Pathophysiological mechanisms of fatigue and multidisciplinary management strategies (Review)

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Abstract. Fatigue is a common clinical symptom, and its complex pathophysiological mechanisms markedly affect the quality of life and social function of patients. With the advancement of omics technologies and artificial intelligence applications, the ability to understand the mechanisms of fatigue has been notably enhanced. Fatigue is a complex process involving the interaction of multiple systems and factors. The occurrence of fatigue involves multilevel regulation of energy metabolism, neuroendocrine and immune systems. Based on omics and molecular biology, abnormal energy metabolism, oxidative stress and mitochondrial dysfunction serve a central role in the pathogenesis of fatigue. Disorders in the neuro-endocrine-immune network and dysfunction of the microbiome-gut-brain axis constitute key systemic integration mechanisms. Clinically, numerous diseases, including chronic fatigue syndrome and endocrine, neurological and autoimmune disease, can manifest as fatigue symptoms. In terms of treatment, individualized, multidisciplinary collaborative comprehensive management models have become nursing standards. In addition, the application of telemedicine technology has markedly improved the accessibility and compliance of fatigue management. The present review aimed to examine the conceptual framework, physiological mechanisms, clinical manifestations and management strategies of fatigue to provide reference for clinical diagnosis and treatment practice. Future research should focus on strengthening the exploration and translational application of molecular mechanisms, developing novel intervention targets, establishing effective fatigue assessment models and optimizing management strategies to provide strong evidence-based support for clinical practice.

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1. Introduction

Fatigue, as one of the most common and complex symptoms in clinical practice, has notable impacts on individual health status, quality of life and socioeconomic development (1-3). According to epidemiological research data from 2020, 15-20% of the global population often experience notable fatigue symptoms (1), and this proportion may be higher in certain populations, especially against the backdrop of the coronavirus disease 2019 (COVID-19) pandemic: 40-60% of recovered patients with COVID-19 experience persistent fatigue symptoms (4).

The widespread application of next-generation multi-omics technologies has revealed novel molecular mechanisms and biomarkers (5,6), providing novel research directions and technical support for early diagnosis, precise treatment and prognosis assessment. Artificial intelligence (AI), machine learning and big data analysis in fatigue diagnosis and management have notably improved clinical practice efficiency and accuracy, opening novel avenues for individualized diagnosis and treatment (7-10). Understanding of fatigue as a complex multisystem disease has shifted treatment paradigms towards integrated multidisciplinary approaches. The present review aimed to provide evidence-based recommendations for

clinical practice, ultimately promoting the improvement of fatigue diagnosis and treatment outcomes.

2. Fatigue: Definition and classification framework

Evolution of definitions. The conceptualization of fatigue has evolved from a unidimensional symptom description to multidimensional syndrome recognition. Traditional definitions emphasize a decline in physical or mental vitality, whereas contemporary perspectives integrate physiological, psychological and functional dimensions. Historical physiological definitions described fatigue as a temporary decrease in the ability of the body to work after sustained or repeated activity (11). Psychology emphasizes the subjective experience of fatigue, defining it as an unpleasant feeling accompanied by decreased motivation, reduced vigor, cognitive slowing and attention difficulties (12).

Research has redefined fatigue from a systems biology and precision medicine as a complex biological process involving energy metabolism, cognitive function and neuroimmune regulation, with marked individual heterogeneity, whose occurrence and development are influenced by genetic, environmental and psychosocial factors (1). This definition reflects a multi-level understanding of the nature of fatigue.

Classification system. Modern medicine has a deeper understanding of fatigue, and its classification system is constantly being improved. Based on the latest research evidence, fatigue can be classified along multiple dimensions (Tables I and II).

3. Common causes of secondary fatigue

Fatigue is an independent syndrome, but it is also often secondary to various types of disease, such as rheumatoid arthritis, Parkinson's disease, viral hepatitis and major depressive disorder. Thus, identifying the causes of fatigue is key for treatment.

Neurological disease. Nervous system diseases are one of the notable causes of secondary fatigue. Manjaly *et al* (13) found that 60-90% of patients with multiple sclerosis (MS) experience fatigue symptoms; in addition, fatigue is not only one of the most common symptoms in patients with MS but may also be an early manifestation. Central fatigue (14) is associated with the inflammatory response, demyelinating lesions and axonal damage in the central nervous system (15). Fatigue is related to factors such as hypothalamus-pituitary-adrenal (HPA) axis dysfunction and increased inflammatory factors (16). A meta-analysis of 7,427 patients with Parkinson's disease showed that the prevalence of fatigue is 50%, which may be related to the hypoactivity of dopaminergic activity in the nigrostriatal pathway (17). In addition, stroke, epilepsy, brain trauma and spinal cord injury cause secondary fatigue (15,18,19).

Endocrine system disease. Fatigue associated with endocrine system disorders has been extensively studied (16,19-21). Fatigue levels in patients with hypothyroidism are positively associated with thyroid stimulating hormone levels, and their symptoms improve with hormone replacement therapy (22). Thyroid hormones affect the metabolism and neural activity of the body through multiple mechanisms such as regulating mitochondrial function and neurotransmitters, whereas hypopituitarism causes multiple hormone deficiencies, resulting in common fatigue symptoms that are difficult to relieve (23). In terms of adrenal insufficiency, Husebye *et al* (24) found that patients with primary or secondary adrenal insufficiency may experience severe fatigue, decreased quality of life and ability to work and increased mortality.

Immune disease. Fatigue is one of the main symptoms of autoimmune diseases. Systemic lupus erythematosus (SLE) fatigue may be associated with neuroendocrine immune regulation disorder mediated by inflammatory factors such as autoantibodies. Previous studies (25,26) have shown that the incidence of fatigue in patients with SLE is 67-90%, and the degree of fatigue is associated with disease activity (27). Data from a fatigue visual analogue scale (VAS) study showed that 50% of patients with rheumatoid arthritis have fatigue symptoms, which are mainly related to joint inflammation and dysfunction, in which inflammatory mediators such as TNF-α serve a notable role (28). Fatigue associated with autoimmune disease has a complex pathogenesis, involving inflammation, autoimmunity and neuroendocrine aspects. Immunomodulatory treatment targeting the primary disease alleviates fatigue symptoms (29).

Chronic infectious disease. Infections such as viruses, bacteria and parasites can cause chronic inflammatory responses, leading to secondary fatigue. In patients with chronic viral hepatitis, symptoms such as depression, anxiety, fatigue, neurocognitive disease and sleep disorder are detected in 50% of cases, which markedly affect the quality of life of patients (30). Elevated levels of IgM and IgA antibodies to the exotoxin lipopolysaccharide (LPS), a potent microbe-associated molecular pattern, as well as elevated blood levels of bacterial LPS, LPS-binding protein and soluble CD14, are observed in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (31). A systematic review of follow-up studies of 45 patients with coronavirus 2019 found that the most common symptoms are long-term, such as shortness of breath, fatigue and sleep disturbance (32). In addition, chronic infection, such as tuberculosis, brucellosis and malaria, also causes notable fatigue (33-35). The mechanism of infection-associated fatigue may involve direct damage from pathogens, inflammatory factors and metabolic disorders (21).

Malignant tumors. Tumor-associated fatigue is one of the most common symptoms in patients with cancer, with the incidence of fatigue being 60-80%, and the incidence of severe fatigue being ~40% (36). Severe fatigue is defined according to the Numeric Rating Scale recommended by the European Society for Medical Oncology, with a cutoff score of ≥4 on a 0-10 scale (37). In a 2020 meta-analysis of 144,813 participants, the diagnostic rate of cancer-related fatigue (CRF) was estimated to be 52% (38). In the treatment of patients with cancer, chemotherapy and radiotherapy are the primary factors leading to CRF. The mechanism of CRF has not been fully elucidated and may be associated with (28,35,36) tumor and host inflammatory response, such as increased IL-1, IL-6 and TNF-α; metabolic disorders, such as increased blood sugar and insulin

Table I. Classification of fatigue.

Classification dimension	Key characteristics	(Refs.)
Etiology		(143)
Primary	Represented by myalgic encephalomyelitis/chronic fatigue syndrome, lacking clear organic etiology	(143)
Secondary	Caused by specific underlying diseases, including neurological disorder, autoimmune disease and endocrine metabolic disorders	(143)
Clinical presentation		(3)
Predominantly physical	Decreased physical strength and exercise endurance; delayed post-exertional recovery	(3)
Predominantly cognitive	Difficulty maintaining attention, working memory decline; executive function impairment; ~40% of patients show marked cognitive dysfunction	(144)
Mixed type	Coexistence of physical and cognitive symptoms; ~45% of patients experience simultaneous decline in physical and cognitive function	(118)
Disease course		(145)
Acute	<1 month	(145)
Subacute	1-6 months	(145)
Chronic	>6 months, typically accompanied by marked neuroimmune functional changes and energy metabolism abnormality	(145)
Functional impact		-
Mild	Slight limitation on daily activity	-
Moderate	Marked impact on work and social functioning	-
Severe	Requires continual bed rest	-
Molecular phenotyping		(146)
Energy metabolism dysfunction	Mitochondrial dysfunction and decreased ATP synthesis	(146)
Neuroendocrine dysregulation	Hypothalamus-pituitary-adrenal axis regulates the stress response of the body	(146)
Immune dysfunction	Abnormal inflammatory factors and altered immune cell function	(146)
Mixed type	Improvements in autonomic nervous system function and cardiovascular parameters	(146)

resistance; HPA axis dysfunction, such as abnormal cortisol circadian rhythm; neurotransmitter imbalance, such as decreased activity of serotonin (5-HT) and dopamine; genetic susceptibility; and psychosocial factors, such as depression, anxiety and coping styles (19,31,39). Therefore, the management of CRF requires multidisciplinary collaboration and comprehensive measures, including symptomatic treatment, psychological intervention and exercise rehabilitation, to improve the quality of life of patients.

Mental illness. Depression and anxiety are common psychological factors of fatigue, with fatigue cited as one of the key items of the Hospital Depressive Symptom Scale (40,41). A study of 323 outpatients with MS showed that 83 patients had scores indicating anxiety (25.7%) and 44 patients had depression (13.6%), and fatigue was positively associated with depression and anxiety (40). The mechanism of depression-associated fatigue is not yet fully understood but may be associated with decreased activity of neurotransmitters such as 5-HT and norepinephrine (19); HPA axis dysfunction and decreased melatonin (16); changes in brain function and structure, such as abnormalities in the frontal lobe and limbic system (20); increased levels of inflammatory factors, such as IL-6 and TNF-α (25); and metabolic disorders, such as mitochondrial dysfunction and decreased energy metabolism (42). Anxiety may induce or aggravate fatigue through mechanisms such as sympathetic nerve excitement and HPA axis activation (16). The association between fatigue, depression and anxiety is complex, and there may be a bidirectional causal association.

4. Pathophysiological mechanisms of fatigue

Energy metabolism dysfunction. Energy metabolism disorder is a key mechanism of fatigue. A total of >90% of the energy for the human body is derived from ATP produced by mitochondrial oxidative phosphorylation (42). Mitochondrial dysfunction and abnormal energy metabolism are common in patients with chronic fatigue (42). Mitochondrial dysfunction, which primarily manifests as decreased activity of respiratory chain complexes, markedly decreases ATP synthesis efficiency, reduces the mitochondrial DNA copy number, and causes mitochondrial metabolic homeostasis imbalance as well as dynamic imbalance leading to abnormal mitochondrial morphology (Fig. 1). Furthermore, contractile load is a key determinant of fatigue resistance improvement induced by isometric intermittent training, potentially via

Table II. Subtypes of fatigue.

Subtype	Biomarkers	Potential mechanism	Treatment	Research priority
Metabolic	Decreased ATP and coenzyme Q10; increased lactate	Mitochondrial dysfunction	Energy support therapy	High
Neuroinflammatory	Increased IL-6, TNF-α and CRP	Immune activation	Anti-inflammatory drugs	High
Neuroendocrine	Decreased cortisol and growth hormone	Hypothalamus-pituitary-adrenal axis dysfunction	Hormone replacement	Medium
Cognitive	Decreased BDNF; abnormal functional connectivity between specific brain regions, including the globus pallidus, left lateral occipital cortex and cuneus	Neural network disruption	Cognitive enhancement	Medium
Mixed	Decreased HRV	Multi-system involvement	Combination therapy	High

The priority level indicates the research value of the research area and whether the consideration of this should be prioritized. CRP, C-reactive protein; BDNF, brain-derived neutrophic factor; HRV, heart rate variability.

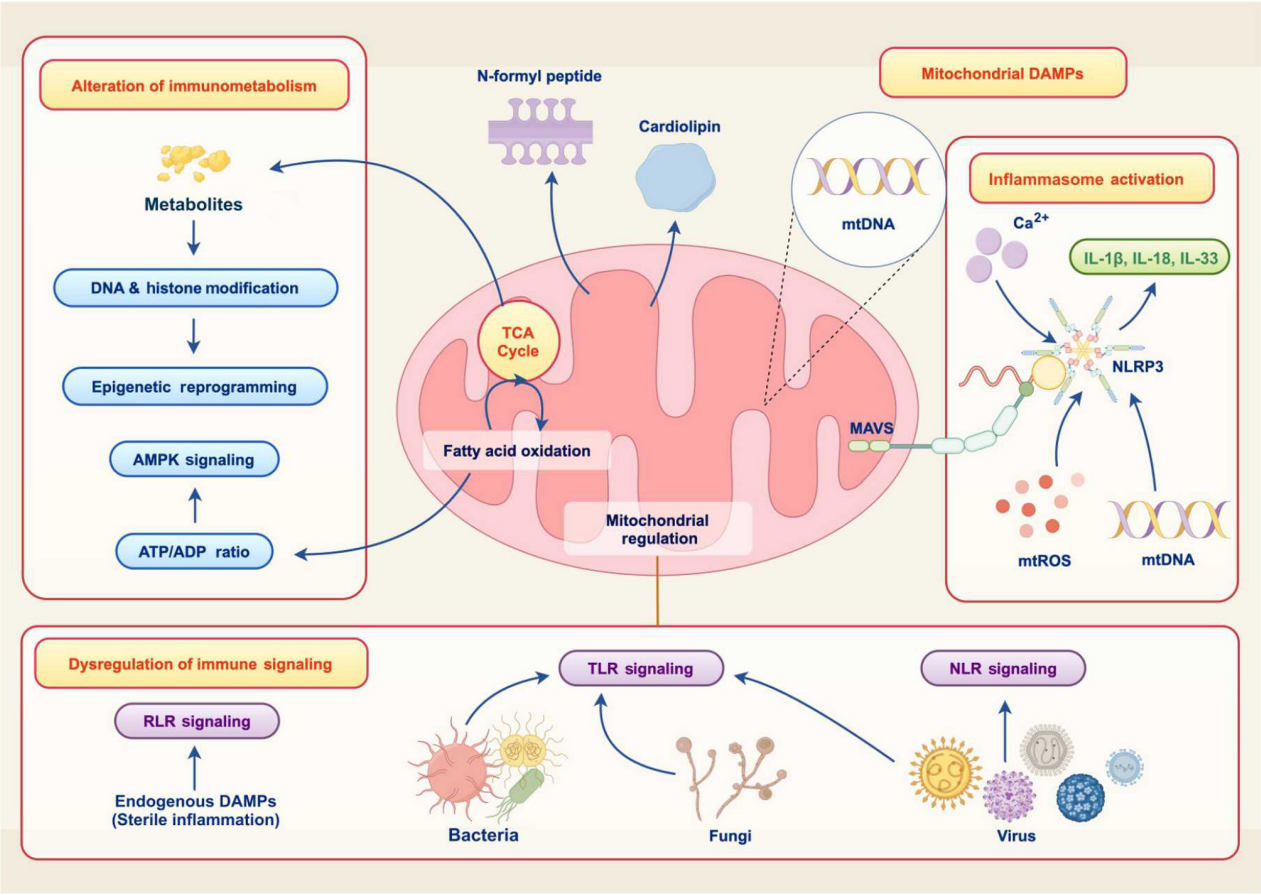

Figure 1. Mitochondria in fatigue. Mitochondrial dysfunction causes cell damage and energy deficiency through multiple pathways, leading to fatigue. These pathways involve the release of mitochondrial DAMPs, including mtDNA, cardiolipin and N-formyl peptide, which activate inflammasomes such as NLRP3 and trigger the release of IL-1β, IL-18 and IL-33. Additionally, mtROS participate in the dysregulation of immune signaling. Meanwhile, disruptions in metabolic processes such as the TCA cycle and fatty acid oxidation impact immunometabolism. For example, metabolites such as acetyl-CoA are involved in DNA and histone modification, epigenetic reprogramming, and the activation of AMPK signaling via the ATP/ADP ratio. AMPK, AMP-activated protein kinase; mtROS, mitochondrial reactive oxygen species; MAVS, mitochondrial antiviral signaling protein; TCA, tricarboxylic acid; RLR, RIG-I-like receptor; DAMP, damage-associated molecular pattern; TLR, toll-like receptor; NLR, NOD-like receptor.

p38 MAPK/peroxisome proliferator-activated receptor γ coactivator-1α-mediated mitochondrial content increase, even in muscles lacking nutrients (43).

In addition to mitochondrial function, other metabolic pathways such as glycolysis and fatty acid β-oxidation are also affected in chronic fatigue (44). Changes in glucose and lipid metabolism primarily manifest as inhibition of the glycolysis pathway, obstruction of fatty acid β-oxidation, decreased efficiency of ketone body utilization and abnormal lactic acid metabolism (42,45).

Oxidative stress and cell damage. Oxidative stress serves an important role in the pathogenesis of fatigue. Proteomic analysis has found that patients with fatigue typically have elevated levels of oxidative stress (2), which manifests as increased production of reactive oxygen species (ROS) (46), weakened function of the antioxidant system, abnormal mitochondrial membrane potential and increased cell apoptosis.

Sweetman *et al* (47) found that oxidative stress markers are notably elevated in the peripheral blood of patients with ME/CFS, while the function of the antioxidant defense system is weakened. Specific manifestations included increased malondialdehyde levels (reflecting lipid peroxidation), increased 8-hydroxydeoxyguanosine (indicating DNA oxidative damage) and decreased glutathione peroxidase activity and superoxide dismutase expression.

Genetic and epigenetic factors. T cells in patients with ME/CFS are epigenetically predisposed to terminal exhaustion. The $CD8^+$ T cells from patients with ME/CFS exhibit specific epigenetic modification patterns that make T cells more prone to exhaustion. Researchers have used assay for transposase-accessible chromatin with sequencing technology to compare chromatin accessibility between memory T cells and naive T cells, identifying 67,189 chromatin accessible regions in the same cohort of ME/CFS patients and healthy controls (the same population enrolled for T cell epigenetic and functional analyses). The authors observed upregulation of key transcription factors associated with T cell exhaustion in the $CD8^+$ T cell effector memory subset, and fatigue markers, including IL-6, TNF-α and CRP, were markedly upregulated following exercise challenges (48).

Previous research analyzed peripheral blood mononuclear cell (PBMC) composition changes through single-cell RNA sequencing, demonstrating increased total T cell frequency in patients with ME/CFS, with notable decreases in natural killer (NK) cells, monocytes, conventional dendritic cells and plasmacytoid dendritic cells (4). The aforementioned study identified excessive communication initiated by monocytes and transmitted to other immune cell components via the estrogen related receptor α/amyloid β precursor protein/CD74 pathway, which serves as a potential biomarker (6).

Additionally, a multi-omics study has shown that genetic variants in genes such as G protein-coupled receptor 180, NOTCH3, supervillin, hydroxysteroid 17-β dehydrogenase 11 and plexin A1 are associated with various fatigue dimensions, including physical fatigue, cognitive fatigue and emotional fatigue. The correlation coefficients ranged from -0.539 to 0.517 ($P<0.05$), providing preliminary insights into potential involvement of lipid metabolism changes, catecholamine biosynthesis disruption, microbial imbalance and specific genetic variants in fatigue among patients with non-communicable disease (5).

Neuroendocrine-immune network. The brain is the key organ for regulating fatigue (18), and brain imaging studies have found that the activity and connectivity patterns of brain regions change when patients are fatigued (18,49-51). The severity of fatigue is positively associated with functional connectivity between the globus pallidus and occipital cortex, and functional connectivity within the cortico-cerebellar network is closely related to fatigue perception, suggesting that the basal ganglia-occipital-cerebellar circuit serves an important role in the neural mechanisms of fatigue (18). A previous two-sample Mendelian randomization analysis confirmed that increased volume in the right lateral orbitofrontal, left caudomedial frontal and right caudal middle and orbitomedial frontal cortices is associated with decreased fatigue susceptibility (10). A previous neuroimaging study has shown similar findings in the prefrontal cortex and basal ganglia regions involved in fatigue regulation in patients with ME/CFS and MS (20).

Neurotransmitters are the basis of the activity of the nervous system. Fatigue is associated with metabolic disorders of neurotransmitters such as monoamines and amino acids (19). Positron emission tomography (PET) shows decreased 5-HT transporter binding, suggesting decreased 5-HT neuron function. Glutamate and γ-aminobutyric acid (GABA) are notable excitatory and inhibitory neurotransmitters in the central nervous system, respectively; a spectral study found that the GABA levels in the brain of patients with CFS are decreased, whereas the glutamate levels are increased, and the ratio of the two is decreased, indicating an imbalance in neurotransmitters (20).

Fatigue involves multiple neuroendocrine axes, and its abnormalities may originate from central nervous system dysfunction, which affects peripheral organs. The HPA axis is a key neuroendocrine system regulating the stress response of the body, and chronic stress can induce dysfunction of the HPA axis, leading to fatigue. Lee *et al* (16) found through a meta-analysis and animal experiments that knocking out glucocorticoid receptors in the mouse brain causes fatigue-like behavior. Low cortisol levels may be the result of long-term stress leading to HPA axis hypofunction, which may be associated with immune dysfunction and inflammatory response.

Chronic fatigue is associated immune dysfunction. Viral infection is considered a potential etiological factor of ME/CFS, accompanied by immune disorders (21). CFS is often secondary to viral infection, suggesting infection-induced immune dysregulation may be involved in the pathogenesis of CFS (52). A systematic review showed that patients with CFS have abnormal PBMC function, which typically manifests as decreased NK cell killing activity and imbalance of T cell subsets. In addition, the levels of inflammatory factors such as IL-4, IL-5, IL-7, IL-12p70 and TNF-α are elevated in patients with CFS (25,26), indicating a chronic low-grade inflammatory state.

Immune inflammatory responses induce fatigue through a variety of pathways (Fig. 2). Inflammatory factors directly act on the central nervous system, causing symptoms such

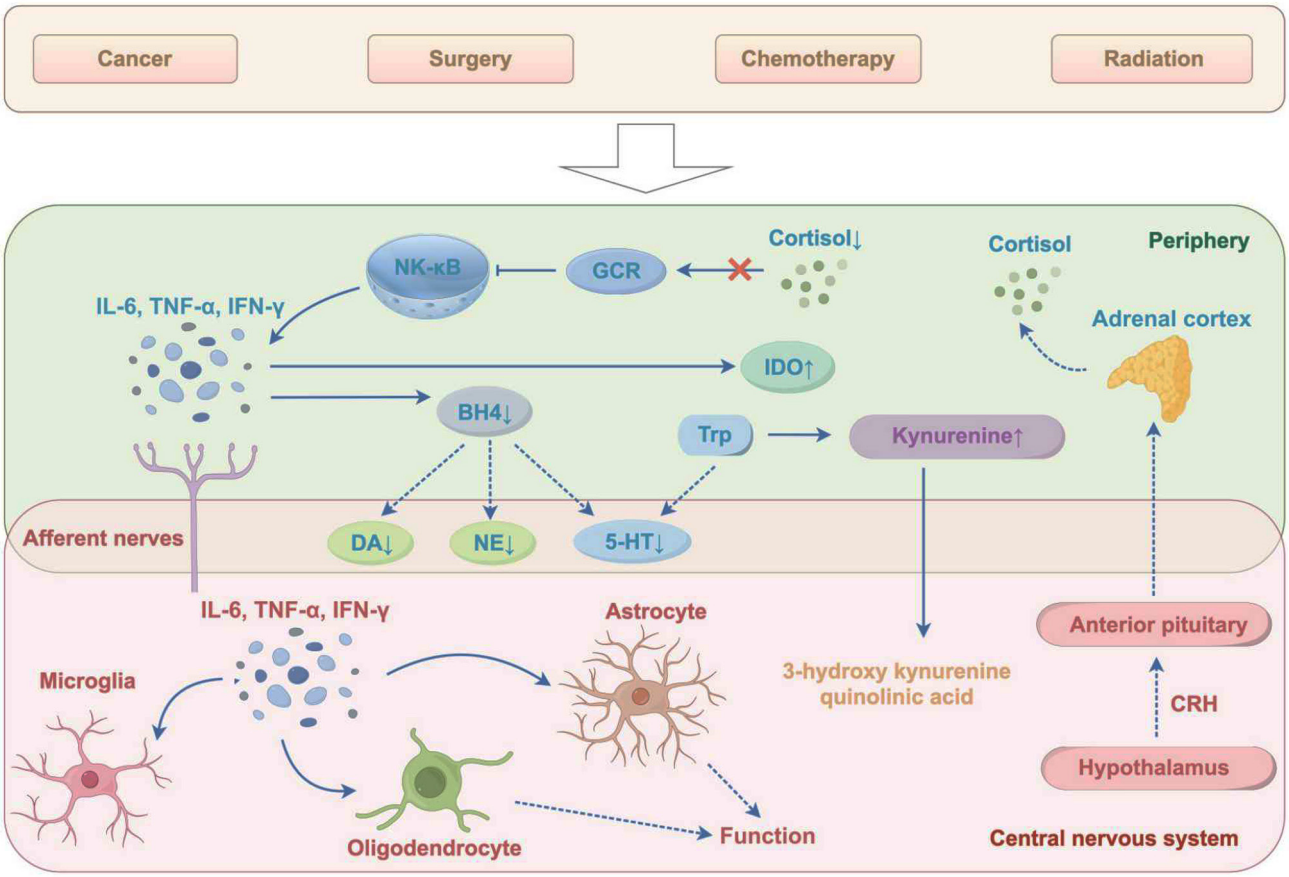

Figure 2. Role of abnormal immune inflammation in fatigue. Cancer, surgery, chemotherapy or radiation activate leukocytes, leading to increased expression of the transcription factor NF-κB, which in turn promotes the release of inflammatory factors such as IL-6, TNF-α and IFN-γ. These inflammatory factors induce fatigue manifestations through multiple pathways: They upregulate IDO and downregulate BH4. IDO promotes the conversion of Trp to kynurenine, the metabolites (3-hydroxy kynurenine and quinolinic acid) of which act on the central nervous system. BH4 deficiency leads to reduced levels of DA, NE and 5-HT. Meanwhile, GCR signaling is impaired due to decreased cortisol, further amplifying inflammatory responses. In the central nervous system, microglia and astrocytes are activated by inflammatory factors, affecting oligodendrocyte function, while the hypothalamic-pituitary-adrenal axis (involving CRH, the anterior pituitary and adrenal cortex) is dysregulated, collectively contributing to fatigue via abnormal immune inflammation and neurochemical imbalance. GCR, glucocorticoid receptor; BH4, tetrahydrobiopterin; GABA, glutamate and γ-aminobutyric acid; DA, dopamine; NE, norepinephrine; 5-HT, serotonin; CRH, corticotropin-releasing hormone; IDO, indoleamine 2,3-dioxygenase; Trp, tryptophan.

as drowsiness, loss of appetite and social withdrawal (21). Inflammatory factors affect the metabolism of neurotransmitters, decreasing the synthesis of 5-HT and dopamine (19,20). Continuous inflammatory response consumes energy and aggravates metabolic disorders (21,25,26). Inflammation induces mitochondrial dysfunction, and increased ROS causes oxidative stress (2,47). Immune complex deposition and autoantibody production are involved in the occurrence of muscle weakness (16,21).

Intestinal flora. The intestinal flora is the largest and most complex microbial system in the human body and serves a key role in maintaining health. Intestinal flora imbalance is involved in the occurrence of chronic fatigue (31). Patients with ME/CFS typically exhibit gastrointestinal symptoms, primarily including intestinal inflammation and changes and disorders in the intestinal microbiota (53). Abundance of Firmicutes in the feces of patients with CFS is markedly reduced, whereas the abundance of *Bacteroidetes* is increased, and the diversity and stability of the bacterial community is decreased (53,54). A metabolomic analysis has suggested that patients with CFS have decreased intestinal bacteria production of tyrosine and tryptophan metabolism, and decreased levels of short-chain fatty acids (SCFAs) such as butyrate (54).

The intestinal flora affects the occurrence of fatigue through pathways such as the gut-brain axis (Fig. 3). Intestinal flora imbalance leads to a decrease in the 5-HT precursor tryptophan. Dysbiosis induces the production of pro-inflammatory factors and aggravates chronic inflammation. Inflammatory factors and oxidative stress damage the intestinal mucosal barrier, leading to reduced expression and impaired function of tight junction proteins, as well as increased intestinal permeability. Decreased levels of SCFAs affect the energy supply of host cells.

5. Clinical manifestations and assessment of fatigue

Clinical manifestations and subtype analysis. The clinical manifestations of fatigue are diverse and complex, involving multiple systems. A large-scale prospective study found that the primary manifestations of fatigue include (55) persistent fatigue, which can manifest as physical weakness or mental exhaustion, ranging from mild discomfort to complete loss of ability to move; cognitive dysfunction, primarily manifesting

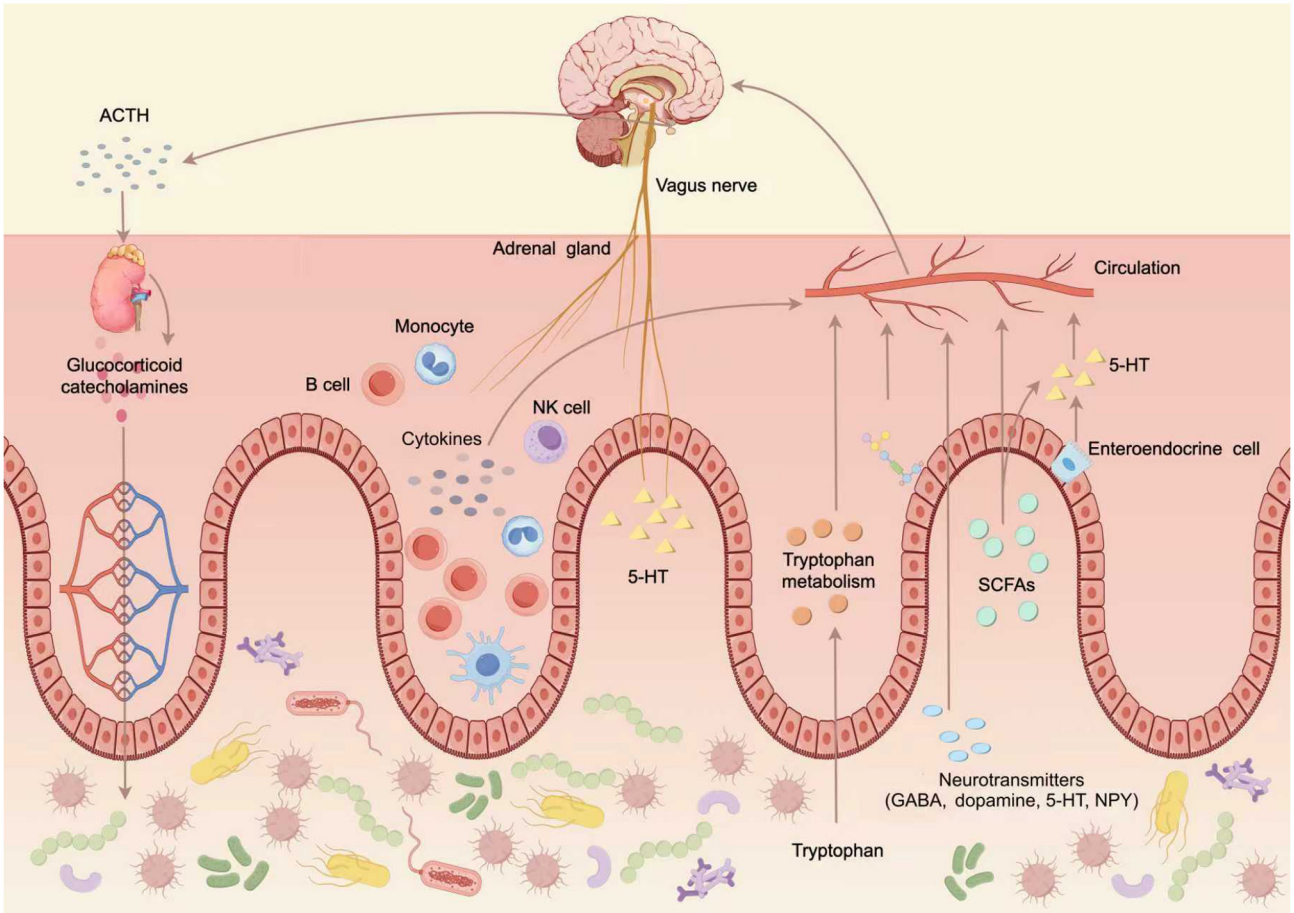

Figure 3. Intestinal flora is involved in the mechanism of fatigue. Dysbiosis causes adverse consequences by affecting host metabolism and immunity. Specifically, gut microbes influence the production of SCFAs and neurotransmitters (GABA, dopamine, serotonin and NPY), as well as tryptophan metabolism. These molecules enter the circulation and act on the brain via the vagus nerve or systemic transport. Meanwhile, the intestinal flora modulates immune cells (monocytes, B cells and NK cells) and cytokines, which interact with the hypothalamic-pituitary-adrenal axis (involving ACTH and glucocorticoid/catecholamine release from the adrenal gland). Additionally, enteroendocrine cells secrete 5-HT, which participates in this gut-brain communication network, collectively contributing to fatigue when the intestinal flora is imbalanced. ACTH, adrenocorticotropic hormone; NK, natural killer; 5-HT, serotonin; SCFA, short chain fatty acid; NPY, neuropeptide Y.

as lack of attention, memory loss and slow reaction (56); sleep disorders, mainly manifesting as difficulty falling asleep, poor sleep quality, frequent dreams and fatigue after waking (57); autonomic nervous system dysfunction, such as palpitations, blood pressure regulation disorder (58), sweating, dry mouth, constipation or diarrhea; musculoskeletal symptoms, such as muscle soreness and weakness and joint pain; discomfort in the throat and neck, swollen and tender lymph nodes in the neck or armpits (59); endocrine and metabolic abnormality, fear of cold and heat and menstrual disorder and mental and psychological problems, such as depression, anxiety and low mood.

The clinical manifestations of patients with fatigue vary and may be related to factors such as the cause, course of disease and comorbidities of fatigue. Vaes *et al* (56) conducted a large-scale cross-sectional study and cluster analysis of patients with ME/CFS based on symptom manifestations. The aforementioned study identified five symptom clusters, as follows: i) Mild symptoms and less limitation in daily function; ii) moderate fatigue and cognitive dysfunction, and limited exercise tolerance; iii) severe symptoms, notable autonomic nervous system symptoms and immune dysfunction; iv) cognitive dysfunction and marked brain fog and v) aggravated symptoms following exercise and notably reduced exercise tolerance.

The study by Vaes *et al* (56) emphasizes the heterogeneous nature of CFS, and that different subtypes may reflect differences in the mechanisms of fatigue development, which may guide the formulation of individualized treatment plans, accuracy of prognostic assessment and clinical stratified management (Tables III and IV).

Table III clinically differentiates four fatigue subtypes (ME/CFS, MS-related, cancer-related and depression-related) by primary mechanism, onset pattern, post-exertional malaise, exercise tolerance, cognitive features and biomarkers, enabling precise differential diagnosis and tailored management.

Table IV outlines the differential diagnosis of fatigue syndrome across disease categories such as neurological, endocrine, autoimmune, infectious, neoplastic and psychiatric. Table IV details specific diseases, key differentiating features, diagnostic tests, warning signs and references to guide accurate identification.

Assessment of fatigue. Fatigue is subjective and multidimensional, and fatigue assessment has undergone a development

Table III. Clinical comparison of fatigue subtypes.

Characteristic	ME/CFS	MS-associated	Cancer-associated	Depression-associated
Primary mechanism	Immune/metabolic	Neuroinflammation	Cytokine-mediated	Neurotransmitter dysfunction
Onset pattern	Post-infectious acute	Progressive/recurrent	Treatment-associated	Episodic/chronic
PEM response	Severe (>24 h delay)	Variable	Mild	None
Exercise tolerance	Severely impaired	Moderately impaired	Temporarily decreased	Variable
Cognitive features	Brain fog	Decreased processing speed	Attention deficit	Executive function impairment
Biomarker profile	Decreased NK cells; increased cytokines	MRI lesions; increased NFL	Increased IL-6 and CRP	Decreased 5-HT and cortisol

PEM, post-exertional malaise; NK, natural killer; CRP, C-reactive protein; NFL, neurofilament light chain; 5-HT, serotonin; MS, multiple sclerosis; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome.

process from a single subjective score to a multidimensional integrated assessment. Single indicators do not fully reflect its severity. Modern fatigue assessment emphasizes combining subjective and objective indicators, and static and dynamic assessments, forming a systematic assessment framework.

Subjective assessment scale. The subjective assessment scale is the most commonly used fatigue assessment tool in clinical practice and obtains information on multiple dimensions of fatigue through patient self-assessment. Commonly used scales include: i) Fatigue Severity Scale, which consists of nine items to assess the impact of fatigue on daily activity. Each item is scored from 1-7 points. The higher the score, the more severe the fatigue. This scale is simple and easy to use and has been validated for the assessment of fatigue caused by numerous diseases (60); ii) the multidimensional fatigue inventory, which consists of 20 items and assesses fatigue from five dimensions, namely general, physical and mental fatigue and decreased activity and motivation. This scale has good reliability and validity, and is widely used in chronic fatigue research (61,62); the fatigue impact scale (FIS), which consists of 40 items and assesses the impact of fatigue on cognitive, physical and social function. This scale has high sensitivity in assessing the functional status and quality of life of patients with fatigue (63); and iv) Fatigue Assessment Inventory, which consists of 29 items and assesses the impact of fatigue on daily and social activity, including the severity of fatigue, situational specificity and consequences of fatigue (64).

These scales have been rigorously validated for reliability and validity, and are suitable for fatigue assessment in different clinical scenarios (62). In addition, the VAS and Chalder fatigue scale (65,66) are used in clinical practice and research. Choice of assessment basis should be individualized according to clinical purposes and patient characteristics (67,68).

Objective evaluation indicators

Exercise physiology indicators. Exercise physiology indicators objectively reflect the energy metabolism state of the body and cardiopulmonary function. Maximum oxygen uptake (VO_2 max) is the gold standard for evaluating aerobic exercise capacity, but is markedly lower in patients with ME/CFS than in healthy controls. Nelson *et al* (69) found that patients with ME/CFS show notable abnormality in exercise capacity assessment through 2-day continuous cardiopulmonary exercise testing. The specific manifestations include marked decrease in VO_2 max, shortened exercise tolerance time and an earlier time to reach the anaerobic threshold during exercise. This serves as an important reference indicator for diagnosis. In the assessment of autonomic nervous function, heart rate variability (HRV) is a key objective indicator. Escorihuela *et al* (70) found that the HRV indicators of patients with ME/CFS are markedly decreased, among which, the root mean square of successive differences parameter value, reflecting parasympathetic nerve activity, is associated with the severity of fatigue symptoms.

Cognitive function tests. Fatigue is associated with cognitive dysfunction. Commonly used tests include the Stroop color-word, paced auditory serial addition, VAS and trail making test cue production test (71). Computerized cognitive testing systems such as the Cambridge Neuropsychological Test Automated Battery provide standardized and sensitive measurements of spatial working memory, rapid visual information processing, paired associate learning and emotion recognition task of patients with ME/CFS, thus providing tools for the assessment of cognitive function in CFS (72).

Imaging examination. Brain imaging technology plays an important role in revealing the central nervous system-mediated mechanisms of fatigue. Using advanced neuroimaging techniques such as PET and diffusion tensor imaging, previous research has identified specific changes in brain structure and function in patients with ME/CFS, such as reduced serotonin neuron function (15,18,20,49). Functional magnetic resonance imaging shows alterations in the functional connectivity of brain regions such as the default and dorsal attention network in patients with CFS, as well as abnormalities in prefrontal and limbic system activity and neurovascular coupling in ME/CFS; these changes are associated with cognitive dysfunction (50,51). In addition, magnetic resonance spectroscopy quantitatively analyzes brain tissue metabolites; patients with ME/CFS have altered N-acetylaspartate levels, and abnormal lactate metabolism and choline compound levels (2).

Table IV. Differential diagnosis of fatigue syndrome.

A, Neurological				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Multiple sclerosis	Progressive, focal deficit	MRI, cerebrospinal fluid oligoclonal bands	Neurological symptoms	(13,16,17,56,144,147)
Parkinson's disease	Motor symptoms; bradykinesia	Clinical evaluation	Tremor, rigidity	(1,15-17,19,20,50,51, 56,86,111,121)
B, Endocrine				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Hypothyroidism	Cold intolerance, weight gain	TSH, T4, T3	Goiter, hair loss	(21-24,52)
Adrenal insufficiency	Hypotension, electrolyte abnormalities	Cortisol, ACTH stimulation test	Hyperpigmentation	(5,16,23,24,46)
C, Autoimmune				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Systemic lupus erythematosus	Arthritis, rash, organ involvement	ANA, anti-dsDNA	Malar rash, nephritis	(1,16,21,25,27-29, 52,91)
Rheumatoid arthritis	Joint inflammation, morning stiffness	RF, anti-CCP	Synovitis, erosions	(2,21,27-29,46, 52,59,90)
D, Infectious				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Chronic viral hepatitis	Abnormal liver function	Serology, liver enzymes	Jaundice, hepatomegaly	(21,30,31,33-35, 43,52,75)
Post-viral syndrome	Recent infection history	Virial titer, inflammatory markers	Acute onset	(21,30,31,33-35,43, 52,75)
E, Neoplastic				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Active malignancy	Weight loss, organ-specific symptoms	Imaging, tumor markers	Systemic symptoms	(2,6,19,21,31,38,39, 47,52,148)
Treatment-associated	History of chemotherapy/ radiotherapy	-	-	-
F, Psychiatric				
Medical condition	Differentiating features	Diagnostic tests	Warning signs	(Refs.)
Major depressive disorder	Mood symptoms, anhedonia	Clinical assessment	Suicidal ideation	(16,19,20,25,42,71,72, 75,85-88,107,109,110)
Anxiety disorder	Worry, panic, avoidance	Clinical assessment	Panic attacks	(16,19,20,25,42,71,72, 75,85-88,107,109,110)

TSH, thyroid-stimulating hormone; T4, thyroxine; T3, liothyronine; ACTH, adrenocorticotropic hormone; ANA, antinuclear antibody; dsDNA, double stranded DNA; RF, rheumatoid factor; CCP, cyclic citrullinated peptide.

Laboratory tests. Although ME/CFS lacks specific diagnostic biomarkers, previous multi-omics studies (2,14,21,45,47) have found that patients with CFS have abnormal PBMC function (25), increased lactate and decreased glutathione peroxidase levels (47), suggesting energy metabolism disorder and increased oxidative stress (2). Serological examinations reveal manifestations of immune dysfunction, such as increased immunoglobulin and decreased complement levels and decreased number and activity of NK cells (21,26,52). Endocrine function tests reveal HPA axis hypofunction, and changes in growth hormones and estrogen (16). Genomics has found that patients with CFS have decreased mitochondrial DNA copy number (42) and ATP synthesis efficiency (73), suggesting increased genomic instability. Transcriptomics shows that the expression of immune and metabolic-associated genes is dysregulated in patients with CFS (47).

Emerging digital health technology. Traditional fatigue assessment methods rely on surveys or physiological signal measurements, which often fail to provide real-time monitoring and are limited by patient discomfort. However, multi-omics approaches and AI offers transformative potential for fatigue research. For example, a novel non-contact fatigue level diagnosis system that uses multimodal sensor data, including video, thermal imaging and audio, minimizes physical discomfort while enabling precise, real-time data collection and analysis for fatigue evaluation (46,74,75).

Classification of the progressive stages of fatigue-induced physiological tremor is achieved using a hybrid bidirectional long short-term memory-gated recurrent unit neural network (76,77). Cross-sectional area (CSA) is measured from muscle volume changes during limb movement, and different feature combinations are fed into the network to evaluate performance metrics for CSA-informed tremor classification (78).

BioMapAI, a supervised deep neural network (75), provides systems-level insights into ME/CFS, refining existing hypotheses and proposing unique mechanisms. It simultaneously models diverse data types to predict clinical severity, identify disease- and symptom-specific biomarkers, and classify ME/CFS in both retained and independent external cohorts, thereby increasing the effective sample size (75).

In recent years (79-81), surface electromyography (sEMG) has emerged as a novel technology for quantitative assessment of exercise-induced fatigue. A study proposed (10) a multi-attention convolutional network (MACNet) for three-tiered evaluation of muscle fatigue based on sEMG signals. MACNet achieved the highest average classification accuracy and F1 score. The F1 score refers to the harmonic mean of precision and recall, balancing the trade-off between false positives and false negatives, which helps comprehensively assess the model's classification performance. This network enhances the extraction of exercise fatigue-related features from sEMG channels and time-domain characteristics (10).

6. Management and treatment of fatigue

General treatment principles. The priority is to establish a clear diagnosis of fatigue, which requires systematic evaluation to exclude secondary causes of fatigue, including endocrine, autoimmune, infection and other disease. The importance of multidisciplinary consultation is emphasized during the diagnostic process to ensure no causes are missed. An individualized treatment plan is developed based on the severity of fatigue, specific clinical manifestations and concurrent symptoms. The choice of treatment regimen should be based on the latest evidence and adjusted dynamically as the disease progresses. At the same time, biological, psychological and social factors should be considered to adopt a multi-pronged approach, including drug treatment, psychotherapy and lifestyle intervention. Clinically, it is necessary to explain the natural course of the disease, treatment plan and prognosis to patients to enhance treatment compliance. Chronic fatigue requires long-term follow-up and rehabilitation plans, regular evaluation of treatment effects and timely adjustment of treatment plans to prevent recurrence.

Drug treatment. Although there are currently no US Food and Drug Administration-approved anti-fatigue medications, certain medications can be used to relieve fatigue-associated symptoms.

Central stimulants. Stimulants relieve fatigue by increasing the excitability of the central nervous system. Commonly used drugs include modafinil [high-quality evidence; Grading of Recommendations Assessment, Development and Evaluation (GRADE)] (82). In a previous study of 141 patients with relapsing-remitting MS accompanied by fatigue, the subjects were randomly assigned to receive four treatment regimens in a cross-over manner. Each treatment phase lasted 6 weeks. Modafinil relieved MS-related fatigue and was well-tolerated (83). Its mechanism may be associated with enhancing noradrenergic, dopaminergic and histaminergic neurotransmission, as well as regulating inflammatory responses (84). Methylphenidate (low-quality evidence, GRADE), which is primarily used in the clinical treatment of attention deficit hyperactivity disorder, has also been used in fatigue management in previous years. Methylphenidate improves fatigue severity, concentration and memory in patients with CFS (85). Its mechanism is primarily associated with dopamine reuptake inhibition (85). Pemoline (low-quality evidence, GRADE) is a non-amphetamine central nervous system stimulant with dopamine-enhancing effects. A previous small-sample study showed that pemoline has a certain effect on relieving symptoms related to depression, such as disturbances in concentration, memory, tension and fatigue in depressed patients, but there is a lack of evidence from large-sample randomized controlled studies (86).

Antidepressants. Antidepressants are used to treat fatigue in patients with comorbid depressive symptoms. Selective 5-HT reuptake inhibitors (SSRIs; high-quality evidence, GRADE) are the most widely used antidepressant drugs in clinical practice, and effectively improve symptoms of depression and fatigue. For example, fluoxetine, a SSRI commonly used for psychiatric disorder, is considered to have neuroprotective effects, thereby decreasing fatigue symptoms in patients with MS (87). However, certain studies have shown that SSRIs are not effective for patients with CFS without depressive symptoms (86,88). Therefore, antidepressants are primarily suitable for patients with CFS with notable depressive symptoms.

Immunosuppressants. Patients with CFS typically have immune dysfunction, suggesting immune regulation may have potential value in improving CFS symptoms. Fluge *et al* (89) conducted a randomized double-blind trial to explore the efficacy and safety of the B cell depleting drug rituximab (moderate-quality evidence, GRADE) in the treatment of CFS. The study included 151 patients with CFS, who were randomly divided into a rituximab (n=77) and a placebo control group (n=74). The fatigue severity scores of patients in the treatment group markedly decreased compared with baseline and were markedly improved compared with those in the placebo group (moderate-quality evidence, GRADE), with therapeutic effects lasting several months. It is hypothesized that rituximab may relieve CFS symptoms by clearing autoreactive B cells and decreasing the production of inflammatory factors. A previous small open-label trial (90) showed that low-dose naltrexone (low-quality evidence, GRADE) could regulate immune function and decrease neuroinflammation. Naltrexone relieves fatigue in patients with CFS, but this effect needs to be confirmed in large-sample studies (90).

Non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs (low-quality evidence, GRADE) primarily exert their antipyretic, analgesic and anti-inflammatory effects by inhibiting cyclooxygenase activity and decreasing prostaglandin synthesis. They can relieve symptoms such as muscle soreness and joint pain in patients with CFS but have limited efficacy on core fatigue symptoms (91).

Coenzyme Q10. Coenzyme Q10 (moderate-quality evidence, GRADE), also known as ubiquinone, serves as an electron carrier in the mitochondrial electron transport chain, participates in ATP synthesis, scavenges free radicals and exerts an antioxidant effect. CFS is related to mitochondrial dysfunction (92,93) therefore, coenzyme Q10 may alleviate fatigue by improving mitochondrial function and enhancing the metabolic and antioxidant capability of the body (94).

Calcium channel blockers. Patients with CFS typically have symptoms of autonomic dysfunction such as palpitations and tachycardia. It is hypothesized that increased sympathetic nerve excitability may be a potential mechanism (95). Calcium ion blockers (low-quality evidence, GRADE) such as amlodipine block L-type calcium channels, inhibit the release of norepinephrine from sympathetic nerve endings and decrease sympathetic nerve excitability, thus relieving CFS-related cardiovascular symptoms (7). To the best of our knowledge, there are few studies on calcium antagonists for the treatment of CFS, most of which are small-sample observational studies or case reports, and there is a lack of evidence-based medicine (96-99).

Vitamins. Methylcobalamin (low-quality evidence, GRADE) is a cobalt-containing vitamin B12 derivative that serves as a coenzyme in the synthesis and metabolism of proteins, nucleic acids, FA and other substances in the body. Previous studies have found that methylcobalamin may have beneficial effects on CFS-associated fatigue (100,101) and cognitive dysfunction by improving cell energy metabolism and enhancing neural repair and neuroprotection (94).

Non-pharmacological treatment

Exercise therapy. Exercise therapy (moderate-quality evidence, GRADE) is a key methods for treating CFS. A Cochrane systematic review included eight randomized controlled trials involving a total of 1,518 patients with CFS (102). The results of the narrative review showed that compared with conventional treatment such as pharmacotherapy and cognitive behavioral therapy, sport and exercise therapy could improve fatigue symptoms in patients with CFS, but had no significant advantages in terms of depression and sleep quality. This suggests that the benefits of exercise therapy are primarily concentrated on physical fitness (103), whereas mood and sleep problems may require coordinated treatment. Another study conducted network meta-analysis on 56 studies, and showed that combing aerobic and resistance exercise, yoga and regular physical activity markedly alleviates CRF (104). The mechanism by which exercise therapy relieves CFS is not fully understood but may include improving cardiopulmonary function and muscle endurance, reversing deconditioning adaptive changes in patients with CFS, improving autonomic dysfunction and reducing sympathetic nerve tone, increasing the levels of β-endorphins and monoamine neurotransmitters in the brain, improving pain and mood, regulating cytokines and immune function, decreasing chronic inflammatory responses and enhancing self-efficacy and sense of control (3,105,106).

Psychotherapy. Psychotherapy (high-quality evidence, GRADE) is a key component of the comprehensive management of CFS and can effectively improve fatigue symptoms, emotional state and coping style. Commonly used psychological treatments include cognitive behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) (107-110). CBT helps patients develop positive disease management strategies by amending cognition and coping styles. A meta-analysis of eight randomized controlled trials involving 1,298 patients with CFS showed that CBT causes marked improvement in fatigue severity, physical function and emotional symptoms compared with standard treatment. The standard treatment in this analysis was defined as supportive care, including symptom management, psychoeducation and general lifestyle advice without structured psychological or behavioral intervention. This beneficial effect was consistent across key patient characteristics, with no significant heterogeneity observed (107). A randomized controlled trial involving 240 patients with CFS found that internet CBT is as effective as face-to-face CBT in reducing fatigue and improving daily function and has higher compliance (108).

MBSR is a meditation-based stress reduction method. A randomized controlled trial compared patients who underwent MBSR with untreated patients, and the results showed that patients with CFS in the MBSR group exhibit marked improvements in fatigue severity and sleep quality, with therapeutic effects maintained for 3 months after the end of the intervention (109). MBSR may alleviate CFS symptoms by regulating autonomic nervous function and alleviating the chronic stress response (110).

Nutriregulation technology. Transcranial magnetic stimulation (TMS; low-quality evidence, GRADE) is a non-invasive neuromodulation technology that generates local currents in the cerebral cortex through electromagnetic induction, affecting neuronal membrane potential and cortical function (43). A previous study used a multimodal approach, combining peripheral neuromuscular electrophysiological assessment and TMS-electroencephalography technology (74), and found

that, following fatigue induction, the oscillation energy of the g frequency band (30-45 Hz) of the motor cortex in the MS group decreases markedly, while the functional connectivity within and between the default and the frontoparietal control networks is weakened, which is negatively associated with the severity of fatigue (43,74,111).

Cryotherapy. There are a number of preliminary studies exploring the effects of cryotherapy (low-quality evidence, GRADE) on symptoms and function in patients with CFS (112-114). A small controlled study involving 24 patients with CFS found that a combined intervention of whole-body cryotherapy (-110˚C; 3 min each; 3 times/week for 4 weeks) plus static stretching could markedly improve fatigue severity (FIS), with beneficial effects sustained for at least 4 weeks post-intervention. No notable adverse reactions were reported, and the improvements were associated with enhanced autonomic nervous system function, a key mechanism underlying symptom relief in patients with CFS (115-117). Another randomized controlled trial compared conventional care combined with local cryotherapy (freezing the limbs for 30 sec each; twice/day for 15 days) with conventional care alone; daily living ability and quality of life scores of patients in the combined group were markedly higher than those in the control group, suggesting cryotherapy can be a beneficial supplement to conventional therapy (118).

Physiotherapy. Certain physical factors (low-quality evidence, GRADE) such as low-intensity laser and static magnetic field may alleviate CFS symptoms. Transcranial low-level laser therapy (LLLT) uses near-infrared light to perform photo biomodulation of specific brain regions (119). It improves mitochondrial respiratory chain function by upregulating the expression of key enzymes such as nitric oxide synthase and cytochrome c oxidase, and enhances ATP synthesis, thereby exerting a role in cell protection and repair (120). This suggests LLLT may alleviate core symptoms such as fatigue and cognitive decline by improving mitochondrial dysfunction in patients with CFS and alleviating neuroinflammation. Extremely low frequency electromagnetic field therapy uses a constant magnetic field of specific intensity to produce a similar electromagnetic induction effect in the human body, regulates the cell membrane potential and ion channel function and enhances the antioxidant activity of enzymes in patients, and improves their functional and psychological status (121). In addition, transcranial electrical stimulation (tES) technology has recently been applied for CFS, tES exerts specific effects in patients with CFS, including alleviating core symptoms such as persistent fatigue, improving cognitive functions and reducing associated emotional distress. These effects are considered to be mediated by its ability to regulate cerebral cortex excitability and induce plasticity changes in neural circuits involved in fatigue perception and cognitive processing. Notably, tES has shown efficacy in diseases such as depression and chronic pain by applying a weak constant or an alternating current to specific parts of the scalp (122).

Traditional Chinese medicine. Traditional Chinese medicine (low-quality evidence, GRADE) of CFS has advantages of overall regulation and multi-target effects (123-125). In terms of traditional Chinese medicine treatment, modern pharmacological studies have shown that tonic herbs can improve fatigue symptoms through various mechanisms. For example, herbs such as ginseng, astragalus and codonopsis can enhance immune function and improve energy metabolism (126). In addition, acupuncture notably improves fatigue severity, depression and anxiety levels and quality of life, while having few adverse reactions and being safe (127). The mechanism by which acupuncture exerts its efficacy may be associated with regulating the neuro-endocrine-immune network, improving autonomic function and decreasing oxidative stress and inflammatory responses (128).

Self-management. Self-management (low-quality evidence, GRADE) is a key part of the comprehensive treatment of CFS. Prognosis is notably improved by imparting disease knowledge, coping skills and behavioral strategies to patients and improving their awareness and ability to actively participate in disease management. A comprehensive review of fatigue self-management education in individuals with disease-related fatigue included 26 randomized controlled trials involving eight disease groups (129). At follow-up, 46% of the included studies reported statistically significant improvements in fatigue, with positive effects observed particularly in patients with cancer and multiple sclerosis. However, the overall evidence for the effectiveness of fatigue self-management education on fatigue and quality of life remains limited and inconsistent (129).

Weight management. Healthy weight loss (very low-quality evidence, GRADE) is a common dietary management goal for patients with CFS. Previous studies have found that obesity aggravates the symptoms of CFS, while moderate weight loss can help improve fatigue, sleep and mood (130-133). However, due to limited physical activity in patients with CFS, weight loss should primarily focus on dietary adjustments, supplemented by exercise within tolerable limits, and should be progressed gradually.

7. Future prospects and research priorities

Despite notable progress in fatigue research, numerous challenges and practical limitations remain. One of the primary challenges in CFS clinical research is the lack of standardized assessment tools. Existing diagnostic tools primarily rely on self-reported multidimensional fatigue scales and contact-based sensor measurements (such as electromyography or respiratory sensors). These methods are cumbersome, time-consuming and impractical, lacking reliable biomarker support. Additionally, due to the complexity of symptoms, self-reported fatigue is not accurate, and psychological, physical and environmental factors affect diagnostic accuracy and treatment timeliness.

Existing clinical studies generally exhibit limitations, including small sample size, insufficient follow-up duration, lack of data on risk factors for fatigue and fatigue severity, and the use of different fatigue assessment tools without standardization, which make comparative studies and result interpretation difficult. These factors compromise the reliability, reproducibility and generalizability of research findings. There are no established standard treatment methods for chronic severe fatigue associated with specific diseases, and the development of individualized treatment plans lacks sufficient theoretical basis and practical guidance.

The development of polygenic risk score (PRS) models is an important direction in precision medicine for CFS. By integrating gene variants associated with CFS, PRS can predict individual susceptibility to fatigue and provide a basis for early intervention (134-136). Future research should focus on developing more accurate PRS models and verifying their applicability in different populations.

Epigenetic profiling provides a method understanding the environment-genetic interactions in CFS. Patients with CFS typically exhibit abnormal DNA methylation patterns, which may be associated with viral infection, psychosocial stress and other factors (5,6,48). Future research should explore the dynamic changes of these epigenetic markers and their association with symptom severity.

The regulatory roles of long non-coding RNA and microRNA in CFS have gained increasing attention (52,137-138). Single-cell RNA sequencing technology has revealed cellular heterogeneity in CFS (139). By analyzing expression differences of different cell types in patients with CFS, specific cell subpopulations and their functional disorder can be identified. Spatial transcriptomics demonstrates tissue-specific gene expression patterns, particularly changes in the brain and immune tissue. Although multi-omics technologies have made progress in CFS research, data standardization and computational infrastructure remain challenges (5,48). There are differences in data formats and analytical methods across different omics platforms (such as genomics, transcriptomics and proteomics), and unified standards need to be established to facilitate data integration. Additionally, processing large-scale omics data requires efficient computational platforms and algorithms to support joint analysis of multi-omics data (75).

The application of AI in CFS diagnosis is developing rapidly: The BioMapAI deep learning model, developed in 2025, has successfully integrated gut microbiome, plasma metabolome and immune cell profiling data from 249 participants, and constructed a microbiome-immune-metabolic interaction network. This model reveals the association between key molecules such as SCFAs, γδT cells, IFN-γ and symptom heterogeneity, providing novel strategies for precision diagnosis and treatment (75,140). Natural language processing technology has also shown potential in CFS research; by extracting key information from electronic health records, AI systems identify clinical features and subtypes of CFS. The application of AI in optimizing CFS treatment primarily focuses on predictive modeling; however, by analyzing multi-omics data, symptom characteristics and treatment responses, AI models can predict the efficacy of specific treatment plans. Additionally, AI guides drug optimization, such as predicting patient responses to specific drugs and decreasing the risk of adverse events.

In terms of identifying therapeutic targets and drug development, the application of respiratory chain modulators such as coenzyme Q10 in CFS treatment remains controversial. Although certain studies have reported improvements in other symptoms of patients with CFS with coenzyme Q10 supplementation, notable efficacy in fatigue relief is lacking (141,142). Future research should explore more effective respiratory chain modulators, such as specific complex enhancers.

Future research on CFS should focus on multi-omics integration, AI applications, development of novel therapeutic targets and improvement of clinical research methodologies. Multi-omics integration may provide biomarkers and mechanistic basis for precise diagnosis and treatment of CFS. AI applications may enhance diagnostic accuracy and treatment efficiency. The development of novel therapeutic targets will offer more effective treatment options for patients with CFS, and improvement of clinical research methodologies may ensure the reliability of research findings and their clinical translational value.

With the advancement of research, CFS may transform from an unexplained syndrome into a disease with precise biological basis and targeted treatment methods. However, this faces numerous challenges, including data standardization, computational infrastructure, cost-effectiveness and patient engagement. Future research needs to overcome these challenges to promote the development of precise diagnosis and treatment for CFS.

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Authors' contributions

LL conceived the study. HZ, WY and JL performed the literature review and wrote the manuscript. WY drew and modified figures. RC, YC and GW conceived the study and provided key discussions for the images. RC, YC and GW constructed the figures. LL and WY revised the manuscript. All authors have read and approved the final the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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