Review of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: an evidence-based approach to diagnosis and management by clinicians

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Abstract: This review was written from the viewpoint of the treating clinician to educate health care professionals and the public about Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). It includes: the clinical definition of ME/CFS with emphasis on how to diagnose ME/CFS; the etiology, pathophysiology, management approach, long-term prognosis and economic cost of ME/CFS. After reading this review, you will be better able to diagnose and treat your patients with ME/CFS using the tools and information provided. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, chronic medical condition characterized by symptom clusters that include: pathological fatigue and malaise that is worse after exertion, cognitive dysfunction, immune dysfunction, unrefreshing sleep, pain, autonomic dysfunction, neuroendocrine and immune symptoms. ME/CFS is common, often severely disabling and costly. The Institute of Medicine (IOM) reviewed the ME/CFS literature and estimates that between 836,000 and 2.5 million Americans have ME/CFS at a cost of between 17 and 24 billion dollars annually in the US. The IOM suggested a new name for ME/CFS and called it Systemic Exertion Intolerance Disease (SEID). SEID’s diagnostic criteria are less specific and do not exclude psychiatric disorders in the criteria. The 2010 Canadian Community Health Survey discovered that 29% of patients with ME/CFS had unmet health care needs and 20% had food insecurity – lack of access to sufficient healthy foods. ME/CFS can be severely disabling and cause patients to be bedridden. Yet most patients (80%) struggle to get a diagnosis because doctors have not been taught how to diagnose or treat ME/CFS in medical schools or in their post-graduate educational training. Consequently, the patients with ME/CFS suffer. They are not diagnosed with ME/CFS and are not treated accordingly. Instead of compassionate care from their doctors, they are often ridiculed by the very people from whom they seek help. The precise etiology of ME/CFS remains unknown, but recent advances and research discoveries are beginning to shed light on the enigma of this disease including the following contributors: infectious, genetic, immune, cognitive including sleep, metabolic and biochemical abnormalities. Management of patients with ME/CFS is supportive symptomatic treatment with a patient centered care approach that begins with the symptoms that are most troublesome for the patient. Pacing of activities with strategic rest periods is, in our opinion, the most important coping strategy patients can learn to better manage their illness and stop their post-exertional fatigue and malaise. Pacing allows patients to regain the ability to plan activities and begin to make slow incremental improvements in functionality.

Keywords: case definition; chronic fatigue syndrome; myalgic encephalomyelitis; pathophysiology and treatment; SEID.

Case study: CL

CL was a 54 year old woman who was referred for investigation of her severe fatigue that had been present for the past 2 years. Before she was sick she worked full time as a kindergarten teacher. She loved her job. She was happily married with two sons who were at university. Before her illness, she went to advanced Pilates classes 3 to 4 X a week and enjoyed entertaining family and friends on weekends. Her illness started 2 years ago when she was at a Christmas party. Everyone at the party got the flu. They all got better but she never recovered. She could not go back to teaching after the Christmas holidays because she was so ill. She was unable to work since that time. At the time of presentation she had the following symptoms: severe fatigue and malaise, so much that she could barely stand long enough to make a meal most days. She had equal numbers of good days and bad days. Her energy on a good day was

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5 out of 10. Her energy on a bad day was 3 out of 10 and she was in bed. Her premorbid energy on the Functional Capacity Scale was 9 to 10/10 (See Appendix 1). She pushed herself to get things done on a good day. For example, she would go to the bank; but after she stood in line for a few minutes she felt very exhausted and felt like she was going to faint. One time she was so embarrassed because she had to sit on the floor to recover enough to go home. She had recurrent sore throats and swollen glands, which were worse after she pushed herself. She had unrefreshing sleep, woke up repeatedly throughout the night and woke up exhausted every morning no matter what time she went to bed. On good days she could be on the computer to do emails for half an hour, but she had to stop because she could not concentrate or focus. She called it “brain fog”. Most days she could not read anything but a few paragraphs because she could not remember the story line. Previously she was an avid reader. She had muscle pain that moved around her body and new headaches she had never had before and which were worse when a storm was coming in.

She had been tried on various antidepressants because her physician thought she was depressed but she did not tolerate them. She had no history of depression and did not think she was depressed; she just did not have the energy to get things done the way she used to. She pushed herself to do things when she had more energy on a good day – but she ended up “crashed” in bed for 2 days afterward with immobilizing post exertional physical and/or mental fatigue. She was sad that she could no longer work at the job she loved and exercise as she had in the past. She was frustrated and angry that after seeing 10 doctors she did not have a diagnosis and no one could help her. She just wanted to get better.

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is known as a very complex chronic clinical condition plagued by having no diagnostic blood test or investigation. Funding for research has been sparse (1). There are 20 consensus research and clinical definitions of ME/CFS in the literature (2) including: Canadian Consensus Criteria (3), Fukuda (4), Holmes (5), International Criteria (6), Oxford (7), etc. with an inability to separate ME and CFS. The United States Institute of Medicine appointed a committee in 2015, which wrote new ME/CFS criteria and renamed it Systemic Exertion Intolerance Disease (SEID). With inconsistent ME/CFS criteria, it has been difficult to carry out definitive studies on patients with ME/CFS that would lead to new understanding of pathophysiology, new diagnostic tests, and treatment methods.

As a result of not having diagnostic blood tests or investigative tools plus the variety of case criteria having different selection and exclusion criteria, many clinicians have been skeptical that ME/CFS was legitimate. As a result, patients with ME/CFS have been maligned and told they did not have a real physical illness and that it was “all in their head”. The IOM acknowledged this in the report Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness and described it as “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.” (8).

ME/CFS case definitions are assessed in terms of sensitivity (ability to identify ME/CFS patients correctly) and specificity (ability to exclude patients that do not have ME/CFS). It is essential to identify ME/CFS patient populations correctly. If patient samples include participants with different conditions, it is impossible to determine what are the core domains or symptoms.

The new SEID criteria were not assessed with patient data sets and controls. Analysis of 796 CFS patients BioBank samples found that the new SEID criteria selected more patients who had less impairment and fewer symptoms than several other criteria. It excluded symptoms of pain and immune system dysfunction. Also, SEID does not exclude “individuals from major depressive disorder illness groups as well as other medical illnesses” (9, 10). The SEID criteria is similar to the 1994 Fukuda CFS criteria and the 1991 Oxford CFS criteria which include other patient populations including major psychiatric illnesses in their criteria. There are “detrimental consequences for research in the interpretation of epidemiological, etiological and treatment” for patients with ME/CFS (11).

The purpose of this article, as long-standing clinicians with considerable experience re ME/CFS, is to inform other clinicians about how to assess and manage patients with ME/CFS as research proceeds, because there remains a severe gap in diagnosis and appropriate management using the available evidence. As a result of its better specificity, by the exclusion of other treatable illnesses (including psychiatric illnesses), and its well defined clinical criteria, we will continue to use the Canadian Consensus Criteria (CCC) when diagnosing patients with ME/CFS. Jason et al. validated the CCC symptoms by using the DePaul Symptom Questionnaire (12) in several patient samples, and assessed function by using the Short Form 36-Item Questionnaire (SF-36) (13). (Both
questionnaires and scoring systems are available online)
A symptom must be present with moderate severity about half of the time to meet criteria for a symptom category, and a patient must score below a certain maximum score on at least two of the three scales of the SF-36 to meet criteria for a substantial reduction in functioning. This validation and development of the Revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition (14) was to operationalize the CCC, make it more reliable as a diagnostic tool and allow its use in future research studies. The CCC is best able to differentiate between ME/CFS and another common cause of fatigue: depression. This makes it very useful for primary care clinicians. The recently published 2014 “ME/CFS: Primer for Clinical Practitioners” published by the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) used the CCC (15).

In order to diagnose ME/CFS using the Canadian Consensus Criteria (CCC) (3), exclusion criteria must first be applied; then the patient must have the following criteria: pathological fatigue, post-exertional fatigue and malaise, sleep dysfunction, pain, cognitive dysfunction, and two symptoms from the following categories: autonomic, neuroendocrine or immune. The patient needs to have had the illness for a minimum of 6 months if an adult and 3 months if a child. See Appendix 2 for the ME/CFS Clinical Diagnostic Criteria Worksheet. Despite the symptom complexity of ME/CFS, doctors can use the same skills to manage ME/CFS that they utilize successfully in patients with other complex conditions.

Prevalence of ME/CFS

Adults

Middle aged women comprise 70% of ME/CFS patients. Women are twice as likely to have ME/CFS as men (16–18).

ME/CFS is found in people of all ages and races. A case as young as 4 years old has been reported. It is more common in adolescents than children. Cases can occur in clusters or sporadically (19).

The prevalence of ME/CFS has been estimated to be between 0.004%–0.0087% (20), 0.42% (16) and 2.54% (21). The large discrepancy in the prevalence statistics is as a result of using different definitions of ME/CFS. The more specific the exclusion criteria in the definition the smaller the number of patients diagnosed with ME/CFS. This translates into between 836,000 and 2.5 million Americans having ME/CFS according to the IOM.

Children

In children and adolescents the prevalence estimates range from 24 to 116 per 100,000 (22). Up until now, existing studies of ME/CFS in youth have conflicting numbers and have lacked the ability to rigorously estimate the overall prevalence of pediatric ME/CFS or examine risk factors for the illness. Weaknesses of the studies were recruiting strategies: only doctors were reporting the patients ill with ME/CFS or the studies involved unconfirmed phone surveys. Jason et al. have published a pediatric case criteria (22). See Appendix 3.

Prognosis

Adults

The prognosis of ME/CFS is variable. Patients may show some improvement over the first five years of the illness and usually plateau at a level below their pre-illness functioning level. Most patients never regain their premorbid level of health or functioning (23, 24).

A review of 14 studies found on average that 5% of patients recovered (range 0%–31%); 40% of patients improved during follow-up (range 8%–63%); 8%–30% returned to work; 5%–20% of patients reported worsening of symptoms (25, 26).

The patients may be functionally impaired mildly (can work with accommodation of hours that are usually reduced or work from home), or moderately or severely (bedridden) (27). During the course of the illness patients commonly have good (remission) and bad (relapse) days with bad days being called crash days (28).

Patients who do recover often need more rest than their contemporaries. Some patients may slowly get worse.

- Risk factors for severity (29–32) of the illness are:
  - The severity of the illness at the time of onset
  - The standard of early management of the illness (e.g. late diagnosis or overexertion in the early stages of the illness are likely to lead to deterioration)
  - Having a mother with the illness
  - Comorbid diagnosis of fibromyalgia

Death certificates, in patients with ME/CFS, are usually documented as the patient’s death being caused by another co-existing illness since the cause of death on the death certificate is not listed as ME/CFS. Therefore, the mortality rate is difficult to determine from reviewing
death certificates of patients with ME/CFS. Preliminary data from one study found suicide, heart disease and cancer to be the leading causes of death in patients with ME/CFS and the mean ages of death from these causes were well below national averages. Another study found that all-cause mortality rates of individuals with ME/CFS were not significantly different from standardized mortality rates (33, 34).

Children

The long term prognosis in children is generally better than in adults even in those with severe disease. Even those who report being in remission do not perform as well as controls. Children with ME/CFS may have been ill for such a long time that they do not remember what it was like to be well and normal (35–38).

Economic costs of ME/CFS

ME/CFS is a severely debilitating chronic disease. As a result there is a tremendous burden for patients and their caregivers, as well as the health care system. Unemployment rates among those with the disorder ranged from 35% to 69%. One study found that as a result of ME/CFS, individual income losses of approximately $20,000 annually occurred in households (39, 40).

There is a huge economic cost for the individual, their family and for society. The annual direct medical costs per ME/CFS patients ranges from $2342 in a community-based sample (previously undiagnosed) to $8675 in a tertiary sample (already diagnosed).

The Canadian Community Health Survey of 2005 and 2010 documented that patients with ME/CFS are significantly impaired compared with Canadians with other chronic conditions such as cancer and heart disease. Patients with ME/CFS reported high levels of permanent in ability to work, needing help with activities of daily living and high number of consultations with doctors (10+ per year). They reported high rates of unmet health care and home care needs and high levels of moderate or severe food insecurity. A sizeable proportion report income and productivity loss of $20,000 per patient, and many report an annual household income <$15,000 (18, 32, 41).

The direct and indirect economic costs of ME/CFS to society are estimated to be in the billions: somewhere between $18 and $24 billion annually in the US (41).

Why do doctors have difficulty making the diagnosis of ME/CFS in their patients?

- **Insufficient training:** Most medical schools do not teach about ME/CFS to their medical students. Medical textbooks are not up to date in this area of medicine. Doctors, both general practitioners and specialists, have not been taught about ME/CFS in a formal systematic fashion as was done in the past with emerging diseases such as HIV/AIDS. As a result of poor practitioner training about ME/CFS, it takes patients many years to get a diagnosis, but this problem can be solved with education. It is estimated that only 20% of the people suffering with ME/CFS have been actually diagnosed (42, 43).

- **Fatigue:** as a symptom comprises 25% of primary care physicians’ appointments (4, 44).

- **Multiple Clinical and Research Definitions** (2, 42).

How to make the diagnosis of ME/CFS using the Canadian consensus criteria

**Exclusion of treatable diseases**

The first step is to rule out all of the treatable active diseases that cause: fatigue, sleep disturbance, cognitive dysfunction and pain (see Table 1). If the symptoms of ME/CFS are the result of another treatable condition the diagnosis of ME/CFS should be deferred until the treatment is attempted. Sometimes it turns out that treatment of the other conditions e.g. sleep apnea causes a partial improvement but the symptom cluster and severity of ME/CFS remains and the diagnosis can still be made.

Laboratory tests and investigations used to rule out the treatable chronic diseases include the following (see Tables 2 and 3).

The purpose of testing is to rule out other conditions which may account for any of the symptoms of ME/CFS. Routine testing cannot rule in ME/CFS however, there are specialty tests available through research centres which can be very helpful.
### Table 1: Exclusion of treatable active disease with laboratory tests or investigations.

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td>Rheumatological diseases: Systemic Lupus, Rheumatoid Arthritis, Polymyalgia Rheumatica</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Infectious Diseases: HIV, Lyme Disease, TB, Chronic Hepatitis,</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Substance Abuse</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Neurologic Disorders: MS, Parkinson’s, Disease, Myasthenia Gravis, B12 deficiency</td>
</tr>
<tr>
<td>Hypothyroidism hyperthyroidism</td>
<td>Primary Psychiatric Disorders</td>
</tr>
</tbody>
</table>

### Table 2: Investigation of ME/CFS: routine laboratory testing.

- complete blood count and differential
- erythrocyte sedimentation rate and C-reactive protein
- iron studies: serum iron, iron-binding capacity, ferritin
- vitamin B12 and serum folate
- electrolytes: sodium, potassium, calcium, phosphate, magnesium
- fasting glucose
- liver function: bilirubin, alkaline phosphatase (ALP), gamma glutamyl transaminase (GGT), alanine transaminase (ALT), aspartate transaminase (AST) (probably GGT is a good single screening test)
- renal function: creatinine clearance, urea, glomerular filtration rate (eGFR), albumin/globulin ratio
- thyroid function: thyroid stimulating hormone (TSH), free thyroidine (T4), free thyroxine
- creatine phosphokinase (CPK)
- 25-hydroxy-cholcalciferol (Vitamin D)
- urinalysis
- infectious disease screen HIV, hepatitis, Lyme disease, Q fever, etc.
- Microbiology: stools, throat, urine, sputum, genital
- am and pm cortisol
- renin/aldosterone ratio
- ACTH
- prolactin
- testosterone
- rheumatoid factor
- serum amylase
- urine drug screen for substance abuse
- MRI if multiple sclerosis suspected
- tilt table test for autonomic function — if available

### Table 3: Investigation of ME/CFS: additional tests to be considered depending on symptoms.

- Cardiac: chest x-ray, electrocardiogram (EKG/ECG), tilt table test for autonomic function
- Endocrine/Metabolic: short ACTH challenge test or cortisol stimulation test, parathyroid hormone, estradiol, follicle-stimulating hormone,
- Gastrointestinal: endoscopy: gastroscopy, colonoscopy; gastric emptying study, gliadin and endomyosal antibodies
- Infectious Diseases: screen for HIV, hepatitis, Lyme disease, Q fever and microbiology of stools, throat, urine, sputum, genital as appropriate
- Immunology/Autoimmunity: antinuclear antibodies, total and subclass immunoglobulins, functional antibodies and lymphocyte subsets
- Neurological: MRI if multiple sclerosis suspected
- Pulmonary: overnight polysomnogram and possibly multiple sleep latency test
- Urinary: cystoscopy

### Co-morbid conditions

A number of co-morbid (non-exclusionary) conditions may co-exist with ME/CFS. These conditions include: fibromyalgia, multiple chemical sensitivity, orthostatic intolerance, irritable bowel syndrome, irritable bladder syndrome, interstitial cystitis, sicca syndrome, temporomandibular joint syndrome, migraine headache, allergies, thyroiditis, Raynaud’s phenomenon and prolapsed mitral valve. These conditions should be investigated in their own right and treated appropriately (45).

### ME/CFS clinical diagnostic canadian consensus criteria (3)

In order to make the diagnosis of ME/CFS the patient must have the following criteria:
- Fatigue
- Post-Exertional Fatigue and Malaise
- Sleep Dysfunction
- Pain
- Cognitive Dysfunction
- At least one Symptom from Two of the Following Categories:
  - Automatic Nervous System Dysfunction
  - Neuroendocrine Dysfunction
  - Immune Dysfunction
Illness length is chronic:
- Adults 6 months
- Children 3 months

See Appendix 2 for the CCC ME/CFS diagnostic criteria worksheet that can be used in your office. The pediatric definition worksheet is Appendix 3.

Fatigue

In ME/CFS the fatigue is “pathological” or abnormal, more intense and different from normal tiredness. It may combine cognitive and physical exhaustion, weakness, heaviness, general malaise, lightheadedness and sleepiness. It can also include the symptom “wired fatigue” in which adrenaline is pumping in the presence of severe fatigue. It is of new onset, not explained by another diagnosis, persistent, has both physical and mental components. The patient’s activity level is reduced by 50% or more. There are ranges of fatigue that patients describe, most often from severe to completely bedridden. The attached validated Functional Capacity Scale in Appendix 1 assists you and your patient to communicate about fatigue and other symptom severity.

The vitality (VT) subscale of the Medical Outcomes Study (MOS)-Short Form-36 (SF-36) questionnaire is used to assess function including mental and physical function (30, 32). The SF-36 includes four questions concerning energy; being full of life/pep, feeling worn out, or feeling tired. The higher scores indicate greater vitality (46). VT scores are consistently much lower in ME/CFS patients with and without comorbidities than in healthy controls and patients with other chronic illnesses. While Jason and Brown demonstrated that the VT scores of ME/CFS patients ranged from 15 to 25 depending on subtyping strategies, other domains often are affected as well and were reliable reflections of fatigue in patients with ME/CFS (47). The RAND-36 is an alternative version of the SF-36 and is freely accessible with a complex scoring algorithm that is available online (13).

Post-exertional fatigue and malaise (PEM)

This symptom, PEM, is considered one of the distinguishing symptom of ME/CFS. It helps differentiate ME/CFS from other conditions in which patients feel better after exertion such as depression. PEM refers to severe physical or mental/cognitive post-exertional fatigue. This means that there are worsening of symptoms after minimal physical or mental/cognitive exertion. For example, the patient does not recover after normal activities of daily living such as: brushing their teeth, taking a shower or doing emails on the computer for 15 min. The mental fatigue or cognitive dysfunction – what patients describe as “brain fog” – includes: poor concentration, groping for words and poor short-term memory. The fatigue may also include malaise or flu-like feelings and/or pain and worsening of the patient’s other associated symptoms. There is a pathologically slow recovery period that lasts anywhere from 24 h to weeks. The patient may become bedridden during this “crash” period. A “crash” is an episode of immobilizing post-exertional physical and/or mental fatigue and malaise.

Sleep dysfunction

The patient’s sleep is unrefreshing. This may be due to difficulty falling asleep, multiple interruptions while trying to sleep or the sleep rhythm is chaotic and sometimes reversed. There may be daytime hypersomnia (excessive sleep) especially early in the illness and in younger patients. Sleep problems are chronic and the dysfunction worsens during a “crash” period. A subset of as many as 20% of patients have sleep apnea, upper airway resistance syndrome, restless leg syndrome or other treatable sleep disorders. An overnight sleep study may help to discern specific problems.

Pain

There is a significant degree of myalgia and joint pain that is often migratory. The pain is chronic and may range from mild to severe and often meets the criteria for Fibromyalgia. There may be significant headaches that are a new type, pattern or severity.

Neurological/cognitive dysfunction

Cognitive function worsens with fatigue. To qualify for this criteria, two or more of the following symptoms must be present: confusion, impaired concentration, poor attention, slowed processing of information, poor short-term memory, disorientation to place, difficulty with categorizing and impaired word retrieval. This cognitive dysfunction is often described by patients as “brain fog”. Neurocognitive impairment involving concentration and memory are cited as some of the most disruptive and functionally disabling symptoms of ME/CFS.
Ataxia, muscle weakness and fasciculations are common. Patients have difficulty with inaccurate body boundaries. This may result in patients having clumsiness and walking into doorjambs while walking through a doorway or losing their balance while walking down stairs. Difficulty with depth perception and focusing of their vision can make it difficult to walk, for example, on uneven/rough surfaces.

There may be overload phenomena, where patients with ME/CFS are hypersensitive to sensory stimulation including: bright lights, noise, odors and temperature extremes. This makes it difficult for patients to attend social functions and go into public places. Some patients with ME/CFS lose the ability to screen out and ignore extraneous stimuli similar to a deaf person at a party with a hearing aid that cannot screen out the background noise. The additional stimulation causes mental exhaustion and patients “crash” as a result. Patients can also become emotionally overloaded which can lead to anxiety.

At least one symptom from two of the following categories

**Autonomic dysfunction manifestations**

Autonomic dysfunction is an umbrella term for various conditions in which the autonomic nervous system (ANS) malfunctions.

The autonomic nervous system (ANS) provides the unconscious control by the brain of the basic bodily functions including: heart rate, body temperature, breathing rate, digestion, bladder and sexual function and other systems. The ANS is composed of two opposing subsystems: the sympathetic autonomic nervous system (SANS) and the parasympathetic autonomic nervous system (PANS). Most organs have nerves from both the sympathetic and parasympathetic systems.

The SANS usually stimulates organs: it increases heart rate and blood pressure when necessary. It causes the fight or flight reaction when in danger. The PANS usually dampens down bodily processes and is often referred to as the relaxation response. For example, it reduces heart rate and blood pressure. It provides rest and digest reactions, and stimulates urination.

**Symptoms of Autonomic Dysfunction:**
- Dizziness and fainting upon standing up (orthostatic hypotension, POTS)
- Inability to alter heart rate with exercise (exercise intolerance)
- Sweating abnormalities, which could alternately be too much sweat or insufficient sweat
- Digestion difficulties due to slow digestion. Resulting symptoms could include loss of appetite, bloating, diarrhea or constipation, and difficulty swallowing.
- Urinary problems. These can include difficulty starting urination, incontinence, and incomplete emptying of the bladder
- Sexual problems. In men, this could be difficulty with ejaculation and/or maintaining an erection. In women, this could be vaginal dryness and/or difficulty with orgasm
- Vision problems. This could be blurry vision, or the failure of the pupils to react quickly enough to changes in light.

Any or all of these symptoms may be present in patients with ME/CFS and range from mild to severe.

**Chronic Orthostatic Intolerance:** is the inability to sustain upright activity including: sitting, standing or walking. The most symptoms in ME/CFS include: overwhelming exhaustion, an urgency to lie down, feeling faint, mental confusion, malaise and the worsening of other symptoms. The symptoms are relieved when reclining. Patients, like Case CL, often develop these symptoms when standing waiting in line e.g. at the bank.

**Documentation of Orthostatic Intolerance:** can be done in the office setting by first setting a baseline blood pressure by measuring the BP after the patient lies supine for 5 min. Next the patient stands still for 10 min and does not move their legs. BP and heart rate are taken every 2 min for 10 min. Symptoms such as fatigue, lightheadedness, nausea, warmth, shortness of breath, headache, pain, reduced concentration/brain fog are recorded on a 0–10 scale when the patient is supine and then every few minutes when standing still. The patient must be monitored at all times due to the possibility of syncope and falling injuries. A positive test documents a drop in blood pressure, increase in heart rate, color or volume changes in the lower legs or the presence of symptoms of orthostatic intolerance.

**Subtypes of Chronic Orthostatic Intolerance:**
- **Neurally mediated hypotension (NMH)** is an abnormality in the regulation of blood pressure during upright posture. There is a drop in systolic BP of 20–25 mm Hg (compared to the BP measured when the person is lying flat) when standing still. Symptoms may include light-headedness, dizziness, pressure-like chest pain over the left chest, visual changes, weakness, slowed verbal response, pallor, an urgency to lie down and syncope.
- **Postural orthostatic tachycardia syndrome (POTS)** is present when the heart rate increases by 30 beats per
minute (bpm) for adults, or 40 bpm for adolescents, or if it reaches 120 bpm or higher over the first 10 min of standing. Symptoms may include: lightheadedness, dizziness, nausea, fatigue, tremor, irregular breathing, headaches, visual changes, sweating, and rarely syncope. POTS is an abnormality in the autonomic regulation of heart rate; the heart itself is usually normal. The increased heart rate may be accompanied by a fall in blood pressure, neurally mediated hypotension, while standing. The two conditions, POTS and NMH, often are found together and can cause chronic, daily, orthostatic symptoms.

c. Delayed postural hypotension happens when there is a delayed drop in blood pressure 10 min or more after the patient stands.

**Neuroendocrine manifestations**

Hypothalamic-pituitary-adrenal axis dysfunction is associated with dysfunction of the autonomic and immune system. This results in loss of thermostatic stability with marked intolerance to heat or cold. There may be marked diurnal fluctuation, sweating episodes and recurrent feeling of feverishness and cold extremities. Patients often experience worsening of their symptoms during changes of the weather (when storms are coming) and are often worse in the winter months when the weather systems change more frequently. There may be marked weight change with some patients experiencing a loss of appetite (anorexia) and others having an increased appetite.

Patients with ME/CFS have loss of adaptability and tolerance for stress. Things they could easily handle before their illness become stressful. Stress builds with physical, mental or emotional exertion beyond their available envelope of energy. Stress may cause symptom relapses and anxiety/panic attacks or may be part of the overload phenomenon. Recovery is slower than normal.

**Immune manifestations**

Some patients have symptoms from immune system activation and these include general malaise or flu-like feelings and feeling feverish. It is more prominent at the outset and may decrease over time. Flu-like symptoms often recur during times of post exertional malaise. Tender lymphadenopathy in the cervical axillary, inguinal or other areas may be present. Patients may have recurrent sore throats with non-exudative pharyngitis with bilateral crimson (red) crescents visible in the anterior pillars (palatoglossal arches) of the soft palate. The erythema may extend and include the uvula.

There may be new sensitivities to food, medications and/or chemicals. Much smaller doses of medications are needed in some patients. Some patients develop environmental sensitivities/multiple chemical sensitivity (ES/MCS) and react adversely to multiple unrelated chemicals in their environment with a range of symptoms. These reactions cause patients to withdraw from social and public events in an effort to avoid becoming unwell. This leads to social isolation.

**The illness persists for at least 6 months in adults**

It usually has a distinct onset, although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children and adolescents.

**Suggestive physical signs and symptoms**

The following signs are suggestive of ME/CFS but are not specific for it. Physical signs are more prominent at the beginning of the illness before patients have had a chance to learn how to accommodate their life to the illness and stay within their energy envelope. Patients look tired. They have drooped postures and slouch with rounded shoulders when sitting in a chair. Some patients need to lie down on the examination table while they wait to be seen. Others come in wheelchairs. The totally bedridden patients cannot come for office visits and need to be seen at their home. Some patients have periorbital shiners indicating allergies and puffy eyes indicating fatigue or edema. They may have a sore throat and examination of their throat shows crimson or red crescents. These are seen during a crash and viral vesicles can also sometimes be seen indicating viral reactivation. This may be accompanied by tender lymphadenopathy in the cervical, axillary and inguinal areas. Examination of the pupils may show oscillation of the pupils or diminished pupillary accommodation. The imbalance of the central sympathetic and parasympathetic nervous system in may be the underlying mechanism (48).

Measurement of the blood pressure may show a drop when changing from a lying to standing position when orthostatic hypotension is present. There may be other features of automatic dysfunction including an increase in pulse indicating Postural Orthostatic Tachycardia Syndrome (POTS). There may be abdominal bloating and tenderness as part of the irritable bowel symptoms. Examination of the central nervous system may show hypersensitivity to vibration sense, a positive Romberg test and a positive Tandem test. Cognitive dysfunction can be
validated by the use of standardized neurocognitive tests where available. These findings help to confirm the diagnosis of ME/CFS.

Some patients also have Fibromyalgia in addition to ME/CFS and have positive tender points on examination.

Etiology and pathophysiology of ME/CFS

A specific cause of ME/CFS has not been found and there is no clinically available diagnostic test. Prior to having ME/CFS, most patients were healthy, fully functional and had active social lives. 50%–80% of patients with ME/CFS started suddenly with a flu-like illness, from which the patient never recovered. ME/CFS is commonly found after an infection by a virus, bacteria or parasite.

The pathophysiological consequences of ME/CFS are multi-systemic. Below is a brief overview of the information available to date. See the 2015 IOM report for a more extensive summary (8).

Genetic predisposition

- Female gender is a predisposing factor in adults. In children there is no gender differential. Genealogy data from three generations of people entered in the Utah Population Data Base shows an increased relative risk among first degree relatives 2.70, second degree relatives 2.34, and third degree relatives 1.93 (49, 50).
- Twin studies show a higher concordance in monozygotic (55%) compared to dizygotic (19%) twins (51–54).
- A study of gene expression was done that identifies differential expression of 88 human genes in patients with ME/CFS. Clustering of quantitative PCR data from patients with ME/CFS reveals seven distinct subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes and severity (55).
- A study was done using single-nucleotide polymorphism (SNP) analysis to identify subtypes of ME/CFS with distinct clinical phenotypes. Twenty one SNPs were significantly associated with ME/CFS compared with depressed and normal groups. One hundred and forty eight SNP alleles had a significant association with one or more ME/CFS subtypes (56).

Immune system dysfunction

The pathological fatigue that is present in ME/CFS is multifactorial and based on several dysfunctional body systems that contribute to the patient’s overall feeling and level of fatigue. These dysfunctional body systems include the following: immune, cognitive, sleep, autonomic nervous system, mitochondrial dysfunction and biochemistry.

“Malaise” is a general body discomfort or weakness, often marking the onset of an of infection/flu-like illness or other disease. Fatigue and flu-like symptoms are linked to activation of the immune system and research scientists are in the process of unraveling these mechanisms in ME/CFS.

Immune system changes in ME/CFS

The immune system abnormalities in patients with ME/CFS are diverse and tend to wax and wane over the course of the illness and with the severity of the symptoms. Some abnormalities are present at the onset but decrease over time and are reinitiated during symptom flares or “crashes”. The immune findings are not specific to ME/CFS and are found in other diseases.

There is strong evidence of immune dysfunction in ME/CFS. Fatigue and flu-like symptoms may be linked to elevated levels of various cytokines, including interferons and interleukins. In addition lower cognitive function is significantly related to low NK cell function. The dysregulation of the RNase L pathway supports the hypothesis that viral infection may play a role in the pathogenesis of the illness. The IOM’s 2015 Report concluded that there was “sufficient evidence to support the finding of immune dysfunction in ME/CFS” (61, 62).

T helper cells (Th cells) trigger and direct immune cells as part of the body’s immune system. They can differentiate into two sub-types: Th1 and Th2 cells. Th1 cells
are involved in producing the body’s cellular immunity. Th2 cells are instrumental in humoral immunity (production of antibodies), mucosal immunity and the allergy response (63–65).

- **T-helper 2 shift in Cellular Immunity**: Dominance of humoral over cell-mediated immunity. Patients are more prone to the development of new allergies to medications, food and environmental chemicals and multiple chemical sensitivity (66, 67).

- **Low natural killer (NK) cell cytotoxicity**: NK cells are part of the innate immune system and provide surveillance against tumor cells and infections and host rejection of bone marrow transplants. Patients with ME/CFS have poorly functioning NK cells. The poor NK function correlates with the severity of illness and disturbed cognitive function in patients with ME/CFS (68–72). Low NK cytotoxicity is also found in rheumatoid arthritis, cancer, HIV, MS, SLE, smokers, major depressive disorder and sleep deprivation.

- **Activation of Cytokines**: There is imbalance in the regulation of immune function as illustrated by the study of cytokine networks by Broderick et al. These cytokine networks were significantly different in geometrical arrangement, more than expected by chance. The ME/CFS network is more hub-like in configuration compared to healthy controls (HC). The cytokine changes in ME/CFS are subtle and not shown by measuring individual cytokine levels. The distinction between the ME/CFS patients and healthy controls is displayed by the hub-like configuration showing differences in the relationships between the cytokines in patients with ME/CFS. “These observations are consistent with several processes active in latent viral infection and would not have been uncovered by assessing individual marker expression alone” (73). See Figure 1.

- CFS patients who experienced significant symptom flare post-exercise showed increased cytokines at the 8 h post-exercise (74).

- Daily fatigue severity was significantly correlated with inflammation in a study of adipokine leptin in women with CFS and not in the controls. A machine learning algorithm differentiated high from low fatigue days in the CFS group with 78.3% accuracy (75).

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**Figure 1**: Cytokine co-expression networks were constructed from the pair-wise mutual information (MI) patterns found within each subject group. Networks for HC and CFS had visibly different topologies (geometric arrangements). A weighted spring-electrical embedding structurally reveals the subject-subject (inset) and cytokine-cytokine associations based on measurements in 59 healthy control subjects (A) and 40 CFS patients (B). All edge weights are significant at p ≤ 0.01. Separation of subjects was consistent with their assignment to diagnostic groups supporting the use of within-group variation in the estimation of mutual information for cytokine-cytokine associations (73). Diagram used with permission.

Another case control study showed that early ME/CFS cases had a prominent activation of both pro- and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks. The newer ME/CFS cases had stronger cytokine variation compared to the patients who were ill longer. These findings suggest that the immunopathology of ME/CFS changes with time (62).

A positron emission tomography study measured a translocator protein expressed by activated microglia or astrocytes. This ligand was elevated in patients with ME/CFS demonstrating that neuroinflammation was present in widespread brain areas in CFS/ME patients versus healthy controls (76).

Figure 2: Pathways associated with secondary fatigue. Prolonged and or excessive stimulation of membrane bound Toll-like receptors (TLRs) results in the production of pro-inflammatory cytokines (PICs) and reactive oxygen and nitrogen species (O&NS) at sufficiently high concentrations to cause macromolecule damage leading to the production of redox-derived damage-associated molecular patterns (DAMPs). The presence of such DAMPs leads to chronic engagement of TLRs and a spiraling, self-amplifying pattern of increasing ROS/RNS and PICs in a TLR radical cycle. Increasing levels of ROS/RNS damage mitochondrial lipids and proteins leading to dissipation of the mitochondrial membrane potential and inhibition of the electron transport chain. This leads to compromised oxidative phosphorylation and the production of ROS making another major contribution to the inflammatory milieu and another element in the development of a vicious spiral of bioenergetics decline. Elevated levels of PICs in the periphery activate microglia and astrocytes in the brain leading to the production of elevated PICs and ROS/RNS causing mitochondrial and metabolic dysfunction (77). Diagram is used with permission.


### Dysregulation of antiviral defense pathway ribonuclease L/2–5A synthetase (RNase L)

- An abnormally low molecular weight (small size) 37 kilo Dalton (kDa) RNase L is produced
- the purpose of normal RNase L is to kill RNA in cells, both cellular and virus
- it is not turned off in the normal negative feedback loop
- RNase L continually destroys cell membranes including mitochondrial membranes causing leaks which lead to cellular damage and dysfunction (78).

### Antibodies in ME/CFS

- ME/CFS has been reported to be associated with autoimmune disorders: hypothyroidism and Sjogren’s syndrome.
- Antibodies found include: antinuclear antibodies, rheumatoid factor, and thyroid antibodies. The significance of this is unknown.
- Antibodies are also found to viruses: Epstein Barr, Cytomegalovirus, Human Herpes Virus 6, Parvovirus, etc. The viruses may become reactivated with elevated antibodies due to impaired immune surveillance (79).

### Post exertional malaise/fatigue (PEM)

**Post Exertional Malaise (PEM) Definition:** PEM is the exacerbation of a patient’s symptoms and deterioration in function after physical or cognitive effort that was easily tolerated premorbidly. The cardiopulmonary exercise test (CPET) is used to assess exercise capacity (maximal oxygen consumption or VO2 max) and provides objective and reproducible indices of functional capacity for cardiovascular and pulmonary disease.

“Energy for physical activities is produced through two physiological systems: 1) Anaerobic metabolism is
the predominant metabolic pathway during the first 90 s of exercise; 2) The aerobic/oxidative system is the primary source of energy during physical activities lasting longer than 90 s. Because most daily physical activities exceed 90 s, the aerobic system is typically utilized to produce the energy-releasing nucleotide adenosine triphosphate (ATP), at a steady rate in order to perform activities of daily living. In patients with ME/CFS, aerobic metabolism may be impaired. Thus, any physical exertion exceeding 90 s may utilize a dysfunctional aerobic system, which leads to increased reliance on anaerobic metabolism. This imbalance may be linked to the prolonged symptoms and functional deficits associated with PEM” (80).

Research studies showed that whereas patients with other conditions including severe cardiac and pulmonary disease are able to replicate their performance on a CPET on two consecutive days, patients with ME/CFS showed decreased functional capacity on the second testing day despite maximal effort both days. Second day decrements found in ME/CFS included: VO2max, VO2 at ventilatory threshold and maximal workload or workload at ventilatory threshold. VO2max measured during repeated CPETs was shown to be reliable with the test-retest showing a difference of <7%. The 2 day CPET testing provided objective evidence that corroborated ME/CFS patients’ subjective reports of impaired functionality with PEM, impaired cognitive function, and validated the severity and duration of their PEM.

It is hoped by the authors that this test will move from research studies into clinical use. Further testing is required to identify which patients with ME/CFS show this unique finding. If found to be diagnostic, the creation of a certified training program for personnel with standardized ME/CFS 2 day CPET protocol and with built in quality assurance measures (to standardize the CPET reliability of the 2 day testing) is needed. This test is not suitable for bedridden patients who would not be able to tolerate the testing. Perhaps in the future a modification of the test will be created (81–84).

The role of impaired aerobic metabolism in producing pathological fatigue, post-exertional malaise and a prolonged recovery time is still being evaluated. Several mechanisms may be involved and patients may have a variety of abnormalities.

**Mitochondrial/energy production abnormalities**

Several studies have shown evidence of impairment of oxidative phosphorylation including decreased ATP production by the mitochondria resulting in reduced aerobic energy production. This may be due to lack of essential substrates and interference in mitochondria function by inflammatory molecules (85–88).

The patients’ physical and mental exertions can exceed patients’ anaerobic threshold; but patients have faulty aerobic metabolism. As a result the anaerobic metabolic pathways are used by these patients. The anaerobic pathways are produce less energy and also cause the production of lactic acid and a disturbance of ATP/ADP metabolic cycling (86, 89, 90). Evidence for mitochondrial abnormalities includes: mitochondrial myopathy, impaired oxygen consumption during exercise; activation of anaerobic metabolic pathways in the early stages of exercise and raised brain ventricular lactate levels (91–95).

In other patients with ME/CFS low mitochondrial ATP levels may be present with normally functioning mitochondria. This may result from the brain’s autonomic dysfunction causing decreased circulating blood volume resulting in decreased transportation of oxygen to the cells and mitochondria in patients with ME/CFS and resulting fatigue (85).

**Cognitive dysfunction**

Cognitive dysfunction is present in the vast majority of patients with ME/CFS. Reported symptoms include slowed information processing, memory impairment, attention deficits, and impaired psychomotor function as measured by a range of neuropsychological tests (see Figure 3). This cognitive dysfunction can be severe enough to impair or prevent ability to work.

An electroencephalogram (EEG) study was done on 50 CFS patients and age matched controls. The EEG data and exact low-resolution electromagnetic tomography (eLORETA) results showed widespread cortical hypoactivation in CFS patients as demonstrated by increased delta and decreased beta2 frequency bands. These findings provided objective quantification of central nervous system dysregulation in CFS patients (99).

Quantitative electroencephalogram (QEEG) is another tool (in addition to neuropsychological tests) that shows abnormalities in patients with ME/CFS. The same research group did a pilot study using quantitative EEG (qEEG) and peak alpha frequency in CFS patients to look at the cognitive impairment known as “brain fog” in 50 CFS patients and 50 age matched healthy controls. The alpha frequency is associated with cognitive and memory performance. The results found decreased peak alpha frequency (PAF) in 58% of the cortex in CFS patients compared to...
controls. qEEG and PAF measurements of cognitive fog and fatigue may have prognostic value in evaluating CFS patients (100).

Sleep dysfunction

Unrefreshing sleep, or feeling just as tired when waking up as when going to bed, is among the most common symptoms reported by ME/CFS patients. Overnight sleep studies (polysomnographic studies) show that patients with ME/CFS have decreased sleep efficiency, decreased total sleep time and reduced time spent in deep restorative – delta wave sleep. Sleep can also be disturbed as a result of multiple arousals with alpha (awake EEG rhythm) wave intrusions during sleep on the overnight sleep study (101–104).

Stage shifts and dynamic stage transitions have been shown to discriminate between ME/CFS patients and healthy controls. The emergence of new, more sensitive techniques that examine the microstructure of sleep are showing promise for detecting differences in sleep between patients and healthy individuals. There is preliminary evidence that alterations in sleep stage transitions and sleep instability may be evident (105).

A recent polysomnographic study of CFS patients showed that they mainly differ in sleep fragmentation and slow wave sleep (SWS) durations. They found lower proportions of very slow oscillations during SWS in Primary Insomnia and CFS. They found normal or increased SWS durations but lower proportions of ultra slow power. Their findings suggest a possible quantitative compensation of altered homeostatic regulation in CFS (106).

The diagnosis of a primary sleep disorder does not rule out a diagnosis of ME/CFS as both can be present in the same patient. As many as 20% of patients with ME/CFS have a primary sleep disorder. However, even when optimally treated, they continue to have symptoms of ME/CFS. In these cases both diagnoses should be made.

Pain

The majority of patients with ME/CFS have pain of varying types and severity. See Figure 4.

Pain is often part of an ME/CFS patient’s symptom cluster that is triggered by physical and/or mental activity and part of the post-exertional malaise (PEM). The types of pain and severity of the pain vary. It could be disabling. The most common pain is described as muscle aches and pains, joint pain, and headaches. Less common are tender lymph nodes, sore throats, abdominal pain, eye and chest pain (96, 107–109).

Autonomic dysfunction

Autonomic dysfunction is thought to be centrally mediated as part of the brain dysfunction found in ME/CFS and can be seriously disabling (110–112).

Documented studies of autonomic dysfunction in ME/CFS have included:

- Tilt table testing – available in large centres to subtype orthostatic intolerance (113). The severity of orthostatic symptoms predicts the functional status of patients with ME/CFS (114) and may cause relapse of symptoms. Patients with low energy, ≤3/10 on the
Heart rate variability (available at specialist centers) is abnormal in patients with ME/CFS with increased sympathetic nervous system tone and decreased parasympathetic tone (114, 115).

- 24 h Holter monitoring may reveal benign cardiac rhythm disturbances and non-specific T wave changes, repetitive oscillating T-wave inversions and/or flat T-waves. On the EKG requisition, clinicians must ask the technician to document the presence of oscillating T-wave inversions or T-wave flattening in the report or they will be reported as non-specific T wave changes (116).

- Low blood volume has also been found in patients with ME/CFS by between 10% and 15% compared to controls (117, 118). This is likely related to the orthostatic symptoms.

- Ehlers-Danlos syndrome and joint hypermobility is higher in ME/CFS patients than in healthy controls and is associated with orthostatic intolerance (119).

Neuroendocrine dysregulation

One or more of the following neuroendocrine abnormalities has been found in studies of patients with ME/CFS:

- Reduced function of the HPA axis, which can affect adrenal, gonad, and thyroid function (93, 120).

- Raised levels of neuropeptide Y (released in the brain and sympathetic nervous system following stress), possibly linked to the dysfunction of the HPA axis. Neuropeptide Y levels in plasma have been correlated with symptom severity (121).

- Mild hypocortisolism and attenuated diurnal variation of cortisol (122).

- Blunted DHEA response to ACTH injection despite normal basal levels (123).

- Low IGF1 (somatomedin) levels and an exaggerated growth hormone response to pyridostigmine (124).

- Increased prolactin response to buspirone (125).

- A disturbance of fluid metabolism as evidenced by low baseline levels of arginine vasopressin (126).

- Relatively lower levels of aldosterone in patients compared with controls (127).

The presence of increased HR and reduced Heart Rate Variability in ME/CFS during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggest a state of sympathetic autonomic nervous system predominance possibly from defective serotonergic signaling in the brain and resulting neuroendocrine alterations.

Approach to treatment

This section draws heavily from the recommendations found in ME/CFS: A Primer for Clinical Practitioners 2014 (15, pages 17–27). This is Level V evidence based on expert clinician opinion. There is no specific treatment for ME/CFS to date. Therefore we recommend providing patient-centred, supportive, symptomatic care.

Goals of treatment

- Improvement of current symptoms, functioning and quality of life.

- Prevention of worsening symptoms.

- Help patients cope with the emotional impact and grieve the losses that have resulted from having a chronic, complex, debilitating illness.
– Prevention of the development of depression and potential suicide by managing the physical and emotional issues resulting from ME/CFS.
– Prevention of new environmentally-associated illnesses with worsening of the condition, such as multiple chemical sensitivity.

Treatment/management begins with validation of the patient’s experience and acknowledging that the patient’s illness is a real physical disease – ME/CFS. Having a diagnosis is the beginning of healing for many patients who have been told “it’s all in your head” for many years. It is estimated that only 20% of individuals with ME/CFS have been diagnosed and even fewer have access to expert management advice.

Management strategies
– Establish supportive therapeutic relationship with the patient
– Educate patient and family about the condition
– Collaborate with patient to develop an individualized treatment program
– Empower the patient to trust his/her own experiences and use his/her symptoms as early warning devices to avoid PEM relapse/crash
– Symptomatic treatment begins with helping patients cope with their most debilitating symptoms.

Easier office visits
To improve the efficiency of an office visit and clinical management, we suggest the following:
– Request the patient write down their medical history before the first visit. Patients often forget parts of their history during an office visit because of physical fatigue and cognitive dysfunction.
– Ask patients to bring a support person (family member or friend) with them at each visit to make notes of what medical advice occurred during the visit for the patient to review later. Offer to record sessions to serve as a memory aid.
– Give the patient your recommendations in writing at the end of the visit. They may not remember oral instructions.
– At each follow-up visit have patients write out on a form you provide the following headings for them to complete before their next visit:
– Improvements from the last visit. Patients may forget to tell you what has improved unless you ask. Celebrate their incremental progress with them. This encourages patients and empowers them to cope with their chronic illness.
– Top 3 most troublesome symptoms. Limit the number of symptoms dealt with at a visit in order to avoid overloading the patient and to deal with the reality of time constraints of an office visit.
– All medications and supplements with doses. Patients do not remember changes.
– Begin new medications at a low dose (1/4 the recommended dose) for a few days and increase slowly to a therapeutic level since patients have increased reactions/sensitivities to new medications.
– Schedule ongoing visits on a regular basis. Preferably, the patient will choose the interval and may alter it as required.
– If new symptoms not in their cluster of symptoms appear, these should be treated as a newly developing illness and investigated accordingly.
– Schedule an annual follow-up assessment to review symptoms and severity, a physical exam, a functional capacity evaluation, routine screening blood tests, and a review of the patient’s management/treatment plan.
– Ensure that all new symptoms are not blamed on ME/CFS. When new symptoms arise that are not in the patient’s symptom constellation they should be investigated.
– Complete the private or public insurance forms to ensure that patients have access to food, shelter and transportation. Understand the meanings of the terms “disabled” in these contracts and document the patient’s degree of disability: partial or total. The long term prognosis is dependent on the severity of ME/CFS and the length of time that the patient has had ME/CFS (30–32).

Management of symptoms
Symptomatic treatment begins with helping patients cope with their most debilitating symptoms. Assist each patient to make a symptom list and then prioritize which are most problematic. Start at the top of the list and work down. As patients experience benefits they will become more confident and motivated towards self-management. Not all patients will improve, but there is potential for modest to a great degree of improvement for most individuals.
Fatigue and Post-exertional Malaise

Patients with ME/CFS experience pathological fatigue and post-exertional malaise (PEM). When they “overexert” all their symptoms worsen. The sleep disturbance during a crash is usually described as “tired but wired”. The body is physically exhausted, but the brain cannot turn off to fall asleep due to increased sympathetic nervous system stimulation (128).

Energy conservation exercise

Many patients were athletic before they became ill and felt good when they exercised. When patients with ME/CFS push themselves to exercise they will develop PEM if they go beyond their body’s available energy envelope. PEM has been documented in patients with ME/CFS on 2-day bicycle ergometry testing (129). Their faulty muscle aerobic metabolism does not produce the energy needed for aerobic exercise. Therefore, patients should stop if symptoms become worse. Increases in exercise are advised only when patients feel they are coping with current activity levels. In ME/CFS any exercise program must be tailored to the individual patient. In the more severely ill patients doing activities of daily living, such as taking a shower, is their exercise (130, 131).

Graded exercise therapy

The Oxford criteria for chronic fatigue syndrome were used to assess graded exercise therapy (GET) and also for the Cochrane analysis (132). The Oxford CFS criteria do not exclude patients with psychiatric disorders: depressive illness, anxiety disorders and hyper-ventilation syndrome. It is known that depressed patients improve with activity. ME/CFS is a physical illness with post-exertional malaise. As a result of including patients with depression in the Oxford studies, the studies erroneously concluded that CFS patients improve with GET. Patients with ME/CFS have documented PEM on 2 day bicycle ergometry testing. Therefore GET is contraindicated and can be harmful for patients with ME/CFS using the CCC criteria (82, 84–86, 129, 133, 134).

Pacing

Pacing is physical energy conservation. Learning to pace by taking breaks or rests in between activities helps to prevent relapsing and spending the next few days to a week in bed recuperating. In this context “rest” means lying down meditating or sleeping in order to minimize postural hypotension symptoms. Pacing is described as staying within the “energy envelope”; staying as active as possible but avoiding overexertion and crashing. Pacing is the most effective tool patients have to help them manage their symptoms. Research shows that those who stay within their energy envelope have significant improvements in physical functioning and fatigue severity compared to those who exceed their envelope (133) (see Figure 5).

It helps patients learn how to pace to reframe how to approach getting their daily activities done. When they were well and wanted to do something e.g. go shopping, it was simple. They grabbed their wallet and drove to the mall and shopped for as long as they liked because they had normal energy. Now their energy is limited and it is

Figure 5: Diagram used with permission (133).
much more limited than when they were well. In order to improve they need to discover their new physical boundary of energy to avoid relapsing. The easiest way to do this is for them to be aware of their body’s needs by taking a moment before they go shopping and check in with their body. Patients can close their eyes and say, “Body, in this moment do I have the energy to go shopping?” If their body says “Yes” then they need to figure out their body’s limits in the present time because this will fluctuate with good and bad days. Patients can close their eyes and ask themselves, “For how many minutes can I go shopping?” Patients can then scroll through the ten times table until they get a number that is comfortable for their body – for example 30 min. In order to stay within the energy envelope or physical boundary patients need an external alarm because as part of their cognitive dysfunction many have lost their sense of time passing or linear time sense. Ask them to set the alarm on their cell phone to let them know when to stop. This takes practice and self discipline. It allows patients to begin to accomplish more because they lose less time in bed recovering from a relapse/crash (113, 135). Pacing is not popular with patients. They think they will never get anything done with this approach. Explain that accomplishing a small number of tasks consistently is more productive than accomplishing a lot 1 day and then taking many days to recover and accomplishing nothing. This is a huge paradigm shift: thinking of themselves and putting their needs and their bodies’ needs first.

Using an activity log and recording their daily routines as they are doing them helps give patients knowledge as to what is working for them. See Activity Log in Appendix 4 (136).

This is an example of pacing when shopping. Break shopping into multiple steps: 1) rest at home before driving the car to the store, 2) drive to the store, 3) rest, lying down in the car after driving to the store, 4) shop for 30 min in the store, 5) rest lying down in the car before going home, 6) drive home and 7) rest at home.

Pacing can also be applied to cooking and housework.

**Functional capacity scale (FCS) ratings from 0 to 10**

Fatigue is an imprecise term which is difficult to operationalize. We wrote the Functional Capacity Scale to better understand what patients are able to do on a given day. Before using this scale, when patients said they “felt better”, they were sent back to work. Much to our dismay 3 months later they had crashed and were much worse than before. How had this happened? The functional capacity scale operationalizes what patients can do physically and mentally on a scale of 0–10 in a given day. It can distinguish between patients’ good and bad days and shows their progress over time. See Appendix 1 for the Functional Capacity Scale.

At the first office visit we introduce the FCS (with a range of 0–10) to the patient and pick out a higher number on the scale for a good day and a lower number on the scale for a bad day. We also determine how many days a week are good or bad days. Normal energy is 9–10/10. The level 0 represents a patient in the ICU requiring total bed care.

- **Severely ill patients**: functional capacity energy rating 0–3. At this severely low level of energy the scale ranges from describing patients who are bedridden – 0/10 to patients who can do independent self-care (washing at the sink) for a few minutes – 3/10. At this level “exercise” consists of exercises to maintain muscle and mobility and include: range of motion exercises, stretching and increasing mobility as tolerated. Patients are bed or house bound. These activities may be done passively with a few repetitions to start for the patient by their caregiver with rest periods before and after as tolerated by the patient and under the guidance of a professional who understands ME/CFS so that symptoms are not triggered by the activity.

- **Less severely ill patients**: functional capacity rating 4–5. At this low level of energy the scale ranges from describing patients who are able to do light housework or walk for a few minutes to patients who can walk 10–20 min a day. These activities include range of motion exercises and stretching to begin with and can be done by the patient in intervals of 90 s or less to keep the patient using mainly their anaerobic metabolism. Patients need to rest between intervals and avoid PEM and further exercise until completely recovered. If orthostatic hypotension is present these may be done lying down as opposed to sitting or standing to avoid triggering symptoms. As stamina improves the addition of leisurely walking can be added, initially inside the house from room to room or walking halls in the apartment. Resistance training using resistance bands or light (1 to 2) pound weights can be added. Again this needs to be done in intervals of time to keep the metabolism working mainly anaerobically. This is the opposite of the aerobic workouts that patients did in the past when they pushed to the maximum and the goal was to get the heart pumping and beating faster.

- **Moderately ill patients**: functional capacity rating 6–8. At this moderately low level of energy the scale
ranges from describing patients who are able to walk 20–30 min a day to being able to work out vigorously three times a week. Exercise can begin with leisurely walking or riding an exercise bike. Riding a bicycle on the street is not recommended because of patients’ difficulty with balance. Tai Chi and supportive yoga may also be helpful. Again patients must be mindful of staying within their energy envelope to avoid crashing. A patient has to be functioning consistently at 6/10 to consider part time, flexible work and 7/10 or above for full time work. Ability to work outside the home also depends on responsibilities inside the home.

Medications for fatigue
Due to limited effectiveness, medications for fatigue are not generally recommended. Very rarely they may be used to help patients manage at exceptional and potentially exhausting events in the patient’s life (e.g. attending a funeral or wedding). Patients should avoid using medication to do more than their body can handle – causing PEM symptoms. Examples of stimulants that can be used on an occasional basis include: caffeine, Dexamphetamine, Methylphenidate and Modafinil.

Sleep
Sleep hygiene
Patients with non-restorative sleep wake up feeling unrefreshed and as tired as they were before they went to bed. The following sleep hygiene suggestions may be helpful to patients (137).
- Establish a nighttime routine so patients go to sleep when their body is winding down. Going to bed for example at 10:00 p.m. and waking 7–10 h later (depending on the body’s needs) helps maintain healthy circadian rhythms.
- Wake at the same time every day to retrain the circadian rhythm.
- Pace activities during the day to avoid aggravating symptoms that interfere with sleep. If patients do not pace during the daytime they will get a second wind, or an adrenaline rush. Patients describe this as going to bed “tired and wired”. The following day patients are “crashed” and wake up exhausted.
- Avoid watching TV or using computer devices before bed. These images are stimulating and include blue light which turns off melatonin production. Blue light blocking glasses can help.
- Meditate, relax and wind down before bedtime for 20 min to an hour. This helps to increase the parasympathetic tone, increase relaxation, reduce active thinking by the brain and reduce pain levels by increasing the body’s endorphins.
- Darken the bedroom with blackout curtains or use a sleep mask at night. This helps the brain to produce the melatonin needed for sleep. In the morning exposure with bright natural light or a seasonal affective disorder (SAD) light is helpful (138).
- Use earplugs or soundproofing for noise, or sleep in a different bedroom from (a snoring) partner or ram-bunctious pet.
- Make sure the bed is comfortable so that it cushions the body and prevents the worsening of pain. Most people prefer a moderate to firm support with a pillow top or eggshell foam on top.
- If unable to sleep use meditation tapes to help the brain to turn off and relax the body or try light reading.
- Take calcium, magnesium, remedies, and medications if needed. Drink non-caffeinated herbal teas e.g. chamomile or peppermint to help the body to relax.
- Pace with rests as required throughout the day but avoid napping past 3 pm because it interferes with nighttime sleep.
- Reduce or eliminate caffeine-containing beverages and food.

Medications (see Table 4)
The medications listed below are a mixture of over the counter and prescription drugs. A list like this emphasizes that one size does not fit all. The list is not all inclusive. Remember that ME/CFS is a chronic, usually lifelong condition. Most patients will require some type of sleep aid ongoing, not just for 2 weeks as the drug monographs state. Sometimes rotating medications is helpful to decrease the development of tolerance. These medications can be started at 1/4 of the normal dose until the effective dose or

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimenhydrinate</td>
<td>25–50 mg</td>
</tr>
<tr>
<td>Melatonin</td>
<td>1–3 mg</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>500 mg–3 g</td>
</tr>
<tr>
<td>Zopiclone/Imovane</td>
<td>5–15 mg</td>
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<tr>
<td>Clonazepam</td>
<td>0.5–1 mg</td>
</tr>
<tr>
<td>Doxepin/Sinequan</td>
<td>2–200 mg</td>
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<tr>
<td>Amitriptyline, Nortriptyline</td>
<td>5–50 mg</td>
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<tr>
<td>Clonidine/Pramipexole</td>
<td>0.125–0.25 mg</td>
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<tr>
<td>Trazodone</td>
<td>12.5–150 mg</td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>5–10 mg</td>
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<tr>
<td>Mirtazapine</td>
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<td>Zolpidem</td>
<td>2.5–10 mg</td>
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<td>Gabapentin</td>
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<td>Pregabalin</td>
<td>50–450 mg</td>
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<tr>
<td>Quetiapine</td>
<td>12.5–100 mg</td>
</tr>
</tbody>
</table>

Table 4: List of medications helpful for sleep.
maximum recommended dose is reached. These medications must be individualized and based on the best match between the patient’s symptoms and the medication available. Sleep medications need to be reviewed with the patient’s entire group of other medications and supplements to ensure there are no contraindications. To help with this, it is best if the patient uses one pharmacy.

Pain

Pain in ME/CFS is often migratory in muscles and joints. It may be mild, moderate or severe. New headaches occur and are often migraines. Fibromyalgia is a co-morbid condition with ME/CFS and needs to be considered if pain is present.

Pain needs to be treated and treatment varies with the severity of the pain and what modalities most help the individual patient. Useful modalities for some patients include: meditation/relaxation response, warm baths, massage, stretches, acupuncture, hydrotherapy, chiropractic, yoga, Tai Chi, TENS (transcutaneous electrical nerve stimulation), physiotherapy and nerve blocks (help migraines).

The pain medications range from over the counter anti-inflammatories and pain medications, muscle relaxants, to prescribed central desensitizers and narcotic analgesics in extreme cases (see Table 5).

- Start with 1/4 doses in more medication-sensitive patients.
- Establish clear goals with the patient for a trial, as well as start and assessment times. Stop the medication if not effective.
- Use the functional capacity scale and activity logs and pain scales to measure the effectiveness of medication.

Cognitive dysfunction

Patients have poor concentration, difficulty focusing and reading, grope for words, get lost in familiar places, have lost their sense of time and have difficulty with short term memory. They think and process more slowly and thinking takes more effort. They need the same treatment as brain injured patients to cope with cognitive dysfunction.

What helps patients to stay organized and in control?
- Write it down. Patients need a place to write down what they need to remember either on their cell phone or in a “memory book”. They need written instructions for any treatments you prescribe. It helps if the same person can come with them to appointments as their designated “memory person”.
- Promote habits to simply their life e.g. key hook to hang their keys on each time they use the car.
- Pace activities that use mental energy e.g. time spent doing emails on the computer. Mental tasks need to be treated like physical activities and have a limit set before started. If they do not stop in time, they will crash/have symptom relapse just as they would from physical activities.

There are no specific medications that have been helpful for cognitive dysfunction to date. Stimulants have not been effective.

Managing depression, anxiety and distress

Education, support and coping skills

To differentiate between symptoms of depression and anxiety secondary to ME/CFS and psychiatric disorders, ask the patient what they will do the next time they have a “good day”. A patient with ME/CFS will have a long list of ideas whereas a patient with major depressive disorder will say they can not think of anything they enjoy any more. Patients with an anxiety disorder will have a list of reasons why they won’t be able to do or enjoy the activities.
Whereas patients with psychiatric disorders generally feel better after exertion, patients with ME/CFS feel worse after exertion or exercise. Patients with ME/CFS are human and get frustrated and angry when they crash and on bad energy days, but it improves on their good energy days. Patients with ME/CFS need to grieve the loss of their lives: their health, jobs, finances, friends, and sometimes family. The hospital anxiety and depression scale (HADS) and the beck anxiety or depression inventories are useful to evaluate anxiety and depression in patients with physical health conditions as they do not assume that all physical symptoms are caused by the psychiatric disorder (139, 140).

Patients with major depressive disorder (MDD) have difficulty initiating activities. They usually have a very low mood, may have suicidal thoughts, loss of interest or desire to do things, lack enjoyment, have a sense of worthlessness or guilt, and feel better after exercise.

In comparison patients with ME/CFS are highly motivated. They want to and try accomplish things that they have not been able to do as a result of their low energy on their bad days.

Patients find hope by getting a diagnosis, a medical plan and by getting their medical, home care and social needs met. If depression does occur with ME/CFS it may develop into MDD and needs to be immediately treated. If suicidal thoughts are present, referral plus hospitalization for the patient’s safety may be necessary.

Anxiety about health and life circumstances can be secondary to ME/CFS. Generalized anxiety disorder (GAD) is characterized by excessive worry about a wide variety of things; whereas people with ME/CFS can distract themselves from anxiety and still enjoy some things in life. People with GAD are anxious all the time.

Helpful interventions
- Start an educational and support group for the mobile patients and families in your practice so that they can improve their coping skills. The group setting with others who “get it” can be immensely reassuring, as well as decreasing isolation (141, 142).
- Explore meaningful fun low level activities patients can do by themselves or with family to find their joy in life (143, 144).
- Patients need time and safety to grieve their losses and to vent their frustration at being ill and losing their jobs and their life. If you cannot offer this support refer to a mental health professional.
- Patients benefit from a good ME/CFS support group where they learn about their illness and are surrounded with supportive people. Avoid groups where the biggest event is “who is the sickest”, as they discourage patients and they feel worse after attending.

Psychotropic medications
Patients who develop a psychiatric disorder should be treated with medications as any other patients with anxiety, depression, obsessive compulsive disorder, etc. Due to their sensitivity, medications should be started at a low dose and increased slowly as tolerated over weeks.

Cognitive behavioral therapy (CBT)
CBT is a counseling strategy that helps patients evaluate the accuracy of their thoughts and assumptions. CBT coping skills reduce worry, sadness and anger which consequently reduces the emotional drain of negative emotions.

Historically in the literature CBT was inappropriately touted as a cure for patients with ME/CFS if they changed their “belief system”. ME/CFS is a physical illness and not a psychological illness, therefore CBT cannot cure ME/CFS. What CBT can do is to help patients cope with being chronically ill and manage their emotional reactions better so that they do not waste valuable energy on worrying or feeling guilty about things that they cannot control. We like to think of CBT as “emotional energy conservation”.

Management of Orthostatic Intolerance (OI) and Cardiovascular Symptoms
Many patients have symptoms suggestive of OI such as feeling light-headed, dizzy, faint or having heart palpitations. Changing positions slowly from lying to sitting and then standing is essential to manage symptoms. Pumping their calves to push the blood back to their core is helpful. Prolonged standing is to be avoided. Pressure stockings (knee highs or full pantyhose) and elevating the legs while sitting helps to manage OI.

It often helps to increase patients’ blood volume for fewer OI symptoms. This can be done by increasing salt and electrolyte intake with fluids. Start with a pinch of salt and increase to a total of 1 tsp of salt to be taken throughout the day. Increasing salty foods is also helpful. This may reduce symptoms of postural hypotension and tachycardia.

Fludrocortisone 0.1–0.2 mg/day or Midodrine 10 mg up to four times daily help some patients. Tachycardia or palpitations from postural hypotension can be treated with low dose beta-blockers, such as Atenolol 25–50 mg or Propranolol 10–20 mg.
Management of gastrointestinal and genitourinary problems

Diet
A well balanced diet is essential for healing. Providing food to eat is a problem for many patients due to lack of money to buy food, lack of energy to shop for and prepare food, and finally lack of energy to chew and swallow food. Income assistance may be needed to buy the food. Home care services may be needed to cook the food. If patients cannot chew they may benefit from mashed meals in a shake form. Bedbound patients may need to be fed. Ideally avoid refined sugars, caffeine, alcohol and deep fried foods. To keep energy maximal, eating small meals and snacks helps many patients. To facilitate this, some patients find it handy to have a small refrigerator in their room so that they can have easy access to pre-cooked prepared food and avoid navigating the stairs to the kitchen.

Patients may have GI symptoms that include irritable bowel, reflux, nausea, and pain. Slow gastric emptying and poor bowel peristalsis can be present. Evidence based treatment of IBS with the Low FODMAP (Fermentable Oligo-Di-Mono-saccharides and Polyols) diet helps some patients. Some patients have small bowel dysbiosis/leaky gut and have developed new food sensitivities. In these patients, reducing and avoiding sensitive foods which worsen symptoms is helpful (145). Ideally, patients could rotate their foods every 4–5 days so they avoid developing more food sensitivities.

If intestinal dysbiosis is present patients may improve their symptoms taking L-glutamine or butyrate (145) or by using evidence based probiotics.

Specific nutrients

- **Vitamins**: Because patients with ME/CFS eat often so poorly they may benefit from a multivitamin/multimineral. Use of supplements should ideally be supervised by a knowledgeable person.

- **Vitamin D3** Levels should be checked as a baseline for this patient population as they are at risk for osteoporosis due to lack of weight bearing exercise and poor absorption (146).

- **Vitamin B12 and B-Complex** Patients with ME/CFS have been found to have low levels of B12 in their cerebrospinal fluid (147). A trial of B12, methylcobalamin, 1000 μg IM weekly for 6 weeks may be helpful. Fatigue symptoms and cognitive symptoms may improve. There have been no reports of side effects, despite the high blood levels.

- **Essential Fatty Acids** Some patients symptoms improve on supplementation with eicosapentaenoic acid, an essential fatty acid that is found in omega-3 fish oil (148, 149). Also vitamin and mineral cofactors including vitamin C, biotin, niacin, folic acid, selenium, zinc, and magnesium, may be supportive in conjunction with essential fatty acids supplementation.

- **Zinc** deficiency may contribute to decreased function of natural killer cells and cell-mediated immune dysfunction (150). Zinc supplements must be balanced with copper in the correct ratio.

- **CoQ10** Plasma CoQ10 is significantly lower in a substantial number of ME/CFS patients compared to healthy controls. Some patients may show improvement with CoQ10 100–400 mg daily. If effective, to maintain improvement CoQ10 needs to be taken long term (151, 152).

Urinary symptoms

Patients with ME/CFS may have symptoms of frequency, dysuria and bladder pain. Low grade bacterial infection should be ruled out. Interstitial cystitis, detrusor instability, urethral syndrome and endometriosis also may occur and may require specialist referral.

Managing Infections and immunological factors

In patients in whom viral, bacterial or parasitic infections have been found (e.g. herpes viruses, enteroviruses, Borrelia burgdorferi, mycoplasma, Giardia lamblia) long-term antibiotics, anti-parasitic or antiviral therapy may be helpful (153).

Isoprinosine (Imunovir) is an immune modulator that may be helpful in selected patients. Specialist advice may be in order if clinical experience is limited.

Based on two randomized trials, the experimental drug Rintatolimod (Ampligen®) has been shown to benefit patients in the first three years of the illness who are more disabled (154, 155). The drug was not FDA approved but is available for fees to recover costs.

Allergies and environmental sensitivities/multiple chemical sensitivity

Allergies
Many patients with ME/CFS suffer from allergies to natural inhalants (such as grasses, trees, pollens, etc.) that may
worsen symptoms during relapse. Treatment with nasal sprays, inhalers or topical skin applications may be adequate, but many will need to use an oral antihistamine. A non-sedating antihistamine (24 h Claritin/Loratadine or Reactine/Cetirizine HCl) can be used in the daytime and a sedating antihistamine (Benadryl/Diphenhydramine) at night.

Environmental sensitivities/multiple chemical sensitivity (MCS)
Rather than an allergic response, patients become sensitive to low levels of specific odors or chemicals, or electromagnetic radiation. On exposure to their sensitizing substances, an exacerbation of symptoms is provoked. For example, perfumes, cigarette smoke, cleaning products, paint, glue and many other odors, as well as excess use of cell phones, may trigger symptoms. These patients may need advice on how to avoid these environmental factors.

Patients with multiple food sensitivities who avoid sensitive foods may need dietary counseling to rotate their foods to avoid malnutrition (156, 157).

Alternative and complementary approaches
The use of acupuncture, massage therapy, meditation and chiropractic treatments have been helpful in some patients. The research of CAM therapies and methods is not well documented in the literature. Patients often try costly therapies hoping for a cure. More detailed information may be found in the reviews (158, 159).

Summary: myalgic encephalomyelitis/chronic fatigue syndrome: what’s in a name?
The above collection of data has shown that ME/CFS is a complex condition that affects every organ system in the body. There is evidence of inflammation at the cellular and biochemical levels: in the muscles, brain and spinal cord in patients with ME/CFS. The name for this illness has had a huge impact on the medical, scientific and patient communities – how it is viewed and how patients are treated by the medical community (160). We are now at the descriptive stage of ME/CFS, delineating symptoms and symptom clusters and reporting on pathological cellular and biochemical observations. Myalgic means muscle pain. Encephalomyelitis means inflammation of the brain and spinal cord. The term myalgic encephalomyelitis is recognizable as a descriptive term for this condition with its host of symptoms. It is listed in the World Health Organization’s classification system of diagnoses under neurology. Research is not yet clear enough about which symptoms are characteristic for ME and which for CFS. For now, let us continue to use ME/CFS in the CCC. It is well recognized in the literature and is currently able to describe this illness with its constellation of symptoms and exclude other illnesses.

When we are able to find a definitive cause that will satisfy the strictest definition of the word “disease” and with consultation from all interested groups; clinicians, scientists and patients; let us convene for a new name then.

The IOM recommended reconvening in 5 years after testing the new SEID criteria in clinical trials. Jason’s research group did test the SEID definition against the CCC definition in different patient data bases and found, that as a result of including the psychiatric disorders and other comorbid conditions, the SEID definition’s specificity was worse and as a result the prevalence rate of ME/CFS was higher (96, 161). It would be prudent to have feedback given now from all concerned groups to the Secretary of US Department of Health and Human Services to ensure that money and effort is not wasted in research and clinical trials that will not be meaningful.

The Canadian Consensus Criteria Definition for ME/CFS has acceptable sensitivity and specificity. It includes essential exclusion criteria and inclusion criteria. We recommend using this definition for your patients.

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Supplemental Material: The online version of this article (DOI: 10.1515/reveh-2015-0026) offers supplementary material, available to authorized users.