# Chronic fatigue syndrome: progress and possibilities

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## Summary

- Chronic fatigue syndrome (CFS) is a prevalent condition affecting about one in 100 patients attending primary care.
- There is no diagnostic test, validated biomarker, clear pathophysiology or curative treatment.
- The core symptom of fatigue affects both physical and cognitive activities, and features a prolonged post-activity exacerbation triggered by tasks previously achieved without difficulty.
- Although several different diagnostic criteria are proposed, for clinical purposes only three elements are required: recognition of the typical fatigue; history and physical examination to exclude other medical or psychiatric conditions which may explain the symptoms; and a restricted set of laboratory investigations.
- Studies of the underlying pathophysiology clearly implicate a range of different acute infections as a trigger for onset in a significant minority of cases, but no other medical or psychological factor has been reproducibly implicated.
- There have been numerous small case–control studies seeking to identify the biological basis of the condition. These studies have largely resolved what the condition is not: ongoing infection, immunological disorder, endocrine disorder, primary sleep disorder, or simply attributable to a psychiatric condition.
- A growing body of evidence suggests CFS arises from functional (non-structural) changes in the brain, but of uncertain character and location. Further functional neuroimaging studies are needed.
- There is clear evidence for a genetic contribution to CFS from family and twin studies, suggesting that a large scale genome-wide association study is warranted.
- Despite the many unknowns in relation to CFS, there is significant room for improvement in provision of the diagnosis and supportive care. This may be facilitated via clinician education.


Chronic fatigue syndrome (CFS) is an enigmatic clinical entity which challenges patients, health care providers and researchers alike.[1] The diagnosis is sometimes avoided by medical practitioners, leaving patients in diagnostic limbo and prone to non-evidence-based labels and potentially harmful treatments. This quandary reflects the lack of a diagnostic test, validated biomarker, clear pathophysiology or curative treatment.

We retrieved publications from MEDLINE, PsycINFO, EMBASE, Cochrane and PubMed databases from 1988 to 2019 to consider aspects of clinical decision making in the diagnosis, assessment of prognosis, and management of CFS; provide an update on understanding of CFS pathophysiology; and identify priorities for improved care of patients with CFS and for future research. This review focuses on adult populations, but the condition also affects children and adolescents (reviewed elsewhere).[2]

## Characterising fatigue

CFS is a label applied to an illness featuring persistent and disabling fatigue present for 6 months or more, causing difficulties in both physical and cognitive tasks. The fatigue has a striking pattern of prolonged post-activity exacerbation, in which tasks previously achieved with ease trigger hours or even days of worsened symptoms, sometimes referred to as post-exertional malaise (Box 1).[3] In addition, patients report an unrefreshing quality of apparently sufficient sleep. The condition is also commonly known as myalgic encephalomyelitis (ME) or ME/CFS, and has also been proposed to be renamed as systemic exercise intolerance disease.[4]

In the English language, "fatigue" is a widely encompassing term, with medical meanings ranging from weakness (associated with neuromuscular disorders) to sleepiness (ie, the somnolence of primary sleep disorder) to loss of interest and motivation (ie, the anhedonia of major depression). When systematically explored, the common descriptors provided by patients with CFS include exhaustion, tiredness, feeling drained of energy, heaviness in the limbs, and foggy in the head.[5] Perhaps the best insight into the illness experience comes from longitudinal analysis of symptom patterns in patients with acute infections such as glandular fever followed into subsequent CFS, which indicates close concordance between the acute infective symptoms and the subsequent fatigue state (with the exception of fever).[6] There are, at most, minor objective deficits in sustained muscle performance on neurophysiological testing in patients with CFS, and formal assessment of cognitive performance indicates only subtle objective deficits, hence the phenomenon of fatigue is considered subjective (analogous to chronic pain, but no less valid).[7–9] The fatigue of CFS is clearly pathological as it does not resolve with rest, sleep, or reduced physical or cognitive demands.

*Summary:* The fatigue state in patients with CFS has physical and cognitive elements, and a characteristic pattern of prolonged post-activity exacerbation.

## Overlapping syndromes

CFS is best considered as a condition with imprecise diagnostic boundaries: first, because the illness manifestations are purely subjective (hence difficult to record reliably); and second, as it is clear that CFS overlaps with several other syndromal diagnoses — a significant minority of patients also meet the diagnostic criteria for additional conditions, including fibromyalgia, irritable bowel syndrome, and postural orthostatic tachycardia syndrome.[3,10,11] In addition, although it is clear that mood disturbance is prevalent in patients with CFS, major depression generally does not provide an alternative diagnosis, and patients with CFS respond poorly to antidepressant medication unless significant features of comorbid depression are present.[12] Further, premorbid psychiatric disorders are not more common in those who develop CFS than those who do not.[13–16] Finally, although the report of an unrefreshing quality of sleep is universal, polysomnography studies have not revealed evidence of a primary sleep disorder.[17,18]

*Summary:* Many patients with CFS also meet diagnostic criteria for other syndromes, including fibromyalgia, irritable bowel syndrome and postural orthostatic tachycardia syndrome.

## Diagnosing CFS

Over the past decade, considerable attention has been placed on the development of new or improved diagnostic criteria. Importantly, most of these criteria sets were primarily intended for research purposes (eg, epidemiology, pathophysiology or

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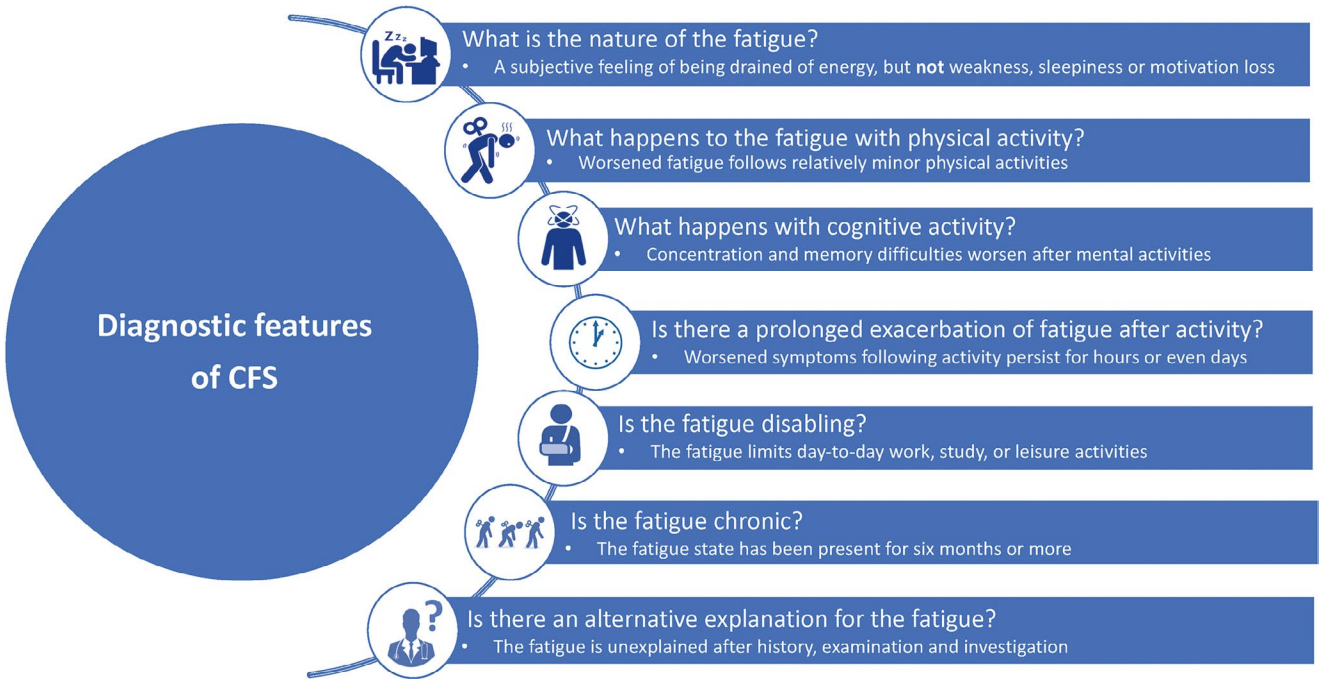
**1 Diagnostic features of chronic fatigue syndrome (CFS)**




treatment trials) and not for routine clinical practice.[19] The most commonly used criteria set was drafted by an international expert group convened by the United States Centers for Disease Control and Prevention.[20] These criteria were operationalised[21] but have been criticised as being overly inclusive of patients with less severe illness.[22] The newer diagnostic criteria sets have also been developed by expert consensus,[3,23–25] and one of these has been partially operationalised.[26] It is clear that these various criteria sets identify overlapping patient groups with somewhat differing symptom features,[27] and generate community prevalence estimates for CFS ranging from 0.5% to 2.5%.[28–30] It is also clear that none have been well validated in broad population studies and, in the absence of a diagnostic test or biomarker, that no significant increase in precision is likely.[30,31]

Although homogeneity within the diagnostic label is potentially critical for research,[32,33] for clinical purposes the somewhat varied syndromal diagnoses and symptom heterogeneity should not be a barrier to providing a diagnosis to mark the transition into supportive care.[11] The core elements of the symptom set across all diagnostic criteria sets are physical and cognitive fatigue with a prolonged post-activity exacerbation, and the absence of an alternative explanation after history taking, examination and investigation. It is important to acknowledge to patients that despite a lack of comprehensive understanding of the condition, or precise diagnostic criteria, the symptoms are valid and the struggles with disabilities are genuine. Most patients with CFS are unable to work or study, and the levels of disability are comparable to those attributable to multiple sclerosis.[34,35]

Existing clinical practice guidelines recommend that the diagnosis of CFS should generally be made in primary care,[11,24] as it does not typically require assessment by a specialist physician or psychiatrist, or complex laboratory investigations. It does require a careful history, a review of mental health, a thorough physical examination, and a few necessary investigations to exclude conditions which may not be suspected on clinical grounds, such as hypothyroidism.[36] The majority of patients with CFS report that it took longer than a year to receive a diagnosis,[3,37] often because the condition is regarded as a diagnosis of exhaustive exclusion rather than a positive recognition of the characteristic fatigue state (Box 1). Necessary investigations include full blood count, urea, electrolyte and creatinine levels, liver and thyroid function tests, C-reactive protein levels or erythrocyte sedimentation rate, and fasting blood glucose tests.[2,36] Reassuringly, a systematic review of 26 studies examining CFS diagnosis in patients attending primary care with tiredness revealed a low prevalence of underlying medical conditions, including anaemia (2.8%), malignancy (0.6%), and other serious physical illnesses (4.3%).[38] Depression was diagnosed in 18.5% of patients.

*Summary:* Diagnosis of CFS should be made in primary care, by recognition of unexplained chronic fatigue affecting both physical and cognitive function, with a prolonged post-activity exacerbation. Alternative explanations should be excluded by history, physical examination and a restricted list of laboratory investigations.

## Assessing prognosis

An assessment of prognosis is key to good patient care. A systematic review of 14 studies that suggested a poor prognosis for complete recovery (a median of 5% over 1–3 years of follow-up) is commonly misinterpreted as being representative of the entire population of patients with CFS, which (by definition) includes all those diagnosed with 6 months or more of symptoms.[39,40] Importantly, the studies included in the review assessed outcomes in individuals who already had many years of illness (median about 5 years) at the commencement of follow-up.[40] By contrast, it is evident from prospective cohort studies of CFS arising as post-infective fatigue,[41] and from the subpopulations with illness of less than 2 years duration, that there is a good prognosis for recovery during several years of follow-up.[40] In addition, studies in paediatric and adolescent populations also suggest a good prognosis, with most patients

recovering over 1–5 years.[39,42] In clinical practice, it is helpful for the individual patient to characterise the typically slow trajectory of improvement in functional status over the preceding months or years (say, 10 percentage points of improvement per annum on a 0–100 scale, with 0 being dead, 30 being largely bedbound, 70 being unable to work or study, and 100 being healthy — analogous to the Karnofsky Performance Scale[43]). This trendline can then be projected forwards to estimate the time to resolution.

*Summary:* The prognosis should be provided to the patient based on the illness trajectory before presentation.

## Pathophysiology

Since the early 1990s, there have been several thousand published case–control studies seeking to identify the biological basis of CFS. Given the variations in diagnostic criteria used, the heterogeneity within the label, the typically small sample sizes, and the lack of standardised investigative tools, independent replication is a key prerequisite for advances in this field. There have been many "breakthrough discoveries" which have failed this test. The most recent of these was initiated by a report describing the detection of genetic sequences of xenotropic murine leukaemia virus-related virus, a retrovirus, in the blood of a majority of patients with CFS (67%) compared with a small proportion (3.7%) of healthy individuals.[44] Multiple subsequent studies failed to replicate the finding, which was ultimately shown to be due to laboratory contamination with murine genomic DNA.[45]

Prospective cohort studies following individuals from acute infection with both viral and non-viral pathogens, including Epstein–Barr virus (EBV), Ross River virus and *Coxiella burnetii* (the causative agent of Q fever), have documented a prevalent post-infective fatigue state meeting diagnostic criteria for CFS.[13,41] By contrast, a well controlled longitudinal study in general practice found that patients presenting with minor symptomatic infections, such as common colds or gastroenteritis, did not experience post-infective fatigue.[46] This clear link with some acute infections at onset led to investigation of persistent infection as a possible disease mechanism. Multiple studies examining patients with well characterised post-infective fatigue and matched control subjects who recovered uneventfully from the same acute infection have not found evidence of abnormal persistence of viable organisms, non-viable pathogen residues, or nucleic acids, including in relation to Q fever, Lyme disease or EBV disease.[47–49] These data argue strongly against the possibility of persistent infection underpinning CFS, and do not provide a rationale for antimicrobial therapy.

The immunological hypothesis for post-infective fatigue has proposed that an abnormally persistent immune response to the pathogen results in chronic cytokine production mediating the protracted symptoms.[50] A comprehensive examination of pathogen-specific immune responses was undertaken in a longitudinal case–control series of individuals followed from acute EBV infection either into a post-infective fatigue or to prompt resolution; no significant differences in immune response patterns or cytokine production were found.[49,51,52] Cross-sectional case–control studies of patients with CFS and healthy control participants have also not revealed any consistent alteration in laboratory measures of immune function.[53–55] In combination, these data argue strongly against an immunological disorder as a likely underpinning of CFS.

Multiple lines of evidence point to the central nervous system as the primary site of the pathophysiology. Cognitive performance testing has revealed relatively subtle but significant changes, including slowed information processing, impaired working memory and poor learning of information.[8,9,56] It has been hypothesised that fatigue and pain may cause excessive interoceptive monitoring causing a decrease in externally directed attention,[56] which is very similar to changes associated with the acute sickness response to infection or inflammation, manifesting as an altered central perception of physical or cognitive effort.[57,58] Structural neuroimaging studies (computed tomography and magnetic resonance imaging) have not revealed any consistent abnormality, but a growing body of evidence from research functional imaging techniques, including functional magnetic resonance imaging, magnetic resonance spectroscopy and positron emission tomography, appears promising.[59–63] The recognition of prevalent postural symptoms (dizziness, palpitations), and the key role the autonomic system plays in responses to stressors, has led to investigation of heart rate variability analysis, galvanic skin responses and tilt table testing to generally document evidence for sympathetic predominance, although the biological basis of this alteration remains unknown.[64–66] Finally, neuroendocrine studies suggest mild hypocortisolism and blunted hypothalamic–pituitary–adrenal axis responsiveness. However, replacement therapy with hydrocortisone or equivalent is not recommended, as benefit was limited and adverse effects were prominent.[67]

Twin studies of fatigue and CFS consistently indicate a genetic contribution to the condition,[68–70] although no candidate gene variant has been consistently associated.[71] The heterogeneity of the diagnostic label and the likelihood of a polygenic risk argue for a large scale genome-wide association study. Gene expression studies have focused on expression in peripheral blood leucocytes with no consistent alteration found, including in whole transcriptome studies in longitudinal case–control series after acute infection.[72,73] These data reinforce the low probability of finding any meaningful abnormality in the blood. A series of interesting but preliminary studies have used proteomics,[74–76] metabolomics[77] and microbiome analyses[77,78] in cross-sectional case–control studies of patients with CFS. As these approaches measure hundreds to thousands of variables, the studies have uniformly included tens of subjects only, and the technologies are relatively new and evolving, any preliminary findings require independent replication in larger cohorts.

*Summary:* The biological basis of CFS remains unknown.

## Treatment

There have been more than 100 controlled trials of treatments for CFS, most with curative intent.[67,79,80] A systematic review in 2015 revealed 35 studies enrolling participants meeting diagnostic criteria, but concluded that trials were limited by size, number, duration and methodological quality.[67] The review included nine trials of medications, seven of complementary and alternative medicines, 14 of behavioural therapies, seven of exercise, and four comparing or combining different therapies. Most of the trials only met criteria for fair quality (24 trials) or poor quality (five trials), and enrolled small sample sizes of predominantly middle-aged women from specialty clinics with long standing illness (27 trials involved < 100 participants). No pharmacological agent had moderate or high

quality evidence for benefit. In particular, there was no evidence to support further use of hydrocortisone, intravenous immunoglobulin, valganciclovir, galantamine, isoprinosine, fluoxetine, or various complementary medicines. The field is plagued by a repetitive history of initial enthusiasm and failed replication in clinical trials, well exemplified by the recent studies of B lymphocyte-depleting agent rituximab (anti-CD20 monoclonal antibody), which appeared to demonstrate clinical benefit in a small case series of patients with CFS.[81] This was followed by similar benefit in a small placebo-controlled trial,[82] but ultimately failed replication in a larger ($n$ = 151) randomised, placebo-controlled trial.[83]

Cognitive behaviour therapy (CBT) is a commonly trialled intervention. In the context of CFS, CBT is best considered as a multifaceted strategy to identify and modify illness behaviours and beliefs to reduce symptom severity and improve functional capacity.[84,85] Beliefs that should be challenged include that more sleep will alleviate the fatigue, that avoiding activity is preferable, and that ignoring symptoms and simply pushing beyond activity thresholds will overcome the illness. The most recent meta-analysis of the four controlled studies of CBT, including the PACE trial, found no significant differences in physical function scores between intervention and control groups.[67,86] However, this analysis excluded several high quality, randomised controlled trials with positive outcomes,[87,88] and contrasts with an earlier Cochrane analysis, which suggested CBT was effective in reducing the symptoms of fatigue compared with usual care.[89] More recently, with the aim of improving access to treatment, a randomised controlled trial of online CBT with clinical psychologist feedback showed a significant reduction in self-reported fatigue and psychological distress, as well as some improvement in physical functioning in those receiving online CBT versus the waitlist control group.[90]

Graded exercise therapy (GET) has more consistent evidence for benefit, with a meta-analysis showing moderate quality evidence for improvement in measures of physical function and fatigue severity.[67] In clinical practice, GET is preceded by activity pacing, which involves identifying thresholds beyond which the prolonged symptom exacerbation follows, and then "pacing" activities in order to maximise use of the constrained energy supplies. GET then involves planned, cautious increases in physical activity without causing sustained worsening of symptoms. A recently updated Cochrane review of eight randomised controlled studies indicated that in comparison to passive control (such as relaxation or flexibility), GET reduced fatigue at end of treatment with moderate certainty.[91,92] However, the review indicated that it was not possible to exclude the potential for an exacerbation of symptoms in patients with severe illness.

It is evident that there is no high quality evidence for any pharmacological or non-pharmacological approach as a cure for CFS. This impasse reflects both the challenges associated with heterogeneity in the diagnostic label, which can only be overcome by larger clinical trials including participants meeting different case definitions, with subgroup analyses to identify responders to specific treatments.[79] The impasse also reflects the need to better understand the pathophysiology to guide rational therapeutic approaches.

Nevertheless, considerable support can be offered in primary care, such as physical and pharmacological approaches for pain relief, management of mood disturbance or sleep disturbances when they are clinically significant, and appropriate counselling regarding the chronic illness (Box 2).[11] In addition, advice and support regarding pacing of activities to manage functional status is appropriate, as well as advice to avoid excessive rest.

*Summary:* There is no known curative treatment for CFS, but supportive care should be provided.

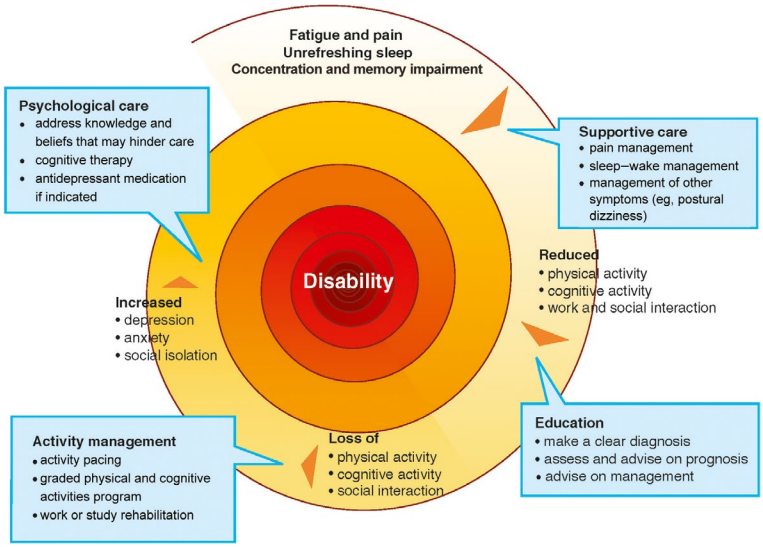
## Future directions

Although delays in diagnosis and a lack of supportive care are commonly reported by patients, data from a large survey of primary care practitioners in the US revealed that the great majority of health care providers were aware of CFS, with over 40% reporting ever giving a CFS diagnosis.[93] The gaps were in the confidence of clinicians in making the diagnosis and providing care.[93] By contrast, an earlier survey in primary care in Wales[94] revealed poor knowledge of CFS, with only half the general practitioner respondents believing that the condition actually exists. In combination, these studies highlight a significant gap in the health sector which may be filled by provision of education to clinicians to improve self-efficacy in diagnosis and management of CFS. This suggestion was a key recommendation of the ME/CFS Advisory Committee recently convened by the National Health and Medical Research Council in response to consumer advocacy, to identify and report on the clinical guidance and research needs for CFS in Australia.[95] Similarly, there is a need to empower patients by providing them with accessible and evidence-based education regarding the diagnosis and supportive care options.

As several decades of research into CFS have not identified a diagnostic test, a validated biomarker, clear pathophysiology or curative treatment, it is evident that the strategic direction of the research needs reconsideration. The weight of evidence suggests that functional neuroimaging, genetics and potentially high throughput -omics studies offer the greatest promise for a breakthrough. In addition, provocation studies seeking to identify correlates of the dynamic changes in symptom severity which characterise the post-activity exacerbation offer a largely unexplored research paradigm.[5]

Given the irreconcilable difficulties in resolving a unified case definition in the absence of a gold standard, and the likelihood of

**2 Management of chronic fatigue syndrome in primary care**



residual heterogeneity within the diagnostic label, the highest research priority is to improve the fundamentals. This will involve moving from small scale, local, investigator-led studies using novel experimental techniques, to large scale, multicentre, international collaborative studies with standardised case definitions and illness characterisation tools (questionnaires, structured interviews) using only well validated investigative approaches.

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