • To exclude HIV infection.	**negative**

Other tests to consider

Test	Result
heads-up tilt table test if symptomatic orthostatic intolerance • Orthostatic tachycardia/hypotension diagnostic for postural orthostatic tachycardia syndrome (POTS).	**excludes POTS**
2-day cardiopulmonary exercise testing • The test's threshold for change in VO2 between days 1 and 2, sensitivity, and specificity have not yet been defined to make this a diagnostic test. • Some people report severe exacerbation of post-exertional exhaustion after testing.[98] [99] [100] [169] Exacerbations should be considered diagnostic of post-exertional malaise.	**a significant decrease in VO2max on the second day's test is strong evidence of CFS**
serum ferritin • Ordered to investigate borderline anaemia that may exacerbate the effects of decreased circulating volume and dysautonomia leading to orthostatic imbalance.	**normal**
HbA1c • Alternative test to fasting blood sugar to exclude diabetes mellitus.	**normal**

Test	Result
urine toxicology screen • Ordered as a baseline investigation to exclude drug abuse if this is suspected by history. • Not diagnostic. • Repeat only as clinically indicated.	**negative**
antibody tests for gluten sensitivity/coeliac disease • If history suggests gluten sensitivity, consider testing for IgG anti-tissue transglutaminase (tTG) autoantibody, and IgA anti-endomysial autoantibody (note: false-negative results if patient is IgA-deficient). • Not diagnostic. • Repeat only as clinically indicated.	**normal**
brain magnetic resonance imaging (MRI) • Only ordered to exclude multiple sclerosis if suspected. • Not diagnostic. Some studies suggest findings of T2 hyperintense signal changes in subfrontal white matter that are nonspecific.[67] • Repeat only as clinically indicated.	**normal**

Differential diagnosis

Condition	Differentiating signs / symptoms	Differentiating tests
Migraine	• Recurrent headaches lasting 4 to 72 hours. • Headache has at least 2 of the following characteristics: unilateral location; pulsating quality; moderate or severe pain intensity; or aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs). • Nausea and vomiting, and/or photophobia and phonophobia must also be present during headache episode. • Auras occur in approximately 33% of chronic fatigue syndrome (CFS) patients with migraine.[170] • Approximately 40% to 70% of patients with migraine meet the criteria for fibromyalgia and/or CFS.	• Clinical diagnosis.

Condition	Differentiating signs / symptoms	Differentiating tests
Anxiety	• Generalised anxiety disorder and other forms of anxiety can present with dizziness, dry mouth, dyspnoea, sensation of choking, palpitations, tachycardia, nausea, stomach churning, excessive sweating, hot flushes, chills, trembling, or paraesthesiae.	• Feelings that objects are unreal (derealisation), that one's self is distant or not really here (depersonalisation), fear of losing control or dying, and restlessness suggest an anxiety disorder. Difficulty falling asleep may be due to excessive worrying.
Major depressive disorder	• Feelings of sadness, hopelessness, helplessness, worthlessness, and/or guilt. • Loss of interest. • Psychomotor retardation or agitation. • Anhedonia. • Somatisation. • Thoughts of suicide.	• Diagnosis is clinical but the affective dysfunction does not follow an infection, and is not typically associated with new onset of pain, migraine, irritable bowel, or autonomic dysfunction. It is generally improved by exercise instead of exhibiting post-exertional malaise and exhaustion. • Other tools such as the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire,[171] and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) (SCID) can be used to assist diagnosis.
Reactions to life crises, other psychological or psychiatric illness	• Signs and symptoms will depend on the psychological or psychiatric condition.[172]	• Diagnosis is clinical. • Other tools such as the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire,[171] and the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) (SCID) can be used to assist diagnosis.
Sleep apnoea	• Periodic breathing, transient dyspnoea, or headaches upon arising may be observed.	• Overnight polysomnography is abnormal.

Condition	Differentiating signs / symptoms	Differentiating tests
Fibromyalgia	• Widespread pain affecting many of the 18 designated anatomical locations (1990 fibromyalgia criteria).[24] • Pain or cramps in the lower abdomen.	• Clinical diagnosis. • Clinical testing of systemic hyperalgesia (tenderness) by tender point counts no longer required.[23] [173] The 2010 criteria that include fatigue, sleep, cognitive, and somatic complaints make it difficult to distinguish CFS from fibromyalgia.
Dehydration or volume depletion (e.g., due to diuretics)	• Postural hypotension, postural tachycardia.	• Recumbent and standing vital signs.
Infectious mononucleosis	• Fever, and enlarged spleen and/or liver. Waxing and waning symptoms. Periods of symptom remission suggestive of dormant EBV. • More likely to be seen in adolescents.	• Positive for Paul-Bunnell heterophile antibody testing. • Positive EBV-specific antibodies. IgM indicates acute infection. IgG indicates prolonged humoral immune response. • Atypical lymphocytes; elevated WBC count. • Positive reaction to the monospot test.
Irritable bowel syndrome (IBS)	• Manning criteria for IBS: abdominal pain or discomfort relieved by defecation; mild tenderness in lower quadrants (without a mass); alteration of bowel habits; abdominal bloating or distention; passage of mucus with stool. • Rome III criteria for IBS: recurrent abdominal pain or discomfort with improvement with defecation; onset associated with a change in frequency of stool; onset associated with a change in form of stool.[174]	• Clinical diagnosis. • Bristol stool scale is a visual scale for assessing the appearance (form) of stool that can be used for IBS subtyping.[175]

Condition	Differentiating signs / symptoms	Differentiating tests
Chronic pelvic pain, vulvodynia	• Complex pain syndrome characterised by constant or intermittent generalised vulva pain (generalised vulvodynia), or localised burning sensations in the vestibule area when pressure is applied (vestibulodynia, or vulvar vestibulitis syndrome), in the absence of infectious, inflammatory, or neoplastic findings, or a specific clinically identifiable disorder of any kind (i.e., idiopathic). • Vulvar pain of at least 3 to 6 months duration. • Pain with insertion during sexual intercourse, which impacts negatively on a woman's quality of life. • Meets International Society of Vulvovaginal Diseases criteria for vulvodynia.[176]	• Physical examination of introitus. • Typically, vulvar tissue with vulvodynia appears normal, without infection or skin disease.
Orthostatic intolerance	• Orthostatic intolerance is defined by the dizziness, lightheadedness, nausea, spatial disorientation, visual changes, or malaise that are specifically linked to assuming or maintaining an upright posture. Symptoms abate once supine.[147] • History may include a cause of autonomic neuropathy (e.g., diabetes), neurological disorder (e.g., Parkinson's disease), volume depletion (e.g., due to diuretics or blood loss), causative medication, or other defined aetiology.	• Focused testing when indicated may provide aetiology.

Condition	Differentiating signs / symptoms	Differentiating tests
Postural orthostatic tachycardia syndrome (POTS)	• Sustained heart rate increment of >30 bpm (>40 bpm for adolescents) within 5 minutes of standing or head-up tilt in the absence of orthostatic hypotension; standing heart rate >120 bpm. Other differentiating symptoms include visual blurring/tunnel vision, palpitations, tremulousness, weakness (especially in the legs), hyperventilation, shortness of breath, chest pain, and acral coldness or pain.[151]	• Exacerbated by exercise. • Tilt-table testing may be required for autonomic nervous system evaluation.
Lyme disease (and other endemic illnesses in different areas)	• Acute presentation of 'bull's eye' rash.	• Clinical observation of rash; exposure to endemic Lyme areas. • Positive enzyme-linked immunosorbent assay (ELISA) and Western blot test.
Hypothyroidism	• Cold sensitivity; brittle fingernails/hair. • New-onset urticaria.	• Thyroid stimulating hormone is raised in primary hypothyroidism.
Cardiovascular dysfunction	• Cardiovascular risk factors or symptoms/signs of cardiac ischaemia or failure may be present.[101]	• Echocardiography. • Cardiology evaluation.
Mild traumatic brain injury (mTBI)	• Many symptoms after mTBI are similar to chronic fatigue syndrome.[177] • History of trauma.	• Brain magnetic resonance imaging.
Gulf War illness (GWI)	• Military exposures in the 1990 to 1991 cohort of the first Persian Gulf War. • The symptoms are similar to chronic fatigue syndrome, but there may be more severe irritable bowel syndrome with diarrhoea, irritability, or PTSD.	• None in clinical practice.

Condition	Differentiating signs / symptoms	Differentiating tests
Cancer and post-chemotherapy fatigue	• Fatigue is a common occurrence during and after cancer, and following treatment with chemotherapeutic drugs.[178]	• Unlike chronic fatigue syndrome, cancer fatigue had good responses to CBT and exercise training,[179] and may not show reductions in regional brain volumes.[180]
Other medical exclusions for CFS	• Medical exclusions for chronic fatigue syndrome include the following.[144] • Chronic infections (e.g., HIV/AIDS, hepatitis B or C). Fatigue has also been reported following recovery from Ebola virus infection.[181] • Rheumatic and chronic inflammatory diseases (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis). • Major neurological diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy, or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurological deficits). • Diseases requiring systemic treatment (e.g., organ or bone marrow transplantation, systemic chemotherapy, radiation of the brain, thorax, abdomen, or pelvis). • Major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency). • Primary sleep disorders (e.g., narcolepsy). • Attention deficit hyperactivity disorder.[182]	• Directed to suspected differential diagnosis.

Diagnostic criteria

A complicating factor in chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is the presence of 9 sets of subjective clinical criteria. The 1994 US Centers for Disease Control and Prevention (CDC) 'Fukuda' criteria are most widely used.[1] The preeminence of post-exertional malaise (PEM) is central to

the Canadian consensus ('Carruthers') criteria[3] [2] and the 2015 US Institute of Medicine (IOM) criteria.[4] The term 'systemic exertion intolerance disease' (SEID) has been proposed by the IOM as an alternative term for CFS/ME. The Oxford criteria[9] and the UK National Institute of Health and Care Excellence (NICE) criteria[155] are not recommended, due in part to their inclusion of mental dysfunction and overlap with psychiatric disease.[156] Caution should be used when interpreting CFS/ME studies using the Oxford criteria.[159] [157] [158] [160] The US National Institutes of Health (NIH) Pathways to Prevention working group has also suggested that the Oxford criteria should be 'retired' as it may impair progress and cause harm.[161] Overall, the Canadian consensus criteria are most widely accepted.[3] [2]

US Institute of Medicine (IOM) 2015 proposed diagnostic criteria for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME)[4]

The IOM revised the clinical diagnostic criteria for CFS/ME in 2015 following a comprehensive analysis of the literature and expert consultation. Furthermore, the term 'systemic exertion intolerance disease' (SEID) has been proposed by the IOM as an alternative term for CFS/ME.

A diagnosis of CFS/ME (SEID) is made if patients have the following 3 symptoms:

- Substantial reduction/impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months, is accompanied by fatigue that is often profound, is of new or definite onset, is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
- Post-exertional malaise (PEM)
- Unrefreshing sleep.

Patients are also required to have at least 1 of the following symptoms:

- Cognitive impairment
- Orthostatic intolerance.

Symptoms must be present at least half of the time and have moderate, substantial, or severe intensity.

Pain symptoms and systemic hyperalgesia were not included in the IOM criteria due to insufficient published data in CFS.

International consensus criteria (2011)[2]

An international panel of researchers, clinicians, and patient advocates have challenged the narrow definition of chronic fatigue syndrome and instead have proposed changing the diagnostic label to myalgic encephalomyelitis. Significant departures from the CDC diagnostic criteria include:

- No longer requiring the 6-month symptomatic period before diagnosis
- Less specific emphasis on fatigue, and rather a broader consideration of symptom clusters.

However, the symptom clusters are not organised by pathophysiological mechanisms, decreasing the value of these proposed myalgic encephalomyelitis diagnostic criteria:

- Post-exertional neuroimmune exhaustion (compulsory feature) characterised by marked, rapid physical and/or cognitive fatigability in response to exertion; post-exertional symptom exacerbation; post-exertional exhaustion; prolonged recovery period; and/or low threshold of physical and mental fatigability resulting in a substantial reduction in pre-illness activity levels.

- Neurological impairments (at least 1 symptom from 3 of the following symptom categories): (a) neurocognitive impairments (difficulty processing information; short-term memory loss); (b) pain (headaches; non-inflammatory somatic pain); (c) sleep disturbance (disturbed sleep patterns; unrefreshing sleep); and (d) neurosensory, perceptual, and motor disturbances (inability to focus; sensory defensiveness; muscle weakness).
- Immune, gastrointestinal, and genitourinary impairments (at least 1 symptom from the following 5 symptom categories): (a) recurrent or chronic flu-like symptoms that worsen with exertion; (b) susceptibility to viral infections with prolonged recovery periods; (c) gastrointestinal tract difficulties; (d) genitourinary problems; and (e) sensitivities to food, medications, odours, or chemicals.
- Energy production/transportation symptoms (at least 1 symptom from the following): (a) cardiovascular intolerance; (b) respiratory difficulties; (c) loss of thermostatic stability; and (d) intolerance of extreme temperature.

1994 US Centers for Disease Control and Prevention (CDC) criteria

The 1994 CDC diagnostic criteria for chronic fatigue syndrome include the following:[1]

Clinically evaluated, unexplained, persistent or relapsing fatigue lasting at least 6 months. The fatigue is not the result of ongoing physical exertion, and resting, sleeping, and downgrading activity is non-restorative. The fatigue causes significant impairment in personal, social, and/or occupational domains and represents a substantial reduction in premorbid levels of activity and functional capacity.

The concurrent presence of at least 4 of the following symptoms over a 6-month period:

- Impaired short-term memory or concentration
- Sore throat
- Tender lymph nodes/glands
- Muscular pain
- Joint pain in multiple areas
- New-onset headaches
- Unrefreshing sleep
- Post-exertional fatigue/malaise lasting longer than 24 hours.

Oxford criteria

The Oxford criteria define CFS as when mild to severe symptoms of fatigue, sleep disturbance, and myalgia are present.[9] No weight was given to the presence or absence of other complaints or their severities. Few medical conditions were articulated as exclusionary illnesses. Instead, there has been a recommendation that other medical conditions be prospectively listed in study publications. Depression, anxiety, and chronic idiopathic fatigue (CIF) were permitted by the Oxford criteria.

Step-by-step treatment approach

The primary goals of management are to provide a supportive healthcare environment with a team of occupational therapists, physiotherapists, and other appropriate therapists who will manage symptoms and improve functional capacity. Physicians provide measured investigations to evaluate the differential diagnosis of each individual patient.

General considerations

There are no curative medications or treatments for chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME). Pharmacotherapy is indicated to treat pain, migraine, sleep disturbance, and comorbid conditions, such as irritable bowel syndrome (IBS), anxiety, and depression. The chronic disability leads to a sedentary lifestyle that may foster deconditioning of muscular, cardiovascular, and autonomic nervous systems. This provides the rationale for supervised, very low impact exercise if a suitable, well-tolerated programme can be individualised for each patient. However, exercise may be counterproductive in severe and/or bedridden CFS because the treatment may induce post-exertional malaise (PEM) and prolonged exercise-induced exacerbations. Mandated exercise programmes with predetermined goals cannot be endorsed because of their potential to harm patients whose primary problem is exercise-induced loss of function.

Long-term management by a coordinated supportive team is beneficial to maximise functional capacity. Compassionate counselling by a doctor, occupational therapist, social worker, or psychotherapist can address many of the concerns of people with CFS; it can also a framework to help them restructure their lives to conserve their energy for necessary activities of daily living and gradually increase social and occupational interactions. Like all other chronic illnesses, about 40% of people with CFS have reduced affect, sadness, or anxiety that may respond to problem-focused cognitive behavioural therapy (CBT) and other allied 'brain-retraining' programmes. Antidepressants may have exaggerated adverse effects, such as weight gain, which promote iatrogenic type 2 diabetes and metabolic syndrome, and their long-term health consequences.

The primary goals of treatment are to manage symptoms and improve functional capacity. A possible strategy may be to provide counsel to patients every 3 months and to reassess any other health issues and treatable diseases.

Treatment is complicated by strong differences in opinions between patients with CFS and their support groups compared with medical specialists. CFS support groups preferred gradual exercise and pacing (91% vs. 50%), complementary and alternative medicine (74% vs. 16%), and pharmacological therapy (71% vs. 42%), while physicians recommended rehabilitative measures (28% vs. 94%).[183] These results indicate a large gulf between patients and doctors about treatment expectations of the rehabilitative therapies national guidelines and systematic reviews recommend, and indicate that patients are disillusioned and wary of the graded exercise and CBT those reviews espouse.

Physicians are encouraged to conduct a thorough treatment history, identify all physicians and healthcare professionals (e.g., chiropractor, acupuncturist) currently involved in the patient's care, and obtain a list of prescribed medications, over-the-counter medications, vitamins, supplements, and homeopathic remedies. For some patients with CFS, their treatment regimens may be complicated and extensive. A general treatment strategy in such cases may involve a stepwise process of simplifying the treatment regimen across time (e.g., gradually reducing the number of medications). Treatment interventions tend to be multidimensional and tailored to each patient's circumstances. The focus of treatment should be

orientated toward symptom management and functional improvement, and away from repeated, extensive diagnostic procedures, or ongoing referrals to additional specialists.

A systematic review has examined 35 randomised clinical trials evaluating pharmacological and non-pharmacological treatments for CFS.[184] There is low-quality evidence showing rintatolimod, an immunomodulatory poly I:C double-stranded RNA, to be effective in improving exercise performance in patients with CFS.[185] [186] [187] Clinical trials evaluating the effectiveness of galantamine,[188] hydrocortisone,[189]immunoglobulin G (IgG),[190] valganciclovir,[123] valaciclovir,[191] inosine pranobex (isoprinosine),[192] fluoxetine,[193] and various complementary medicines in patients with CFS have yielded inconclusive results. Counselling therapies and graded exercise therapy have been shown to improve fatigue, function, global improvement, and work impairment in some CFS clinical trials when compared with no treatment, relaxation, or support.[184] Counselling therapies have also been shown to improve quality of life.

Anxiety, depression, and the risk of suicide are important issues in all chronic illnesses, including CFS. Antidepressant treatment effects in clinical trials may be biased toward the approximately 40% of people with chronic diseases who develop affective disorders. The presence of inflammation in CFS pathology may contribute to inflammatory dysaffective disorders (IDD) that will require a reassessment of potential treatment options. The subset of CFS patients with comorbid depression may have biased the clinical trials of antidepressants leading to their recommendation for CFS treatment. Furthermore, antidepressants do not correct the exertional malaise, cognitive dysfunction, pain, orthostatic intolerance, or other cardinal features of CFS.

Initial treatment plan

After infectious and medical causes have been excluded, a treatment plan can be developed with the patient. Initial treatment should be individualised based on the spectrum of most severe complaints. One approach is to focus on the most severe symptoms and address each one at a time through a series of scheduled visits. The objective is to improve functional capacity.

Initial treatment begins with counselling and supportive care.[194] The evidence base for CFS treatments is limited.[184] Treatments for CFS are palliative and restorative; there are no curative treatments. Time and patience are required to assist the newly diagnosed patient in developing the skills needed to cope with this debilitating condition. A supportive family, medical team, and home environment will facilitate adaptation to a new diagnosis of CFS and its management. A comforting environment may include pleasurable low-effort activities such as listening to music or observing nature. These activities may generate wellbeing; reduce symptoms of anxiety, depression, and distress; and lessen the perception of fatigue.[195] [196] Cognitive strategies such as coping skills to reduce anger, worry, and catastrophising can improve tolerance of this condition.[197] [198] Many resources are available through CFS and ME support groups. Successful support groups have effective leadership and positive programming that avoids simply exchanging complaints.

Graded exercise

Exercise programmes that are low-intensity, individualised to the patient and their personal activities, and allow for variation in effort based on each day's symptoms will provide patients with CFS with a 'paced' approach to treatment, graded low-impact exercise, CBT, or medications.[101] [199]

The 'deconditioning hypothesis' proposes that CFS is perpetuated by reversible physiological effects of bed rest and avoiding activity, and that exercise will reverse consequences of deconditioning.[157] [200]

[201] Exercise is presumed to prevent and reverse muscle atrophy and loss of sympathetic orthostatic reflexes, and therefore improve physical function. Exercise may be beneficial for recovery of athletes, healthy individuals, cardiac patients, and others who may experience temporary immobility, but it is not clear whether patients with CFS respond in the same way. Graded exercise has been proposed to treat 'typically Western diseases' associated with reduced activity in the modern lifestyle, such as accelerated ageing, premature death, low VO2max, cognitive dysfunction with reduced short-term memory and recall, anxiety, depression, chronic pain, constipation, and metabolic syndrome.[202] [203] Low grade inflammation related to interleukin-6 (IL-6) has been proposed as a common denominator.[204] However, this highly generalised view and exercise prescription may not apply to the theories of metabolomics dysfunction and post-exertional malaise in CFS.

There is widespread concern among CFS physicians that mandated exercise programmes can cause significant patient deterioration because of the exercise-induced musculoskeletal pain, neurocognitive impairment, weakness, and prolonged bed rest patients may require to recover from them.[205] What appears to be deconditioning may in fact represent the inability to generate adequate ATP for muscular work,[12] and intolerance of exercise-induced acidosis as the diagnostic PEM epitomises.[205]

Exercise to about 75% of predicted heart rate (220 minus age) was fatiguing but reasonably well tolerated by people with CFS in a small study.[206] Exercise-induced symptoms may be reduced by mindfulness, meditation, and structured breathing programmes that attempt to reduce the heightened sense of effort intrinsic to PEM, and instead allow the patient to focus on reducing on the symptom severity generated by the exercise protocol itself.[201] [207] [208] It is not clear whether exercise has benefits for the perception of muscular or cognitive efforts, maintenance of muscle strength, or correction of autonomic instabilities in CFS.

A meta-analysis of RCTs has suggested that exercise therapy is generally beneficial for sleep, physical function, and self-perceived general health in patients with fatigue diagnosed using the outmoded Oxford criteria of minimal fatigue.[160] However, this analysis did not report drop-out rates or measure the consequences of exercise therapy on immediate and delayed PEM, pain, and cognitive dysfunction. Furthermore, no conclusions could be drawn on the effects of exercise therapy on quality of life, anxiety, depression, and use of health service resources. Exercise therapy was shown to be more effective than pacing, but similar to passive non-physical CBT. The use of the Oxford criteria in 5 of the 8 studies included in the analysis is an important limitation of the review. These criteria include patients with altered mood and depression, which will bias study outcomes because exercise has a direct beneficial effect in affective dysfunction.[209] It is not clear whether these results from people with mild fatigue can be applied to those with more severe CFS.[210] The potential selection bias is supported by the high prevalence of antidepressant medication use among patients in the analysis. The lack of stratification by severity of PEM symptoms, non-adherence among patients with moderate and severe disease due to intolerance to the exercise programmes, and potential under-reporting of harms (e.g., delayed exercise-induced cognitive dysfunction or chronic pain) are also potential limitations of the review.[211] The concerns regarding harms reporting are supported by results of 2-day maximal exercise stress tests, where people with CFS/ME do well on the first day, but have reduced cardiopulmonary function on the second day,[100] followed by exacerbation of fatigue and other CFS symptoms.[169] Future graded exercise studies should stratify people with CFS/ME by severity, start at the lowest tolerated exercise level, identify reasons for patient withdrawal, and report levels of exercise that induced PEM.

Patients with CFS may tolerate an individualised activity plan developed in collaboration with knowledgeable and experienced professionals.[37] The activity plan must aim to minimise the negative

effects of exertion on impaired aerobic function. Exercise therapy should not take priority over activities of daily living, but should be designed to improve lifestyle habits and stamina, rebuild self-confidence, and definitely not cause iatrogenic PEM.

Guidelines from the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) suggest that patients with severe CFS (i.e., functional capacity rating of 1 to 3) may benefit from in-home assisted range-of-motion and strengthening exercises by a skilled provider as these patients are generally bedbound or homebound. [International Association for CFS/ME: Functional capacity scale] [37] Exercises can be carried out lying down if the patient is unable to sit or stand. Interval training can begin with gentle passive stretching for intervals of 90 seconds or less to improve mobility, with a rest between intervals until complete recovery has occurred. Additional intervals can be added if stretching exercises do not trigger post-exertional symptoms. For patients with mild to moderate CFS (i.e., functional capacity rating of 4 to 5) resistance training can begin with elastic bands or light weights. As endurance improves, short-duration interval training such as leisurely paced walking can be added. This may start with 1 minute of walking per day, with increases of 1 minute per day at weekly intervals as tolerated. The brain training involved in cognitively preparing and planning exercise may be as beneficial as the exercise itself. Patients with higher functioning (i.e., functional capacity rating of 5 to 9) can begin interval training with leisurely paced walking, swimming, or peddling on an exercise bike.[196] The initial duration may vary from 1 to 10 minutes per day depending on how much the patient can do without provoking symptom flares. Adaptive yoga and tai chi may also be beneficial.[37]

Multidisciplinary rehabilitation treatment

Multidisciplinary rehabilitation treatment is more effective in reducing long-term fatigue severity than CBT in patients with CFS.[212]

Body awareness therapy, coached by a physiotherapist, aims to establish an increased awareness and consciousness of healthy bodily symptoms and their relation to physical function, psychological wellbeing, and social interaction.

CBT facilitates the patient to identify unhelpful, negative emotion-provoking thoughts, dysfunctional behaviours, and cognitive patterns, and uses a goal-oriented, systematic procedure to enhance self-esteem. Unlike conventional CBT, immediate feedback is provided. Gradual reactivation is then scheduled, with the gradual increase in activities (e.g., fitness and swimming) under close supervision by physiotherapists and occupational therapists. The therapy aims to meet the patient's personal goals for increased activity at home.

Pacing refers to the self-managed recognition and awareness of psychological and physical limitations, which allow the patient to complete activities before the onset of extreme fatigue or pain.

Mindfulness is non-elaborative, non-judgemental awareness state centred within the present, in which each thought, feeling, or sensation is acknowledged and accepted as it is. The emphasis is on the immediate experience in the present moment. Thoughts, emotions and sensations are observed without making judgements about their truth, importance, or value, and without trying to escape, avoid, or change them. The intent is to increase self-awareness and self-acceptance, reduce reactivity to passing thoughts and emotions, and improve the ability to make adaptive choices. In patients who have been chronically ill, mindfulness skills have a positive effect on depression, mood, and activity level.[213]

Normalisation of the sleep/wake rhythm begins by stopping daytime napping, and proceeds to improving the quality of sleep through relaxation therapy. Social reintegration is supervised by the occupational

therapist and social worker by making plans to return to work or school, and to increase social activities. Instruction is provided to prevent relapse.

Cognitive behavioural therapy (CBT)

The biopsychosocial model of CFS and its treatment with CBT has been adopted by many governmental organisations with the aims of eliminating many presumed psychogenic and socially induced factors that maintain illness behaviours.[205] The literature does not justify the biopsychosocial model of CFS when studies are limited to CFS patients with moderate to severe fatigue, and PEM in accordance with the Centers for Disease Control and Prevention (CDC) and Canadian Consensus Criteria.[1] [2] [3] Protocols are not standardised as there are significant differences in outcomes between different countries.[214] General practitioners and patients have reported negligible to minimal improvements in patients receiving CBT, with the improvements equivalent to counselling and supportive care.[194] Studies of CBT in people with CFS report significant improvements in mental health scores, fatigue scores, and 6 minute walking,[215] but effect sizes were low (Cohen's d estimated at 0.30 to 0.35),[216] and were not corrected for multiple comparisons.[217] Studies using the Oxford criteria of mild fatigue may not be applicable to CFS diagnosed by CDC or Canadian Consensus Criteria that require moderate to severe fatigue with PEM.[1] [2] [3]

Around 40% of patients with CFS have clinical depression and/or anxiety, which is similar to many other chronic medical illnesses.[162] There is little investigation of reactive depression, anxiety, or stress reactions secondary to the illness compared with interest in a premorbid history of depression or generalised anxiety disorder. A suicide evaluation is standard practice for all patients who appear to be clinically depressed or highly stressed. In one UK-based study, suicide-specific mortality was found to be significantly increased in patients with CFS compared with the general population (standardised mortality ratio 6.85, 95% confidence interval: 2.22 to 15.98; P = 0.002) indicating the need for physician awareness and compassion in the care of these patients.[131] Age at death from suicide was younger in people with CFS (41.3 years) compared with that in the overall US population (47.4 years).[101]

CBT is a psychotherapeutic intervention aimed at modifying thinking, feeling, and behaviour, and focuses on current problems. Therapists lead discussions and follow a structured style of graded interventions to address problems one at a time. For patients with CFS, CBT is usually accompanied by a graded activity programme. CBT may help in dealing with a new diagnosis of CFS, improve coping strategies, and assist with rehabilitation. CBT and low-impact exercise therapy are cost-effective with a good probability of yielding symptom and functional improvements relative to speciality medical care alone.[218] Cost may also be decreased by self-management programmes.[219] However, the prospect that CBT can change the illness beliefs of a patient, and that graded activity can reverse or cure CFS, is not supported by post-intervention outcome data.[157] [220] [221] Furthermore, in routine medical practice CBT has not yielded clinically significant long-term benefits in CFS.[222] [223] [224] [225] A retrospective analysis of several stress management studies found small benefits for exertional malaise, chills, fever, and restful sleep, but only in the face-to-face rather than the telephone-administered therapy.[226]

CBT should be planned by the practitioner as 'brain retraining sessions' to improve attention, working memory, and organisation of daily routines (e.g., going to social events, shopping, and other outings) to take advantage of periods during the day where fatigue is felt the least. Family sessions can help educate and inform spouses, children, parents, and other significant persons about the disabling nature of CFS.[225] Although referral to a mental health professional with expertise in CBT has been recommended regardless of CFS severity, the absence of a qualified CBT psychologist, social worker, nurse, or other practitioner with CFS training limits its availability.

Medications

Few medications have had beneficial effects on the post-exertional malaise, fatigue, cognitive dysfunction, or long-term sleep disruption in CFS.[227] Pain medications improve this symptom but do not alter the systemic hyperalgesia. No drug therapies have been licensed for CFS. Palliative treatments are directed at specific symptoms.

There is currently no evidence showing that any single drug therapy regimen is more effective than another for CFS.[184] RCTs assessing antidepressants, anticholinergics, corticosteroids, and hormones in CFS have produced equivocal findings.[29] [228]

In depressed CFS patients, adjunctive pharmacotherapy with selective serotonin-reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants may be prescribed in an effort to treat comorbid depression, improve mood, and reduce fatigue.1[B]Evidence In one RCT, fluoxetine (an SSRI) was shown to be effective for depression in patients with CFS, but not for functional work capacity or fatigue.[193] In another RCT, duloxetine (an SNRI) improved mental fatigue, pain, and global measure of severity in patients with CFS, but had no effect on the primary outcome of fatigue.[229]

A meta-analysis of SNRIs in fibromyalgia examined 5 studies of duloxetine against placebo, and 5 studies of milnacipran (an SNRI) against placebo (n = 6,038 participants). The drugs had small incremental benefits over placebo in reducing pain, with limited benefits for fatigue and quality of life but none for sleep.[230] Anticonvulsants may be used for mood regulation, sleep disruption, and pain control, although the effectiveness of these medications is limited. Improvements with drug therapy may take several weeks, but more severe levels of depression may predict a slower treatment response.[231]

Choice of antidepressant drug should be based on the side-effect profile of the drug and the patient's initial response to treatment. Possible side effects of SSRIs, SNRIs, and tricyclic antidepressants include sedation, orthostatic hypotension, and increased appetite and weight gain, which may worsen fatigue and autonomic lability in some patients. Given that some patients may not tolerate the side effects of certain drugs, starting drug treatment at a low subtherapeutic dose, and gradually increasing to therapeutic levels over time as tolerated is usually recommended. Moreover, drug treatments are mostly used off-label and, therefore, should be managed carefully to prevent synergistic or other adverse events.

The absence of effective therapies indicates a significant need for research to clarify the pathophysiology of CFS and to identify rational drug targets. Randomised double-blind placebo-controlled studies will be needed to identify drugs that are beneficial in CFS.

Other treatments

Migraine appears to be present in around two thirds of patients with CFS.[170] Migraine may be present but overlooked if an aura is absent. A trial of a selective serotonin (5-HT1) receptor agonist (triptan) may show whether they are beneficial or not, and is the usual starting point for migraine therapy. Chronic daily headache may be present, and may respond to topiramate based on anecdotal findings.

Nasal symptoms of congestion, fullness, and rhinorrhoea (sinus) may respond to frequent nasal saline sprays and menthol gels. Menthol stimulates a cooling sensation via transient receptor potential M8 ion channels on nasal mucosal A-delta nerve fibres, which in turn induces a reduction in the work of breathing.[232] Anticholinergic drugs such as ipratropium reduce rhinorrhoea. Products that are indicated for mucosal use should be used to avoid damaging the nasal epithelium. Nasal decongestant sprays (e.g., oxymetazoline) should be avoided because of the risk for rhinitis medicamentosa (rebound nasal

congestion), but olopatadine (an H1 antagonist) nasal spray protected against vasomotor challenge in one small study of people with severe vasomotor rhinitis.[233] Phenylephrine had a small benefit for working memory during tilt-table testing in CFS, but cannot be recommended as a therapy.[234]

Chronic pelvic pain, vulvodynia, interstitial cystitis, IBS, and other functional somatic syndromes should be treated as significant components of the CFS panoply, with appropriate diagnosis and treatment.

Diagnosis and treatment of obstructive sleep apnoea is indicated.

Vitamin and mineral supplementation in standard daily doses has also been advocated for CFS.[235]

Occupational therapists, physiotherapists, and massage therapists may play valuable roles in the overall treatment plan. Symptom-specific treatments, such as activity pacing and sleep hygiene, can also be helpful.

The use of commercial online cognitive training plans has not been established for CFS. Lumosity and other brain-training programmes are now under review by FDA for unsubstantiated claims.

Treatment of orthostatic intolerance is focused on mild, gradually increasing levels of structured exercise to overcome deconditioning, and to rehabilitate the dysfunctional perceptions of instability. Patient education, vestibular rehabilitation, and CBT reduce morbidity.

Special circumstances

In the setting of treatment resistance, the diagnosis should be reevaluated including the possibility of comorbid conditions.

Non-adherence with prescribed exercise protocols may indicate that the protocol is too aggressive for the patient. Patients should be provided time to recover between each exercise session. Imposing strict adherence to a uniform exercise regimen will generally not be tolerated by patients with CFS. Other factors contributing to non-adherence include severe fatigue, pain, difficulties in travelling to the physician, and severity of PEM following visits to the physician.

Family, financial, and other conflicts may interfere with the physician-patient relationship. Sleep disruption with reversal of day-night cycles may confound patient travel plans and appointments. Furthermore, concomitant problems such as IBS with uncontrolled explosive diarrhoea can be an embarrassment that keeps the patient housebound. Social withdrawal with depression should be addressed, and all such patients asked about suicidal ideation. Adjunctive drug treatment with antidepressants, sedatives, and analgesia may be of value in these situations. Pain medications can help, especially if the patient has systemic hyperalgesia.

Patients with severe CFS may be bed-ridden and require home visits and in-home therapy sessions because severe pain and discomfort will prevent them from travelling. Severe CFS represents about 5% to 10% of cases. It is not known if this group represents a separate disease or aetiology, or is the extreme end of a continuous distribution of CFS severity.

Treatment details overview

Consult your local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing. (see Disclaimer)

Ongoing (summary)

Patient group	Tx line	Treatment
all patients	1st	multidisciplinary rehabilitation treatment
	adjunct	cognitive behavioural therapy (CBT)
	adjunct	treatment of comorbid depression and/or anxiety
	adjunct	treatment of comorbid migraine
	adjunct	other pharmacotherapy
	2nd	individual tailoring of treatment
with mild fatigue	adjunct	consider individualised exercise program

Treatment options

Ongoing

Patient group	Tx line	Treatment
all patients	**1st**	**multidisciplinary rehabilitation treatment**
		» Multidisciplinary rehabilitation treatment is more effective at reducing long-term fatigue severity than CBT in patients with CFS.[212] Body awareness therapy, coached by a physiotherapist, aims to establish an increased awareness and consciousness of healthy bodily symptoms and their relation to physical function, psychological wellbeing, and social interaction. Unlike conventional CBT, immediate feedback is provided. The intent is to increase self-awareness and self-acceptance, reduce reactivity to passing thoughts and emotions, and improve the ability to make adaptive choices. » In patients who have been chronically ill, mindfulness skills have a positive effect on depression, mood, and activity level. » Normalisation of the sleep/wake rhythm begins by stopping daytime napping, and proceeds to improving the quality of sleep through relaxation therapy. » Occupational therapists and social workers supervise social reintegration by making plans to return to work or school, and to increase social activities. Instruction is provided to prevent relapse.
	adjunct	**cognitive behavioural therapy (CBT)**
		» CBT is a psychotherapeutic intervention aimed at modifying thoughts, feelings, and behaviours. » In patients with chronic fatigue syndrome (CFS), CBT can be used with a graded activity programme. CBT may help in dealing with a new diagnosis of CFS, improve coping strategies, and assist with rehabilitation. » CBT should be planned by the practitioner as 'brain retraining sessions' to improve attention and working memory, and to improve organisation of daily routines (e.g., going to social events, shopping, and other outings) to take advantage of periods during the day where fatigue is felt the least. Family sessions can help educate and inform spouses, children, parents,

Ongoing

Patient group	Tx line	Treatment
		and other significant persons about the disabling nature of CFS.[225] » Goals of treatment involve learning strategies to behaviourally manage symptoms and gradually regain or improve function over time. » A referral to a mental health professional with expertise in CBT is recommended. » CBT and graduated exercise therapy are cost-effective with a good probability of yielding symptom and functional improvements relative to specialty medical care alone.[218] » The agenda for CBT and exercise should be discussed with the patient to ensure the programme is not too rigorous for their personal pain, fatigue, and cognitive status. » CBT is most effective when comorbid depression is present.[160] [209]
	adjunct	**treatment of comorbid depression and/or anxiety** » The prevalence of clinical depression and/or anxiety in patients with chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is about 40%,[162] which is similar to other chronic conditions. » Standard CFS criteria do not include diagnosis of depression, suggesting that major 'melancholic' depression is not a typical feature of CFS. An unanswered issue is the extent of overlap between symptoms of anxiety, and major and reactive depression, with the disabilities caused by the chronic illness. » A suicide evaluation is standard practice for all patients who appear to be clinically depressed or highly stressed.[37] » There are few randomised double-blind placebo-controlled studies of treatments for CFS to direct logical treatment.[184] [236] [237] [238] [239] » Selective serotonin-reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), or tricyclic antidepressants (e.g., amitriptyline, nortriptyline) may be prescribed to treat comorbid depression.1[B]Evidence An alternative antidepressant such as trazodone may be

Ongoing

Patient group	Tx line	Treatment
		used for insomnia. A benzodiazepine (e.g., clonazepam) may be used for anxiety symptoms. Improvements with drug therapy may take several weeks, but more severe levels of depression may predict a slower treatment response.[231] » Recommendations for the use of SSRIs (e.g., citalopram, fluoxetine, paroxetine) in fibromyalgia are instructive for CFS given the paucity of clinical trials in this condition.[240] The evidence for SSRIs in treating the key symptoms of fibromyalgia (pain, fatigue, and sleep problems) is generally weak and biased. However, SSRIs might be considered for treating depression in people with fibromyalgia. » In one study, fluoxetine was shown to be effective for depression in patients with CFS, but not for functional work capacity or fatigue.[193] In another study, duloxetine (an SNRI) improved mental fatigue, pain, and global measure of severity in patients with CFS, but had no effect on the primary outcome of fatigue.[229] Studies in fibromyalgia indicate that duloxetine and milnacipran (another SNRI) have a small incremental effect over placebo in reducing pain, but no significant effect on fatigue, quality of life, or sleep.[230] Also, drop-out rate with these two drugs was greater than with placebo. » Anticonvulsant medications (e.g., pregabalin, gabapentin), typically used in the treatment of neuropathic pain conditions, may be prescribed as an alternative to antidepressants for co-occurring pain, and to address problems such as mood regulation, sleep disruption, and pain control, although their effectiveness is limited. Cyclobenzaprine used in low doses may also be useful for pain and sleep. » There is currently no evidence showing one drug regimen to be more effective than another.[184] Choice of drug should be based on the side-effect profile of the drug and the patient's initial response to treatment. Some patients have hypersensitivity to medication side effects. » It is recommended to start drug treatment (including liquid forms of medication) at a low dose and gradually increase to therapeutic levels as tolerated by the patient. Moreover, drug treatments are mostly used off-label and, therefore, should be managed carefully to prevent synergistic or other adverse events.

Ongoing

Patient group	Tx line	Treatment

Primary options

» clonazepam: 0.5 to 1 mg orally once daily

OR

Primary options

» trazodone: 25-100 mg orally once daily at bedtime

OR

Primary options

» citalopram: 20 mg orally once daily

OR

Primary options

» fluoxetine: 20 mg orally once daily

OR

Primary options

» paroxetine: 20 mg orally once daily

OR

Primary options

» duloxetine: 60 mg orally once daily

OR

Primary options

» milnacipran: 50-100 mg orally twice daily

OR

Secondary options

» amitriptyline: 10-150 mg orally once daily at bedtime

OR

Secondary options

» nortriptyline: 10-150 mg orally once daily at bedtime

OR

Secondary options

» pregabalin: 75-225 mg orally twice daily

Ongoing

Patient group	Tx line	Treatment
		OR **Secondary options** » gabapentin: 300 mg orally once daily initially, increase gradually according to response, maximum 2400 mg/day given in 3 divided doses **OR** **Secondary options** » cyclobenzaprine: 2.5-10 mg orally once daily at bedtime initially, increase gradually according to response, maximum 30 mg/day
	adjunct	**treatment of comorbid migraine** » Studies of migraine associated with chronic fatigue syndrome (CFS) suggest that around two-thirds of patients with CFS have migraine. » Migraine may be present but overlooked if an aura is absent. » A trial of a selective serotonin (5-HT1) receptor agonist (triptan) may show whether or not they are beneficial, and is the usual starting point for migraine therapy. » Topiramate (in low doses) may be considered if migraines occur 3 days per week or more. However, higher doses of topiramate can mimic the fatigue and cognitive dysfunction of CFS. **Primary options** » sumatriptan: 25-100 mg orally as a single dose, may repeat in 2 hours, maximum 200 mg/day **OR** **Primary options** » zolmitriptan: 1.25 to 5 mg orally as a single dose , may repeat in 2 hours if necessary, maximum 10 mg/day **OR** **Primary options** » topiramate: 25 mg orally once daily at night initially, increase gradually according to response, maximum 100 mg/day given in 2 divided doses

Ongoing

Patient group	Tx line	Treatment
	adjunct	**other pharmacotherapy** » Symptom-specific treatments if necessary are indicated. » Nasal symptoms of congestion, fullness, and rhinorrhoea may respond to frequent use of over-the-counter nasal saline sprays and menthol gels. Anticholinergic drugs such as ipratropium reduce rhinorrhoea. Products that are indicated for mucosal use should be used to avoid damaging the nasal epithelium. Nasal decongestant sprays such as oxymetazoline should be avoided because of the risk for rhinitis medicamentosa (rebound congestion). However, olopatadine (an H1 antagonist) nasal spray protected against vasomotor challenge in one small study of people with severe vasomotor rhinitis.[233] Phenylephrine had a small benefit for working memory during tilt-table testing in CFS, but cannot be recommended as a therapy.[234] » Chronic pelvic pain, vulvodynia, interstitial cystitis, irritable bowel syndrome (IBS), and other functional somatic syndromes should be treated as significant components of the chronic fatigue syndrome (CFS) panoply with appropriate diagnosis and treatment. » Diagnosis and treatment of obstructive sleep apnoea is indicated. » Vitamin and mineral supplementation in standard daily doses has also been advocated for CFS.[235] **Primary options** » ipratropium nasal: (0.06%) 84 micrograms (2 sprays) in each nostril three to four times daily for up to 3 weeks **OR** **Primary options** » olopatadine nasal: (665 micrograms/spray) 1330 micrograms (2 sprays) in each nostril twice daily
	2nd	**individual tailoring of treatment** » In the setting of treatment resistance, the diagnosis should be revaluated including the possibility of comorbid conditions.

TREATMENT

Ongoing

Patient group	Tx line	Treatment
		» Non-adherence with recommended low-impact exercises is a common problem and may indicate that the intensity of the exercise is too great for the patient to tolerate. Provide sufficient time between treatments for complete recovery. If pain or post-exertional malaise (PEM) occurs, decrease the intensity of the exercise. Other factors contributing to non-adherence include severe fatigue, pain, difficulties in travelling to the physician, and severity of PEM following visits to the physician. » Family, financial, and other conflicts may interfere with the physician-patient relationship. Sleep disruption with reversal of day-night cycles may confound patient travel plans and appointments. » Treatment strategies may need to involve family members and friends in accordance with patient privacy and confidentiality. » In-home physiotherapy may be necessary to slowly optimise flexibility exercises. » Adjunctive pharmacotherapy may also be recommended to manage comorbid conditions such as depression, sleep disruption, and pain that contribute to sedentary behaviour. » Patients with severe CFS may be bed-ridden and require home visits and in-home therapy sessions because severe pain and discomfort will prevent them from travelling. Severe CFS represents about 5% to 10% of cases. It is not known if this group represents a separate disease or aetiology, or is the extreme end of a continuous distribution of CFS severity. » Minor improvements in fatigue have been reported for nicotinamide adenine dinucleotide hydride (NADH), probiotics, high cocoa polyphenol-rich chocolate, and a combination of NADH and coenzyme Q10. However, there is still insufficient evidence to recommend the use of nutritional supplements, or elimination or modified diets for CFS.[241]
with mild fatigue	**adjunct**	**consider individualised exercise program** » The primary goals of treatment are to manage symptoms and improve functional capacity. » After infectious and medical causes have been excluded an individualised treatment plan can be developed with the patient.

Ongoing

Patient group	Tx line	Treatment
		» Patients may tolerate an individualised activity plan developed in collaboration with knowledgeable and experienced professionals.[37] The activity plan must aim to minimise the negative effects of exertion on impaired aerobic function. Exercise therapy should not take priority over activities of daily living, but should be designed to improve lifestyle habits and stamina, and rebuild self-confidence. Exercise therapy may start with 1 minute of walking per day, with increases of 1 minute per day at weekly intervals as tolerated. Patients should be provided time to recover between each exercise session. » Recommended low-impact exercises include walking, stationary biking, stretching, yoga, and swimming.[37]Adaptive yoga and tai chi may also be beneficial. » The 'brain training' of the cognitive preparation and planning of exercise may be as beneficial as the exercise itself. » Over time, more aerobic exercises can be introduced. Structured exercise programmes should be monitored routinely over time. » Exercise appears to be most effective in patients who have comorbid depression.[160] [209]

Emerging

Rituximab

Rituximab has had the best outcome in chronic fatigue syndrome (CFS) with 60% improvement rates in randomised placebo-controlled and open studies.[12] [41] [42] [104] Rituximab is a chimeric monoclonal antibody targeting the pan-B-cell antigen CD20,[242] which suggests the hypothesis that B lymphocytes synthesise autoreactive antibodies that contribute to CFS pathology.[44] In one small phase II randomised placebo-controlled double-blind study that compared rituximab versus placebo (saline) in 30 patients with CFS, self-reported improvement in fatigue was rated as 'major' by 9/15 (60%) patients in the rituximab group compared with 1/15 (7%) in the placebo group (P = 0.002) at 12-months follow-up.[42] In a post-hoc inspection of the study, one patient in the rituximab group did not respond, while two patients in the placebo group had long-lasting improvement. This finding suggests there are subsets of rituximab responders and non-responders, and a small subset of spontaneously resolving, potentially post-infectious CFS/myalgic encephalomyelitis (ME) patients. The outcomes were consistent with the suspected heterogeneity of CFS/ME pathogenesis. In an open-label study assessing efficacy and relapse after rituximab withdrawal, self-reported 'lasting' improvement in fatigue was achieved in 21 of 29 patients (72%, 95% CI 54% to 85%).[104] In a post-hoc analysis, patients were divided into major, moderate, marginal, and non-responders. Major responders (n = 14) had an onset of action after 22 weeks that lasted 115 weeks. Moderate responders (n = 4) took 56 weeks to reach the criterion with a 67-week duration of action. Marginal responders (n = 3) had benefit at 86 weeks that lasted 25 weeks. There were 7 non-responders. The major and moderate responders improved their composite fatigue scores by 83%, while marginal and non-responders had a 10% change. This is an unprecedented level and duration of improvement when compared with randomised clinical trials of rintatolimod (an immunomodulatory poly I:C double-stranded RNA),[186] [187] antivirals,[123] [243] cognitive behavioural therapy,[157] and graded exercise.[157] [158] Further randomised placebo-controlled studies are being planned to further evaluate the efficacy of rituximab in CFS. Rituximab is not licensed for use in CFS or ME.

KPAX002

A combination of methylphenidate hydrochloride and mitochondrial support nutrients, KPAX002, improved Checklist Individual Strength (CIS) by 34% at 12 weeks (P <0.0001), corresponding to a ≥25% decrease in 87% of the participants.[244] KPAX002 was well tolerated and significantly improved fatigue and concentration disturbance symptoms in >50% of patients with CFS.

NADH +/- coenzymeQ

Studies investigating nicotinamide adenine dinucleotide (NADH) alone,[245] and combined with coenzyme Q10,[246] have shown small benefits in treating fatigue in some patients with CFS.

IL-1 receptor inhibitors

Inhibition of IL-1 receptors with anakinra for 4 weeks does not alter severity in women with CFS and severe fatigue.[247] However, IL-1 beta is only elevated early in CFS, suggesting there may be a narrow window for potential treatment.[248]

Rintatolimod

Rintatolimod, an immunomodulatory poly I:C double-stranded RNA that has toll-like receptor 3 (TLR3) agonist properties, has low-quality evidence for improvement of exercise in patients with CFS.[185] [186] [187] [249] Publication of case series to identify factors that may be involved in anecdotal improvements of exercise in some patients with CFS may be useful to clarify the issues surrounding use of this immunomodulator.

Other drug therapies

Antivirals (alone or with intravenous immunoglobulin),[120] [122] [123] clonidine,[16] citalopram (in patients without depression),[250] hydrocortisone,[251] fludrocortisone,[189] methylphenidate,[252] melatonin,[253] [254] galantamine,[188] intravenous immunoglobulin (IgG),[117] [255] [256] and staphylococcal toxoid[257] have been studied in CFS, but results have been equivocal, or they have shown limited or no effect.[258] Furthermore, these studies may provide misleading results due to small sample sizes and poor study designs; therefore, results should be in interpreted with caution. Clonidine failed to improve symptoms of orthostatic intolerance in adolescents compared with placebo.[16] [259] The subset who were homozygous for the rs4680 high-activity allele of catechol-O-methyltransferase (COMT) had reduced sleep, quality of life, and number of steps taken per day (decreased by 2500).[226] Three months of oral guanidinoacetic acid increased muscular creatine but had no effects on fatigue or other subjective parameters.[260] Subcutaneous human placental extract was reported to be effective in CFS.[261] However, this therapy has a high risk for transmission of prions, viruses, and other agents, and should not be condoned in human research.

Low-intensity behavioural treatments

Multiple barriers exist for patients with CFS to access care. Studies have begun investigating 'low-intensity' alternative delivery methods for evidence-based care, such as telephone, internet, and brief primary care interventions. Studies suggest comparable improvements in physical functioning, fatigue, and patient satisfaction among patients receiving face-to-face or telephone-based CBT, even at 12-month follow-up.[262] Furthermore, a randomised trial for adolescents found that an internet-based CBT with graduated exercise (Fatigue in Teenagers on the InterNET - FITNET) resulted in significantly fewer symptom complaints and functional impairments relative to usual care.[263] A recent study compared the effectiveness of a home-delivered (in-person nurse visit or telephone coaching) 'pragmatic rehabilitation' intervention to either supportive listening or treatment as usual.[159] Self-reported fatigue significantly improved for patients allocated to the home-based programme relative to the other groups by the end of the trial at 20 weeks. However, at 70-week follow-up, no between-group differences were found on self-reported measures of fatigue and physical functioning. A randomised trial conducted in patients with CFS in primary care compared a 2-session fatigue self-management intervention with either a 2-session symptom monitoring or usual care group. Post-test and 12-month follow-up found clinically significant improvements in self-reported fatigue in the self-management group relative to the other conditions, although dropout rates were high in this study.[264] Another low-intensity, guided self-instruction CBT programme has been found to significantly reduce fatigue at 6 months relative to a usual care group.[265] Future research will need to explore the effectiveness of different treatment delivery modalities to help improve access to behavioural interventions.

Heart rate variability biofeedback therapy and graded exercise training

The combination of heart rate variability biofeedback therapy (HRV-BF) and graded exercise training (GET) reduced fatigue. HRV-BF had additional effects on depression, while GET improved physical health.[266] Centers for Disease Control and Prevention (CDC) criteria were used during study participant recruitment.

Qigong exercise

Qigong exercise involves a series of gentle, repetitive stretching and strengthening exercises to promote balance, fluid motion, and enhanced bodily awareness. Relative to controls, fatigue symptoms and mental functioning significantly improved among those patients randomised to Qigong therapy.[267] Another randomised trial comparing a 5-week, 10-session Qigong exercise group with a wait-list control among CFS-like patients found that the intervention group produced significant improvements in self-reported physical fatigue, mental fatigue, and depression, but not anxiety.[268]

Essential fatty acid and magnesium supplements

Randomised trials of essential fatty acid and magnesium supplements suggest possible benefits.[228] [269] Larger-scale randomised trials are needed. These interventions are generally not recommended in the treatment of CFS as they lack sufficient evidence.

Alternative and complementary approaches

Emerging studies suggest possible benefits of massage therapy and homeopathic interventions.[228] [270] Larger-scale, well-designed randomised trials are needed. These interventions are generally not recommended in the treatment of CFS as they lack sufficient evidence. Various forms of meditation and wellness programmes may be beneficial. Meditation may reduce the heightened sense of effort that is intrinsic to post-exertional malaise (PEM), and help the patient focus on reducing symptom severity. Isometric yoga has been evaluated in a small randomised controlled trial where it showed some benefit in treatment-resistant patients.[271] Vitamin D, polynutrients,[272] homeopathics,[273] phototherapy,[254] tryptophan depletion,[274] and traditional Chinese medicines[275] have been studied in CFS, but results have been equivocal, or they have shown limited or no effect. Furthermore, these studies may provide misleading results due to small sample sizes and poor study designs; therefore, results should be in interpreted with caution.

FOLLOW UP

Recommendations

Monitoring

Chronic fatigue syndrome (CFS) is a chronic medical condition, with a waxing and waning of symptoms and impairments. Long-term management with a single primary care physician is recommended. Emphasis is placed on maximising functional capacity and improving symptom management. Medications, redundant diagnostic and laboratory testing, and ongoing consultant referrals should be kept to a minimum. Patients should be periodically reassessed for depression as untreated and more severe levels of depression may lead to a slower treatment response.[231] One strategy may be to provide counsel to patients every 3 months and to reassess them for other health issues and treatable diseases.

Patient instructions

Patients should be educated on how secondary physical deconditioning can emerge due to increased resting and activity restriction. Difficulties and fears associated with attempting to increase levels of physical activity should be normalised. Patients are instructed in establishing and maintaining a daily low-impact physical activity routine (e.g., walking, stationary biking, stretching, and swimming). Graded exercise programmes should be structured and monitored to prevent cycles of over-exertion and prolonged inactivity. A referral to a specialist in cognitive behavioural therapy (CBT) may also be recommended. Patients should be routinely monitored for depression and encouraged to engage with personally meaningful activities and social supports. Where indicated, patients should be assisted in accessing appropriate mental health care.

Complications

Complications	Timeframe	Likelihood
major depressive disorder	**variable**	**medium**
Chronic symptom presentation, loss of functional capacity, and limited social support may place people at risk for depression. Depression may also predate the onset of chronic fatigue syndrome (CFS). Mild-to-moderate levels of depression are treated with cognitive behavioural psychotherapy or evidence-based pharmacotherapy. More severe levels of depression (e.g., suicide risk) should be referred to psychiatry and treated with evidence-based pharmacotherapy. In one UK-based study, suicide-specific mortality was found to be significantly increased in patients with CFS compared with the general population (standardised mortality ratio 6.85, 95% confidence interval: 2.22 to 15.98; P = 0.002) indicating the need for physician awareness and compassion in the care of these patients.[131]		

Prognosis

Longitudinal studies indicate that 17% to 64% of patients improve with treatment; however, less than 10% meet criteria for full recovery, and up to 20% of patients may worsen over time.[276] [277] [278] It is important to review the severity of fatigue and criteria used for chronic fatigue syndrome (CFS) diagnoses in these studies. Longitudinal studies also suggest that recovery rates for patients who develop CFS after infectious mononucleosis are better in younger patients than in older patients, with over 50% returning to work after average disease duration of 11.4 years.[279] Findings from one small observational study also suggest that adolescents with CFS after infectious mononucleosis have a higher remission rate than adults and that

they also tend to return to full functional capacity.[113] In contrast, less than 10% of CFS patients without mononucleosis returned to premorbid levels of functioning despite standard therapies.[113] One study carried out in a single tertiary-referral centre found improvements within 5 years in a subset of patients with post-infectious CFS who presented with a history of sudden-onset fatigue, fever, tender lymph nodes, and myalgia.[280] Poor prognostic factors include arthralgia, older age, longer illness duration, greater fatigue severity, presence of comorbid psychiatric illness (self-reported depression), and a physical attribution for CFS.[281]

Mortality from cardiovascular and all causes is significantly higher in CFS than the overall US population.[101]

Diagnostic guidelines

Europe

Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children

Published by: National Institute for Health and Care Excellence **Last published:** 2007

Summary: Recommends that the possibility of chronic fatigue syndrome (CFS) should be considered if a person has fatigue with all of the following criteria: 1) new or recent onset; 2) persistent or recurrent; 3) unexplained by other conditions; 4) results in marked reduction in activity (e.g., post-exercise malaise and fatigue that is delayed by at least 24 hours) and which is accompanied by one or more of the following conditions: 1) sleep problems; 2) non-inflammatory muscle or joint pain at multiple sites; 3) painful lymph nodes that are not pathologically enlarged; 4) sore throat; 5) cognitive dysfunction; 6) malaise or flu-like symptoms; 7) dizziness and/or nausea; 8) palpitations not of cardiac pathology; 9) symptoms made worse by mental or physical exertion. In addition, recommends investigation of: 1) C-reactive protein; 2) screening blood tests for gluten sensitivity; 3) serum calcium; 4) serum ferritin (in children and young people only). The NICE guidelines are in need of updating by inclusion of newer information about CFS/ME pathology and treatment.

International

Chronic fatigue syndrome/myalgic encephalomeyelitis: primer for clinical practitioners

Published by: International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomeyelitis **Last published:** 2014

Summary: Discusses chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME) and provides advice on diagnosis.

North America

Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness

Published by: Institute of Medicine of the National Academies **Last published:** 2015

Summary: Provides revised clinical diagnostic criteria for ME/CFS, and recommends the term 'systemic exertion intolerance disease' (SEID) as an alternative to ME/CFS.

Chronic fatigue syndrome: diagnosis

Published by: Centers for Disease Control and Prevention **Last published:** 2012

Summary: A diagnosis of chronic fatigue syndrome (CFS) is assumed in patients with typical symptoms following the exclusion of other medical conditions associated with persistent fatigue.

Treatment guidelines

Europe

Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management of CFS/ME in adults and children

Published by: National Institute for Health and Care Excellence **Last published:** 2007

Summary: NICE have made the following general recommendations regarding treatment strategies: individual management plans should be developed for each person with chronic fatigue syndrome (CFS); health care should be convenient for the patient including, where possible, the provision of treatments at home with telephone and email support; physicians should give patients advice on managing activity and detailed advice should be provided in the form of individualised exercise regimens; exercise and cognitive behavioural therapy should be offered to people with mild or moderate CFS and to those who choose it. NICE guidelines also make provision for managing quality of life (i.e., sleep management, relaxation techniques, and diet), education, and employment issues. The NICE guidelines are in need of updating by inclusion of newer information about CFS/ME pathology and treatment.

Occupational aspects of the management of chronic fatigue syndrome: a national guideline

Published by: National Health Service Plus **Last published:** 2006

Summary: NHS evidence-based guidelines for managing chronic fatigue syndrome (CFS) in the workplace. Key findings as follows: cognitive behavioural therapy and managed exercise regimens can facilitate the return to work; cognitive behavioural therapy may have the potential to lower the 5-year risk of relapse; depression and co-existing physical symptoms are associated with poor work outcomes and should be treated.

Evidence-based guideline for the management of chronic fatigue syndrome/ myalgic encephalopathy in children and young people

Published by: Royal College of Paediatrics and Child Health **Last published:** 2004

Summary: Guidelines for the management of chronic fatigue syndrome (CFS) in children and young adults. These follow the same principles as those described for the general population with CFS.

International

Chronic fatigue syndrome/myalgic encephalomeyelitis: primer for clinical practitioners

Published by: International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomeyelitis **Last published:** 2014

Summary: Discusses therapies for managing symptoms in chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME) patients. There are no curative treatments for CFS/ME.

Online resources

1. International consensus criteria: Myalgic encephalomyelitis *(external link)*
2. US Institute of Medicine: CFS/ME criteria *(external link)*
3. International Association for CFS/ME: Functional capacity scale *(external link)*

Evidence scores

1. Fatigue: there is medium-quality clinical evidence to show that fluoxetine is no more effective than placebo at improving fatigue.
Evidence level B: Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.

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