

BEYOND MYALGIC ENCEPHALOMYELITIS/
CHRONIC FATIGUE SYNDROME

Redefining an Illness

Report Guide for Clinicians

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Introduction

About the IOM Report

Myalgic encephalomyelitis/chronic fatigue syndrome, commonly referred to as ME/CFS, is a disease characterized by profound fatigue, cognitive dysfunction, sleep abnormalities, autonomic manifestations, pain, and other symptoms that are made worse by exertion of any sort. ME/CFS can severely impair patients' ability to conduct their normal lives, yet many struggle with symptoms for years before receiving a diagnosis. Fewer than one-third of medical school curricula and less than half of medical textbooks include information about ME/CFS. Although many health care providers are aware of ME/CFS, they may lack essential knowledge about how to diagnose and treat it.

ME/CFS is a serious, chronic, complex, systemic disease that often can profoundly affect the lives of patients.

The Department of Health and Human Services, the National Institutes of Health, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Social Security Administration asked the Institute of Medicine (IOM) to convene an expert committee to examine the evidence base for ME/CFS. In *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*, the committee proposes new diagnostic criteria that will facilitate timely diagnosis and care and enhance understanding among health care providers and the public. These criteria, based on expert analysis and the most up-to-date scientific literature, are streamlined for practical use in the clinical setting. The IOM committee also recommends that the name of the disease be changed—from ME/CFS to systemic exertion intolerance disease (SEID)—to more accurately capture the central characteristics of the illness.

The following guide, derived from the IOM report, is intended to help primary and specialty care clinicians better understand this complex, debilitating, and often-misunderstood illness.

Background

About ME/CFS

- ME/CFS affects 836,000 to 2.5 million Americans.
- An estimated 84 to 91 percent of people with ME/CFS have not yet been diagnosed, meaning the true prevalence of ME/CFS is unknown.
- ME/CFS affects women more often than men. Most patients currently diagnosed with ME/CFS are Caucasian, but some studies suggest ME/CFS is more common in minority groups.
- The average age of onset is 33, although ME/CFS has been reported in patients younger than age 10 and older than age 70.
- At least one-quarter of ME/CFS patients are bed- or house-bound at some point in their illness.
- ME/CFS patients experience loss of productivity and high medical costs that contribute to a total economic burden of \$17 to \$24 billion annually.
- The cause of ME/CFS remains unknown, although symptoms may be triggered by certain infections, such as Epstein-Barr virus (EBV).
- There are therapies available for the management of symptoms of ME/CFS, but their efficacy is not well understood. There is no existing cure for ME/CFS.
- There is an urgent need for more research to discover what causes ME/CFS, understand the mechanisms associated with the development and progression of the disease, and develop effective diagnostic markers and treatments.

Symptoms can persist for years, and most patients never regain their pre-disease level of functioning.

A new name for ME/CFS

- Several studies have shown that the term “chronic fatigue syndrome” affects patients’ perceptions of their illness as well as the reactions of others, including medical personnel, family members, and colleagues. This label can trivialize the seriousness of the condition and promote misunderstanding of the illness.
- The IOM committee recommends a new name to replace ME/CFS: systemic exertion intolerance disease (SEID). This name captures a central characteristic of the disease—the fact that exertion of any sort (physical, cognitive, or emotional)—can adversely affect patients in multiple organ systems.

Diagnostic Criteria for ME/CFS (SEID)

Diagnosis requires that the patient have the following three symptoms:

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

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS (SEID) should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Key Considerations in Diagnosing ME/CFS (SEID)

- ME/CFS (SEID) is a serious, chronic, and systemic disease that frequently and dramatically limits the activities of affected patients.
- A thorough history, physical examination, and targeted workup are necessary to determine a differential diagnosis and are often sufficient for diagnosis of ME/CFS (SEID).
- Physicians should diagnose ME/CFS (SEID) if diagnostic criteria are met following an appropriate history, physical examination, and medical workup, including appropriate specialty referrals.
- It is essential that clinicians assess the severity and duration of symptoms over the past month or more. Chronic, frequent, and moderate or severe symptoms are required to distinguish ME/CFS (SEID) from other illnesses.
- The proposed criteria require symptom duration for 6 months to make a diagnosis in light of evidence that most other causes of similar fatigue do not last beyond 6 months.
- Patients who do not meet the criteria for ME/CFS (SEID) should continue to be diagnosed by other criteria as their symptoms and evaluations dictate. These patients should also receive appropriate care. (Conditions that may approach but not meet the criteria for ME/CFS [SEID] include, for example, protracted recovery from EBV mononucleosis or gradual emergence of a different chronic illness, such as multiple sclerosis, colon cancer, or a primary sleep disorder.)
- Comorbidities such as fibromyalgia and irritable bowel syndrome are common in ME/CFS (SEID) patients. These comorbidities should be diagnosed and treated when caring for patients. The presence of other illnesses should not preclude patients from receiving a diagnosis of ME/CFS (SEID) except in the unlikely event that all symptoms can be accounted for by these other illnesses.

“When I do any activity that goes beyond what I can do—I literally collapse—my body is in major pain. It hurts to lay in bed, it hurts to think, I can’t hardly talk—I can’t find the words. I feel my insides are at war.”

—Patient communication to IOM committee

Core Symptoms

Fatigue and impairment

There is sufficient evidence that fatigue in ME/CFS (SEID) is profound, not the result of ongoing excessive exertion, and not substantially alleviated by rest. This fatigue must be accompanied by a substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities and persist for more than 6 months. Fatigue, and particularly the impact of illness on function, should be assessed in making a diagnosis of ME/CFS (SEID).

Post-exertional malaise (PEM)

PEM is worsening of a patient's symptoms and function after exposure to physical or cognitive stressors that were normally tolerated before disease onset. Subjective reports of PEM and prolonged recovery are supported by objective evidence in the scientific literature, including failure to normally reproduce exercise test results (2-day cardiopulmonary exercise test) and impaired cognitive function after exertion. There is sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS (SEID) from other conditions.

Unrefreshing sleep

Despite the absence of a specific objective alteration in sleep architecture, the data are strong that the complaint of unrefreshing sleep is universal among patients with ME/CFS (SEID) when questions about sleep specifically address this issue. While polysomnography is not required to diagnose ME/CFS (SEID), its use to screen for treatable sleep disorders when indicated is appropriate. Diagnosis of a primary sleep disorder does not rule out a diagnosis of ME/CFS (SEID).

Cognitive impairment

Cognitive impairment in ME/CFS (SEID) includes problems with thinking or executive function exacerbated by exertion, effort, or stress or time pressure. There is sufficient evidence that slowed information processing is common in patients with ME/CFS (SEID), and a growing body of evidence shows that it may play a central role in overall neurocognitive impairment associated with the disease (memory impairments, attention deficits, and impaired psychomotor function). Such a deficit may be responsible for disability that results in loss of employment and loss of functional capacity in social environments.

Orthostatic intolerance

Orthostatic intolerance is a general term that implies worsening of symptoms upon assuming and maintaining upright posture. Symptoms are improved, although not necessarily abolished, by lying back down or elevating the feet. Sufficient evidence indicates a high prevalence of orthostatic intolerance conditions in ME/CFS (SEID) as measured by objective heart rate and blood pressure abnormalities and physical findings during standing, bedside orthostatic vital signs, head-up tilt testing, or by patient-reported exacerbation of orthostatic symptoms with standing in day-to-day life. These findings indicate that orthostatic intolerance is a common and clinically important finding in ME/CFS (SEID).

“My personal experience of having ME/CFS feels like permanently having the flu, a hangover, and jet lag while being continually electrocuted (which means that pain plays at least as much of a role in my condition as fatigue).”

—Patient communication to IOM committee

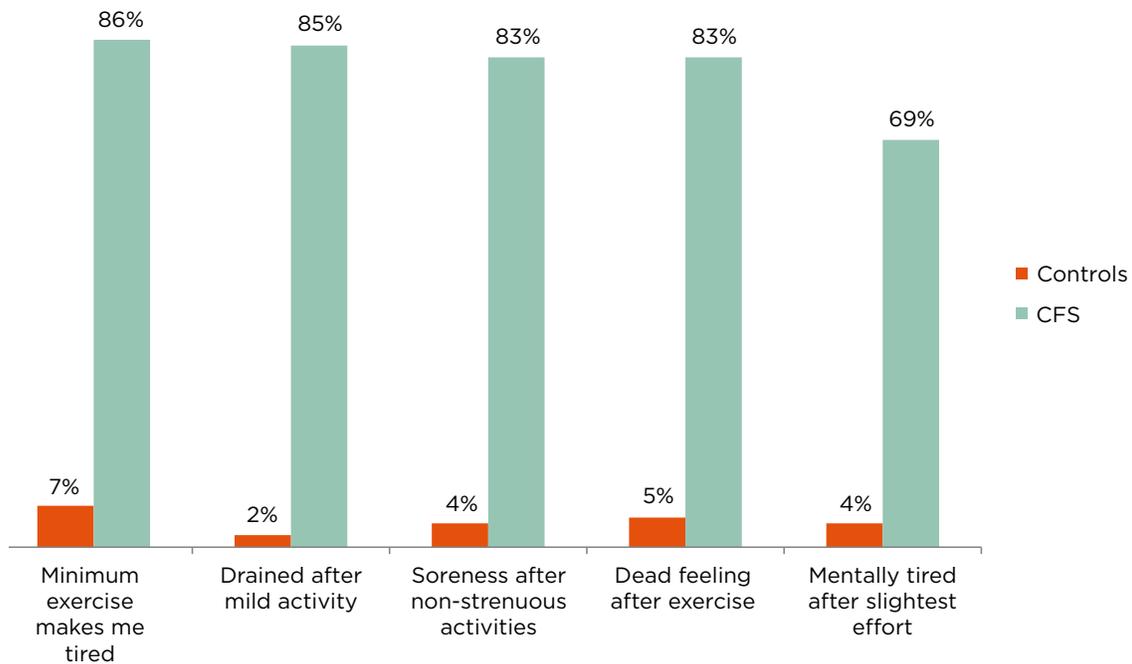


FIGURE 1 Percentage of ME/CFS patients and healthy controls reporting PEM symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.

NOTE: See complete report, Figure 4-1, for note and source information.

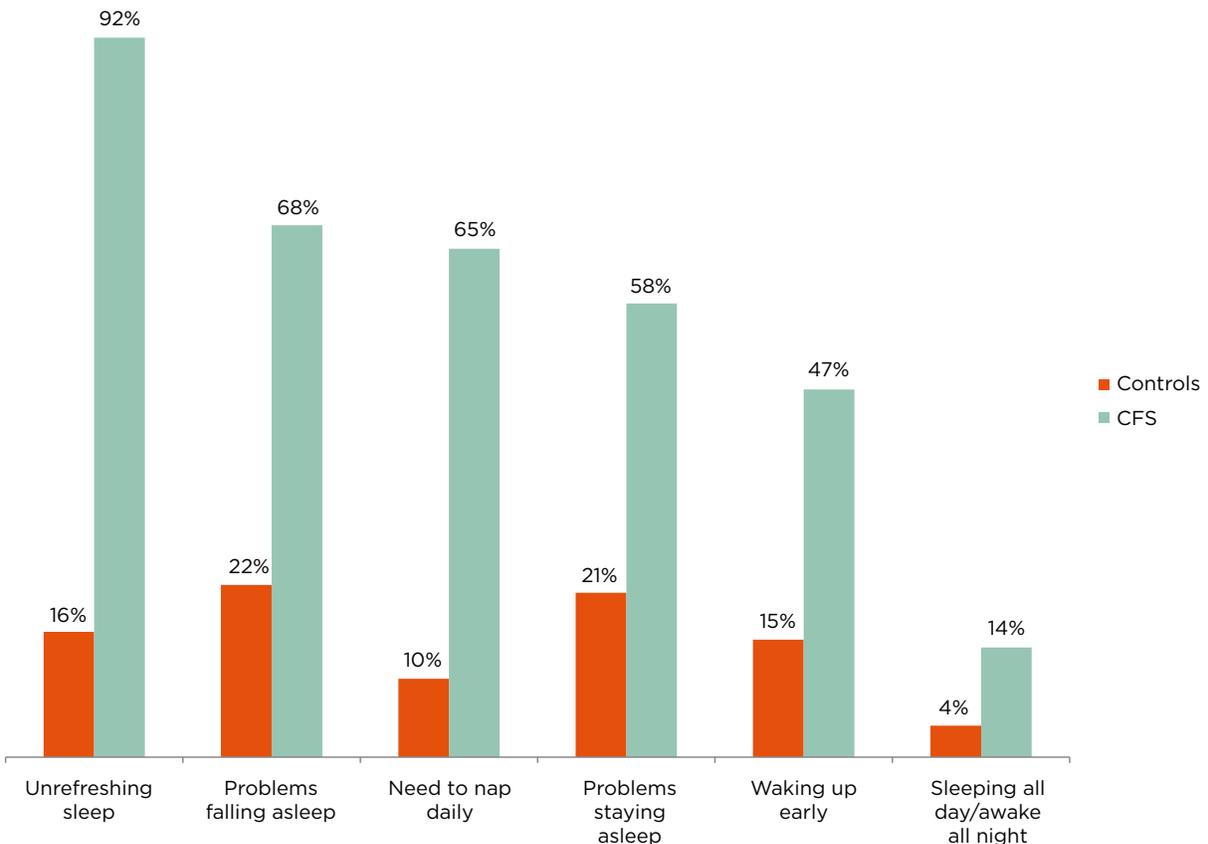


FIGURE 2 Percentage of ME/CFS patients and healthy controls reporting sleep-related symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.

NOTE: See complete report, Figure 4-2, for note and source information.

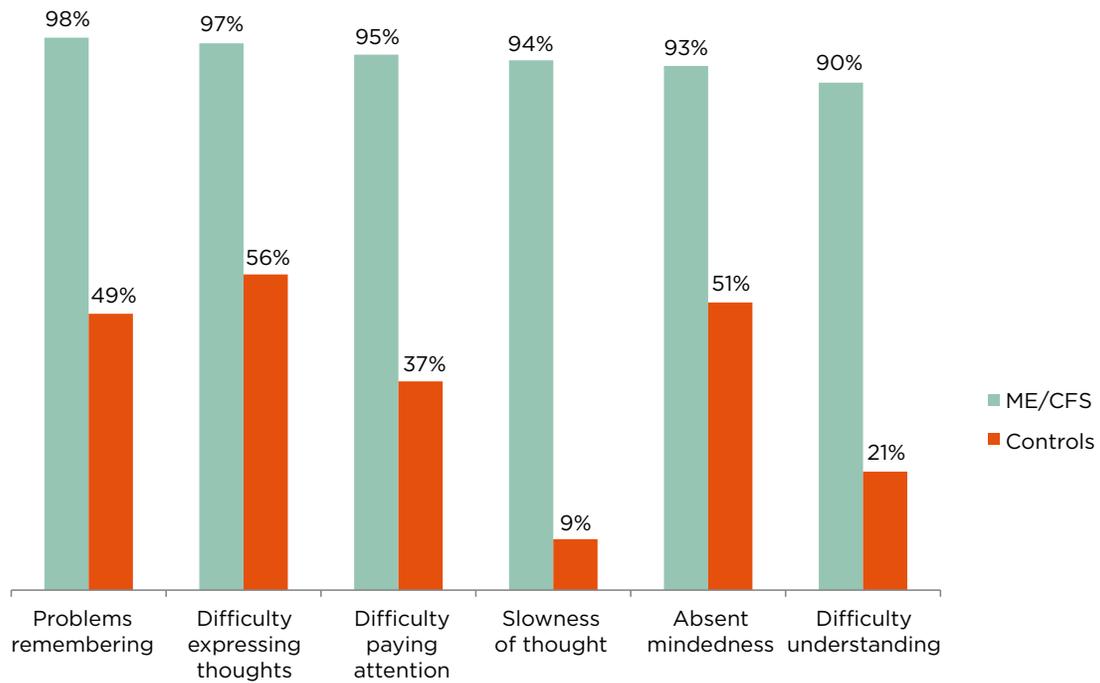


FIGURE 3 Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least moderate severity that occurred at least half of the time during the past 6 months.

NOTE: See complete report, Figure 4-3, for note and source information.

Additional Symptoms

The committee found evidence of other manifestations of ME/CFS (SEID):

Pain

Pain is common in ME/CFS (SEID), but highly variable in presence, nature, and severity (with a higher prevalence in more severe cases). However, there is no conclusive evidence that pain experienced by ME/CFS (SEID) patients can be distinguished from that experienced by healthy people or those with other diseases. Pain associated with ME/CFS (SEID) can come in many forms, including headaches, arthralgia, and myalgia.

Immune impairment

Sufficient evidence supports the finding of immune dysfunction in ME/CFS (SEID). Specifically, the committee's literature search yielded data demonstrating poor NK cell cytotoxicity (NK cell function, not number) that correlates with illness severity in ME/CFS (SEID) patients and could serve as a biomarker for the severity of the disease, although it is not specific to ME/CFS (SEID).

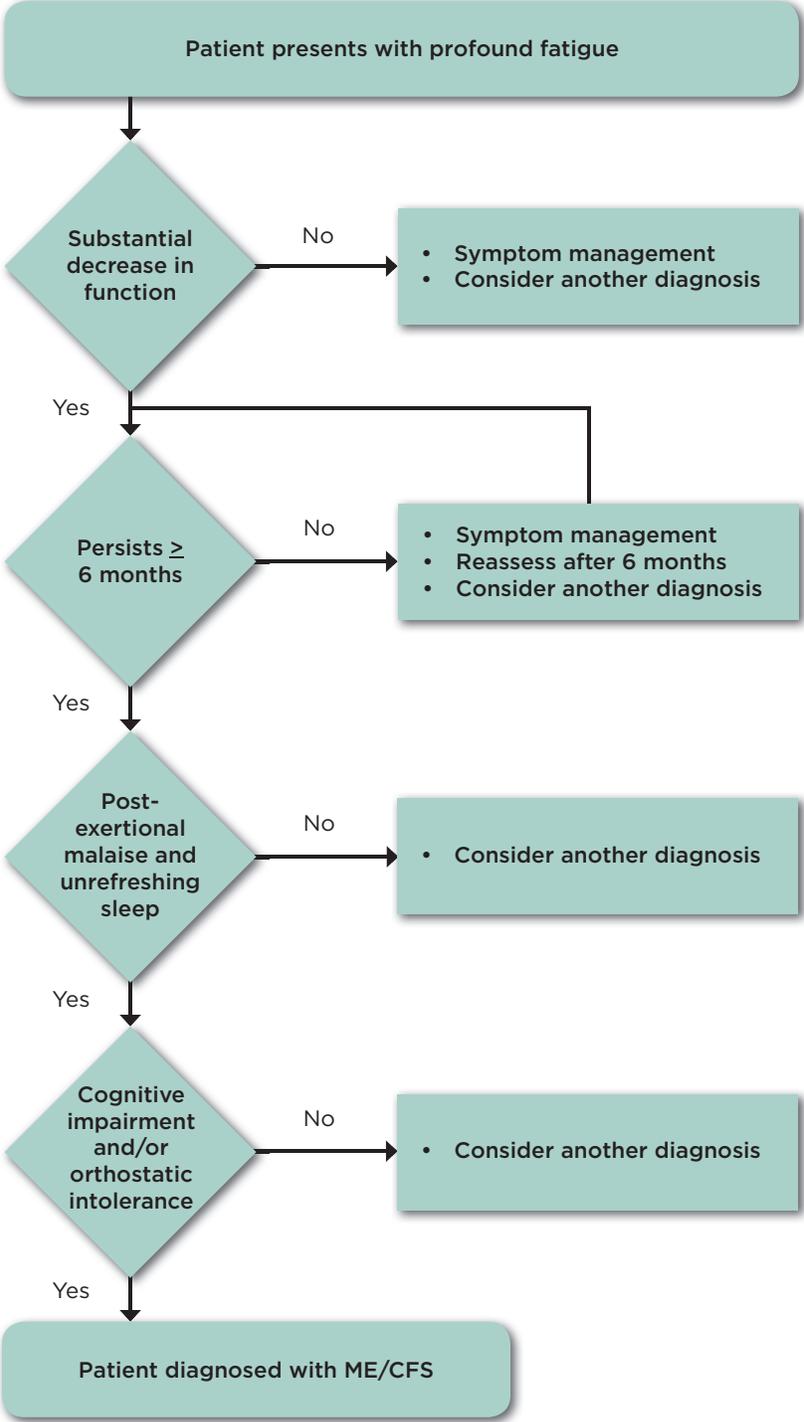
Infection

There is sufficient evidence to suggest that ME/CFS (SEID) can follow infection with EBV and possibly other specific infections, but there is insufficient evidence to conclude that all cases of ME/CFS are caused by EBV or that ME/CFS (SEID) is sustained by ongoing EBV infection. There is also insufficient evidence for an association between ME/CFS (SEID) and bacterial, fungal, parasitic, and other viral infections.

There are several other symptoms that are reported less frequently but may support a diagnosis of ME/CFS (SEID). These include

- Gastrointestinal impairments
- Genitourinary impairments
- Sore throat
- Painful or tender axillary/cervical lymph nodes
- Sensitivity to external stimuli (e.g., foods, drugs, chemicals)

Diagnostic Algorithm for ME/CFS (SEID)



Operationalizing the Diagnosis

Symptom	Patient descriptions	Questions to ask (all questions should explore frequency and severity)	Observations to make; tests to conduct
Impairment in function with profound fatigue	<ul style="list-style-type: none"> • “flu-like fatigue/exhaustion” • “I feel like a battery that is never able to be recharged fully despite resting a lot and limiting my activities to only the bare essentials needed to get by” • “Thinking takes a lot more work than it used to” • “My arms, legs, body feel heavy and harder to move” • severe limitations in personal and household management • loss of job, medical insurance, and career • being predominantly housebound • decreased social interaction and increased isolation 	<ul style="list-style-type: none"> • How fatigued are you? • What helps your fatigue the most (resting, lying down, quiet situations, not exercising or avoiding exercise)? • What makes the fatigue worse? • What are you able to do now? How does it compare with what you were able to do before? • Think back to what you were able to do before you became sick. How much has this illness affected: (a) your ability to work? (b) your ability to take care of yourself/your family and to do chores? • What happens when you try to push through the fatigue? 	<p>Observe for progressive fatigue (physical or mental), need for help or need to lie down during a prolonged exam.</p>
Post-exertional malaise	<ul style="list-style-type: none"> • “crash,” “relapse,” “collapse” • mentally tired after the slightest effort • physically drained or sick after mild activity • the more demanding, prolonged, or repeated the activity, the more severe and prolonged the payback 	<ul style="list-style-type: none"> • What happens to you as you engage in normal physical or mental exertion? Or after? • How much activity does it take you to feel ill? • What symptoms develop from standing or exertion? • How long does it take to recover from physical or mental effort? • If you go beyond your limits, what are the later consequences? • What types of activities do you avoid because of what will happen if you do them? <p>PEM may be delayed related to the trigger. Consider asking patients to keep a diary for a week or two, documenting activities and symptoms.</p>	<p>Using two cardiopulmonary exercise tests (CPETs) separated by 24 hours, look for marked inability to reproduce maximal or anaerobic threshold measures on the second day (note that this test may induce severe exacerbation of symptoms in these patients).</p>

Symptom	Patient descriptions	Questions to ask (all questions should explore frequency and severity)	Observations to make; tests to conduct
Unrefreshing sleep	<ul style="list-style-type: none"> • “feeling like I never slept” • “cannot fall asleep or stay asleep” • “After long or normal hours of sleep, I still don’t feel good in the morning” 	<ul style="list-style-type: none"> • Do you have any problems getting to sleep or staying asleep? • Do you feel rested in the morning or after you have slept? • Tell me about the quality of your sleep. • Do you need too much sleep? • Do you need to take more naps than other people? (There may be other sleep disruptors as well) 	<p>There is no evidence that currently available sleep studies contribute to the diagnosis of ME/CFS.</p>
Cognitive impairments	<ul style="list-style-type: none"> • “brain fog” • “confusion” • “disorientation” • “hard to concentrate, can’t focus” • “inability to process information” • “can’t find the right words” • “inability to multi-task” • “problems with decision making” • “absent-minded/ forgetful” 	<ul style="list-style-type: none"> • Do you have problems doing the following activities: driving, watching a movie, reading a book/magazine, completing complex tasks under time constraints, following/participating in conversation, doing more than one thing at a time? • Compared with before your illness, how is your performance at work or school now? 	<ul style="list-style-type: none"> • Observe for difficulties with thinking during the clinic visit—unusual trouble remembering medications, relating details of history or understanding questions/recommendations, expressing self. • Using formal neuropsychological testing, observe slowed information processing, memory impairments, reduced attention, impaired psychomotor function
Orthostatic intolerance	<ul style="list-style-type: none"> • lightheadedness • dizziness • spatial disorientation or imbalance • fainting • feeling unwell, dizzy, or lightheaded when sitting up or standing still for extended periods (note “extended” can mean a few minutes for the severely affected) 	<ul style="list-style-type: none"> • How do you feel when you have been standing still for more than a few minutes? • What happens to you after you get up rapidly after lying down or sitting for a long time? • How long can you stand before feeling ill? For example, can you do the dishes? Can you stand in line for a bus or movie? Are you able to grocery shop or go to a mall? • How does hot weather affect you? • Do you study or work lying down, in bed or a recliner? Why? • Do you prefer to sit with knees to your chest or legs under you? 	<ul style="list-style-type: none"> • Severely affected patients may need to lie down while they are being interviewed. • Using a standing test or tilt test, evaluate for postural tachycardia syndrome, neurally mediated hypotension, and orthostatic hypotension. • Other signs include: pallor, general discomfort, blue discoloration of extremities, cold hands and feet, diminished peripheral pulses, sway, efforts to compensate by moving around.

NOTE: See the complete report, Table 7-1, for source information.

Questionnaires and Tools That May Be Useful for Assessing ME/CFS (SEID) Symptoms

Symptoms/ Manifestations	Tools or Questionnaires	Access Link
Fatigue	The Chalder Fatigue Scale ^a	http://www.goodmedicine.org.uk/files/assessment,%20chalder%20fatigue%20scale.pdf
	Multidimensional Fatigue Inventory ^a	http://www.cdc.gov/cfs/pdf/wichita-data-access/mfi-doc.pdf
	Fisk Fatigue Impact Scale ^a	http://www.actaneurologica.be/acta/download/2003-4/01-Kos%20et%20al.pdf
	The Krupp Fatigue Severity Scale ^a	http://www.abiebr.com/set/17-assessment-outcomes-following-acquiredtraumatic-brain-injury/177-fatigue-severity-scale-fss
	Checklist of Individual Strength ^b	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1739950/pdf/v057p00353.pdf
	DePaul Symptom Questionnaire ^{b,c}	http://condor.depaul.edu/ljason/cfs
	CDC Symptom Inventory for CFS ^{b,c}	http://www.institutferran.org/documentos/cdc_full_symptom_inventory.pdf
Substantial decrease or impairment in function: adults	NOVA form ^d	http://www.nova.edu/nim/patients/forms/fatigue-scale.pdf
	Work and Social Adjustment Scale (WSAS) ^a	serene.me.uk/tests/wsas.pdf
	Energy Index Point Score ^a	http://www.treatmentcenterforcfs.com/energy_index_score
	SF-36 ^b (RAND-36 is available as a free version of SF36)	http://www.sf-36.org/tools/pdf/SF-6v1_Standard_Sample.pdf
	The Lawton Instrumental Activities of Daily Living (IADL) Scale ^d	http://consultgerirn.org/uploads/File/trythis/try_this_23.pdf
	Katz Index of Independence in Activities of Daily Living ^d	http://clas.uiowa.edu/socialwork/files/socialwork/NursingHomeResource/documents/Katz%20ADL_LawtonIADL.pdf
	FIQR (Fibromyalgia Impact Questionnaire Revised) ^d	http://fiqrinfo.ipage.com/FIQR%20FORM.pdf

Symptoms/ Manifestations	Tools or Questionnaires	Access Link
Substantial decrease or impairment in function: children	Short form of the Child Health Questionnaire ^b	http://jech.bmj.com/content/59/1/75.full.pdf+html
	Pediatrics Quality of Life Inventory (PedsQL) ^d	http://www.pedsql.org
	Functional Disability Inventory (FDI) ^d	http://www.actaneurologica.be/acta/download/2003-4/01-Kos%20et%20al.pdf
Post-exertional malaise	CDC Symptom Inventory for CFS ^{b,c}	http://www.institutferran.org/documentos/cdc_full_symptom_inventory.pdf
	DePaul symptom questionnaire ^{b,c}	http://condor.depaul.edu/ljason/cfs
Sleep problems	Sleep Assessment Questionnaire ^d	http://www.completehealthsleep.com/DesktopModules/DocumentViewer/Documents%5CDocumentId5_%5CSleep%20Assessment%20Questionnaire.pdf
	Pittsburgh Sleep Quality Index (PSQI) ^d	http://consultgerirn.org/uploads/File/trythis/try_this_6_1.pdf
	PROMIS sleep questionnaire ^d	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261577/pdf/nihms335121.pdf
Cognitive symptoms	Wood Mental Fatigue Inventory ^a	http://www.pubfacts.com/detail/7902751/A-brief-mental-fatigue-questionnaire
	Checklist Individual Strength Questionnaire ^b	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1739950/pdf/v057p00353.pdf
	The Cognitive Failures Questionnaire ^b	http://www.yorku.ca/rokada/psyctest/cogfail.pdf
Orthostatic intolerance	Orthostatic Grading Scale ^d	http://www.thestudentroom.co.uk/attachment.php?attachmentid=139109&d=1333233284
	COMPASS 31 ^d	http://www.nymc.edu/fhp/centers/syncope/COMPASS%2031.pdf
Pain	PROMIS ^b	http://www.assessmentcenter.net
	SF-36 ^b	http://www.sf-36.org/tools/pdf/SF-6v1_Standard_Sample.pdf
	McGill Pain Questionnaire ^d	http://www.ama-cmeonline.com/pain_mgmt/pdf/mcgill.pdf
	Brief Pain Inventory ^d	http://www.npcrc.org/files/news/briefpain_short.pdf
	Pain diagram ^d	http://alaska.providence.org/locations/pvmc/Documents/Pain%20Diagram.pdf

^a Questionnaires used or tested in SEID patients that may be useful tools in a clinical setting.

^b Questionnaires used or tested in SEID patients that may be difficult to apply in a clinical setting.

^c Questionnaires that evaluate the full range of SEID symptomatology (fatigue, decrease in function, post-exertional malaise [PEM], sleep problems, cognitive symptoms, pain).

^d Questionnaires not formally tested in SEID patients that may be useful tools in a clinical setting.

For more information

Visit www.iom.edu/MECFS for more resources, including

- Free PDF download of the complete report
- 4-page lay summary
- ME/CFS fact sheet
- Downloadable files for diagnostic criteria and diagnostic algorithm
- Other key figures
- PDF version of the Report Guide for Clinicians

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