Pharmacological Treatment Approaches in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Abstract

Background. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a neuroimmunological disease whose diverse symptom profile is associated with dysregulation of the nervous system, the endocrine system, the immune system, and cellular energy metabolism. To date, no causal pharmacological therapy is available for this condition.

Methods. This narrative review summarizes current clinical experience from physicians, patient-reported experiences, and the results of existing studies on symptomatic therapy in ME/CFS. The latter were selected according to criteria typical of narrative reviews, namely practical relevance and feasibility.

Results. Symptomatic therapy tailored to the individual ME/CFS symptom profile, in combination with consistently implemented pacing, may have a positive impact on patients' clinical status. The medications used for this purpose are predominantly prescribed off label. Some of these drugs target the neuroimmunological pathophysiology of ME/CFS (e.g., dopamine agonists and opioid antagonists, cholinesterase inhibitors and parasympathomimetics, H1/H2 blockers and mast cell stabilizers). Others are primarily selected based on their established use in the treatment of the most common ME/CFS symptoms (e.g., quetiapine and pregabalin for sleep disturbances).

Conclusions. Since only a limited number of clinical studies have investigated the efficacy of drugs currently used in ME/CFS, comprehensive clinical trials evaluating these symptomatic therapies are needed. Beyond their therapeutic benefit, such studies could also contribute to substantiating current pathophysiological hypotheses regarding the development of individual ME/CFS symptoms.

Keywords: myalgic encephalomyelitis; chronic fatigue syndrome; pharmacotherapy; causal therapy; symptomatic therapy; off-label use

1 Background

Over recent years, there has been an increasing body of substantial evidence indicating that myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease in which regulatory processes within the human body are disrupted in multiple ways, likely as a result of neuroinflammatory mechanisms [1–5]. These disturbances in the function of regulatory systems (nervous system, endocrine system, immune system) and in energy supply (particularly in muscle cells and cells of the nervous system) lead to an impaired ability to maintain dynamic equilibrium (homeostasis), i.e. stable physiological conditions within the body [6–13]. They include, among other factors, dysfunctions of serotonin autoregulatory pathways with impaired adrenocorticotropic hormone (ACTH) and cortisol release [14], as well as altered adrenergic and cholinergic signal transmission [15–16]. Increasing evidence suggests that immune-mediated mechanisms may contribute to symptom development after infection. For example, autoantibodies isolated from patients with long COVID have been shown to induce neurological symptoms in experimental models, supporting a potential causal role of autoimmune processes in postinfectious syndromes [17].

A hallmark of this condition, which most commonly develops following an infectious trigger [18–19], is postexertional malaise (PEM). PEM is defined as a prolonged exacerbation of all symptoms following even minimal physical or cognitive exertion [20]. Earlier studies suggested that the chronic course of ME/CFS was characterized by a wide range of symptoms that fluctuated in type and severity in an apparently unsystematic manner [21]. More recent research, however, indicates that symptom expression changes systematically over the course of the illness and that sex-related differences also exist. For example, Hornig et al. demonstrated that immune signatures vary with disease duration, with patients in the early phase showing a more pronounced pro-inflammatory profile [22].

Prior to the COVID-19 pandemic, the prevalence of ME/CFS in the United States was approximately 0.42% [23]. A recent study estimates that in 2024 (postpandemic), there were more than 650,000 individuals with ME/CFS in Germany, corresponding to a prevalence of more than 0.78% of the population [24]. Women are affected more than twice as often as men [25]. ME/CFS frequently results in substantial disability and a marked reduction in quality of life [26]. More than 60% of affected individuals are unable to work [27]. A reduced life expectancy has been suggested,

although current evidence remains insufficient to draw firm conclusions [28]. However, multiple studies indicate an increased risk of suicide in people with ME/CFS [28]. To date, no causal pharmacological therapy exists for this disease, which is diagnosed according to international consensus criteria [6, 29–30]. However, early implementation of symptom-oriented management strategies and pacing may improve symptom control, functional status, and quality of life, although no evidence currently demonstrates reversal of the underlying disease process [31].

The aim of this review is to provide an overview of the medications currently used in clinical practice for the treatment of ME/CFS. It examines whether randomized controlled trials on symptomatic therapies for ME/CFS are already available and seeks to collate existing clinical experience from physicians as well as experiential knowledge reported by patients.

2 Methods

The present work is a narrative review that synthesizes clinical experiential knowledge acquired in routine practice, patient-reported experiential knowledge, and the results of selected key studies published to date in this field. The literature search was conducted using databases accessible via the FernUniversität Hagen library, including PubMed/MEDLINE, Embase, Web of Science, Scopus, the Cochrane Library and PsycINFO. These databases were selected because previous methodological studies have shown that combining multiple biomedical databases improves retrieval of relevant literature [32].

2.1 Search Strategy

The search focused on literature addressing the pathophysiology of ME/CFS and its symptomatic pharmacological management. Representative search terms and Boolean combinations included “ME/CFS,” “myalgic encephalomyelitis,” “chronic fatigue syndrome,” “pharmacological treatment,” “symptomatic therapy,” “off-label,” “autonomic dysfunction,” and “mast cell activation,” as well as the names of selected drug classes and active substances used off-label in the pharmacological management of ME/CFS, including “dopamine agonist,” “ivabradine,” “pyridostigmine,” and “low-dose naltrexone” (LDN). Search terms were derived from commonly used therapeutic approaches described in the literature [33]. The search was complemented by backward and forward snowballing to identify additional relevant publications. Given the limited

evidence base, emphasis was placed on clinical feasibility and practical relevance, consistent with the methodological framework of narrative reviews.

Eligible sources comprised publications addressing pharmacological or symptomatic treatment approaches for ME/CFS, including clinical studies, observational studies, case series, case reports, mechanistic studies, and expert consensus statements published in English or German between 1994 and 2026. Studies focusing exclusively on non-ME/CFS chronic fatigue or lacking clear clinical relevance were not considered.

As is characteristic of narrative reviews, the selection and evaluation of studies were guided primarily by their practical relevance and feasibility for clinical application, and were therefore conducted according to pragmatic criteria guided by clinical relevance rather than a formal systematic review protocol [34-35].

3 Pharmacological Treatment of ME/CFS

To date, there is no scientifically evaluated pharmacological therapy that targets the underlying causes of ME/CFS [36]. However, several research approaches and advanced studies appear promising and raise hope that causal treatment options for ME/CFS may become available in the future. In addition, there are indications that an individually tailored symptomatic therapy, adjusted to the current symptom profile and disease status, may—under certain circumstances—contribute to symptom stabilization and improved daily functioning when initiated early and implemented consistently in combination with equally consistent pacing [36].

At present, in clinical practice, pharmacological support is often limited, even though patients' complex constellation of symptoms severely impairs their daily lives. Instead, patients are frequently informed that no effective treatment options are available.

Figure 1 illustrates the conceptual framework proposed here for precision medicine in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Biomarker-based stratification, potentially supported by AI-assisted clustering approaches, may help identify biologically relevant patient subtypes characterized by overlapping patterns of immune dysregulation, autonomic dysfunction, and impaired cellular energy metabolism. These subtype-specific profiles may inform more individualized therapeutic strategies, including symptom-targeted treatment and pacing, anti-

inflammatory or immunomodulatory therapy, autonomic modulation, and metabolic or vascular support approaches. The overlapping connections between subtypes and therapeutic domains reflect the complex, multifactorial, and non-linear nature of ME/CFS and underscore the need for individualized, multimodal treatment concepts.

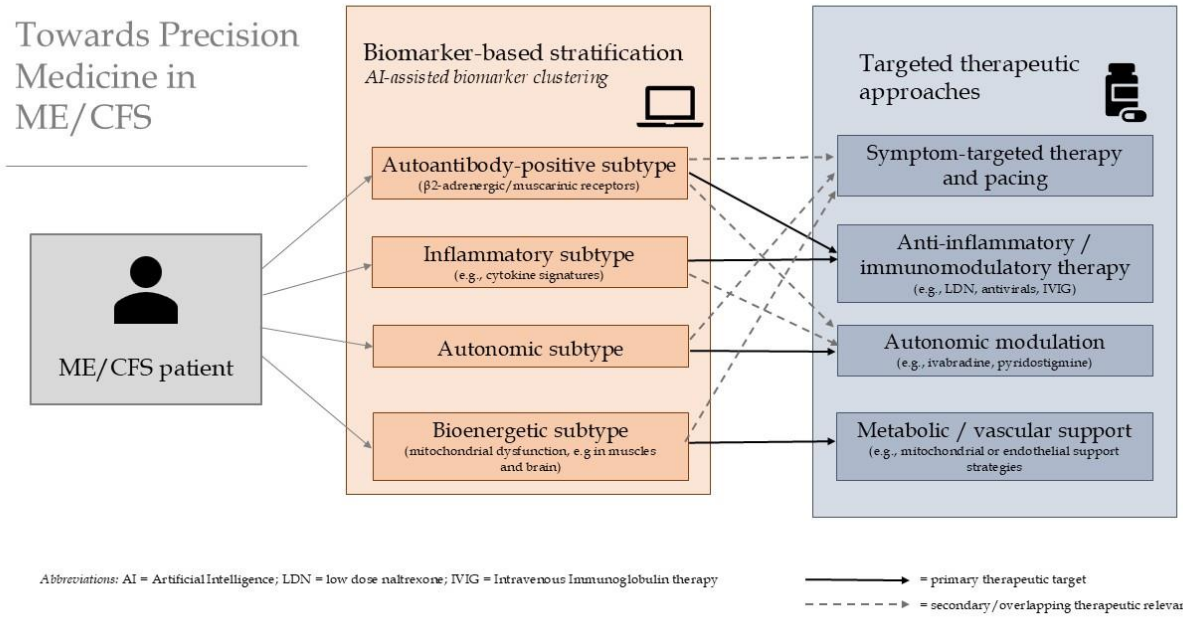

Figure 1. Conceptual framework for biomarker-based stratification and subtype-oriented therapeutic targeting in ME/CFS. AI-assisted clustering may identify immunological, autonomic, and bioenergetic subtypes linked to overlapping targeted treatment approaches.

3.1 Symptomatic Therapies

In current clinical practice, symptomatic treatment approaches play a central role. In contrast to causal therapies, these approaches focus on the treatment of disease-related symptoms. Given the wide range of symptoms associated with ME/CFS, which may vary considerably between individuals depending on sex and illness duration, numerous therapeutic strategies exist to alleviate the symptoms reported by patients. Many of these interventions directly target different components of the neuroimmunological pathophysiology of ME/CFS. Identifying the symptom

cluster that is currently most prominent in a patient can support more targeted pharmacological decision-making (see 3.4).

Recent studies illustrate this: Accumulating evidence supports a central role of skeletal muscle pathology in both ME/CFS and post-COVID syndrome. Recent work by Scheibenbogen and Wirth synthesizes mechanistic and histopathological findings. It proposes that impaired microcirculation and β-adrenergic dysregulation lead to intracellular sodium and calcium overload, ultimately driving mitochondrial dysfunction and structural muscle damage. Importantly, this model is supported by biopsy-based evidence demonstrating subsarcolemmal mitochondrial abnormalities as well as signs of muscle fiber damage and regeneration, particularly following exertion, consistent with the phenomenon of postexertional malaise [37].

Complementing this framework, Bizjak et al. provide direct ultrastructural and functional evidence of mitochondrial impairment in skeletal muscle, including altered cristae morphology and reduced oxidative phosphorylation capacity [38]. Notably, these alterations appear more pronounced in ME/CFS compared to post-COVID syndrome, suggesting a progression from primarily functional disturbances toward more established structural pathology in chronic disease states.

At the clinical level, Paffrath et al. demonstrate that reduced hand grip strength correlates with both symptom severity and functional disability in post-COVID ME/CFS, supporting the notion that muscle dysfunction is not merely an epiphenomenon but a key determinant of clinical status [39]. The convergence of mechanistic, structural, and functional data thus supports a unifying model in which skeletal muscle represents a primary site of pathology linking impaired bioenergetics to hallmark clinical features.

This integrated perspective provides a strong rationale for therapeutic strategies targeting neuromuscular transmission, autonomic regulation, and mitochondrial function. In this context, the ongoing Life Improvement Trial (LIFT[1]), investigating pyridostigmine and low-dose naltrexone, is of particular interest, as both agents may modulate pathways implicated in muscle perfusion, ion homeostasis, and neuroimmune signaling.

[1] https://clinicaltrials.gov/study/NCT06366724

3.1.1 Off-Label Use

The symptomatic therapeutics discussed below are predominantly prescribed off label in patients with ME/CFS. Off-label use refers to the prescription of medicinal products outside their approved indications, which may relate to the indication itself, the age group of patients, the dosage, or the route of administration. Such use outside the scope of official approval is generally permitted. In Germany, for example, the associated costs are only reimbursed by statutory health insurance in exceptional cases [40].

3.1.2 Dosing and Timing

Individually tailored dosing, taking into account sex, age, and body weight [41], as well as the timing of medication intake, can have a substantial impact on drug efficacy [42–44]. This may be particularly relevant in ME/CFS, where circadian rhythm disruption and autonomic dysregulation are frequently observed [45-46] and may alter pharmacokinetics and pharmacodynamics. As a consequence, nocturnal dosing may be required in some cases. In addition, for certain medications, low-dose therapy may be more effective in some cases than standard dosages. In principle, treatment should always be initiated with the lowest possible dose [47]. Furthermore, emerging evidence in ME/CFS suggests that disease stage and duration may influence underlying pathophysiological mechanisms, raising the possibility that the timing of therapeutic interventions could affect treatment response and clinical outcomes [22, 37–38].

3.1.3 Why Mechanistically Promising Therapies Often Fail in Clinical Practice

A major and frequently underestimated reason for the limited success of mechanistically targeted therapies in ME/CFS is the insufficient definition and stratification of study populations. Many clinical trials include participants who do not meet the Canadian Consensus Criteria (CCC), despite these representing the most specific and pathophysiologically coherent case definition. As a result, heterogeneous cohorts are created in which different conditions, severity levels, and biological mechanisms are mixed, making it unlikely that any single intervention will demonstrate a clear therapeutic effect.

In addition, disease duration is rarely considered, even though early-stage and long-standing ME/CFS differ substantially in symptom patterns, immune signatures [22], and treatment responsiveness. Similarly, sex-specific differences—which affect autonomic regulation, immune

responses, pain processing, and hormonal modulation—are typically ignored, further diluting potential treatment signals.

These fundamental issues in patient selection and characterization precede and amplify other well-known challenges, including biological heterogeneity, unvalidated mechanistic hypotheses, negative randomized trials despite promising pilot data, circadian dysregulation, altered pharmacokinetics, and underpowered study designs.

Taken together, these factors underscore that biomarker-driven patient stratification, strict diagnostic criteria, and consideration of disease duration and sex differences are essential prerequisites for generating reliable therapeutic evidence in ME/CFS. Machine learning may represent a promising approach [48].

3.1.4 Biomarkers

Given the marked clinical heterogeneity of ME/CFS, there is increasing interest in identifying biomarkers that may support patient stratification and guide individualized therapeutic decisions. Several candidate biomarkers have emerged from recent research, although none are yet validated for routine clinical application. Autoantibodies against β2-adrenergic and muscarinic acetylcholine receptors, for example, have been detected in a subset of patients and may indicate dysregulation of autonomic and vascular signaling pathways [49]. These findings have stimulated interest in therapies targeting autonomic dysfunction, such as ivabradine, pyridostigmine, or low-dose β-blockers.

Elevated inflammatory mediators—including IL-8 [22,50], TGF-β, and soluble CD14—have been reported in multiple studies although findings across cohorts remain heterogeneous [51]. These patterns may reflect stage-dependent immune activation or neuroinflammatory processes [22]. However, direct evidence linking cytokine profiles to treatment response remains limited, and targeted interventions such as IL-1 blockade have not consistently demonstrated clinical benefit [51].

Patients with such profiles may be more likely to respond to agents with anti-inflammatory or microglia-modulating properties, such as low-dose naltrexone [52] or gabapentinoids (gabapentin and pregabalin). Similarly, abnormalities in endothelial function and reduced cerebral blood flow

have been associated with cognitive dysfunction and orthostatic intolerance suggesting a potential role for therapies such as vericiguat or other agents targeting vascular regulation.

Emerging evidence also points to disturbances in metabolic pathways, particularly in energy production, lipid metabolism, and oxidative stress [53]. Metabolomic studies have identified alterations in amino acid metabolism, lipid profiles, and mitochondrial function, which may help explain differences in fatigue severity, postexertional malaise, and pain phenotypes. Although these findings are not yet actionable in clinical practice, they highlight the potential for future biomarker-driven treatment algorithms.

Overall, the integration of immunological, autonomic, metabolic, and vascular biomarkers into clinical research may enable a precision-medicine approach in ME/CFS. This would allow pharmacological therapies to be more effectively tailored to individual pathophysiological profiles. Current therapeutic approaches in ME/CFS remain largely symptomatic and are frequently guided by dominant clinical phenotypes rather than validated disease-specific treatments. As summarized in Figure 2, neurocognitive, autonomic, immunological, and muscular/metabolic symptom clusters may reflect overlapping and dynamically interacting biological mechanisms, including neuroinflammation, autonomic dysfunction, immune dysregulation, vascular abnormalities, and impaired cellular energy metabolism. Consequently, current management strategies frequently combine mechanism-based pharmacological interventions, symptom-oriented off-label therapies, and non-pharmacological approaches such as pacing. This framework illustrates the biological and clinical heterogeneity of ME/CFS and supports the need for individualized and multidisciplinary treatment approaches.

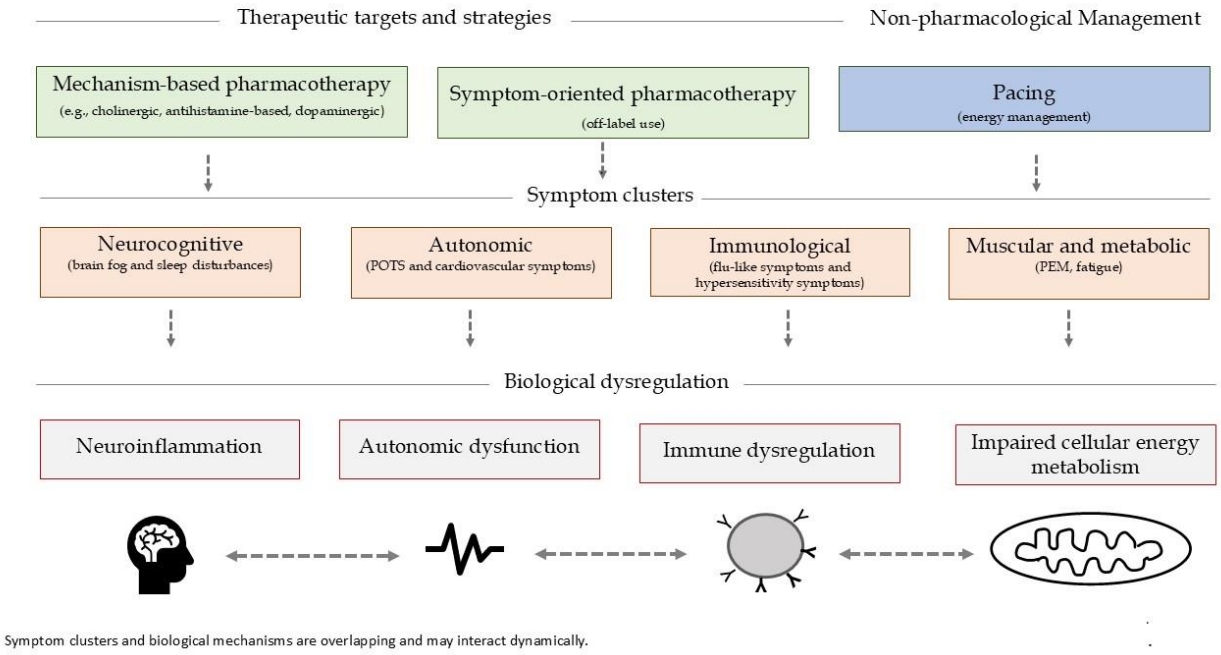

Figure 2 Conceptual framework of therapeutic strategies, symptom clusters, and biological dysregulation in ME/CFS. Mechanism-based and symptom-oriented pharmacological approaches, together with non-pharmacological management strategies such as pacing, may target distinct but overlapping symptom clusters, including neurocognitive, autonomic, immunological, and muscular/metabolic manifestations. These symptom domains are associated with interacting biological mechanisms such as neuroinflammation, autonomic dysfunction, immune dysregulation, and impaired cellular energy metabolism. The figure illustrates the dynamic and interconnected nature of symptom presentation and underlying pathophysiology.

3.2 Drug Classes Targeting Neuroimmunological and Autonomic Dysregulation in ME/CFS

A substantial proportion of ME/CFS symptoms appears from disturbances in signal transmission within the central and autonomic nervous systems [9,12,15-16,54] (see *Neuroinflammatory/neurocognitive symptom cluster, including sleep disorders,* and *Autonomic symptom cluster* in Section 3.4). For instance, elevated serotonin levels may contribute to impaired muscle contraction, sleep disturbances, cognitive dysfunction, hyperalgesia, and migraine [10]. In addition, serotonin excess may alter dopamine and noradrenaline release [55,56], leading to further pathophysiological consequences. Persistently increased serotonin activity may also result in

chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, thereby contributing to additional symptom burden [3, 56].

Beyond neurotransmitter dysregulation, ME/CFS may also be associated with excessive production and synergistic activity of inflammatory and vasoactive mediators such as histamine, which can trigger a wide range of symptoms [57]. Furthermore, there is evidence of impaired function of muscarinic acetylcholine (ACh) receptors [58]; notably, autoantibodies targeting β-adrenergic and muscarinic ACh receptors have been identified [49, 59].

The pharmacological approaches described below aim to modulate these regulatory disturbances [55]. An example of improved grip strength in patients with ME/CFS following targeted modulation of cholinergic systems is provided by Schlömer et al. [58]. Where available, these strategies are supported by published evidence from ME/CFS or related conditions such as postural orthostatic tachycardia syndrome (POTS) [60], mast cell activation syndromes [61], or neuropathic pain [52]. In the absence of formal studies, however, the therapeutic concepts are primarily based on clinical experience and expert opinion and should therefore be regarded as eminence- rather than evidence-based [60].

At the same time, it must be emphasized that the clinical relevance of the pathophysiological mechanisms described here has not yet been conclusively established in all cases. Nevertheless, clinical experience indicates that medications targeting these mechanisms—many of which are used off-label and provide symptomatic relief in at least a subset of patients with ME/CFS (see Table 1). References supporting the statements regarding these medications are provided in the corresponding sections below.

Table 1 provides an overview of symptomatic therapeutics used in ME/CFS, including typical dosing ranges and the corresponding level of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) classification. Given the limited number of controlled trials in ME/CFS, many agents fall into Level 4 or 5, reflecting case series or clinical experience.

Drug	Typical indication in ME/CFS	Dosage	Level of Evidence (LoE)	Evidence / Rationale	Key References
Aripiprazole	Fatigue, cognitive dysfunction	Start 0.25 mg/day, increase by 0.25 mg every 2 weeks; max 2 mg/day	4	Small retrospective case series in ME/CFS	[62]
Cromoglicic acid	Mast cell activation symptoms	100–200 mg orally four times daily; max 800 mg/day	4	Case reports; MCAS literature	[61]
Fludrocortisone	Orthostatic intolerance	0.1 mg once or twice daily; max 0.5 mg/day	3	Evidence from orthostatic hypotension studies	[60]
Gabapentin	Neuropathic pain, sensory hypersensitivity	Start 300 mg/day, titrate up to 3,600 mg/day	2–3	Strong evidence for neuropathic pain	[72]
H1/H2 receptor antagonists	Mast cell activation symptoms	Example: cetirizine 10–20 mg/day + famotidine 20–40 mg/day	4	MCAS case series	[61]
Hydrocortisone (low dose)	Anti-inflammatory	2.5–10 mg/day	3	Small clinical studies; clinical experience	[60]
Ibuprofen	Musculoskeletal pain	400 mg every 8 h; max single dose 800 mg	3	Analgesic evidence in general population	Pain therapy literature
Ivabradine	Sinus tachycardia, POTS	Start 2.5 mg/day, titrate; typical 7.5–10 mg/day, max 20 mg/day	3–4	Small studies in POTS; case series in ME/CFS	[68,69]

Drug	Typical indication in ME/CFS	Dosage	Level of Evidence (LoE)	Evidence / Rationale	Key References
Melatonin (prolonged release)	Sleep disturbance	2–5 mg 1–2 h before bedtime; max 10 mg/day	3	RCTs for insomnia	Insomnia literature
Metamizole	Moderate to severe pain	500–1000 mg per dose; max 4–5 g/day; WARNING: risk of agranulocytosis	3	Analgesic evidence; no ME/CFS-specific trials	Pain therapy literature
Midodrine	Orthostatic intolerance	Start 2.5 mg, repeat every 3–4 h; max 30 mg/day	3	Evidence from POTS and orthostatic hypotension	[60]
Mirtazapine	Sleep disturbance, appetite loss	3.75–7.5 mg at night; do not use in patients with restless legs symptoms	4–5	Clinical experience	Clinical experience
Naltrexone (low-dose)	Pain, neuroinflammation	Start 0.5–1 mg/day, increase to 4 mg/day	4	Pilot studies and case series	[52,63,64]
Paracetamol (acetaminophen)	Mild pain	10–15 mg/kg per dose; max 60 mg/kg/day	3	General analgesic evidence	Clinical experience
Pilocarpine	Autonomic dysfunction, sicca symptoms	2.5 mg several times daily, max 30 mg/day	3–4	Evidence from autonomic disorders	[81]
Pregabalin	Neuropathic pain, sensory hypersensitivity	Start 150 mg/day, titrate up to 600 mg/day	2–3	Evidence for neuropathic pain and fibromyalgia	[82]
Pyridostigmine	POTS, autonomic dysfunction	Start 10 mg, titrate up to 3 × 30 mg/day, max 180 mg/day	2-3	Rcts in POTS	[58,65,67]
Quetiapine	Severe insomnia	25–150 mg at night (off-label), max 300 mg/day	4–5	Clinical experience	Clinical experience
Rotigotine	Dopaminergic dysfunction, RLS	1 mg/24 h patch, titrate weekly to 3 mg/24 h	3–4	Evidence from RLS/Parkinson's disease	Standard RLS literature

Drug	Typical indication in ME/CFS	Dosage	Level of Evidence (LoE)	Evidence / Rationale	Key References
Trimipramine	Sleep disturbance	10–20 drops at night, max 50 drops/day	4–5	Evidence extrapolated from insomnia literature	[76]

Levels of Evidence (Oxford Centre for Evidence-Based Medicine):

- **Level 1:** Systematic reviews or high-quality randomized controlled trials
- **Level 2:** Low-quality RCTs or prospective cohort studies
- **Level 3:** Case–control studies
- **Level 4:** Case series or case reports
- **Level 5:** Expert opinion or clinical experience

Note: Because controlled pharmacological trials in ME/CFS remain scarce, most therapeutic approaches rely on Levels 3–5 evidence.

- *Dopamine Agonists and Opioid Antagonists*

Aripiprazole (Abilify®), a partial dopamine D2 receptor agonist, blocks postsynaptic dopamine D2 receptors while stimulating presynaptic autoreceptors. At low doses, small observational studies have shown that it may have beneficial effects on overall ME/CFS symptomatology, particularly cognitive function and subjective illness perception [62]. Quetiapine also primarily blocks dopamine D2 receptors, as well as serotonin 5-HT2 receptors, and is primarily used in ME/CFS for the treatment of sleep disturbances. The centrally acting dopamine receptor agonist rotigotine (Neupro®) activates D3, D2, and D1 receptors and may be used at low doses for moderate to severe restless legs symptoms in the form of a transdermal patch. Naltrexone is a long-acting opioid antagonist that predominantly blocks the μ-opioid receptor and, to a lesser extent, κ- and δ-opioid receptors. In ME/CFS, it is prescribed off label primarily for pain management [63–64] (for possible dosing see Tables 1 and 2).

- *Cholinesterase Inhibitors and Parasympathomimetics*

Pyridostigmine bromide (Mestinon®) is a cholinesterase inhibitor that prevents the breakdown of acetylcholine (ACh). In patients with ME/CFS, this may increase the availability of ACh in synaptic clefts of the parasympathetic nervous system. A similar effect may be achieved with the direct parasympathomimetic pilocarpine hydrochloride (Salagen®). At the neuromuscular junction, these agents may increase muscle strength [58] and also alleviate restless legs symptoms, bladder emptying disorders, constipation, tachycardia, and vascular dysfunction [65]. In patients with sicca symptoms, dryness of the mucous membranes may be reduced.

Improved perfusion and increased secretion of the mucous glands of the nasal cavity and paranasal sinuses may, based on clinical observations, have a beneficial effect on headache symptoms in ME/CFS. However, adverse effects such as hypersalivation, exacerbation of accommodation disorders of the eye, bronchoconstriction, bradycardia, diarrhea, or abdominal cramps may occur. Treatment should therefore always be initiated at the lowest possible dose.

- *Antihistamines (H1/H2 Blockers) and Mast Cell Stabilizers*

In a subset of patients with ME/CFS, increased mast cell activation occurs [61], resulting in enhanced release of mediators such as histamine and leukotrienes. In these patients, H1 blockers

(second-generation, e.g., cetirizine; third-generation, e.g., levocetirizine) and mast cell stabilizers (e.g., cromoglicic acid, ketotifen) may have a beneficial effect on symptoms.

Mast cell stabilizers inhibit chloride channels in the cell membranes of activated mast cells, thereby stabilizing these cells and reducing histamine release. Due to their very short half-life, agents such as cromoglicic acid must be administered at least four times daily (possible dosing see Tables 1 and 2).

Histamine H1 receptors are located primarily in blood vessels, bronchi, the gastrointestinal tract, adrenal glands, and the brain. Indications for the use of H1 blockers therefore include not only mast cell activation and allergies, mucosal irritation, and food intolerances commonly observed in ME/CFS, but also postural orthostatic tachycardia syndrome (POTS) and evidence of increased vascular permeability. Owing to their higher central nervous system penetration, first-generation H1 antihistamines may be used to treat sleep disturbances and to improve circadian rhythm.

H2 blockers not only inhibit gastric acid secretion but also may influence smooth muscle function and modulate neurotransmitter and adrenergic signaling as well as signal transduction via inhibition of adenylate cyclase. In addition, they exert negative inotropic and chronotropic effects. In the context of increased mast cell activation, they may therefore complement the effects of H1 blockers in certain domains.

3.3 Therapeutics for the Treatment of Specific ME/CFS Symptoms

In the following section, various symptoms that commonly occur in ME/CFS are presented together with the most relevant pharmacological agents used for their symptomatic treatment. As with the therapies discussed above, these agents are predominantly prescribed off label.

- *Agents for the Treatment of Hypo- and Hypertensive Circulatory Disorders*

Patients with ME/CFS who present with tachycardic hypertension or tachycardic cardiac arrhythmias may, for example, be treated with the β-blocker propranolol. Propranolol antagonizes the effects of adrenaline and noradrenaline by binding to adrenergic receptors, thereby lowering elevated blood pressure and normalizing heart rate. Its onset of action occurs no earlier than several

hours after administration. Heart rate may also be reduced by the cholinesterase inhibitor pyridostigmine (Mestinon®; see above).

Treatment is particularly challenging in cases of centrally mediated reversal of the circadian rhythm with nocturnal hypertension. In therapy-refractory cases, evening administration of clonidine, α-blockers, or calcium channel blockers is recommended [66]. Especially in older patients, clonidine should be initiated at a very low dose (< 75 µg), as its long duration of action may lead to pronounced hypotension not only at night but also during daytime hours.

For the treatment of hypotensive circulatory disorders such as postural orthostatic tachycardia syndrome (POTS), various agents are used, including pyridostigmine [67] (see above), midodrine, the If channel blocker ivabradine, the synthetic aldosterone analogue fludrocortisone, and the glucocorticoid hydrocortisone [60, 66, 68–69]. The active metabolite of the prodrug midodrine is desglymidodrine. Like the mineralocorticoid fludrocortisone, it is used in the treatment of orthostatic hypotension, often in combination with ivabradine, which specifically affects heart rate. Reduced cerebral and muscular perfusion in ME/CFS may be treated with the soluble guanylate cyclase (sGC) stimulator vericiguat (Verquvo®). This agent stimulates soluble guanylate cyclase in blood vessels, leading to vasodilation and facilitating cardiac output. Particularly in the treatment of POTS, it is assumed that lower doses of several medications may be more effective than high doses of a single agent. As with the treatment of other ME/CFS symptoms, achieving a balance between therapeutic efficacy and adverse effects is often challenging (possible dosing see Tables 1 and 2).

- *Agents for the Treatment of Pain*

For symptomatic pain management, paracetamol from the group of nonopioid analgesics is frequently used, although its precise mechanism of action has not yet been fully elucidated. This group also includes metamizole (Novalgin®), which has analgesic, antipyretic, and spasmolytic properties. Ibuprofen, which inhibits cyclooxygenases COX-1 and COX-2 and thereby suppresses prostaglandin synthesis, may also be used to treat pain in ME/CFS. Like metamizole, it also modulates inflammatory processes. These medications may be used in an alternating or combined regime to minimize adverse effects.

Unlike traditional pain relievers, low-dose naltrexone (LDN) is not associated with a significant risk of addiction at low doses. LDN not only has a positive effect on inflammatory processes but

also increases endorphin production, which in turn has a beneficial effect on the chronic pain symptoms associated with ME/CFS [52].

Additional analgesic options include the gamma-aminobutyric acid (GABA) analogue pregabalin and the structurally related compound gabapentin. Pregabalin reduces neuronal excitability in the central nervous system by inhibiting the release of neurotransmitters such as glutamate, noradrenaline, and the neuropeptide substance P, primarily through binding to the α2δ subunit of voltage-gated calcium channels [70]. Gabapentin modulates neuronal excitability via related α2δ-mediated mechanisms and thereby inhibits neuronal signal transmission, making it useful in the treatment of neuropathic pain [71]. Both substances are established treatments for neuropathic pain and central sensitization syndromes [70,72]. Experimental studies further suggest anti-neuroinflammatory properties and effects on synaptic plasticity, although direct evidence in ME/CFS remains limited [73] (possible dosing see Tables 1 and 2).

Cannabidiol (CBD) oil is occasionally used by patients for symptom management, particularly pain and sleep disturbances, although robust clinical evidence in ME/CFS is currently lacking [74].

- *Agents for the Treatment of Sleep Disorders*

In addition to H1 antihistamines, the atypical antipsychotic quetiapine, the GABA analogue pregabalin, and CBD oil (see above), other agents that may be used to treat sleep disorders in ME/CFS include melatonin, mirtazapine, and trimipramine. Melatonin is a hormone that regulates the sleep–wake cycle and promotes the expression of antioxidant enzymes via signaling through activated melatonin receptors.

Mirtazapine is used at low doses in ME/CFS for the treatment of severe sleep disturbances and also as an adjunctive analgesic. It acts centrally as an antagonist at the α2-adrenergic receptor, while also enhancing noradrenergic and serotonergic neurotransmission mediated via 5-HT1 receptors and blocking 5-HT2 and 5-HT3 receptors. Trimipramine is likewise used for more severe sleep disturbances. This compound, which binds to 5-HT2/5-HT1, D2/D1, and α1/α2 receptors, is a potent H1 antagonist and exhibits a pronounced binding affinity for muscarinic acetylcholine receptors (possible dosing see Tables 1 and 2). Evidence for trimipramine derives primarily from insomnia research rather than ME/CFS-specific studies [76].

Benzodiazepines such as lorazepam may be used only on a short-term basis for the treatment of sleep disturbances in ME/CFS. These agents bind to GABA receptors in the central nervous system and enhance the inhibitory effects of GABA. Owing to its sedative, anxiolytic, and muscle-relaxant properties, lorazepam may be used as a rescue medication in cases of severe postexertional malaise, sleep disturbances, sensory overload, tachycardia, and muscle tension [6]. However, there is a high risk of dependence, and paradoxical effects may occur.

There are repeated reports suggesting that the aromatic amino acid tryptophan (TRP) may have a beneficial effect on sleep disturbances in ME/CFS. Through decarboxylation, TRP can be converted into various biogenic amines the metabolism of which may be disrupted in ME/CFS. These include tryptamine, melatonin (which influences the sleep–wake cycle), and serotonin (which, among other functions, affects sleep, pain perception, memory, and thermoregulation). Although tryptophan has historically been used to improve sleep, concerns regarding altered kynurenine-pathway metabolism in ME/CFS currently limit its routine pharmacological use [75].

- *Supportive Neuro-Cognitive and Psychotherapeutic Interventions*

The sGC stimulator vericiguat (see above) may improve cerebral blood flow and thereby potentially support cognitive function. Some agents with neuromodulatory and anti-inflammatory properties, such as the antipsychotic aripiprazole and the opioid receptor antagonist low-dose naltrexone (LDN) may exert positive effects on cognition in some patients, although evidence is currently limited to observational studies and mechanistic hypotheses [62–64].

Psychotherapy and psychosomatic rehabilitation play an important role as supportive interventions for patients with ME/CFS insofar as they help individuals cope with their limited energy resources, social isolation, and frustration, thereby improving health-related and social well-being [77]. Guideline-concordant antidepressant therapy is primarily indicated in patients with comorbid depressive symptoms, where appropriate in combination with cognitive behavioral therapy.

- *Agents for Infection Control*

There is evidence that prolonged antibiotic therapy with azithromycin or minocycline may improve the condition in a subgroup of patients [78]. This effect is attributed to the immunomodulatory properties of these antibiotics. In cases of documented immunoglobulin deficiency with recurrent

bacterial infections, subcutaneous immunoglobulin replacement therapy may be indicated. Frequent herpesvirus reactivations may be managed with suppressive antiviral therapy (e.g., aciclovir 200 mg twice daily or valaciclovir 500 or 1,000 mg/day for at least eight weeks).

3.4 Clinical Symptom Clusters and Symptom-Cluster–Specific Pharmacotherapy

ME/CFS presents with substantial clinical heterogeneity, and accumulating evidence suggests that distinct symptom clusters1 may reflect partially different underlying pathophysiological mechanisms. Although formal symptom clusters are not yet standardized, several clinically relevant patterns have emerged in observational studies and expert consensus. Preliminary findings suggest that, in addition to a symptom cluster characterized primarily by muscular-metabolic symptoms, there may be other clusters in which immune-dominant, neuroinflammatory/neurocognitive (including sleep disorders), autonomic-dominant, and gastrointestinal symptoms are predominant [79]. There are indications that the dominance of these symptom complexes changes over the course of the disease [80] and that there may also be differences between men and women regarding the predominant symptoms [79]. Recognizing these predominant symptom clusters can support more targeted pharmacological decision-making (Table 2).

[1] We are not referring here to clinical subtypes, but rather to clinical symptom complexes, since different clinical symptom clusters may come to the fore as the disease progresses. The term “clinical subtype” suggests that this type does not change over the course of the disease in an individual.

Table 2 Assignment of selected off-label therapeutic agents to common ME/CFS symptoms and domains of dysfunction.Prevalence values were compiled from data reported in Ref. [33]. The table was created by the author.
Please note: These are not monocausal classifications.

Domain of dysfunction		*Symptoms*	Prevalence [%]	*Examples of off-label therapeutics*
Cellular energy metabolism of muscle and nerve cells		Brain fog, Memory impairment, Wordfinding difficulties	91.4	· Aripiprazole, · Vericiguat, · Naltrexone
		Muscle problems (e.g., pain, "muscle soreness", fasciculations, cramps, restless legs)	89.2	· Rotigotine, · Pilocarpine hydrochloride, · Pyridostigmine bromide
		Dyspnea (e.g., when climbing stairs, prolonged speaking)	68.1	
		Pain, headache (e.g., migraine-like)	70.6	· Naltrexone, · Paracetamol, · Metamizole, · Ibuprofen, · Pregabalin, · Gabapentin, · CBD oil
Neurological/endocrine regulatory dysfunction	Central nervous system	Sleep disturbances (e.g., difficulty maintaining sleep, altered circadian rhythm)	88.0	· Quetiapine, · H1 blockers, · Pregabalin, · CBD oil, · Melatonin, · Mirtazapine,

				· Trimipramine, · (Benzodiazepines)
		Hypersensitivity (e.g., to light, noise, touch)	85.5	· Aripiprazole, · Quetiapine · Low-Dose, Gabapentin, · Pregabalin, · LDN
		Impaired temperature regulation (cold sensation, chills, hot flashes)	81.2	· Midodrine / Fludrocortisone / Pyridostigmine · Clonidine, · Guanfacine
		Intolerance to high or low ambient temperatures	73.6	
		Visual disturbances (e.g., blurred vision, tunnel vision, zigzag lines)	65.3	· Gabapentin/Pregabalin, · Lamotrigine, · Melatonin
	Autonomic nervous system	Cardiovascular complaints (e.g., palpitations, blood pressure fluctuations, dizziness during prolonged stan-ding or positional changes, POTS)	83.8	· Pyridostigmine bromide, · H1 blockers, · Beta blockers, · Midodrine, · Ivabradine, · Hydrocortisone, · Vericiguat
		Gastrointestinal complaints (e.g., bloating, diarrhoea, intestinal cramps)	71.8	· H2 blockers
		Urinary and sexual organ complaints (e.g., sudden urge to urinate)	42.4	· H1 blockers, · H2 blockers
Immunological dysfunction		Flu-like symptoms (chills, pronounced malaise)	78.5	

	Intolerances and hypersensitivities to foods, medications, and/or chemicals	62.0	· H1 blockers, · H2 blockers, · Cromoglicic acid
	Increased susceptibility to infections with prolonged recovery phases	48.1	· Azithromycin, · Minocycline, · Immunoglobulin replacement therapy

4 Limitations

This study represents a narrative review. Due to the still very limited scientific evidence base, the clinical experience already published and the experiences reported by patients with symptomatic therapies were compared with the results of the available efficacy studies. In accordance with the principles of narrative reviews, the selection and evaluation of the studies included were based on pragmatic criteria guided by clinical relevance and feasibility.

5 Conclusion and Future directions

As no causal pharmacological therapy for the treatment of ME/CFS is currently available, existing treatment approaches continue to focus on symptomatic therapies individually tailored to the patient's specific ME/CFS symptom profile. A range of pharmacological agents is available that target neuroimmunological pathophysiological mechanisms in ME/CFS, while others are selected primarily based on their applicability to the most common ME/CFS symptoms (Table 2). Most of these medications are currently prescribed off label.

Available clinical experience and limited studies suggest that such symptomatic treatment approaches may have a positive effect on symptom burden and quality of life in some patients when combined with consistent pacing [31,36]. As long as there is no causal therapy available, this currently represents one of the primary approaches to improving patients' health status. In addition to ongoing clinical trials evaluating the efficacy of potential causal therapeutics, future studies should therefore also focus on the symptomatic pharmacological agents already in use. Beyond their direct therapeutic benefit, such studies may further substantiate current pathophysiological concepts underlying the development of individual ME/CFS symptoms.

Abbreviations:

Ach: **A**cetyl**ch**oline

ACTH: **A**drenoco**r**ticoto**r**opic **H**ormone

CBD: **C**anna**bid**iol

CFS: **C**hronic **F**atigue **S**yndrome

GABA: **G**amma-**A**mino**b**utyric **A**cid

HPA: **H**ypothalamic–**P**ituitary–**A**drenal

LDN: **L**ow-**D**ose **N**altrexone

MCAS: **M**ast **C**ell **A**ctivation **S**yndrome

ME: **M**yalgic **E**ncephalomyelitis

OCEBM: **O**xford **C**entre for **E**vidence-**B**ased **M**edicine

PEM: **P**ost**e**xertional **M**alaise

POTS: **P**ostural **O**rthostatic **T**achycardia **S**yndrome

RCTs: **R**andomized **C**ontrolled **T**rials

RLS: **R**estless **L**egs **S**yndrome

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