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Comprehensive review of myalgic encephalomyelitis/chronic fatigue syndrome

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Abstract

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, debilitating disease that is unexplained and is characterised by persistent unexplained fatigue, Post Exertional Malaise (PEM), cognitive impairment, unrefreshing sleep and multisystem impairment. Despite the high burden of symptoms and the worldwide prevalence, ME/CFS has been poorly understood, underdiagnosed and underfunded. This large-scale review summarises the available evidence regarding the epidemiology, diagnostic progress, main clinical characteristics, pathophysiological theories and therapeutic approaches for ME/CFS. Despite problems with diagnostic consistency, the lack of validated biomarkers, and historical linkage to psychiatric illness, the recognition of this condition has been delayed and has led to patient marginalisation. The review highlights PEM as a cardinal symptom and reviews the weaknesses in earlier diagnostic criteria, as well as current changes in treatment guidelines, including the formal withdrawal of Graded Exercise Therapy, which has evidence of harm. New pathophysiological evidence suggests mitochondrial dysfunction, immune dysregulation, autonomic imbalance, neuroinflammation, and alterations in gut microbiome. New diagnostic and therapeutic strategies, such as metabolomic and electrophysiological assays, mTOR inhibitors, and decentralised clinical trial designs, are being studied. This intersection with Long COVID offers a chance to rapidly advance studies of post-infectious chronic diseases. The paper also argues for stringent subtyping, uniform data collection, and ongoing patient participation in research as strategies to surmount challenges of heterogeneity. Finally, it underscores the critical need for fair funding of research, so biomarker discovery and development of disease-modifying treatments can be achieved. The care of people with ME/CFS is not only a clinical obligation, but also a public health one.

Registration and protocol

The review was not registered prospectively and a study protocol was not published.

Clinical trial number

Not applicable.

Keywords Myalgic encephalomyelitis, Chronic fatigue syndrome, Post-Exertional Malaise, Mitochondrial dysfunction, Neuroinflammation, Diagnostic criteria

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Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, chronic and disabling multisystem disease that can significantly affect the lives of those who suffer. The complexity of the subscale makes it difficult to define, diagnose and treat. The purpose of this review article is to present a critical review of the literature and an analysis of ME/CFS from an evidence-based perspective, covering its historical background, diagnosis, clinical features, proposed pathophysiological mechanisms, treatment options, prognosis, and future directions of research.

The essential feature of CFS is profound, disabling fatigue lasting more than six months, often accompanied by muscle weakness or feeling tired and unrefreshed, even after rest [1]. This deep tiredness can make it harder for people to do some of their daily activities, such as up to 50% [1]. Fatigue is generally classified according to duration, as recent (lasting less than one month), prolonged (more than one month), or chronic (more than six months) fatigue [1].

In the past, the diagnosis and understanding of this condition have been hampered by multiple difficulties, mainly because its aetiology is still unknown and the symptomatology is complex to assess objectively [1]. The ambiguity led to a variety of different names, based on various historical interpretations and purported origins. The names given to it include allergic encephalomyelitis, immune dysfunction syndrome, neuroendocrine immune dysfunction syndrome, post-viral syndrome, Iceland disease, neurasthenia and Royal Free disease [1]. For example, "neurasthenia" was a common 19th -century diagnosis for a collection of symptoms that includes fatigue, depression, headache, and neuralgia, which are all symptoms of ME/CFS [2]. The numerous historical terms used for what is now known as ME/CFS reflect the challenges historically encountered in classifying and understanding a condition that did not conform to prevailing disease models. The names were frequently used to emphasise a symptom or a suspected source of the disease, and represented a lack of coherence and uniformity in the way the disease was perceived. This confusion had a direct impact on diagnostic issues and on the distrust and trivialisation of patients for decades [3]. The naming alone is a testimony to the lack of clarity in the pathogenic mechanisms, which has led to the marginalisation of the disease.

Today, the World Health Organisation (WHO) International Classification of Diseases (ICD-10) has Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) grouped within the category of neurological disorders. Furthermore, it recognises terms such as post-viral fatigue syndrome (PVS) and benign myalgic encephalomyelitis [4]. In 2015, the Institute of Medicine (IOM) (now called the National Academy of Medicine (NAM)) recommended that the name of ME/CFS be changed to "Systemic Exertion Intolerance Disease" (SEID) [3]. The reason was that SEID more fundamentally reflects the centrality of the symptom, namely that any type of physical, cognitive or emotional activity can significantly and negatively impact patients across various organ systems and components of their life [5]. This proposed name was not accepted, however, largely because of major backlash from patient advocates that the name lacked the complexity and severity of the disease and could potentially demean it [5]. This dispute over terminology highlights an ongoing battle for ME/CFS to be accepted as a genuine, recognisable organic illness, rather than a vague, ill-defined or psychosomatic disorder. If there is no uniformity in nomenclature within the medical community, it breeds confusion, ignorance on the part of health care practitioners [6] and slows science and clinical progress. The shift from general concepts such as "neurasthenia" [1] to ME/CFS and the suggested "Systemic Exertion Intolerance Disease" (SEID) [3] marks an essential progression in medical knowledge. This trend is due to a better understanding of the condition as a multisystem disease involving neurological, immunological, and other physiological systems. The evolution of the terminology reflects the growing body of research, from a merely descriptive and sometimes derogatory understanding to one in which a deep biological basis is recognised, even if it is not precisely known.

Searching the literature and evaluating its quality

Literature search strategy and quality assessment

A thorough literature search was conducted in a narrative format to identify relevant literature in the epidemiology, pathophysiology, diagnosis, and management of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The electronic databases PubMed/MEDLINE, Scopus, and Web of Science were searched from January 2000 to June 2025, with a special focus on publications in the last five years to reflect recent progress in biomarker discovery, subtyping, and post-viral/Long COVID research. The search terms and MeSH headings encompassed combinations of the terms "Myalgic Encephalomyelitis," "Chronic Fatigue Syndrome," "Post-Exertional Malaise," "Fatigue Syndrome, Chronic" [MeSH] with those related to pathophysiology (e.g., immune dysfunction, neuroinflammation, mitochondrial dysfunction, gut microbiome, autoantibodies), diagnosis (e.g., biomarkers, diagnostic criteria, cardiopulmonary exercise testing), and treatment (e.g., rehabilitation, pharmacotherapy, clinical trial). The inclusion criteria were peer-reviewed, original research articles, systematic reviews, meta-analyses, and authoritative clinical guidelines in English. Non-peer-reviewed publications (e.g., unpublished preprints,

blog commentary), case reports/case series (n<5), and publications not in English were not included unless of extraordinary historical significance. Hand searching was also done to retrieve additional relevant primary studies not found through electronic searching, using the reference lists of retrieved reviews and guideline documents. This search strategy was not systematic and did not follow a protocol for a systematic review, but was an exploratory one to prioritise breadth and relevance based on expert input.

The literature on ME/CFS is diverse and often includes methodological weaknesses such as a lack of rigour in methods of inclusion or exclusion, sample size, the criteria used to define cases, the selection of control groups, and the way outcomes were established in the studies. Small sample sizes, lack of blinding, cross-sectional study design, and use of subjective patient-reported outcome measures instead of objective physiological outcome measures are limitations in many studies, especially early immunological and biomarker studies. Where such limitations materially affect the interpretation of a finding, their impact is explicitly addressed in the accompanying text. Results from studies conducted with these limitations (such as small pilot biomarker studies, single-centre cohorts, and uncontrolled or open-label intervention studies) should be viewed as preliminary or exploratory and are not intended to represent the results of a definitive study and should be interpreted as hypothesis-generating until replicated in larger, adequately powered, and, where possible, blinded and controlled studies.

Prevalence, demographics and global impact

The prevalence of ME/CFS is not influenced by socioeconomic status, gender, age or race [7]. The prevalence of the disorder varies markedly across the world, with the variations being related to the number of diagnostic criteria used. Clinically diagnosed, population-based prevalence rates vary from 0.2% to 3.48% [7], from 0.4% to 2.5% [8], or from 0.2% to 2.8% [9]. A recent systematic review calculated the prevalence at 0.89% overall [10]. In Europe, prevalence ranges from 0.1% to 2.2% [9]. There are estimated to be 836,000 to 2.5 million people in the United States who have ME/CFS [3] and estimates of 5–9 million people worldwide [11]. One epidemiological fact is the greater prevalence of ME/CFS in women than men, the ratio being reported from 1.5:1 to 4:1 [11]. In England, for instance, the ratio was 3.88:1 [12]. Women also tend to have higher fatigue scores, less physical function, more bodily pain and more impairment with work activities [13] in ME/CFS. The prevalence of ME/CFS varies across different age groups, with a peak around 50 years of age in females and about 10 years later in males [12]. Age is also recognised as a poor prognosis factor, and age > 38 years is a poor prognosis [13].

Major racial differences in diagnosis have been found. There is a significant difference in the risk of a diagnosis of ME/CFS by ethnicity, with a risk of up to 5-fold higher in white individuals than in other ethnic groups, and a very low risk in Black, Asian or Chinese ethnic individuals [12]. This diagnostic bias has been reported to be greater than other common conditions, such as clinical depression and fibromyalgia [12]. The wide range of reported prevalence estimates reflects diagnostic difficulties and the absence of uniform criteria. The alarming number of people who are undiagnosed with ME/CFS (84% to 91% of people) [3] is an indicator of a large public health crisis that exists. Additionally, the demographic trends in diagnosis (with females being more likely to be diagnosed and significant racial differences) point to systemic problems in the health care system with access, provider awareness, and possibly implicit biases in diagnostic processes. All these factors contribute to the underdiagnosis and neglect of patients with ME/CFS, meaning that the actual incidence of ME/CFS is likely much higher than current estimates and some groups may be more vulnerable to this lack of recognition and care [5]. The universal observation that females were more affected, and that middle-aged females were more affected, also raises questions beyond the reporting of demographic data. This may be due to biological factors, such as hormonal influences or differences in the immune system, which render women more vulnerable to the effects, or to diagnostic practices that are more likely to diagnose women's symptoms as "psychosomatic" [14]. The near-equal gender distribution in the 4th and 5th decades further reinforces that age-related physiological changes and gender-specific health experiences are likely to be complex. This gap underscores the importance of sex-disaggregated data and research into possible biological mechanisms – those that vary between men and women – and the need to consider possible gender-specific bias in clinical practice.

The debilitating nature of ME/CFS and its effect on life's quality

ME/CFS is a chronic, multisystem, disabling illness with a significant impact on the daily functioning and productivity of those who suffer [3]. The functional impairment is significant and estimated to affect 25% of patients at some point in their lifetime [5], and a significant proportion of 16.2% are bedridden and need nursing care [15]. Many cannot sustain full-time work [9]. For people with ME/CFS, the effects on quality of life related to their health are massive and all-encompassing [8]. The impairment of all domains of HRQoL is severe, especially in the physical domain, such as persisting pain, with lower health functioning in relation to activities of daily living and work [16]. Research shows that ME/CFS

sufferers experience more pain and disability than RA or MS patients [17]. The most frequent HRQoL problems are problems with walking, moving around, maintaining self-care, pain, and inability to do usual activities (97%, 83%, 64%, 92%, and 67%, respectively) [18]. It should be noted that anxiety/depression was reported by 540 of 876 patients (62%) and was not the most prevalent of the five EQ-5D-3 L domains [18]. This separation stands in contrast with the historical tendency to misdiagnose ME/CFS as purely psychological. The economic impact of ME/CFS is significant, and in the United States alone, costs have been estimated between $149 billion and $362 billion USD [14]. The high cost of care places a heavy financial burden on individuals and society [15]. Its name features the word "fatigue", but the many lines of evidence reinforce the idea that ME/CFS is a complex, multisystem disease with many physical, cognitive and autonomic symptoms [1]. The high impact it has on daily living, work capacity and quality of life [5] underscores the disabling nature of its impact, which can be equal to or even worse than multiple sclerosis or heart disease, other severe chronic conditions [19]. The economic costs [14] also highlight that ME/CFS is not just a personal health issue, but a major public health problem with the need for increased research funding and public health resource prioritisation. There is a long history of misconceptions that it is essentially a psychological disorder [5], which is directly contradicted by the patient-reported QOL results [18]. It is a major factor in patient neglect, misdiagnosis and the continuation of suffering. Because symptoms are "invisible to others" [11], it is difficult to understand and to be understood by family, friends and the public, resulting in isolation [18]. This lack of awareness, alongside the belief that ME/CFS is largely a psychological disorder [5], causes a huge gap between what the patient feels and experiences as severely disabled and what society sees. This gap directly affects access to disability and social support services that are essential to the survival of the individual [15], where disability policies are often not in place to account for the disabling effect of disease [16]. Insufficient awareness, particularly among the public and professionals, of the serious physical nature of ME/CFS will continue to result in neglect, misdiagnosis and inadequate care for patients, and continue to cause unnecessary suffering. A summary of key epidemiological characteristics and indicators of disease burden is presented in Table 1.

Table 1 Global prevalence and demographic characteristics of ME/CFS

Characteristic	Data	Source
Global Prevalence	0.2% – 3.48% (depending on criteria)	[7]
US Prevalence	836,000–2.5 million Americans	[3]
Undiagnosed in US	84% – 91%	[3]
Female-to-Male Ratio	1.5:1 to 4:1 (up to 6:1 in 4th/5th decades)	[13]
Mean Age of Onset	31.6 years (15% before 18)	[9]
Peak Prevalence Age	~ 50 years (females), > 60 years (males)	[12]
Racial Disparities	White individuals 5x more likely to be diagnosed than others; lowest in Black, Asian, Chinese ethnicities	[12]
Housebound/Bedbound	~ 25% at some point; 16.2% bedridden requiring nursing care	[5]
US Economic Impact	$149 - $362 billion USD annually	[14]

Evolution and challenges in the diagnostic criteria

While no definitive diagnostic test or pathognomonic signs are available, the diagnosis of ME/CFS is largely based on excluding other medical conditions that cause fatigue [1]. There have been many changes in the diagnostic criteria over the years, however, which have helped to better define the clinical presentation of ME/CFS, thus contributing to our understanding of the disease and to possible treatment [1]. There are a number of widely used sets of diagnostic criteria, with slightly different requirements and implications:

Holmes criteria: This is an early set of criteria, which includes a severe disturbance in daily functioning due to new-onset debilitating fatigue, accompanied by exclusion of other fatiguing conditions. It also requires that a doctor record three physical signs: low-grade fever (37.6–38.6 °C, or rectal temperature 37.8–38.8 °C), no exudative tonsillopharyngitis, and tender lymph nodes [20].

Fukuda criteria (CDC 1994): The Fukuda criteria require that chronic fatigue is associated with significant disability for at least six months and is not due to another medical or psychiatric condition and are widely used in both clinical and research settings [1]. Most importantly, it must also be accompanied by at least four of the eight 'minor' symptoms: pharyngitis, cervical or axillary lymphadenopathy, myalgia, polyarthritis (without erythema or oedema), headache, non-restful sleep, fatigue after exercise, and/or cognitive impairment (short-term memory and concentration) [1]. One crucial difference between the Fukuda criteria and the others is that Post-Exertional Malaise (PEM) is not required as a diagnosis [5]. This greater inclusiveness can be a strength in that it may include a more diverse range of the condition, but can also be a weakness, leading to heterogeneity in the research cohorts [21].

The Canadian consensus criteria (CCC) and revised CCC (2003, 2010): These are more conservative criteria. The four core symptoms that patients must have to be diagnosed include significant physical and mental fatigue that is new onset, unexplained, persistent, and activity reducing; Post-Exertional Malaise (PEM); sleep

dysfunction (unrefreshing sleep or disturbances); and pain (significant muscle or joint pain, new headaches) [20]. Moreover, two or more neurological/cognitive disturbances (such as information processing difficulties, confusion, perceptual disturbances, impaired concentration, memory consolidation difficulties, motor disturbances, overload phenomena) and at least one symptom of two or three categories (autonomic, neuroendocrine, immune) should be present [21]. The disease should last for a minimum of 6 months (3 months for children) [21]. The most important difference is that CCC does not include patients who are suffering from signs or symptoms of mental illness [20], and PEM is regarded as one of the cardinal features of the CCC [21]. These increased symptom criteria may also result in fewer people being diagnosed than with Fukuda, which may increase the homogeneity of the study samples and facilitate research specificity and the ability to draw more definitive conclusions, although this may also reduce the generalizability of the study results [21].

The International Consensus Criteria (ICC) (2011): ICC is an international consensus document based on the Canadian Consensus Criteria, created by a multidisciplinary international team of clinicians, researchers, teaching faculty, and patient advocates [20]. Must have PEM, neurological symptoms (neurocognitive impairments, pain, sleep disturbance, neurosensory/perceptual/motor impairments); and at least one symptom from three of five areas: flu-like symptoms, easy viral susceptibility, gastrointestinal symptoms, genitourinary symptoms, sensitivities to food, medicines, or chemicals [20]. Of particular note, chronic fatigue is not listed as a symptom required by ICC, and the symptom duration requirement does not specify a minimum of six months; however, it does state that children may have different and more variable symptoms [20].

The IOM 2015 (now NAM) criteria are based on the committee's main symptoms of the disease, and they are stated as being "quite similar" to the Canadian Consensus Criteria [5]. The three core symptoms required for diagnosis are a substantial reduction in activity levels before the illness; profound new-onset fatigue that is not caused by excessive exertion and is not substantially eased by rest (Post-Exertional Malaise [PEM]); and unrefreshing sleep [3]. Also, there need to be at least two symptoms: cognitive impairment and orthostatic intolerance [3]. These symptoms must occur for 6 months or more, and must occur at least half of the time at moderate, substantial or severe intensity [3]. The criteria's lack of specificity on exclusionary conditions, seen as being ambiguous with respect to previous definitions, including the Fukuda definition, has been raised as a concern with the IOM criteria [5].

Multiple, conflicting diagnostic criteria are a major obstacle to ME/CFS research. Patient populations in different studies may not be comparable, owing to the different requirements, particularly for PEM and psychiatric exclusions [21]. This explains the "heterogeneity and complexity of the disease" [22] and makes it difficult to find markers of the disease to elucidate pathophysiology and treatment effectiveness [7]. This means that strong and generalisable results will be hard to come by, and progress in developing effective diagnostics and treatments will be limited. This also helps maintain the "disputed clinical diagnostic criteria" [23] that physicians use to make their diagnoses, thus allowing diagnostic delay to continue.

Critical analysis of diagnostic criteria: emphasis on post-exertional malaise and psychiatric exclusions

Increased awareness of the cardinal and defining symptom of ME/CFS, namely Post-Exertional Malaise (PEM), has led to its use to distinguish ME/CFS from other chronic conditions and illnesses with persistent fatigue symptoms [5]. One issue of contention is that the widely adopted Fukuda criteria do not require PEM [5], and this may account for some of the heterogeneity of the patient populations diagnosed using the different criteria. This shift in diagnostic criteria, especially the greater focus on PEM as a cardinal and sometimes mandatory symptom [3], represents a significant change in the understanding of ME/CFS. This shift from a fatigued-only definition (as in previous Fukuda) to one that acknowledges the specific and disproportionate exacerbation of symptoms following physical exertion [24] provides good evidence for the disease's unique and biological nature, not a psychological or deconditioning problem. This recognition of the centrality of PEM is further highlighted by the IOM's proposed change of the name to SEID (Systemic Exertional Intolerance Disease) [3] although the name itself was controversial and was eventually abandoned by the patient community because, as mentioned above in the history of the nomenclature of the disease, it failed to convey a fuller understanding of the complexity and severity of the illness [5]. This change is crucial for directing research to specific physiological processes responsible for PEM, such as energy metabolism defects and immune system dysfunction [25].

The Canadian Consensus Criteria (CCC) and the updated version of the criteria clearly exclude patients with any symptoms of mental illness from an ME/CFS diagnosis [20]. This contrasts with some criteria, such as the Oxford definition, which allow psychiatric symptoms to be part of a diagnosis [20]. This basic distinction in the criteria of exclusion has significant consequences for the makeup of patient populations in research protocols and for diagnostic and treatment workflows in

clinical practice [21]. The fact that psychiatric disorders are excluded in some criteria (such as CCC) [20] and the IOM's reasoning behind their opposition to the use of the word encephalomyelitis [3] shows that there is ongoing effort to separate ME/CFS from psychosomatic explanations and old allegations of mass hysteria [5]. This historical bias has had a significant impact not only on the diagnostic criteria but also on research funding priorities and the quality of care for patients. In ME/CFS, psychiatric comorbidities, although present, are not the focus of the exclusion, and are actually a rhetorical, but probably necessary, manoeuvre to separate ME/CFS from other illnesses for the purposes of making it a separate, biological disease. This approach also has the potential to miss nuances and complexity of the bidirectional relationship between physical and mental health in chronic disease. This controversy over the "encephalomyelitis" part [3] is a good example of the changing picture of the scientific understanding of the neurological basis of the disease, which is growing in strength.

Underdiagnosis, misdiagnosis and delays in diagnosis

In clinical practice, the diagnosis of ME/CFS is still a major challenge [3]. Many affected people are not diagnosed, and estimates range from 84% to 91% of people in the United States [3]. Those in the patient community often suffer a long diagnostic journey, yearning for a certain diagnosis for years until it is confirmed. A survey found that 67%-77% of patients took over a year for their diagnosis, and around 29% took over five years [3]. These serious and potentially harmful delays have been confirmed recently, with a large proportion of people being diagnosed after over 10 years and the mean time to diagnosis of 14 years in one cohort [18].

Getting diagnosed for ME/CFS and having it confirmed by a health practitioner can be frustrating because of the widespread scepticism and misunderstanding of the condition, for example by being dismissed as a "psychogenic" illness or "a figment of the patient's imagination" [3]. This perception may lead to misdiagnosis as a psychological condition, and ME/CFS is often diagnosed as a diagnosis of exclusion [5]. One of the main reasons for these delays and inconsistencies is the absence of standardised diagnostic criteria and, importantly, objective biomarkers [7]. A diagnostic bottleneck still exists because there are no quantitative, objective tests, and clinical signs are subjective, non-specific and are often disputed. In addition, sometimes, doctors prefer to diagnose fibromyalgia over ME/CFS, as there are treatments available for fibromyalgia, which may affect the course of diagnosis [26]. These long delays in diagnosis [3] are not only inconvenient but also a 'diagnostic odyssey' that prolongs the anguish of the cause, postpones appropriate care, and exacerbates patient mistrust of the health system. This leads to a vicious circle: patients are either sent away or misdiagnosed [5] due to underlying reasons such as scepticism among providers, the absence of objective tests, and exclusion [3]. This delay in diagnosis will only further limit the chances of a better prognosis [27] and the possibility of taking advantage of early interventions that could lead to better outcomes [22]. The preference for diagnosis of fibromyalgia [26] points to the fact that there is a systemic problem in which there are some conditions that are treatable and others that are not, despite having similar underlying pathology, but may not have a clear diagnostic path or approved treatment. The major diagnostic criteria for ME/CFS are shown in Table 2 in comparison.

Table 2 Comparison of major ME/CFS diagnostic criteria

Criteria Name (Year)	Core Fatigue Requirement	Post-Exertional Malaise (PEM) Requirement	Psychiatric Exclusions	Duration Requirement	Other Key Features / Notes
Holmes (1988) [28]	Debilitating, new onset, interferes with daily activities	Not explicitly required	Elimination of other fatiguing conditions	Not specified	Low-grade fever, nonexudative pharyngitis, tender lymph nodes
Fukuda (CDC 1994) [29]	Chronic (≥ 6 months), incapacitating	Not explicitly required	Exclusion of psychiatric conditions	≥ 6 months	4 of 8 minor symptoms (e.g., sore throat, myalgia, cognitive impairment)
Canadian Consensus (CCC) (2003/2010) [21]	Significant physical & mental, new onset, unexplained, persistent, activity-reducing	**Required**	Explicitly excludes patients with mental illness symptoms	≥ 6 months (≥ 3 months for children)	Pain, sleep dysfunction, 2 + neurological/cognitive, 1 + from 2 of 3 (autonomic, neuroendocrine, immune)
International Consensus (ICC) (2011) [30]	Not explicitly required	**Required**	Not explicitly stated, based on CCC	Not explicitly required (variable)	Neurological (cognitive, pain, sleep, sensory), 1 + from 3 of 5 (flu-like, viral susceptibility, GI, GU, sensitivities)
IOM (NAM) (2015) [31]	Substantial reduction in activity, profound, new onset, not exertion-alleviated, not rest-alleviated	**Required**	Ambiguity, potential for overdiagnosis	≥ 6 months (present ≥ 50% of time with moderate/severe intensity)	Unrefreshing sleep, plus 1 of 2 (cognitive impairment, orthostatic intolerance)

Key symptoms of ME/CFS

The symptoms associated with ME/CFS are not just fatigue but a combination of symptoms that impact on a number of physiological systems. The symptoms experienced are frequently disabling, variable and intense. These complex and multisystem presentations are summarised in Fig. 1.

Profound fatigue

Fatigue is a hallmark of ME/CFS, and is severe and debilitating [1]. This is tiredness of sudden or definite onset that is not due to continuing excessive exertion and, importantly, is not significantly reduced by rest [1]. This fatigue is often described as being 'overwhelming' and unique, and is not experienced by patients before [3]. The difference between "fatigue" (which many conditions can cause) and the "profound, unremitting, and unalleviated" fatigue of ME/CFS [1] is important. This is not just fatigue; it's a condition that affects the whole person and affects one's everyday life. Understanding that the symptoms were not improved by rest and became worse with exertion [1] is important, because it differs from what would happen if it were just a state of deconditioning.

Post-Exertional Malaise (PEM)

Post-Exertional Malaise (PEM) is regarded as the cardinal and defining symptom of ME/CFS and one of the most important features that can distinguish ME/CFS from other chronic conditions and illnesses that involve chronic fatigue [5]. PEM is characterised by an extended exacerbation of core symptoms, or the onset of new flu-like symptoms, after a minor physical, mental, emotional or orthostatic challenge [5]. Severity of PEM is often out of proportion to the efforts that caused it [32]. Symptoms may be immediate or commonly delayed until 12–48 h after the activity, but can occasionally take as long as a week to appear [33]. The convalescence following a PEM episode is typically prolonged and may last more than 24 h, and sometimes days, weeks or months [33]. Objective signs of PEM have been found by a 2-day cardiopulmonary exercise test (CPET), which shows a unique performance drop on the second day of CPET testing in ME/CFS patients compared to healthy controls and people with unexplained chronic fatigue [25]. PEM may occur with even minor activities, such as sitting up, brushing teeth, taking a shower, or walking; cognitively demanding tasks, such as reading or writing; and social stimulation, emotional stress, or sensory stimulation, such as loud noises or bright lights [32]. PEM is not only a symptom, but is perhaps the most defining feature of ME/CFS [5]. The delayed onset and disproportionate severity [33] are important in elucidating underlying physiological dysfunction, especially in energy metabolism [25]. This phenomenon is strongly supported by

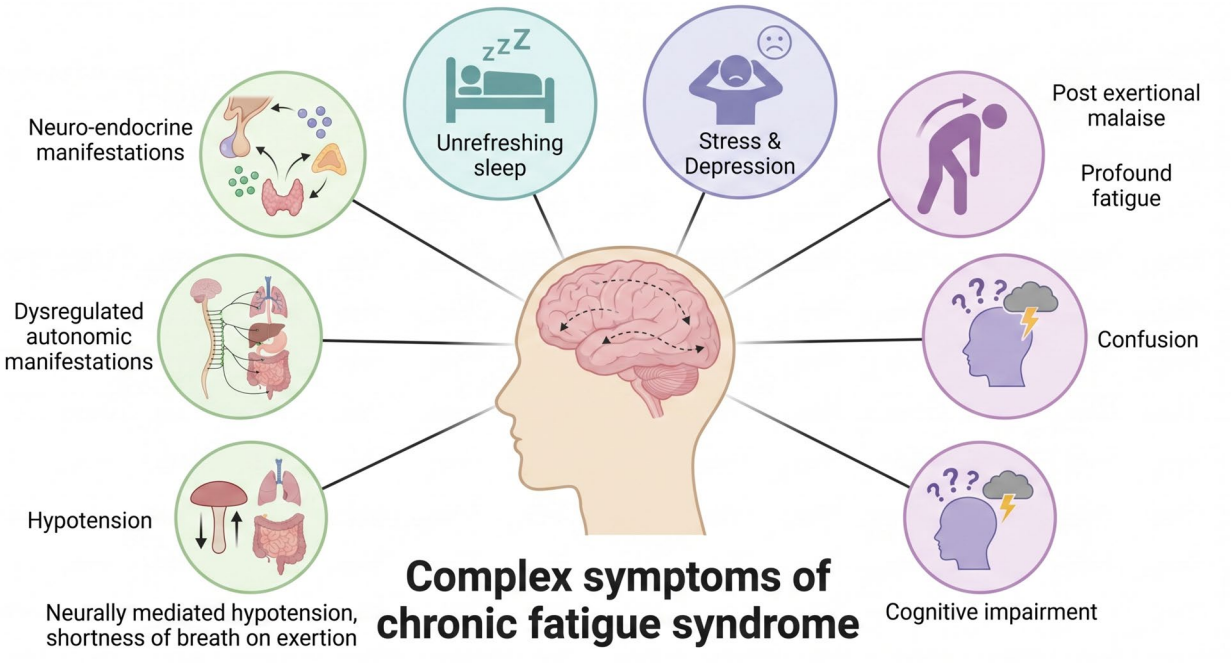


Fig. 1 Complex symptoms of chronic fatigue syndrome. A multi-sector radial diagram mapping the principal clinical features of ME/CFS across physiological domains: energy metabolism (profound fatigue, post-exertional malaise), sleep (unrefreshing sleep), mood (stress & depression), cognition (confusion, brain fog), autonomic function (neurally mediated hypotension, dysregulated autonomic manifestations), and neuro-endocrine regulation (temperature instability, hormonal dysregulation)

objective evidence from 2-day CPET [25], which can be measured as a biological marker. This renders PEM a key point of interest for research and therapy.

Unrefreshing sleep

One of the clinical diagnostic criteria for ME/CFS is unrefreshing or non-restorative sleep, even though an individual has enough or even more than enough hours of total sleep [2]. Patients consistently report waking up feeling as if they have not slept at all, even if they have slept long enough [34]. Common sleep disturbances include insomnia (difficulty falling or staying asleep), frequent waking, excessive daytime sleepiness and dreams or nightmares [2]. This symptom is intrinsically linked to other core features, which will increase the pain, fatigue, anxiety, depression, low functional capacity and quality of life [34]. Research has identified subtle but measurable differences in sleep behaviours in people with ME/CFS. These include abnormalities of brain waves in various sleep stages, substantial decreases in sleep time, excessive time spent awake in bed, decreases in REM sleep, and other REM abnormalities [35]. Importantly, low nighttime HRV has been noted, indicating underlying dysfunction of the autonomic nervous system (ANS) [25]. The ANS is critical to the regulation of bodily homeostasis, and an imbalance, such as increased sympathetic arousal, may contribute to poor sleep. Moreover, there are structural differences in the medial prefrontal cortex (mPFC) related to sleep unrefreshment in ME/CFS patients, a brain region involved with memory and decision-making [35]. Poor sleep hygiene is not the only problem with sleep; unrefreshing sleep reveals a deeper physiological imbalance [2]. The noted brain-wave disturbances, the shift in REM sleep and particularly the reduction of heart-rate variability during sleep [35] indicate a possible dysfunction of the ANS (autonomic nervous system) [25]. The ANS is essential for maintaining homeostasis, and its imbalance (e.g. sympathetic hyperactivity and parasympathetic hypoactivity) may account for increased arousal during sleep, and thus restrict restorative processes. This indicates that sleep disturbance is not only a behavioural symptom of ME/CFS but is also a physiological symptom.

Cognitive dysfunction or "brain fog"

One of the many symptoms of ME/CFS is known as 'brain fog' [1] and is a very debilitating experience for many people. This is a subjective experience of the patient, and they describe it as slow thinking, inability to concentrate, confusion, forgetfulness, and difficulty focusing, among other symptoms [36]. It is also commonly reported as one of the most disabling symptoms of ME/CFS, impacting life activities and productivity [37]. These deficits have been identified through objective neurocognitive testing as deficits in attention, information processing speed and efficiency, working memory, and reaction time [37]. There are suggested physiological underpinnings to the brain fog: chronic orthostatic intolerance (OI) [37], reduced cerebral blood flow (CBF) [4] and the observation that people with ME/CFS need more activation in the cortex and subcortical regions of the brain to do tasks that typically do not require a lot of activation in healthy individuals [37]. There is objective evidence of neurocognitive deficits to support the subjective experience of "brain fog" [37, 38]. When paired with reduced cerebral blood flow [4] and elevated levels of brain activation [37], this indicates a neurological and possibly metabolic inefficiency. It is not simply fatigue, but a measurable impairment of brain function, which may be related to neuroinflammation [4] and energy deficits [25] which are worsened by exertion, like PEM.

Pain

Muscle (myalgia) and/or joint (arthralgia) pain are very common and often very severe symptoms of ME/CFS. However, it is often diffuse, widespread and variable in location and intensity [1]. The most common painful symptom reported is muscle pain (68% of patients) [17]. Surveys show that 79% of patients have severe pain sometimes, often or all the time; and 84–94% of patients report some muscle or joint pain in formal research studies [17]. In past studies, ME/CFS patients have reported more intense pain than those with rheumatoid arthritis and multiple sclerosis—the conditions in which pain is known to be a prominent symptom [17]. Patients report pain as "throbbing, aching, tender, gnawing, and burning", and burning pain is common with neuropathic disorders, indicating potential involvement of the nerves [17]. The most common sites of pain are the cervical spine (66%), anterior thigh (44–46%), lumbar spine (42%) and posterior calf (38%), and most patients report pain at multiple sites [17]. Overall level of disability is strongly related to severity of pain [17]. The high level of pain in ME/CFS [17] is not only due to fatigue, but can be significant and more severe than in recognised painful disorders, such as rheumatoid arthritis [17]. The term 'burning' pain [17] implies a neuropathic component which would indicate involvement in the central nervous system, in addition to a musculoskeletal component. The pain is widespread, debilitating and is a major source of functional impairment and decreased quality of life, and is a very important symptom to manage and study.

Other common symptoms

In addition to fatigue, PEM, unrefreshing sleep, cognitive dysfunction and pain, ME/CFS patients often present with many other symptoms which illustrate the multisystem nature of the disorder.

Orthostatic intolerance (OI) is very common and is associated with a variety of symptoms that improve when lying flat and worsen when standing upright, including dizziness, lightheadedness and fainting. Postural Orthostatic Tachycardia Syndrome (POTS) is defined by a rise in heart rate when people stand [21]. Other autonomic symptoms include palpitations and/or cardiac arrhythmias, marked pallor, dyspnea on exertion, nausea, and irritable bowel syndrome (IBS) and urinary frequency or bladder dysfunction [21].

Neuroendocrine Manifestations: Some patients complain of instability of body temperature, intolerance to hot and cold temperatures, and repeated episodes of chills and fever; some also report cold extremities [11]. Other common features are a change in appetite (anorexia or unusual eating habits) and deterioration of symptoms that occur with stress [21]. Hypothalamic dysfunction, a major brain target region involved in temperature regulation and hormone production (such as cortisol), has been seen [4].

Immune Manifestations: common immune-related symptoms are tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, feeling ill and feverish, as well as new sensitivities to food, medicines and chemicals [11].

The long list of symptoms, as seen in autonomic, neuroendocrine, and immune systems [11], further underscores that ME/CFS is a complex, multisystem disorder [3]. These signs and symptoms are interrelated and indicate a more systemic dysfunction, not just a localised one. Orthostatic intolerance, for example, and sleep can be explained by autonomic dysfunction [25]. It has been linked with disturbances and gastrointestinal symptoms, thus signalling a core regulatory dysfunction. This complexity can lead to diagnostic problems and requires an integrated approach to research and treatment.

Common comorbidities

ME/ CFS also often co-occurs with other medical conditions, which can make diagnosis and management more difficult. The most prevalent overlapping condition reported is fibromyalgia [11]. The prevalence of ME/CFS that has been reported is highly variable depending on the study design and setting; 35% to 70% of patients diagnosed with ME/CFS also have fibromyalgia, and vice versa, and a pooled meta-analytic estimate of clinical overlap between the two conditions was 47.3% (95% CI: 46.0-48.6%) based on 21 studies [39]. Another very common condition associated with OI is NMH and POTS [11]. Irritable bowel syndrome (IBS) is a common condition that often coexists, with a range of 38–92% of patients suffering from it [11]. A few other conditions that are similar to ME/CFS that may overlap include interstitial cystitis, temporomandibular joint disorder or TMJ, chronic pelvic pain and multiple chemical sensitivity or MCS [11]. Autoimmune diseases, including Hashimoto's Disease, Sjögren's Syndrome and Lupus, are also reported as comorbidities, and some clinicians have reported seeing an ME/CFS diagnosis before the diagnosis of an autoimmune disorder. There is a high rate of comorbidity [11], raising important questions about shared underlying pathophysiological mechanisms. For instance, autonomic dysfunction is also a feature of both IBS and OI and immune dysregulation plays a role in autoimmune diseases. These might also be separate, but often overlapping diseases which combine to make diagnosis and treatment more challenging. This is especially interesting because fibromyalgia was also highly represented and there is a considerable overlap between the two conditions [11], with the interesting observation that fibromyalgia was the preferred diagnosis over ME/CFS [26]. This indicates that shared pathways research may provide some interesting insights into both conditions and that a comprehensive, integrated approach to managing these people is necessary.

Pathophysiological hypotheses

Infectious triggers

There is often a triggering event at the onset of ME/CFS, such as an acute infection, and many factors are cited as possible triggers – microbial and viral [1]. One study found that about 60% of patients with ME/CFS experience the onset of symptoms after an acute infection [10]. In one cohort, more than 70% recognised an infectious disease as one or more triggering events [9]. Viral infections were recalled by 77.8% of the respondents, and the most commonly reported infectious agent was Epstein-Barr Virus (EBV) [9]. Other viruses extensively studied for their possible involvement are cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), HHV-7, HHV-8, human parvovirus B19 (B19V), enteroviruses and Ross River Virus (RRV) [7]. Despite this strong connection, in most cases of ME/CFS there is no definitive evidence of an active chronic viral infection [7]. The "hit and run" hypothesis has been suggested as a result of this observation. This theory suggests that viruses initially cause acute immune abnormalities and physiological changes, and that they leave behind a defective immune system and/or autoimmunity, even if they are no longer persistently active or detectable [7]. The very strong link between the onset of ME/CFS and previous infections and the absence of consistent evidence of prolonged active infections suggests the "hit and run" hypothesis. This is important, since it moves the research agenda from the mere detection of a pathogen to understanding the effects of the virus in the host after it is gone or latent – the post-infectious sequelae, where the initial viral insult permanently alters host physiology (immune,

neurological, and metabolic systems). This is why the classical antiviral therapies could be ineffective and why it's necessary to use drugs that act downstream of the initial trigger.

Immune system dysregulation

There is an almost constant association with immune system abnormalities in ME/CFS [7]. Often observed in many studies was reduced activity of natural killer cells (NK), which are cells of the immune system that play an important role in the detection and elimination of virus-infected and tumour cells [25]. In addition, the metabolic activity of T cells in ME/CFS patients is also decreased, potentially indicating an exhausted state, and therefore impaired against pathogens [25]. A role for autoimmunity has been suggested, and some patients have high levels of autoantibodies, which may be related to viral mimicry in which viral proteins are similar to human proteins [7]. Several specific autoantibodies have been identified, including those against muscarinic acetylcholine receptors and β2-adrenergic receptors, which might affect blood flow [25]. The idea of 'immune exhaustion' is becoming more common, especially given the shared features of immune dysregulation and cellular signalling mechanisms between ME/CFS and Long COVID [40]. In patients with ME/CFS, there is evidence of immune suppression through differential gene expression analysis, which shows genes encoding immunoglobulins and interferon (IFN) signalling are downregulated [41]. Pathway analysis also identifies dysregulated macrophage activation, cytokine production, and immunodeficiency signalling as further implicated processes [41]. This is the condition in which the immune system is incapable of responding properly due to its long-term activation or chronic infection [41]. Low-level inflammation and chronic immune activation are also common in ME/CFS [7]. In ME/CFS, there is paradoxical activation of the immune system [7], and at the same time there are signs of exhaustion and suppression [41], including in NK cell function [25]. This indicates the immune system is always "on" but not functioning properly, causing chronic low-grade inflammation and failure to control pathogens or regulate immune responses. This "immune exhaustion" [41] may account for recurrent infections and persistent symptoms, and may therefore be an important bridge connecting infectious triggers and chronic illness.

Neurological abnormalities

The WHO ICD-10 [4] lists ME/CFS as a neurological disorder, and it is now becoming regarded as a "neuroimmune disease" [11]. Neurologic symptoms vary from patient to patient, from alcohol/drug intolerance to disequilibrium (loss of balance, vertigo, nausea), to headaches and migraines, hypothalamic dysfunction, neuropathic pain (burning, stabbing, searing), sensory disturbances (loss of sensation, paraesthesia, sensitivity to light, sound, touch), and profound sleep dysfunction [4]. Studies of brain images have consistently shown structural, biochemical and functional abnormalities in the brains of ME/CFS patients [4]. Common findings include:

Grey Matter Reduction: Reduction of grey matter, especially in the right prefrontal cortex, which is associated with the degree of fatigue [4].

White Matter Reduction: Overall decrease in white-matter content, related to functional status [4]. Over time, studies have also indicated progressive loss of white matter volumes in particular fasciculi [4].

Combined Reductions: marked reductions in both white and grey matter volume, which is in line with the typical complaints of poor memory [4].

Metabolic and Functional Changes: Low metabolism in some regions of the brain, decreased serotonin transporters and neurovascular coupling issues [25]. Reduced blood flow (hypoperfusion) has been noted in different areas of the brain, such as the brainstem [4].

There have also been chemical changes in the brain, such as decreased uptake of acetylcarnitine, increased levels of choline, decreased N-acetylaspartate (a marker of neuronal function), increased lactate in the ventricles, and decreased glutathione in the cortex [4]. Neuroinflammation has been suggested to be involved in the underlying mechanisms [25]. Improved studies, notably from groups in Japan, have shown abnormalities in multiple brain regions associated with neuroinflammation that relate to symptom severity [4]. Differences in levels of some key markers of neuroinflammation and elevated brain temperature have also been seen using Magnetic Resonance Spectroscopy (MRS) analysis [4]. A consistent finding is dysfunction of the Autonomic Nervous System (ANS), including blunted heart rate response to exercise, higher heart rate during tilt-table testing and reduced nocturnal heart rate variability [25]. This suggests a lack of balance between the sympathetic and parasympathetic nervous systems, which may contribute to various systemic symptoms. In contrast, the large body of neurological evidence also suggests that there is more than peripheral or muscular involvement of the CNS in ME/CFS [4]. The biological evidence for symptoms such as cognitive dysfunction, pain and sleep difficulties, including structural changes (grey/white matter reduction), chemical imbalances (lactate, choline, N-acetylaspartate) and direct evidence of neuroinflammation [4], is strong. In addition, autonomic nervous system dysfunction [25] connects neurological pathology to a generalised systemic clinical presentation such as gastrointestinal disturbances and orthostatic intolerance, emphasising the brain's involvement in multisystem dysfunction.

Contrary to some historical "hysteria" accusations [14], there is a need for neurologically focused research and interventions.

The abnormalities in energy metabolism and mitochondrial dysfunction

There is strong emerging evidence that energy metabolism is significantly altered in ME/CFS and that it is a key factor in the pathogenesis of important symptoms [42]. Mitochondrial dysfunction is thought to play a major role in the underlying pathophysiological mechanisms responsible for the main symptoms of Post-Exertional Malaise (PEM) and profound fatigue [25]. Impaired production of adenosine triphosphate (ATP) [42], impaired oxidative phosphorylation (OXPHOS) [43], and reduced spare respiratory capacity in cells (SRC) [41] have been observed in ME/CFS patients. This implies that ME/CFS cells cannot function more energetically when energy demands are raised, leading to energy crises during stress and/or exertion, which directly affects the experience of disabling fatigue and PEM [41]. One-day cardiopulmonary exercise tests done after two days (2-day CPET) confirm this metabolic inefficiency, as ME/CFS patients reach a clinically significant decrease in work rate at the anaerobic threshold on the second test day, which is not seen in any other disease [25]. Patients are also assessed to switch to anaerobic metabolism at very low activity levels, suggesting that they are unable to maintain aerobic energy production. Compensatory metabolic adaptations are reported, including shifts towards less efficient glycolysis and abnormal lactate production [41], and increased lactate levels in the ventricles, which are also seen in the brain [4].

Redox imbalance, the imbalance between ROS and antioxidant defences, is a fundamental characteristic of ME/CFS and results in oxidative stress [41]. Increased oxidative stress and decreased antioxidant capacity are regularly noted in ME/CFS patients, which leads to mitochondrial dysfunction [41]. Reactive nitrogen species (RNS) have also been reported as a marker of nitrosative stress [41]. The consistent associations of mitochondrial dysfunction, decreased ATP production and decreased spare respiratory capacity [25] give a strong biological basis for the hallmark symptoms of extreme fatigue and PEM. When moving at low intensities and producing high levels of lactate, the body is able to produce less energy for this exertion level, resulting in "crashes" after low-intensity activity [43] and high levels of lactate [4]. This metabolic dysfunction is also associated with oxidative and nitrosative stress [41], indicating cell damage and cell inflammation. This renders energy metabolism an ideal field in which to identify biomarkers and therapeutic interventions.

Gut microbiome alterations

There has been a growing number of recent studies pointing to the microbiota-gut-brain axis as a key pathway involved in the pathophysiology of ME/CFS [33]. The complex nature of this relationship implies that changes in the composition of gut microbiomes could be associated with variations in immune responses, neurochemical signalling and neuronal health, and consequently have a significant influence on the wide-ranging symptoms of ME/CFS [33]. There is evidence of gut dysbiosis, which refers to changes in the composition of the gut microbiota of people with ME/CFS. Although no consistent, specific microbial signature has yet been established in all studies, there is overall evidence of dysbiosis, such as decreased bacterial diversity and richness, lower levels of anti-inflammatory bacterial species, and increased levels of pro-inflammatory bacterial species, such as Enterobacteriaceae [33]. In particular, a decrease in Faecalibacterium, one of the most important butyrate producers, has been found to be a potential biomarker and has been observed in several studies [44]. There is some evidence that people with ME/CFS have more permeable guts (leaky gut), which may result in bacterial translocation into the systemic circulation [44]. Several studies have reported that blood IgA and IgM antibody levels against lipopolysaccharide (LPS) of bacteria are significantly elevated in ME/CFS patients, which has been suggested to be related to illness severity and increased gut permeability [44]. This bacterial translocation can lead to a systemic immune response and inflammation [44]. A consistent pattern is reduced abundance of short-chain fatty acid (SCFA) producers, in particular butyrate producers, though some studies have reported higher faecal SCFA levels [44], making this pattern more complex to interpret.

The microbiota-gut-brain axis refers to the two-way relationship between the gut microbiome and the brain, impacting multiple physiological and neurological processes [33]. These pathways include metabolites (SCFAs), hormones (neurotransmitters, e.g., GABA, serotonin, dopamine), neural (vagus nerve, spinal pathway), and immune system pathways (cytokines) [44]. There is growing evidence of dysbiosis and gut permeability in the gut [33], which implies that the gut may play a major role in systemic inflammatory and immune dysfunction in ME/CFS. The "leaky gut" theory, bacterial translocation, and immune system activation [44] are likely explanations for how gut problems may cause symptoms that extend beyond the gastrointestinal tract, such as neurological and immune system effects through the gut-brain axis [33]. This provides a rationale for the possibility of interventions in the gut, but cause and effect require further longitudinal investigation.

Genetic predispositions

The exact genetics of ME/CFS remain to be fully understood, but there is a genetic susceptibility to developing ME/CFS. Several factors suggest an inherited component to ME/CFS. There have been reports of familial clustering of ME/CFS, and twin studies have shown that the incidence of ME/CFS is higher in identical (monozygotic) twins than in fraternal (dizygotic) twins [45]. Familial clustering and increased risk of CFS in first-, second-, and third-degree relatives also suggest a genetic component [45]. The Centres for Disease Control and Prevention (CDC) says, however, there have not been specific definitive genetic associations [45]. Ongoing research is underway to discover potential risk genes for ME/CFS. An initial pilot study (with acknowledged methodological limitations) found a number of relatively common variants of the genes that were more frequent in patients with ME/CFS, such as CYP2D6, PRRT4, PRSS56, C14orf37, ANKDD1B, GPBAR1, LHB, ADAMTS19, VARS2, and CPLX2 [45]. The indolamine-2,3-dioxygenase (IDO) metabolic trap hypothesis was developed as a mathematical model proposing that a series of common harmful mutations in the IDO2 gene may result in abnormal tryptophan metabolism, which may be involved in disease pathogenesis [44]. Moreover, some studies have revealed associations between gastrointestinal, neurological and inflammatory symptoms and mitochondrial DNA haplogroups of patients [45]. The associations of genes in the Human Leukocyte Antigen (HLA) region, a characteristic of autoimmunity, have likewise been studied, and two HLA associations have been shown to be more prevalent in a sub-group of patients with ME/CFS [45]. A genetic 'ME/CFS gene' has yet to be found, but there is strong circumstantial evidence of a genetic susceptibility as familial clustering and twin studies suggest. This implies that although environmental factors (such as infections) can trigger the illness, genetics can also affect a person's susceptibility and their actual symptoms [45]. This means that ME/CFS is probably a complex polygenetic condition with many genetic risk factors and environmental triggers. Knowing these genetic factors is essential for recognising at-risk individuals, creating precision diagnostics, and precision therapies [46]. Table 3 highlights some key pathophysiological findings in ME/CFS.

Research is underway to integrate the pathophysiological cascade in ME/CFS

It is important to note that while each of the aforementioned mechanisms represents an infectious trigger, immune exhaustion, neuroinflammation, mitochondrial dysfunction, gut dysbiosis, and genetic susceptibility are not parallel processes; rather, they appear to be part of a plausible interconnected cascade, as summarised in a schematic representation (Fig. 2). In a certain subset of individuals, an infectious trigger (e.g., Epstein-Barr virus, enteroviruses, or SARS-CoV-2) does not lead to a usual recovery, but to dysregulated and incompletely resolved immune activation, in a genetically susceptible host (e.g., HLA-DQA1*05:01 allele or variants relevant to the immune system and/or the nervous system identified by the genome-wide association study DecodeME) [47]. This is manifested as immune exhaustion, with persistently low levels of cytotoxicity from natural killer (NK) cells, one of the most consistent immunological changes found in ME/CFS [48]. Chronic low-grade immune dysregulation and adrenergic/muscarinic receptor autoantibody production are thought to contribute to neuroinflammation and drive secondary mitochondrial/metabolic dysfunction, as demonstrated by abnormal metabolomic signatures indicating energy strain [42]. Gut dysbiosis, characterised by decreased bacterial diversity and loss of anti-inflammatory bacterial taxa like Faecalibacterium prausnitzii [49], may also feed back into the neuroimmune axis via increased intestinal permeability and bacterial translocation, perpetuating the chronic symptom state, such as post-exertional malaise.

Table 3 Summary of key pathophysiological findings in ME/CFS

System/Factor	Key Findings/Abnormalities	Supporting References
Infectious Triggers	Frequent onset after acute viral/microbial infection (e.g., EBV, HHV-6, enteroviruses); "hit and run" hypothesis	[7]
Immune System	Decreased NK cell function; T cell exhaustion; Autoantibodies (e.g., acetylcholine receptors); Downregulated IFN signaling; Dysregulated macrophage activation, cytokine production; Chronic low-level inflammation	[25]
Neurological System	Reduced grey/white matter volume; Decreased cerebral blood flow; Abnormal brain chemicals (e.g., elevated lactate, choline, reduced N-acetylaspartate); Neuroinflammation; Autonomic nervous system dysfunction (e.g., OI, POTS, altered heart rate variability)	[4]
Energy Metabolism	Mitochondrial dysfunction; Reduced ATP production; Impaired OXPHOS; Diminished spare respiratory capacity; Shift to anaerobic metabolism; Elevated lactate; Redox imbalance (oxidative/nitrosative stress)	[25]
Gut Microbiome	Gut dysbiosis (reduced diversity, altered species); Increased gut permeability ("leaky gut"); Bacterial translocation; Reduced SCFA-producing bacteria; Altered microbiota-gut-brain axis communication	[33]
Genetic Predisposition	Familial clustering; Higher concordance in identical twins; Identification of potential risk genes (e.g., IDO2, HLA associations); Mitochondrial DNA haplogroup correlations	[46]

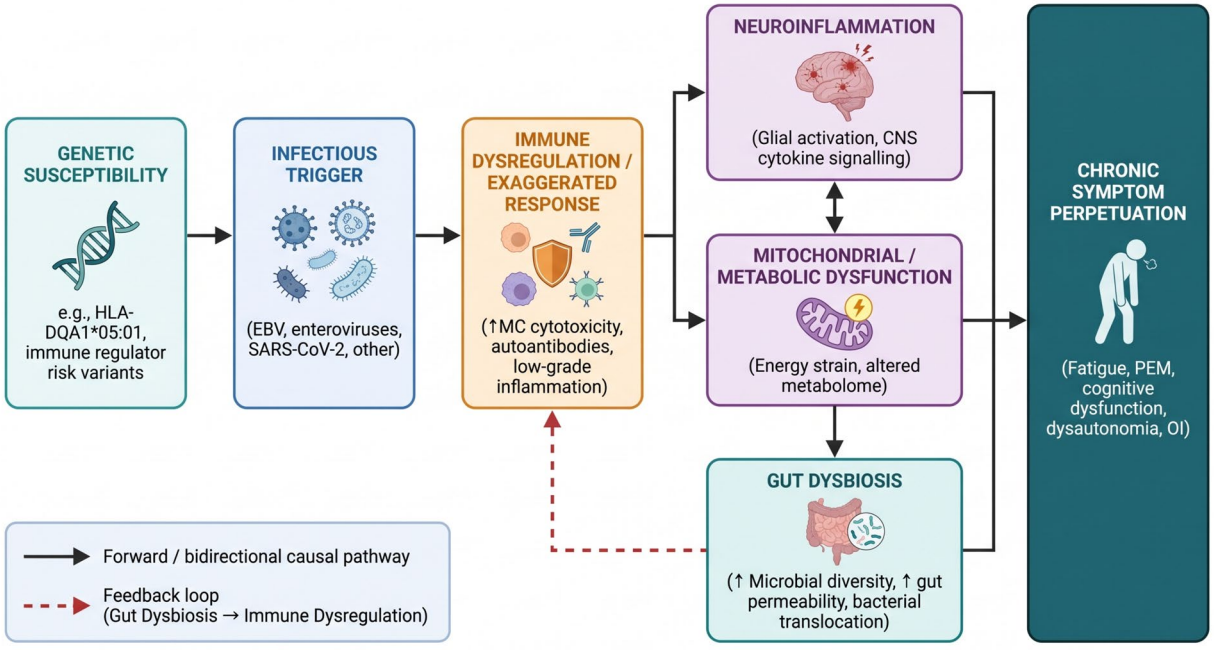


Fig. 2 Proposed unified pathophysiological cascade in ME/CFS. A genetically susceptible host encounters an infectious trigger, precipitating immune dysregulation/exhaustion, which drives parallel and mutually reinforcing neuroinflammation and mitochondrial/metabolic dysfunction. These processes promote gut dysbiosis, which feeds back to sustain immune dysregulation (dashed feedback arrow), collectively perpetuating the chronic symptom state characteristic of ME/CFS

Diagnostic biomarkers: present and future

The urgent demand for objective biomarkers.

Currently, there is no consensus on standardised biological markers or objective diagnostic tests to facilitate progress in research and clinical care of ME/CFS [7]. Diagnoses remain based on subjective, non-specific and controversial clinical diagnostic criteria, and diagnosis often takes many years to accomplish [23]. This subjectivity and absence of a quantitative biomarker are major factors in the trivialisation, scepticism, marginalisation, and misunderstanding of ME/CFS by the medical profession and the public [23]. A validated diagnostic biomarker is not simply a research convenience but an essential step to increase diagnostic accuracy and timeliness, develop targeted treatments, and conduct research studies across collaboration, ensuring homogeneous patient cohorts [22]. It is important to note the repeated focus on the lack of validated biomarkers [7]. This "biomarker bottleneck" is a key source of many problems such as delayed diagnosis [5], misdiagnosis [5], inconsistent research cohorts [22] and scepticism by healthcare providers [3]. With the lack of objective measurements, the disease is expressed subjectively and is prone to misunderstanding, which makes it difficult to treat and to advance research. Hence, the development of a biomarker is not only a research objective but fundamental to validating the disease and making effective treatment possible.

Promising research avenues

While the difficulties are many, recent studies have reported significant, quantifiable differences in the biochemical and electrophysiological properties of blood cells that can distinguish ME/CFS from non-ME/CFS participants with high sensitivities and specificities [23]. These new opportunities can lead to novel diagnostic technologies that are accessible and relatively non-invasive. Some areas of promising research are:

Raman Spectroscopy: Raman Spectroscopy has been found to be useful in distinguishing patients with ME/CFS [23] through profiling of immune cells.

Nano-electronic Assays: Electrical impedance of blood samples during hyperosmotic challenge with a nano-electronic assay has shown promising results [33].

Metabolomic assays: Small molecule metabolite assays (metabolomics assays) can be used to gain insight into metabolic pathways and to differentiate ME/CFS patients [23].

As energy metabolism is so important in ME/CFS, a variety of mitochondrial dysfunction assessment methods are being investigated as potential biomarkers [23].

Ion Channel Dysfunction: Dysfunction of the acetylcholine receptor and transient receptor potential ion channels is increasingly being proposed as a cause of ME/CFS and is being explored as a potential biomarker for the diagnosis of ME/CFS [23].

The adoption of sophisticated technologies like Raman spectroscopy, nanoelectronic assays and metabolomics [23] is a step beyond the use of traditional biochemical markers. These methods have the potential to reveal subtle changes at the cellular and molecular level, which are commensurate with the multisystem nature of ME/CFS. The emphasis on electrophysiological properties [23] is especially relevant, as it might reflect dynamic cellular responses related to energy metabolism and ion channel dysfunction, and thus provide a more functional biomarker than static measurements.

Development of biomarkers is a challenge. While the research directions are promising, there are still major hurdles to overcome to use these findings as clinically applicable biomarkers. To be widely used in clinical practice, the specificity of these possible biomarkers for ME/CFS should be further investigated with a larger number of other disease controls to confirm that they will reliably discriminate ME/CFS from other diseases with similar clinical features [23]. Their easy implementation in everyday clinical practice needs to be taken into account as well [23]. Cytokine changes in ME/CFS have been described, and, as there is a great heterogeneity in the disease, a stable, consistent and reproducible cytokine signature might be difficult to identify in all patients [23]. The challenges of disease heterogeneity and complexity in disease presentation, combined with the lack of agreement on the exact criteria that should be applied to patient selection for research, further undermine the identification and validation of strong biomarkers [22]. Although promising biomarkers are emerging [23], the big problem is that they must be specific to ME/CFS and not to other fatigue-producing illnesses [23]. As there is a high degree of overlap with other diseases [40], a biomarker has to be reliable in distinguishing ME/CFS. This is also complicated by the fact that the disease itself is heterogeneous and the different subtypes could have different biomarker signatures. This suggests that future studies should be performed on larger cohorts with good characterisation and be validated with a wide range of control groups to enable clinical usefulness. The principal candidate biomarkers, together with the supporting evidence and limitations to their clinical translation, are summarised in Table 4.

Treatment and management strategies

As of yet, there is no cure for ME/CFS, and no specific FDA-approved drug for treating ME/CFS [1]. Thus, treatment is centred around symptom management and often includes a number of diverse modalities [1].

Pharmacological strategies

Pharmacological treatments are mainly targeted for alleviating certain symptoms. Mild pain relievers and non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen are frequently prescribed to alleviate pain, muscle pain, headaches and fever [56]. Gabapentin and pregabalin, anti-convulsants used to treat epilepsy, may be used occasionally for nerve pain and sleep disorders [56]. Secondary depression, anxiety, concentration and sleep disturbance are often treated with antidepressant medication [56]. The doses of tricyclic antidepressants (e.g. amitriptyline) required for patients with ME/CFS are often significantly less than those that are used for the treatment of depression, and doses that are higher than normal may not be well tolerated [56]. However, antidepressants are controversial in the treatment of ME/CFS, as there is limited evidence of improvement in core symptoms of ME/CFS [56]. Narcotics are rarely used for a prolonged period of time and are reserved for severe pain where there is a risk of addiction [56]. Different drugs are prescribed for the symptoms of ME/CFS, since there is no known cure: this confirms the current knowledge gaps regarding the pathophysiology of ME/CFS. These treatments may be used to improve symptoms, but have no effect on the underlying disease processes. There has also been a historical confusion over the treatment of ME/CFS, viewing it mainly as a psychiatric disorder, so antidepressants may be viewed as a cure for the condition instead of support for it. This is another reminder that there is a great need for therapies that modify the disease.

Nutritional supplements

Many ME/CFS patients use dietary supplements as a way to reduce the fatigue and symptoms of ME [57]. The evidence for their effectiveness, however, is weak owing to the methodological shortcomings of many of the studies conducted (small sample sizes, missing data) [57]. Some interventions can be cited that have statistically significant reductions in fatigue, but these limitations make it hard to draw firm conclusions for these interventions, including L-carnitine, guanidinoacetic acid, oxaloacetate, CoQ10–selenium combination, NADH and NADH-CoQ10 combination. The secondary outcomes, such as cognitive function and inflammatory markers, have also shown mixed results [57]. Some studies report adverse effects such as nausea and insomnia [57]. In patients with biochemical evidence of deficiency, supplements can be of great use [56]. This is reflected in the widespread use of dietary supplements [57], which is indicative of patients' desperation to find relief when no effective conventional treatment is available. Some supplements are aimed at proposed metabolic pathways (e.g., CoQ10 for mitochondrial function, NADH), but the mixed results suggest a need for well-controlled, large-scale randomised controlled trials (RCTs). The term "biochemically proven deficiencies" [56] is an important distinction, in that it

Table 4 Summary of key diagnostic biomarker candidates in ME/CFS, with supporting evidence and clinical translation limitations

Biomarker/Test	Biological System	Key Finding	Diagnostic Potential/Limitation	Reference
NK cell cytotoxicity	Innate immune system	Meta-analysis of 28 studies (2,982 subjects) found NK cytotoxicity reduced to ~50% of healthy control levels (Hedges' g = 0.96, 95% CI 0.75–1.18)	Most consistent immune finding in ME/CFS, but high heterogeneity across assay methods; not standardised for clinical use; reproducibility across independent cohorts remains a concern given inconsistent replication of group differences	[49, 50]
2-day cardiopulmonary exercise test (CPET)	Cardiopulmonary/exercise physiology	Decrease of 6.3–9.8% in workload at ventilatory threshold on day 2 distinguishes ME/CFS from controls with high sensitivity/specificity, objectively capturing post-exertional malaise	Only test to objectively reproduce PEM; resource-intensive, not universally available, and carries risk of triggering post-exertional symptom exacerbation in patients	[51]
Autoantibodies against β2-adrenergic and M3/M4 muscarinic receptors	Autonomic nervous system/autoimmunity	~29.5% of patients showed elevated autoantibodies against one or more of these receptors; levels declined in clinical responders to rituximab	Identifies an autoimmune-linked subgroup (~20–30% of patients) but not universal; more recent studies failed to replicate significant group differences in an independent cohort, highlighting inconsistency	[48, 49]
Serum metabolomic profile ("metabotypes")	Metabolic/energy metabolism	k-means clustering of 159 significantly altered metabolites identified 3 distinct metabolic phenotypes (M1-M3) in 84% of ME/CFS patients, reflecting energy strain patterns	Supports biological subtyping and precision-medicine approach; exploratory, requires validation in independent, larger cohorts before clinical application	[42]
Raman microspectroscopy of peripheral blood mononuclear cells	Cellular/biophysical	Distinguished ME/CFS patients from healthy and disease (multiple sclerosis) controls with 91% accuracy in a cohort of 98 participants; could discriminate mild/moderate/severe disease	Promising novel diagnostic approach combining spectroscopy with machine learning; single-center pilot data, needs large-cohort external validation	[52]
Nanoelectronic (nanoneedle) impedance assay	Cellular immune stress response	Blood-based test distinguished all 20 ME/CFS patients from 20 healthy controls with no false positives/negatives in a pilot study, using cellular impedance response to hyperosmotic (salt) stress	High initial discriminative accuracy but extremely small pilot sample; requires replication in larger, more heterogeneous cohorts and is not yet clinically validated	[53]
Cytokine panels (e.g., IL-6, TNF-α)	Systemic immune/inflammatory	Findings are inconsistent across studies; some report cytokine signatures correlating with symptom severity or illness duration, but no single cytokine profile is reproducibly diagnostic	Limited by high inter-study heterogeneity in assay platforms and patient selection; considered exploratory rather than diagnostic	[49]
Heart rate variability (HRV)/cardiac autonomic regulation	Autonomic nervous system	Meta-analysis found altered heart rate parameters (reduced HRV, sympathetic predominance) in ME/CFS versus controls, associated with fatigue severity	Reflects autonomic dysfunction common in ME/CFS (including comorbid POTS) but is nonspecific, overlapping with other fatiguing and dysautonomic conditions	[54]
Gut microbiome composition (16 S rRNA sequencing)	Gastrointestinal/microbiome	Reduced bacterial diversity and depletion of anti-inflammatory taxa (e.g., Faecalibacterium prausnitzii), with increased pro-inflammatory species, in ME/CFS patients versus controls	Reflects an associated but non-specific gut dysbiosis signature; causality not established, and findings vary in composition across cohorts	[55]

means this is an individualised, evidence-based approach that would be more suitable for supplementation than a blanket recommendation.

Non-pharmacological interventions: pacing strategies and energy management

One of the key non-pharmacological interventions for managing ME/CFS is pacing, which is a crucial measure to avoid the worsening of symptoms that follows any exercise or activity, known as Post-Exertional Malaise (PEM) [58]. The basic concept of pacing is to keep within an individual's "energy envelope" through careful control of activity and avoiding the development of OVE [59], which may lead to the onset of PEM. This requires eliminating activities that are more demanding than the body can produce ATP [59].

Some good strategies that will work in practice are

Reducing Overall Activity Level: It is a two-step process that entails assessing one's activities and thereafter delegating, simplifying or discarding activities to operate within one's energy limits [58].

Rest Between Activities: Patients are encouraged to rest in between activities, no matter what they are doing [59].

Preventing Overexertion: One of the most important matters is to stop an activity before becoming exhausted; otherwise, PEM may occur later [59].

For orthostatic intolerant patients, activities that can cause a high heart rate should be avoided, such as walking up/down stairs or standing for extended periods of time [59].

Not Pushing Limits: Healthy people may get better from "no pain, no gain" with exercise, but in ME/CFS, pushing through tiredness can result in serious and lasting harm [59].

Adjusting to doing less than perceived capacity: patients with ME/CFS tend to overestimate their capacity because of pre-illness memory, and it is important that they adjust to doing much less [59].

Planning Ahead: For patients who are moderately sick, a daily plan for activities to avoid doing more than one big task at a time (such as a doctor appointment and shopping) is essential [59].

This patient-developed, patient-validated strategy called pacing [58] directly targets the main symptom of ME/CFS, PEM. It respects physiological limits due to energy metabolism disorder [25] and does not try to overcome them through exertion. The focus on "stopping before you feel like stopping" and "always do less than you think you can do" [59] emphasises the counterintuitive nature of ME/CFS and the need for a paradigm shift from the typical 'no pain, no gain' approach. This patient-centred approach is an important part of treatment and prevention of the disease and further deterioration.

Controversies in treatment: critical analysis of CBT and GET

Historically, Cognitive Behavioural Therapy (CBT) and Graded Exercise Therapy (GET) have been strongly recommended treatments for ME/CFS, and this was based on the assumption that symptoms were caused by deconditioning and "unhelpful illness beliefs" [60]. PACE trial (2011) was a large, highly controversial study which found that CBT and GET are "moderately" effective for ME/CFS [61]. The trial, however, was subject to heavy criticism from patient organisations and researchers for its many methodological shortcomings:

One of the criticisms was "Outcome Switching", which involved changing the definition of "recovery" after data collection. For example, it was reduced from a physical functioning score of > 85 to > 60 [61]. However, re-analyses with the original pre-specified protocol did not show any statistical significance and recovery rates were lower (approximately 20% vs. 60% reported with switched outcomes) [61].

Use of subjective (patient-reported) primary outcome measures in an unblinded trial was a concern due to possible bias of these measures [61]. The authors reported that objective measures were performed, but none of these (fitness tests, employment, disability benefits) demonstrated a statistically significant improvement, with the exception of a minor improvement in the 6-minute walking distance, which was also questioned because of the high dropout rates among individuals in the GET group [61].

As more biomedical evidence emerges of physiological abnormalities in ME/CFS, the underlying assumption of the PACE trial and the biopsychosocial model that ME symptoms are mainly due to deconditioning and misbeliefs is increasingly being challenged [60].

There is no harm in Graded Exercise Therapy (GET)

The growing body of research has suggested that GET is contraindicated and may be detrimental for people with ME/CFS [60]. In people with ME/CFS, there is a fundamental physiological defect that reduces aerobic capacity and GET does not increase VO2 max and may have adverse effects [43]. Patients with ME/CFS switch to anaerobic metabolism at very low levels of activity [43]. The 2-day CPET is uniquely able to demonstrate that exercise does not benefit aerobic capacity, but in fact makes it worse in ME/CFS as compared to most other chronic conditions [25]. The main drawback of GET, as used in the trials that have been carried out, is that it focuses on "fixed incremental increases in activity" driven by a set schedule, regardless of the patient's symptoms [62]. This is an approach that directly contradicts the physiology of ME/CFS patients, where energy pushing inevitably causes PEM, producing serious exacerbations and relapses and causing progressive deterioration of health status or leaving patients bedridden [43]. There have also been troubling examples of advice given in GET manuals, such as expressing confidence that patients will experience an increase in symptoms, but that this is "uncomfortable but not harmful" [62] in contrast to patient experience and objective evidence of harm. The high drop-out rates in the GET programs highlight their inappropriateness and adverse effect on patients even more [62].

NICE guideline changes (UK 2021)

The National Institute for Health and Care Excellence (NICE) in the UK issued new recommendations for ME/CFS in October 2021. After a comprehensive literature search, NICE concluded that GET is harmful and should no longer be used [63]. Plus CBT is currently

recommended only as an adjunctive, supportive treatment, and not as a curative treatment for ME/CFS [62]. The updated guidelines highlight the concept of the individual "energy envelope" and the importance of staying within that envelope when undertaking any activity, in keeping with the concept of pacing [62]. The controversy surrounding the PACE trial and the reversal of the GET recommendations by NICE [61, 62] is the biggest paradigm shift in the field of understanding and treatment of ME/CFS that we are aware of. Patient advocacy and the increasing body of biomedical evidence have led to this shift away from psychosocial models [60] of attributing symptoms to "unhelpful beliefs" or deconditioning, and towards an acceptance of the underlying biological pathology [43]. The damage from GET (52) makes it clear that evidence-based medicine should be used to treat ME patients and that the physiological effects of other conditions should not be imposed on ME patients.

Products in the pipeline that have novel therapeutic approaches

The need for effective treatment methods for ME/CFS is urgent and ongoing [15]. A variety of novel interventions are under clinical investigation, such as behavioural changes, new drugs and medical devices [64]. Some drugs being studied are:

Rapamycin: A phase 1 trial that began in early stages showed statistically significant improvements in patient-reported outcome measures (PROMs) for fatigue, sleep, PEM and orthostatic intolerance [65]. Its therapeutic action is believed to be related to its autophagy-promoting and mTOR-inhibiting effects [65].

A trial is currently in progress to investigate the use of baricitinib to enhance neurocognitive function and other symptoms in Long COVID, as there is a symptomatic overlap with ME/CFS [64].

Bezisterim (NE3107): An investigational drug under study to help decrease brain fog and fatigue in persons with Long COVID [66].

There is an open-label study underway for patients with severely debilitating ME/CFS with the drug Poly I: Poly C12U (Ampligen®) [66].

Pyridostigmine or Mestinon, and Low Dose Naltrexone or LDN: These are being tested in a randomised trial in ME/CFS [66].

Ivabradine: This is a drug being tested for its impact on POTS symptoms associated with Long COVID [66].

Other creative solutions are available, such as using battery-powered stimulators for balance modulation, and Enhanced External Counterpulsation (EECP) for Long COVID fatigue [66]. In addition, traditional Chinese Medicine (TCM) interventions such as Xiaoyao San (XYS) have yielded some beneficial effects on fatigue, anxiety and depression in CFS patients, albeit with low levels of evidence [15]. Besides, the use of decentralised clinical trial (DCT) models is a big step forward because it enables patients to screen, recruit, and follow clinical trial procedures remotely from their homes, increasing the patient experience by providing more flexibility and convenience, especially for severely ill patients [67]. A pipeline of new therapeutic strategies [67] indicates a shift from merely symptomatic management to a focus on underlying mechanisms. Drugs such as rapamycin [65] that affect pathways inside the cell (autophagy, mTOR inhibition) directly connect to the energy metabolism hypothesis [25]. The use of decentralised clinical trials [67] is an important development, as it makes research more inclusive and patient-centred, tackling a big hurdle for severely ill patients with ME/CFS to participate. Shared mechanisms are also a great positive development in synergy with the Long COVID research [64] since this would speed up drug discovery for both conditions. The investigational pharmacological and device-based interventions currently in the therapeutic pipeline are summarised in Table 5.

The prognosis and long-term outcomes of this condition

The course of the disease and recovery rates vary

Prognosis for ME/CFS is extremely individual and unpredictable [19]. The course of illness is often unpredictable, with some periods better and some worse [19]. It is uncommon for people with ME/CFS to recover fully or completely. A systematic review of 14 studies showed that only the median 5% of patients recovered in the follow-up [19]. A large percentage of patients (39.5% on average) experience some level of improvement [19], but only 8% to 30% of sufferers are able to return to their workplace after improvement [27]. However, a significant number of people experience worsening symptoms over time (5% to 20%) [27]. Half (50.3%) of patients in one group said their condition was getting worse [9]. If full recovery does not occur, health and functioning are not restored to previous healthy levels; most individuals who feel recovered level off at a lower functioning level than prior to the illness [19]. Few cases are expected to have symptoms lasting longer than 5 years before full recovery [19]. Children and adolescents who get ME/CFS tend to have a much higher likelihood of getting better than adults [19]. In addition, the Centres for Disease Control and Prevention (CDC) suggest that the earlier the diagnosis and treatment, the better the likelihood of recovery [11]. Low recovery rates and high rates of chronic illness or worsening symptoms [9] highlight the serious, and often permanent, effect of ME/CFS. This goes directly against previous accounts that claimed it was a shortcoming or that one could simply get over it. The unpredictable course of the disease and fluctuation in symptoms further add to the burden of the disease for the patient, making

Table 5 Summary of investigational drugs and device-based interventions for ME/CFS and related post-infectious fatigue syndromes

Drug/Intervention	Mechanism	Trial Phase/Status	Key Findings	Reference
Rintatolimod (Ampligen)	TLR-3 agonist; immunomodulator	FDA-approved for expanded access in the U.S.; approved in Argentina; Phase III completed (AMP-516)	Phase III RCT ($n=234$) showed statistically significant improvement in exercise tolerance versus placebo, with a 51.2% positive response in a subgroup with early-stage disease	[68]
Low-dose rapamycin (sirolimus)	mTOR inhibitor; restores autophagy, reduces senescent cell burden and inflammatory cytokine secretion	Ongoing open-label/observational and randomised trials	Open-label study of 86 ME/CFS patients receiving 6 mg weekly for 90 days reported improvements in fatigue, PEM, and orthostatic intolerance; results are preliminary and non-placebo-controlled	[69]
Baricitinib (Olumiant)	JAK1/2 inhibitor; reduces systemic inflammation	Phase 3 RCT ongoing (REVERSE-LC), enrolling ~550 Long COVID patients, sponsored by NIH RECOVER initiative	Trial evaluating effects on neurocognitive function, physical function, post-exertional malaise, and inflammatory biomarkers over 6 months; results not yet reported	[70]
Bezisterim (NE3107)	Anti-inflammatory, insulin-sensitising small molecule; inhibits NF-κB-mediated inflammatory signalling without immunosuppression	Phase 2b RCT (ADDRESS-LC), ~200 patients, funded by U.S. Department of Defense	Evaluating safety, tolerability, and effect on neurocognitive ("brain fog") and fatigue symptoms over 12 weeks of twice-daily oral dosing versus placebo; results pending	[71]
Pyridostigmine + low-dose naltrexone (combination)	Pyridostigmine improves venous return/orthostatic tolerance; LDN provides immunomodulatory/anti-inflammatory effects at low dose	Phase 2 RCT (LIFT trial), $n=160$, double-blind, placebo-controlled, four-arm design	Ongoing trial testing each drug alone, in combination, and versus double placebo in patients with orthostatic intolerance; protocol published, results pending	[72]
Low-dose naltrexone (LDN) monotherapy	Opioid antagonist; at low doses modulates microglial activation and reduces neuroinflammation	Phase II RCT in post-COVID fatigue syndrome (British Columbia, Canada)	Randomised, double-blind, placebo-controlled trial assessing LDN 1-4.5 mg/day for reduction of fatigue severity; protocol published, results pending	[73]
Ivabradine	Selective sinoatrial node If channel inhibitor; reduces heart rate without affecting blood pressure, targeting POTS	Multiple completed RCTs and case series in POTS; included in the NIH RECOVER-AUTONOMIC platform trial	Randomised trial in hyperadrenergic POTS ($n=22$ completers) showed significant reductions in supine/standing heart rate and improved physical/social functioning	[74, 75]
Enhanced External Counterpulsation (EECP)	Mechanical augmentation of venous return and cardiac preload/afterload, targeting exertional intolerance	Investigator-initiated trial (EXPECT trial) in Long COVID-associated fatigue	Ongoing trial evaluating effect on Long COVID fatigue; supported by the Solve M.E. Ramsay Research Grant program; results pending	[76]

planning and sustained engagement in life difficult. Early diagnosis has been shown to be associated with a better prognosis [11], which further highlights the importance of overcoming diagnostic delay [5].

The most commonly quoted systematic review of this prognosis is the review by Cairns and Hotopf (2005) [77], who identified 28 eligible articles describing follow-up of patients with chronic fatigue and chronic fatigue syndrome with a clinical outcome. If only those 14 studies investigated were the ones performed with subjects who met the formal operational criteria for CFS, the median rate of full recovery was 5% (range 0–31% across individual studies) and a median rate of improvement of 39.5% (range 8–63% across individual studies) [77].

Following these, a systematic review of RCTs on CBT/GET for adult CFS, published in 2022, noted that there was clinical heterogeneity and that most outcomes were self-reported [78], while a systematic review of RCTs in paediatric CFS published in 2022 reported recovery rates ranging between 4.5% and 83% across studies, due to at least eleven different definitions of CFS "recovery" [79]. Based on available evidence, therefore, full recovery from ME/CFS seems uncommon, whereas partial improvement in symptoms, a significant amount of which, again, should be used with caution, is much more common.

Factors influencing prognosis

The causes of treatment differences have not been fully understood [19], but a number of factors have been identified which could impact the severity and/or long-term course of ME/CFS. A younger age at onset is always correlated with a better prognosis [13]. Older age at onset is associated with the likelihood of chronic disease and reduction in physical functioning [13]. A lack of concurrent psychiatric disorders also may be correlated with a more favourable course of treatment [1]. Common comorbidities, such as Fibromyalgia, can have a significant effect on outcomes, as people with both ME/CFS

and FM are 3.2 times more likely to be non-improvers than people with ME/CFS [13]. Although recovery rates are low, information on factors that affect prognosis, such as age, comorbidities, etc. [13]., is important when attempting to subtype and target interventions. As these patient subgroups are associated with worse outcomes when fibromyalgia is present [13], it might be logical to consider different management approaches or specific research. It is important to note that there is a significant research gap in the understanding of prognostic variation [19], which could result in more personalised, effective treatments.

Speaking with one voice, the research gaps, challenges, and future directions are as follows.

Dealing with disease heterogeneity and subtyping

ME/CFS is known to be a complex, heterogeneous, systemic illness, and not everyone with it experiences the same symptoms or severity of illness [22]. This variation in disease presentation is believed to be associated with differences in severity, type, and duration of illness, disease comorbidities, and disease triggers [80]. One possible explanation for the inconsistent results reported from the laboratories is the failure to do subgroup analyses in most studies, despite the use of a single group of patients [81]. Research has shown that people with ME/CFS are a varied and heterogeneous population with different symptoms and other health conditions [47]. The study of separate onset sub-groups, such as those with onset after glandular fever, after COVID-19 infection, after other infections and without an infectious trigger, may help to elucidate the underlying pathological mechanisms [47]. There is a strong scientific basis for a new professional and scientific review of the criteria for diagnosing ME/CFS, which must include the application of subgroup analysis and incorporate the lived experience of patients [81]. One of the main problems with research in ME/CFS [22] is the widespread heterogeneity of the disease, which can obscure real signals from biological processes and result in inconsistent outcomes. It is important to recognise that disease onset may vary between types (post-infectious vs. non-infectious) and may exhibit different symptom patterns [47]. This strongly indicates that a "one-size-fits-all" research and treatment approach is unlikely to work. Future studies should focus on identifying more homogeneous patient subsets through robust subtyping based on clinical presentation, biomarkers, and triggers to better pinpoint specific disease mechanisms and targeted, precision-based therapies.

The expanding understanding that ME/CFS is a clinically and biologically diverse disorder has led to attempts to identify clinically relevant patient subgroups in the hope that this will facilitate precision medicine and enhance the efficacy of clinical trial responses to treatment. Three complementary subtyping strategies have arisen. The first is subtyping based on onset type, which discriminates between infectious and non-infectious triggers. In the largest genetic and phenotypic study of ME/CFS to date (DecodeME, $n = 17{,}074$ UK participants), there were two distinct subgroups - those with an infectious onset (e.g., glandular fever, COVID-19 or other infections) (approximately two-thirds) and those with no antecedent infection (roughly 16%), with significant differences in symptom profile, comorbidities, and duration of illness [47]. Second, symptom cluster/subtyping is done by symptom domain, which classifies patients by predominant symptom domain (e.g., cognitive, autonomic, musculoskeletal) or by severity (mild, moderate, severe, very severe) as reflected in the DecodeME severity analyses [47]. The study found significant clinical heterogeneity. Females had more symptoms and comorbidities than males, while increasing age, female sex, and longer disease duration (> 10 years) were independently associated with greater disease severity. Distinct symptom patterns were also observed according to onset type. For example, glandular fever onset was associated with swollen glands and relapsing-remitting illness, whereas COVID-19 onset showed greater associations with chest tightness and alcohol sensitivity. Overall, the DecodeME study provides strong evidence that ME/CFS is not a single homogeneous condition. Instead, stratification by infection at onset, sex, and clinical characteristics may improve future genetic studies, biomarker discovery, and the development of precision medicine approaches, although further molecular validation is required [47]. Third, subtyping by biomarker profile involves clustering metabolomic or immune data without supervision; one study found three metabolic phenotypes (also called "metabotypes") in patients with ME/CFS, broadly distinguished by energy-strain signatures that differed from those of healthy controls [42]. This subtyping is essential because it could explain discrepancies in biomarker results and treatment responses across trials, facilitate refined clinical trial designs, and ultimately lead to "personalised" treatment approaches that are mechanism-targeted instead of a "one-size-fits-all" disease therapy.

The ongoing research on how to use synergy to support people with long COVID

Long COVID (Post COVID-19 Condition, PCC) has brought a new focus on post-infectious fatigue syndromes [63] and significant research and clinical interest. ME/CFS and Long COVID are both chronic, debilitating and multisystem diseases with a remarkable amount of overlapping symptoms; one study found 20 of 25 shared symptoms [40]. Of particular note, there is a significant percentage of patients with Long COVID (40–60%) who meet criteria for ME/CFS [16]. This important overlap

implies that findings from studies of one disorder will be directly relevant to the other, adding to the understanding of both disorders [40]. Some studies suggest there is a synergistic relationship between ME/CFS and Long COVID in creating a range of problems including physical activity restrictions, anxiety, depression and fatigue [40]. Progress in Long COVID treatment could thus directly influence ME/CFS research and speed up advances in the field [16]. The extensive overlap and symptomology of ME/CFS and Long COVID [63] is a unique and unprecedented opportunity for accelerated research. Because of its well-defined infectious cause and large, identifiable group of patients, Long COVID can be considered a "natural experiment" [22]. This will provide a window of opportunity to investigate ME/CFS-like illness from its onset, with the hope that early biomarkers and interventions can be identified that may alter the trajectory of the illness. Synergy is a concept whereby funding and research on one condition can have a direct cross-over impact on the other condition, thus accelerating the understanding and advancement of treating post-infectious chronic illness.

Standardised data collection (Common Data Elements - CDEs) is important

The use of Common Data Elements (CDEs) to standardise data collection is an important step towards achieving increased uniformity in diagnosis, improved treatment, and collaboration across research studies [82]. The National Institutes of Health (NIH) and the National Institute of Neurological Disorders and Stroke (NINDS) are currently backing a revision and expansion of the CDEs for ME/CFS led by a multidisciplinary team that includes patients with lived experience [82]. Core CDEs are essential for all studies related to ME/CFS [82]. Detailed characterisation of post-exertional malaise (causes and duration), objective assessment of general disease activity and measurement of cognitive impairments are key areas of interest for the CDE development [82]. There has been enormous variation in the diagnostic criteria and study methodologies used historically [5], which has significantly hindered the comparability and generalisability of research findings in the study of ME/CFS. The push for Common Data Elements (CDEs) [82] is a critical step towards overcoming this. Standardised data collection will enable larger and more powerful studies, provide opportunities for meta-analysis and enable identification of subtle patterns or sub-groups which are not identified in smaller, more scattered data sets. That is necessary to establish a collective knowledge, as well as to speed up the identification of biomarkers and therapies.

Involving patients in research design

To address the challenges of the unique features, complexity and heterogeneity of ME/CFS, strong partnerships with patients are crucial for the design and implementation of research [22]. Direct patient engagement in the generation of research questions, selection of outcome measures and design of interventions will ensure that research is clinically relevant, appropriate, safe and effective. The NIH/NINDS ME/CFS Research Roadmap Working Group is one example of how this can be done, bringing together clinicians, researchers, leaders from non-profit advocacy groups and individuals with lived experience [83]. The main purpose of engaging individuals with lived experience is to pinpoint research priorities that are most suitable and useful for people affected by ME/CFS, ensuring lived experience is taken into account for the final research roadmap [83]. Patient advocacy has played a key role in challenging old guidelines, like those for Graded Exercise Therapy (GET) and Cognitive Behavioural Therapy (CBT), and in keeping the biomedical research push for the underlying biological mechanisms of the disease alive [63]. It is important to emphasise patient engagement, given the history of underfunding and misdiagnosis of ME/CFS [5]. Patients have the first-hand knowledge of their lived experience with the disease, including the specifics of triggers for PEM [22] as well as the effect of interventions and fluctuations over the course of the day. Incorporating their perspective into research design [22] helps ensure that research studies address clinically relevant questions, use clinically relevant measures, and avoid interventions that do harm. Such a collaborative strategy is pivotal to fostering trust, optimising recruitment and, ultimately, to making more relevant and impactful scientific discoveries.

Increased funding disparities and advocacy work

Underfunding, as compared to disease burden, is a major and chronic problem in the field of ME/CFS research [14]. ME/CFS is funded at only about 3–7% of the funding of comparable diseases despite having significant economic impact [14]. There is a huge lack of proper government and corporate funding to carry out comprehensive, scientific research to understand the intricacies of the disease, find objective markers, and trial new therapies [22]. The total cost of ME/CFS is hundreds of billions of dollars per year in the U.S. alone [14] and is far larger than the investment in current research. Patient advocacy groups have been key – and sometimes decisive – in drawing attention to this lack of funding, in arguing for greater research funding, and in challenging the misleading or damaging research and clinical guidelines [14]. Advocacy and public awareness campaigns must be ongoing to correct the imbalance and ensure that resources are made available to enable meaningful

scientific progress. This significant lack of research funding for ME/CFS [14] is directly attributable to the historical lack of faith and support for the disease. This financial divide also makes it difficult to carry out the extensive and comprehensive research necessary to fully understand the intricacies of this situation, create a biomarker, and test new treatments on a large scale. The economic impact of the disease [14] is much greater than the amount of research invested, and constitutes a major public health failure. Advocacy and public awareness campaigns must continue to help even the balance and get the resources needed to make scientific progress that matters.

Conclusion

Despite advances in understanding ME/CFS, major diagnostic challenges remain, particularly the lack of validated biomarkers and standardised diagnostic criteria. The complexity of the disease highlights the importance of accurate subtyping for targeted treatments. Long COVID has brought attention to it and provides a novel research opportunity because of the clinical similarities. Data collection and patient participation are improving in studies, with standardisation. New research exploring the cause of ME/CFS demands coordinated research and funding for objective diagnostics and to develop disease-modifying treatments. It will not only benefit the people who have ME/CFS but also increase the understanding of post-infectious chronic illnesses.

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