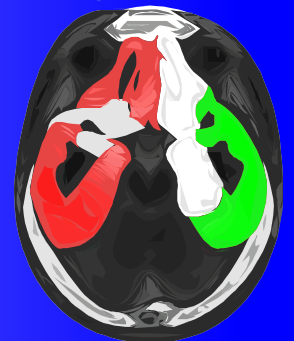
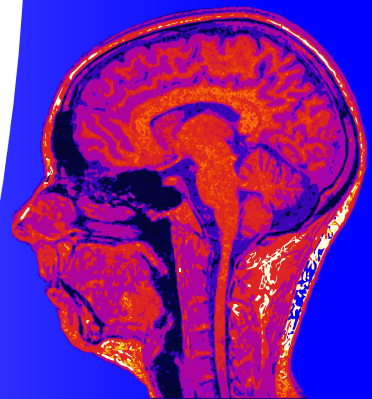
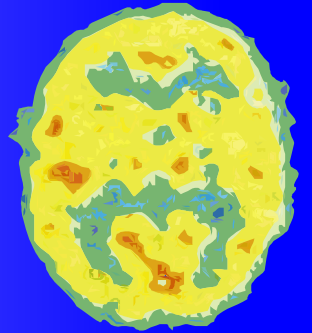
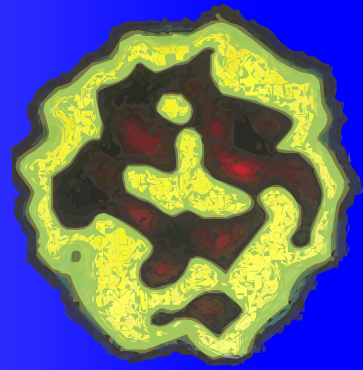


Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome:

A Clinical Case Definition and Guidelines for Medical Practitioners

An Overview of the Canadian Consensus Document

Bruce M. Carruthers
Marjorie I. van de Sande



The Canadian Consensus Document on ME/CFS

Our comparison study examined differences between patients meeting the Canadian clinical and the Fukuda et al. criteria for ME/CFS, with people who had chronically fatiguing illness explained by a psychiatric condition. The Canadian Clinical Criteria selected patients with more physical functional impairment, more fatigue/weakness, neurocognitive and neurological symptoms and had more variables that significantly differentiated them from the psychiatric comparison group than did the Fukuda et al. criteria. The findings do suggest that the Canadian criteria point to the potential utility in designating post-exertional malaise and fatigue, sleep dysfunction, pain, clinical neurocognitive, and clinical autonomic/neuroimmunoendocrine symptoms as major criteria.

The selection of diagnostic signs and symptoms has major implications for which individuals are diagnosed with ME/CFS and how seriously the illness is viewed by health care providers, disability insurers, rehabilitation planners, and patients and their families and friends. I hope the results of this comparison study will encourage more physicians to USE THE CANADIAN CLINICAL CRITERIA.

Leonard A. Jason, Ph D

Director: Center for Community Research, DePaul University, Chicago IL
Board of Directors: American Association for Chronic Fatigue Syndrome

The Canadian Clinical Case Definition has brilliantly rewritten the guidelines to capture, at last, what ME/CFS is really all about. It is not that patients are fatigued. Healthy people get fatigued. Rather the definition specifically selects patients who worsen with exercise. This takes the emphasis away from the subjective sensation of "fatigue" and forces one to clearly describe the connection between fatigue and activity. This also embraces mental fatigue (loss of cognitive function and alertness) as well as physical fatigue (lack of energy and strength, often felt in the muscles). The patient must become symptomatically ill after exercise and must also have evidence of neurocognitive, neuroendocrine, dysautonomic (e.g. orthostatic intolerance), and immune malfunction.

The Adelaide Forum agreed to UNANIMOUSLY EMBRACE THE CANADIAN CASE DEFINITION with a strong recommendation that it also be taken up by ME/CFS societies.

(Excerpt from the final address at the Adelaide Forum, Australia, 2005)

Michael Barratt, MBBS, FRCPA
Adelaide, Australia

In my opinion, and in the opinions of the other doctors at the Environmental Health Clinic, the ME/CFS Consensus Document is EXTREMELY PRACTICAL AND USEFUL. We have used it repeatedly in helping to develop comprehensive individual treatment plans in collaboration with patients. At the behest of the Ontario College of Family Physicians' (OCFP) Environmental Health Committee, and with approval of the publisher, the consensus diagnostic checklists were posted on the OCFP website. We also use the diagnostic criteria, checklists, and treatment suggestions as teaching tools in the OCFP's Environmental Health Day at their Annual Scientific Assembly.

Lynn Marshall, MD, FAAEM, FRSM

Medical Director: Environmental Health Clinic,

Sunnybrook & Women's College Health Sciences Centre

Member: Environmental Health Committee, Ontario College of Family Physicians

Lecturer: University of Toronto Department of Family and Community Medicine

Assistant Professor of Family Medicine: Northern Ontario School of Medicine

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners An Overview of the Canadian Consensus Document

**Bruce M. Carruthers, M.D., C.M., FRCP(C)
Marjorie I. van de Sande, B. Ed., Grad. Dip. Ed.**

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The National Library of Canada Cataloguing-in-Publication Data:

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document. Carruthers, Bruce M., van de Sande, Marjorie I.

ISBN: 0-9739335-0-X

Soft cover, alkaline paper. Includes authors' affiliations, table of contents, 1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) – Clinical Definition/Diagnostic Criteria, 2. Diagnosis, Differential, 3. Clinical Diagnostic Guidelines, 4. Treatment Guidelines. Copyright 2005 by B. M. Carruthers and M. I. van de Sande.

Published by: Carruthers & van de Sande

Correspondence to: Dr. Bruce M. Carruthers, email: bcarruth@telus.net

#2, 3657 West 16 Ave, Vancouver, B.C. V6R 3C3, Canada

Reprint permission requests to: Marjorie van de Sande, email: mvandes@shaw.ca

151 Arbour Ridge Circle N.W., Calgary, Alberta T3G 3V9, Canada

Cover Design by Robert J. van de Sande, B. Sc, E.E.

Cover Pictures (top to bottom): Xenon SPECT scan reveals pronounced worsening of hypoperfusion following exercise; PET scan reveals decreased glucose utilization; sMRI voxel-based morphometry technique indicates the volume of gray matter of the brain is significantly reduced and there is an average of 8% reduction of brain tissue, although not discernable by the naked eye; and the bottom two pictures using qEEG topography indicate the electrical sources in the gray matter (cortex). ME/CFS patients have increased sources (indicated in red) in the left hemisphere whereas the controls have increased sources (indicated in green) in the right hemisphere in the frontal and superior temporal cerebral regions in beta frequencies. Patients' reduced sources in the right hemisphere may be due to interference with the left brain inhibitory regulation of the right hemisphere during cognitive processing.

***This booklet is an Overview of* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Guidelines A Consensus Document**

Bruce M Carruthers, Anil Kumar Jain, Kenny L De Meirleir, Daniel L Peterson, Nancy G Klimas, A Martin Lerner, Alison C Bested, Pierre Flor-Henry, Pradip Joshi, AC Peter Powles, Jeffrey A Sherkey, Marjorie I van de Sande.

Journal of Chronic Fatigue Syndrome 11(1):7-115, 2003. ISBN: 0-7890-227-9 © Haworth Medical Press Inc.

This journal is available from The Haworth Document Delivery Service: Phone (Canada & USA) 800-722-5857.

E-mail address: docdelivery@haworthpress.com <http://www.HaworthPress.com>

Authors and Affiliations: ME/CFS Consensus Document

Bruce M. Carruthers, MD, CM, FRCP(C): Specialist in Internal Medicine, Vancouver, B.C., Canada

Anil Kumar Jain, B Sc, MD: Ottawa Hospital, Ottawa, ON, Canada

Kenny L. De Meirleir, MD, Ph D: Professor of Physiology and Medicine (KDM, IC, PDB); Director of the Human Performance Laboratory and member of the Vakgroep Internal Medicine; Vrije Universiteit Brussel, Brussels, Belgium

Daniel L. Peterson, MD: Specialist in Internal Medicine, Affiliate of the Sierra Internal Medicine Associates, Incline Village, NV, USA; ME/CFS researcher and clinician; a board member of the American Association of Chronic Fatigue Syndrome; and member of the International Chronic Fatigue Syndrome Study Group

Nancy G. Klimas, MD: Clinical Professor of Medicine in Microbiology/Immunology/Allergy and Psychology, University of Miami School of Medicine; Co-Director, E.M. Papper Laboratory of Clinical Immunology, University Miami School of Medicine; Director of AIDS Research and Co-Director of AIDS Clinical Research Unit, Miami VA Medical Center, Miami, FL, USA

A. Martin Lerner, MD, PC, MACP: Clinical Professor of Internal Medicine, Wayne State University School of Medicine; William Beaumont Hospital, Royal Oak, MI, USA

Alison C. Bested, MD, FRCP(C): Haematological Pathologist; Environmental Health Clinic; Sunnybrook & Women's College Health Sciences Centre, Toronto, ON, Canada.

Pierre Flor-Henry, MB, Ch B, MD, Acad DPM, FRC, CSPQ: Clinical Director, General Psychiatry; Director, Clinical Diagnostics and Research Centre; Clinical Professor of Psychiatry, University of Alberta, Edmonton, AB, Canada

Pradip Joshi, BM, MD, FRCP(C): Clinical Associate Professor, Memorial University of Newfoundland, St. John's, NF, Canada

A. C. Peter Powles, MRACP, FRACP, FRCP(C), ABSM: Professor Emeritus, Faculty of Health Sciences, McMaster University, Hamilton, ON; Professor, Faculty of Medicine, University of Toronto; Chief of Medicine and Sleep Disorder Consultant, St Joseph's Health Centre, Toronto; Sleep Disorder Consultant at the Sleep Disorder Clinic at St. Joseph's Healthcare, Hamilton, and Central West Sleep Affiliation, Paris, ON, Canada

Jeffrey A. Sherkey, MD, CCFP(C): Formerly in Family Medicine, University Health Network, Toronto, ON, Canada. We sincerely regret that Dr. Sherkey has since passed away.

Marjorie I. van de Sande, B Ed, Grad Dip Ed: Consensus Coordinator; Advisor to the National ME/FM Action Network, Canada

Acknowledgements for the Canadian Consensus Document

Lydia Neilson, MSM, President, and the National ME/FM Action Network for spearheading the drive for the development of a clinical case definition, and diagnostic and treatment protocols for ME/CFS.

National ME/FM Action Network, Canada. www.mefmaction.net

Health Canada for establishing the "Terms of Reference" and selecting the Expert Consensus Panel

Crystaal, for sponsoring the Expert Consensus Panel Workshop without any direct involvement

James McSherry, MB, ChB, CCFP, FCFP, FABMP, FAAFP, who was a member of the Expert Consensus Panel and contributed in the review process but was unable to attend the consensus meeting. We sincerely regret that Dr. Mc Sherry has since passed away.

Kim D. Jones, RNC, Ph D, FNP, exercise physiologist, for her contribution to the exercise section.

Kerry Ellison, OT (non-practicing), for her contribution to the patient management/treatment, and assessing disability sections

Hugh Scher, LLP, for his contribution to the assessing disability section

Additional Acknowledgements for this Overview

Expert Consensus Panel for ME/CFS, for reviewing the overview

Robert J. van de Sande, B. Sc. E.E., for the cover design and formatting of the booklet

Pictures on Cover (Reprinted with permission): **Dr. Floris de Lange** - sMRI voxel-based morphometry scan; **Dr. Pierre Flor-Henry** - qEEG topography; PET & Xenon SPECT scans: **Goldstein JA.** "Chronic Fatigue Syndromes: The Limbic Hypothesis". pp. vi, ix © 1993 Haworth Medical Press. Available from document delivery service:

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Judith A. Brock, MA, for proof-reading

CONTENTS	
DEVELOPMENT OF THE CANADIAN CONSENSUS DOCUMENT	iv
INTRODUCTION	1
Classification	1
Etiology	1
EPIDEMIOLOGY	
Prevalence	1
Natural Course	1
DIAGNOSTIC GUIDELINES	1
CLINICAL WORKING CASE DEFINITION OF ME/CFS	2
Exclusions	2
Co-morbid Entities	3
Application Notes	3
SYMPTOMS AND SIGNS	3
1. Fatigue	3
2. Post-Exertional Malaise and/or Fatigue	4
3. Sleep Dysfunction	4
4. Pain	4
5. Neurological/Cognitive Manifestations	5
6. Autonomic Manifestations	6
7. Neuroendocrine Manifestations	6
8. Immune Manifestations	7
Features of ME/CFS in Young People	7
CLINICAL EVALUATION OF ME/CFS	7
Differences Between ME/CFS and FMS	9
Differences Among ME/CFS and Psychiatric Disorders	9
TREATMENT GUIDELINES	10
Goals	10
Guidelines	10
SELF-HELP STRATEGIES	10
SELF-POWERED EXERCISE	12
SYMPTOM MANAGEMENT & TREATMENT	12
1. Sleep Disturbance	12
2. Pain	13
3. Fatigue	13
4. Cognitive Manifestations	13
5. Autonomic Manifestations	13
6. Neuroendocrine Manifestations	14
7. Immune Manifestations	14
Blood Donations	14
Immunization	14
APPENDICES	15
Symptom Severity and Severity Hierarch Profile	15
Sleep and Pain Profile	16
Assessing Occupational Disability	17
REFERENCES	19

DEVELOPMENT OF THE CANADIAN CONSENSUS DOCUMENT

The National ME/FM Action Network of Canada spearheaded the drive for the development of an expert consensus document for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). In response to increasing numbers of patients inquiring about doctors knowledgeable about ME/CFS, the Network sent a questionnaire to doctors across Canada asking what items would be most helpful in assisting them with their ME/CFS patients. The physicians concurred that a clinical definition, as well as diagnostic and treatment protocols were of prime importance.

The National ME/FM Action Network then approached two clinicians knowledgeable about ME/CFS and experienced in its diagnosis and treatment. Dr. Bruce Carruthers of British Columbia and Dr. Anil Jain of Ontario kindly agreed to co-author a draft document. Lydia Neilson, President of the National ME/FM Action Network, met with the Honourable Alan Rock, then Minister of Health, to discuss the results of the doctors' survey and the draft document. The Honourable Alan Rock responded by stating the draft clinical definition was "a milestone in the fight against this complex and tragic condition".

Health Canada established the "Terms of Reference". One stipulation was that at least one member of the panel must be nominated by each of the five stakeholder groups of government, universities, clinicians, industry, and advocacy. There had to be at least ten members on the panel, four of whom could come from outside of Canada. Panel members had to be practicing MDs actively treating and/or diagnosing ME/CFS, or MDs or Ph.Ds involved in clinical research of the illness. Their

mandate was to develop a clinical definition that addressed a broader spectrum of the pathogenesis of the illness, as well as to provide diagnostic and treatment protocols for medical practitioners. The members of the panel would have autonomy over their consensus document.

Health Canada selected an Expert Consensus Panel for ME/CFS. The eleven-member Expert Consensus Panel received more than forty nominations including numerous nominations from each stakeholder group. The members of the Consensus Panel represented clinicians, university medical faculty, and researchers in the area of ME/CFS. Collectively, the members of the panel had diagnosed and/or treated more than twenty thousand ME/CFS patients.

Health Canada planned for a Consensus Workshop to be held on March 30 to April 1, 2001. Crystaal (Biovail Pharmaceuticals) funded the workshop without having any involvement with or influence over the Consensus Document. They hired Science and Medicine Canada to organize and facilitate the workshop.

The draft document went through three rounds of revisions prior to the Consensus Workshop where the document received consensus, in principle, with directives for various members to revise some sections. The document was compiled by Marjorie van de Sande and the revised document was sent to the panel. There was 100% consensus by the panel members on the final Consensus Document¹. The Consensus Document has become known as the "Canadian Consensus Document for ME/CFS".

Importance of a Clinical Definition

The Greek origin of syndrome is *syn*—together, and *-drome*—a track for running. One must determine the tracks of travel and observe the travel of a patient's syndrome components. Because research definitions define a static collection of symptom entities, they have ignored or downplayed the critical dynamic features of this syndrome, as lived by patients. The normal fatigue/pain pattern directly related to felt causal action and adjusted by activity/rest rhythms is broken in ME/CFS. As a result there are cumulative physical and cognitive fatigue/pain and "crashing" patterns, which are critical in this Clinical Definition. The objective postural cardiac output abnormalities correlate with the degree of reactive fatigue and overall severity of ME/CFS. These findings could supply an objective marker for fatigue severity and duration, and help explain why ME/CFS can be so disabling. It is important for the clinician to observe the dynamics of the whole cluster of symptoms in their interaction, additive effects, and the disruption to patients' lives over longer periods of time.

INTRODUCTION

“Myalgic Encephalomyelitis” and “Chronic Fatigue Syndrome” are used interchangeably and this illness is referred to as “ME/CFS”. The Expert Consensus Panel, selected by Health Canada, established clinical criteria, and developed an integrative diagnostic and treatment approach to ME/CFS.

Classification

ME/CFS is an acquired organic, pathophysiological, multi-systemic illness that occurs in both sporadic and epidemic forms. Myalgic Encephalomyelitis (ICD 10 G93.3), which includes CFS, is classified as a **neurological disease** in the World Health Organization’s International Classification of Diseases (ICD). Chronic fatigue must not be confused with ME/CFS because the “fatigue” of ME/CFS represents pathophysiological exhaustion and is only one of many symptoms. Compelling research evidence of physiological and biochemical abnormalities identifies ME/CFS as a distinct, biological, clinical disorder.

Etiology

Most patients enjoyed a healthy, active lifestyle prior to the onset of ME/CFS. The importance of viral involvement is supported by frequent infective triggers. Elevated levels of a wide variety of intracellular pathogens suggest that a dysfunction in the body’s response to infection plays a significant role. The presence of activated immune complexes is supported by activation of elevated levels of T lymphocytes; poor cellular function is suggested by low natural killer cell cytotoxicity². There are confirmed findings of biochemical dysregulation of the 2-5A synthetase/ribonuclease L (RNase L) antiviral defense pathway in monocytes^{3,4} in many cases. Other prodromal events include immunization, anesthetics, physical trauma, exposure to environmental pollutants, chemicals and heavy metals, and rarely blood transfusions. A rapid and dramatic deterioration of health in acute onset cases often occurs while others have a gradual onset with no obvious cause. In addition to infectious causes, a genetic predisposition⁵ may be considered when more than one separated family member is afflicted.

EPIDEMIOLOGY

Prevalence

Epidemiological studies indicate a wide range of prevalence. However, in a large American sample of more than 28,000 adults⁶, 422 per 100,000 had ME/CFS, suggesting that between 125,000 and 150,000 adult Canadians suffer from ME/CFS. It is more prevalent than lung cancer and AIDS⁶. This illness affects all age groups, including children, all racial/ethnic groups, and all socioeconomic strata. There is a higher prevalence in females. Lower blood volume and lower blood cell mass may be contributing factors in their difficulty in coping with the genesis of ME/CFS.

Natural Course

ME/CFS can be debilitating. In a review study of prognosis⁷, 5 of 6 studies indicated that 0% to 6% (the sixth study indicated 12%) of adults return to their pre-illness level of functioning. Relapses can occur several years after remission. Progressive degeneration of end organs, particularly cardiac or pancreatic failure, may result in death, and suicide is a risk. The prognosis for children and youth is much better. Symptom severity is the best indicator of outcome, but accurate prognosis for an individual cannot be predicted with certainty. Objective postural cardiac output abnormalities correlate with symptom severity and reactive exhaustion.

DIAGNOSTIC GUIDELINES

The Clinical Definition encompasses the broad cluster of symptoms and signs that give ME/CFS its distinctive character. Diagnosis is based on these

characteristic symptom patterns, which reflect specific areas of pathogenesis.

CLINICAL WORKING CASE DEFINITION OF ME/CFS

A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine, and immune manifestations; and adhere to item 7.

___ **1. Fatigue:** The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.

___ **2. Post-Exertional Malaise and/or Fatigue:** There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period - usually 24 hours or longer.

___ **3. Sleep Dysfunction:*** There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.

___ **4. Pain:*** There is a significant degree of myalgia. Pain can be experienced in the muscles, and/or joints, and is often widespread and migratory in nature. Often there are significant **headaches** of new type, pattern or severity.

___ **5. Neurological/Cognitive Manifestations: Two or more** of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances – e.g. spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload¹ phenomena: cognitive, sensory – e.g. photophobia and hypersensitivity to noise - and/or emotional overload, which may lead to "crash"² periods and/or anxiety.

___ **6. At Least One Symptom from Two of the Following Categories:**

___ **a. Autonomic Manifestations:** orthostatic intolerance - neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.

___ **b. Neuroendocrine Manifestations:** loss of thermostatic stability – subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change - anorexia or abnormal appetite; loss of adaptability and worsening of symptoms with stress.

___ **c. Immune Manifestations:** tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.

___ **7. The illness persists for at least six months:** It usually has a distinct onset, **although it may be gradual. Preliminary diagnosis may be possible earlier. Three months is appropriate for children.

To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 & 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day. *There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. **Some patients have been unhealthy for other reasons prior to the onset of ME/ CFS and lack detectable triggers at onset or have more gradual or insidious onset.

Exclusions: Exclude **active** disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnea; rheumatological disorders such as rheumatoid arthritis, lupus,

¹ "Overload" refers to hypersensitivities to stimuli that have changed from pre-illness status.

² "Crash" refers to a temporary period of immobilizing physical and /or cognitive fatigue.

polymyositis and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. *Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise.*

Co-morbid Entities: Fibromyalgia Syndrome (FMS), Myofascial Pain Syndrome (MPS), Temporomandibular Joint Syndrome (TMJ), Irritable Bowel Syndrome (IBS), Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities (MCS), Hashimoto's thyroiditis, Sicca Syndrome, etc. *Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes".*

Idiopathic Chronic Fatigue: If the patient has unexplained prolonged fatigue (6 months or more) but has insufficient symptoms to meet the criteria for ME/CFS, classify it as idiopathic chronic fatigue.

Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles ACP, Sherkey JA, van de Sande MI. **MYALGIC ENCEPHALOMYELITIS / CHRONIC FATIGUE SYNDROME: Clinical Working Case Definition, Diagnostic and Treatment Protocols.** *Journal of Chronic Fatigue Syndrome* 11(1):7-116, 2003. © Copyright 2003, Haworth Press Inc., Article available from The Haworth Document Delivery Service: 1-800-722-5857, docdelivery@haworthpress.com, www.HaworthPress.com Reprinted with permission.

Application Notes

- **Total illness burden** is determined by observing and obtaining a complete description of the patient's symptoms, their interactions, and functional impact.
- **Variability and coherence of symptoms:** The cluster of symptoms exhibited will vary; however they are connected by their temporal, coherent, and causal relationships.
- **Symptom severity and impact:** Symptom severity is significant if it substantially impacts the patient's *premorbid activity level* (by an approximate 50% reduction). Confirm symptom severity and impact by dialogue with the patient over time.
- **The hierarchy of symptom severity** will vary over time and among patients. Periodic ranking of the severity and hierarchy of symptom severity helps orient the treatment program and monitor its effectiveness.
- **Separate primary symptoms from secondary symptoms and aggravators.** Symptom dynamics and interactions, and the effects of aggravators should be noted.

Dr. Leonard Jason's study⁸ compared patients meeting the Canadian clinical criteria and Fukuda criteria for ME/CFS and control patients with chronic fatigue due to depression. Patients meeting the Canadian criteria were more physically ill, had greater physical functional impairment, greater fatigue/weakness, and more neurocognitive, neurological and cardiopulmonary abnormalities and had more impairments that significantly differentiated them from the psychiatric comparison group than did patients meeting the Fukuda criteria.

Symptoms and Signs

1. Fatigue

"Fatigue" is an inappropriate label because the fatigue experienced in ME/CFS is not normal fatigue whereby energy is promptly restored with rest. The pathological "fatigue" experienced in ME/CFS may combine exhaustion, weakness, heaviness, general malaise, lightheadedness, and sleepiness that can be overwhelmingly debilitating. By

definition, the patient's activity level is reduced by approximately 50% or more. Some patients are housebound or bedridden and dependent on others for their daily care. ME/CFS "is actually more debilitating than most other medical problems in the world"⁹ including patients undergoing chemotherapy and HIV patients (until about two weeks before death). Cognitive fatiguing may be evident when the

patient's responses become slower, less coherent, and s/he experiences more difficulty in word and information retrieval. The pathological components of fatigue should be identified in order to provide appropriate treatment. Orthostatic intolerance, the inability to tolerate sustained upright activity, may be associated with the overwhelming exhaustion, weakness, and urgency to lie down experienced in ME/CFS. Often there is arousal fatigue due to poor sleep quality and sometimes quantity. Oxygenation fatigue is caused by insufficient oxygen being delivered to the brain and tissues. In metabolic fatigue, the cells are unable to transform substrates of energy into useful functions. Muscle fatigue is common. Patients who also meet the criteria of FMS usually experience structural fatigue.

2. Post-Exertional Malaise and/or Fatigue

Physical or mental exertion often causes debilitating malaise and/or fatigue, generalized pain, deterioration of cognitive functions, and worsening of other symptoms that may occur immediately after activity or be delayed. Patients experience rapid muscle fatigue and lack endurance. These symptoms are suggestive of a pathophysiology which involves immune system activation, channelopathy with oxidative stress and nitric oxide related toxicity¹⁰, and/or orthostatic intolerance. Recovery time is inordinately long, usually a day or longer, and exercise may trigger a relapse. The following chart indicates some of the documented dysfunctional reactions to exercise that patients may exhibit¹¹:

Response to Exercise	Healthy People	ME/CFS Patients
Sense of well-being	Invigorating, anti-depressant effect	Feel malaise, fatigue and worsening of symptoms ^{1,12}
Resting heart rate	Normal	Elevated ^{13,14}
Heart rate at maximum workload	Elevated	Reduced heart rate ^{13,14}
Maximum oxygen uptake	Elevated	Approximately 1/2 of sedentary controls ¹³
Age-predicted target heart rate	Can achieve it	Often cannot achieve it and should not be forced ^{13,14}
Cardiac output	Increased	Sub-optimal level ^{13,14}
Cerebral blood flow	Increased	Decreased ^{15,16}
Cerebral oxygen	Increased	Decreased ¹⁵
Body temperature	Increased	Decreased ¹⁷
Respiration	Increased	Breathing irregularities: shortness of breath ¹⁷ , shallow breathing
Cognitive processing	Normal, more alert	Impaired ¹⁸
Recovery period	Short	Often 24 hours but can last days or weeks ^{1,12,19}
Oxygen delivery to the muscles	Increased	Impaired ¹³
Gait kinematics	Normal	Gait abnormalities ²⁰

3. Sleep Dysfunction

Research²¹ suggests that ME/CFS patients have disrupted circadian rhythm, sleep onset difficulties, sleep maintenance disturbances and do not get into or spend enough time in the deeper phases of sleep. The EEG indicates alpha waves intrude into delta waves within non-REM sleep²².

Hypersomnia is common, particularly in the acute stage. Sleep onset difficulties, fragmented sleep, non-restorative sleep, morning exhaustion, and abnormal diurnal variation of sleep rhythms and energy levels are

common. Vivid, disturbing dreams may occur. Sleep problems are usually chronic rather than intermittent. Insomnia often increases when the patient is overly exhausted. Restless leg syndrome and periodic limb movement disorder may occur. A subset of patients may have upper airway resistance syndrome, sleep apnea or other treatable sleep disorders.

4. Pain

The chronic pain is thought to be due to a dysfunction of the pain processing areas of the central nervous system²³. Inappropriate pain signals are sent to and from the brain and

body. Dysregulation of sodium channels and cellular ion transport may be involved in pain symptoms.

Generalized myalgia or nonanatomical pain may occur randomly and is often migratory. The pain may be described as sharp, shooting, deep aching, burning, throbbing, tingling, etc. Muscle spasms, and new onset headaches, including tension headaches and migraines, are common. A subset of ME/CFS patients also meets the criteria of fibromyalgia syndrome and/or myofascial pain syndrome.

5. Neurological/Cognitive Manifestations

Structural and functional neuroimaging suggest that neuropathic involvement plays a primary role in causing a disruption of the normal coordination between the brain and the body. In patients with ME/CFS, PET scans indicate decreased glucose metabolism in the right mediofrontal cortex,²⁴ and significant hypoperfusion and hypometabolism in the brain stem²⁵. SPECT brain scan analysis²⁶ reveals significantly lower cortical/cerebellar regional cerebral blood flow (rCBF) of the frontal, parietal, temporal, occipital, and brain stem and may play a role in cognitive impairment and activity limitations. MRI studies reveal elevated numbers of irreversible punctuate lesions consistent with demyelination or edema, predominantly in the frontal lobes²⁷ and subcortical areas²⁸. A controlled study²⁹ using structural MRI voxel-based morphometry technique for measuring brain volume and tissue concentration showed that the volume of gray matter of the brain was significantly reduced and there was an average of 8% reduction of brain tissue, which was a global problem in patients. A previous MRI voxel-based morphometry study³⁰ indicated an average reduction of 11.8% in gray-matter volume in the bilateral prefrontal areas of patients compared to controls. fMRI studies^{31,32} demonstrate that patients use more areas of the brain when involved in auditory cognitive activities, thus greater effort is required to do cognitive activities and may contribute to cognitive fatigue. qEEG topography indicates elevated activity of intracerebral electrical sources in theta and beta frequencies³³. Delta and beta frequencies were particularly elevated in the left frontal region in eyes closed condition. qEEG suggests reduced sources in the right hemisphere (beta) due to interference with the

left brain inhibitory regulation of the right hemisphere during verbal cognitive processing³³. Quantitative assessment shows enlargement of the lateral cerebral ventricular volumes that may be associated with white matter loss in the frontal and parietal lobes³⁴. Some degree of encephalomyelitis may occur in the upper spinal motor and sensory nerve roots and nerve networks transvering the brain stem³⁵. Abnormal function of ATP binding cassette (ABC) transporters may contribute to significant neurological dysfunction³.

Cognitive manifestations vary and become more pronounced with fatigue. "Cognitive fog" or confusion, slowed processing of information and reaction time, difficulty in word retrieval or speaking, concentration, attention, short-term memory consolidation, and forgetfulness are common. Susceptibility to interference and difficulty in processing complex information are prominent. Selective memory processing deficits, such as experiencing more difficulty in recalling information when it is presented with greater semantic structure and contextual clues, may occur against a relatively normal cognitive background. Patients may become dyslexic when overly fatigued. Neurocognitive impairments involving concentration and memory are cited as some of the most disruptive and functionally disabling symptoms of ME/CFS.

Overload Phenomena: Patients are often hypersensitive to sensory stimulation including noise, bright lights, temperature extremes, and odours. They have difficulty focusing their attention when there is more than one source of input, such as concomitant auditory and visual input, cognitive and physical activity, and in fast-paced or confusing environments. Emotional overload may be unduly stressful. Overload phenomena may trigger a "crash" where the patient becomes temporarily immobilized by physical and/or mental fatigue and recovery is slow.

Motor and Perceptual Disturbances: Muscle weakness and fasciculations are common. The patient may appear clumsy due to loss of cognitive map, inaccurate body boundaries, poor muscle coordination, and/or loss of balance. Difficulty with depth perception and focusing vision may result in an inability to accommodate walking on uneven surfaces, as well as spatial instability and disorientation.

Other symptoms: Visual accommodation and focusing difficulties, blurred or double vision and dry eyes are common. Tinnitus may occur.

6. Autonomic Manifestations

Chronic Orthostatic Intolerance (COI), the inability to sustain upright activity (standing, sitting or walking), is very common and may be an important component in ME/CFS. Upon limited standing, the patient experiences overwhelming exhaustion, an urgency to lie down, confusion, malaise, and worsening of other symptoms. Sitting and light walking are tolerated better than standing still, but no upright activity is tolerated well. Lying down helps alleviate symptoms. Tilt-table testing may be helpful in diagnosis but some patients may have a normal tilt-table test and still have severe COI. Quiet standing in the office allows for observation and monitoring the blood pressure and pulse. **Note:** This must only be done with extreme CAUTION with someone standing beside the patient at all times in order to support him/her if s/he begins to feel weak!

Research³⁶ suggests a low circulating erythrocyte volume (approximately 70% of normal on average), but not plasma volume in ME/CFS patients. Blood may pool in the legs, abdomen, and sometimes hands. This may decrease effective blood volume and contribute to COI. Lower stroke volume and cardiac output, and reduced circulation correlate with symptom severity³⁷. Treadmill walking suggests significantly reduced vagal power³⁸. Autonomic dysfunction underlies COI and its subtypes of neurally mediated hypotension, postural COI, orthostatic hypotension, and orthostatic narrowing of pulse pressure.

- **Neurally mediated hypotension (NMH)** involves a precipitous drop of more than 20-25 mm of mercury of systolic blood pressure upon standing, or standing still. Symptoms may include lightheadedness, dizziness, pressure-like chest pain over the left chest, visual changes, weakness, slowed verbal response, pallor, an urgency to lie down, and sometimes syncope.
- **Postural orthostatic tachycardia syndrome (POTS):** Upon standing there is rapid action of the heart, either an increase of over 30 beats per minute or a rate greater than 120 beats per minute during 10 minutes of standing, plus or minus a drop in blood pressure. Tachycardia is more common than low blood pressure.

Symptoms may include lightheadedness, dizziness, nausea, fatigue, tremor, irregular breathing, headaches, visual changes, sweating, and rarely syncope.

- **Delayed postural hypotension** occurs when there is a drop in blood pressure ten minutes or more after the patient stands.
- **Palpitations with or without cardiac arrhythmias**
- **Chest pain resembling angina and/or thrombosis**

Other common ANS symptoms

- **Breathing dysregulations** include breathing irregularities, sudden attacks of breathlessness, exertional dyspnea, and holding the breath inappropriately.
- **Intestinal irregularities:** Constipation, diarrhea, alternating diarrhea/constipation, irritable bowel syndrome (IBS), abdominal pain, cramps, and nausea are common.
- **Bladder dysfunction** may include bladder pain, urinary frequency, dysuria, and nocturia.
- **Alternating sweating and shivering episodes**
- **Painful vascular spasm in extremities with cold or hot feelings**

7. Neuroendocrine Manifestations

Centrally mediated dysfunction (impaired activation) of the hypothalamic-pituitary-adrenocortical axis³⁹ may be associated with dysfunction of the autonomic and immune system. Significantly reduced pancreatic exocrine function may lead to malabsorption.

- **Loss of thermostatic stability:** Altered body temperature (often subnormal but occasionally febrile), marked diurnal fluctuation, alternating feelings of hot or cold (sometimes with unusual distribution), recurrent feelings of feverishness, and sweating episodes may occur.
- **Heat/cold intolerance** is common and may be accompanied by worsening of other symptoms.
- **Marked weight change**
- **Hypoglycemia**
- **Hypothalamic/pituitary/adrenal axis** and ANS dysregulation may lessen patients' adaptability to stressful and overload situations. Stress may cause disorientation, anxiety, worsening of other symptoms, and trigger a "crash". Recovery is slow.

8. Immune Manifestations

Many infectious agents may trigger ME/CFS. A subset of patients appears to have human cytomegalovirus or Epstein-Barr herpes virus infection of the heart⁴⁰, and viral infections of the brain have been discovered in autopsies. As human herpesvirus-6 (HHV-6)⁴¹ is regarded as an important pathogen, those patients testing positive should be referred to an infectious disease specialist. Hypercoagulation may be triggered by dysfunction of the endothelial cells in patients with active HHV6. The elevated levels of many intracellular pathogens suggest that immune dysfunction plays a primary role. The upregulation of the 2-5A synthetase/RNase L pathway in ME/CFS patients indicates an activated immune state. This state has been linked to a perturbed apoptotic (cellular suicide) process resulting in an accumulation of RNase L fragments because the nuclei cannot ingest all the resulting fragments and cannot reutilize them. The cell death and scattering of RNA debris may alter immunological functions and lower ATP reserves, magnesium and particularly cell potassium levels⁴². Although testing for cleavage of the native 80 kDa RNase-L molecule using patients meeting the Clinical Definition is yet to be done, we postulate that the results would be similar to the 80% of patients testing positive using the 1988 Holmes definition. The ratio of abnormal low 37 kDa RNase-L to normal 80 kDa RNase-L³ is associated with low oxygen consumption of patients and corresponds to clinical status. PKR is simultaneously upregulated. Perforin, a cell lytic protein that correlates with the cell's cytolytic potential, is reduced in Natural Killer (NK) cells suggesting a molecular basis for NK cytotoxicity⁴³. Cytokine profiles suggest a shift of Th1, which controls intracellular infection, to Th2². Activated lymphocytes and elevated immunoglobulins, particularly IgG, have been found. Immune tests indicating low NK cell levels and function per cell, measurements of protein kinase 1, and activated immune complex may be helpful². Interferon induced production of 2-50 AS

enzymes may lead to hypothyroidism while the thyroid hormone levels in the blood are normal.

Acute onset patients usually exhibit more immune dysfunction. Immune activation symptoms, particularly in the acute onset stage, may sometimes occur in the absence of known viral exposure. Physical exercise and overload situations may trigger or exacerbate immune symptoms.

- **General malaise**
- **Tender lymphadenopathy**, particularly in the cervical, and axillary inguinal regions
- **Recurrent sore throat**
- **Faucial injection and crimson crescents** may be seen in the tonsil fossae
- **New sensitivities** to food, medication and/or chemicals

Features in Young People

Children may be diagnosed when suggestive symptoms last more than 3 months. Numerous symptoms may have similar severity but the hierarchy of severity differs more dramatically from day to day than in adults. Severe exhaustion, weakness, pain, and mood changes make life very challenging. Cognitive abilities deteriorate particularly in topics requiring analysis, multi-task activities, fast-paced or confusing environments, and with physical and mental fatigue. Severely affected young people may be bed-ridden. Because activity level is reduced by about 50% or more, young people have difficulty or are unable to maintain a full school program⁴⁴. Unlike school phobia, these young people spend most of their out-of-school time resting. 51% of British students with long-term school absenteeism suffered from ME/CFS⁴⁵. A supportive letter from the treating physician outlining the patient's medical condition and limitations, and open communication between physician and school is helpful. *TEACH-ME: A Sourcebook for Teachers of Young People with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Fibromyalgia Syndrome*,⁴⁴ will assist teachers and parents in understanding symptoms in young people and provide strategies for educational planning and accommodations.

Clinical Evaluation of ME/CFS

It is important to recognize the characteristic features of ME/CFS, as well as to exclude alternate explanations for a patient's symptoms.

- A. PATIENT HISTORY:** A thorough history, including a complete description of patient's symptoms as well as their severity and functional impact must be taken before attempting to classify them.
- 1. FOCUS ON THE PRINCIPAL SYMPTOMS OF ME/CFS:** including post-exertional malaise, fatigue,

sleep dysfunction, pain and symptoms from neurological/cognitive, autonomic, endocrine and immune dysfunctions. Examine the course of the symptoms, with special attention to the worsening of symptoms after exertion, prolonged recovery and fluctuating course.

2. PRESENTING COMPLAINT AND AGGRAVATING/AMELIORATING EVENTS

- **Date of onset**
- **Trigger or prodromal event**
- **Symptoms at onset**
- **Progression of symptoms**
- **Duration of symptoms**
- **Hierarchy of quality and severity of current symptoms**
- **Worsening of symptoms with exertion: symptoms which require prolonged recovery**
- **Secondary symptoms & aggravators**
- **Energy/Fatigue (great 100%):** good day _____%, bad day _____%.
- **Sleep Quality:** good _____, moderate _____, poor _____
- **Pain Severity:** absent _____, mild _____, moderate _____, severe _____
- **Total burden of symptom severity & current level of physical function**

3. MEDICATION HISTORY: current, past, prescribed & other therapies, & sensitivities

4. SENSITIVITIES AND ALLERGY HISTORY: including new sensitivities and allergies and change in status of pre-existing ones

5. PAST HISTORY: earlier illnesses, exposure to environmental, work, and other toxins

6. FAMILY HISTORY

7. SYSTEMS REVIEW: Many symptoms involve more than one system. Attention paid to:

- **Musculoskeletal:** myalgia, muscle weakness, or arthralgia
- **CNS:** fatigue with post-exertional exacerbation, neurocognitive complaints, headaches, sleep disturbance
- **ANS & Cardiorespiratory:** palpitations, exertional dyspnea, symptoms suggestive of neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural orthostatic intolerance, vertigo, light-headedness, respiratory disturbances, extreme pallor
- **ANS & GI & GU:** intestinal or bladder disturbances with or without IBS
- **Neuroendocrine:** loss of thermostatic stability, heat/cold intolerance, marked weight change, loss of adaptability and tolerance for stress and slow recovery, emotional lability
- **Immune:** general malaise, 'flu-like' feeling, recurrent sore throat, hypersensitivity to foods, medications or chemicals

B. PHYSICAL EXAMINATION: Standard physical exam, with **attention paid to:**

- **Musculoskeletal System:** including FMS tender point exam (appendix 6). Check joints for inflammation, hypermobility, & restricted movement. Muscle strength: _____
Positive tender points _____/18. Meets criteria for FMS _____, MPS _____
- **CNS:** including reflex examination (*Reflex examination during neck flexion and extension may accentuate abnormalities arising from cervical myelopathic changes*). _____
Tandem walk: forwards _____ backwards _____ Romberg test _____
- **Cognitive:** ability to remember questions, cognitive fatiguing (e.g. serial 7 subtraction) & cognitive interference (e.g. serial 7 subtraction & tandems done simultaneously)
- **Cardiorespiratory System:** Arrhythmias, BP (first lying down), BP (immediately after standing).
- **GI System:** increased bowel sounds, abdominal bloating and/or tenderness
- **Endocrine System:** thyroid, adrenal and pituitary dysfunction
- **Immune System:** tender lymphadenopathy in the cervical, axillary, & inguinal regions (especially in acute stage) _____ Crimson crescents in the tonsillar fossae _____

C. LABORATORY AND INVESTIGATIVE PROTOCOL: A thorough work up must be done.

- **Routine Laboratory Tests:** CBC, ESR, Ca, P, Mg, blood glucose, serum electrolytes, TSH, protein electrophoresis screen, CRP, ferritin, creatinine, rheumatoid factor, antinuclear antibody, CPK and liver function, as well as routine urinalysis.

ADDITIONAL TESTING: *In addition to the routine laboratory tests, additional tests should be chosen on an individual basis depending on the patient's case history, clinical evaluation, laboratory findings, risk factors & co-morbid conditions.*

- **Further Laboratory Tests:** diurnal cortisol levels, 24 hour urine free cortisol; hormones including

free testosterone, B12 and folate levels, DHEA sulphate, 5-HIAA screen, abdominal ultra sound, stool for ova and parasites, NK cell activity, flow cytometry for lymphocyte activity, Western blot test for Lyme disease, chest x-ray, TB skin test, and HIV. Do testing for 37-kDa 2-5A RNase L immunoassay. • Differential Brain Function & Static Testing: for those with positive neurological findings • X-RAY &/or MRI of Brain and Spinal Cord: to rule out multiple sclerosis (MS) and other primary neurological disorders. <i>MRI interpretation: it is important to look for changes that are easily overlooked such as dynamic disc bulges/herniation or minor stenosis, which can be important in the pathogenesis.</i> • Tilt Table Test: (If indicated, test prior to giving medication for orthostatic intolerance.) • Sleep Study: to show decrease in time spent in stage 4 sleep or rule out treatable sleep dysfunctions. • qEEG, SPECT and PET Scans and Spectography: if indicated • 24-HOUR HOLTER MONITORING: repetitively oscillating T-wave inversions and/or T-wave flats during 24-hour monitoring. Note: this pattern may not be reported or subsumed under non-specific T-wave changes.	
_____	ME/CFS: If the patient's presentation meets the criteria for ME/CFS, classify the diagnosis as ME/CFS, except when the specified exclusions are present. Idiopathic chronic fatigue: chronic fatigue but does not meet the criteria for ME/CFS or have alternative explanation
NEW SYMPTOMS: People with ME/CFS can develop other medical problems. New symptoms need to be appropriately investigated.	

Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Joshi P, Powles ACP, Sherkey JA, van de Sande MI. **MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME: Clinical Working Case Definition, Diagnostic and Treatment Protocols.** *Journal of Chronic Fatigue Syndrome* 11(1):7-116, 2003, pp.105-6. © Copyright 2003, Haworth Press Inc., Journal of Chronic Fatigue Syndrome. Available from Haworth Document Delivery Service: 1-800-722-5857, docdelivery@haworthpress.com www.HaworthPress.com Patient Evaluation Worksheet reprinted slightly condensed, with permission.

A clear diagnosis often has a considerable therapeutic benefit as it reduces uncertainty and orients therapy. Early diagnosis may assist in lessening the impact of ME/CFS.

Differences Between ME/CFS and Fibromyalgia Syndrome (FMS)

ME/CFS is commonly triggered by a viral infection. There is usually greater fatigue, post-exertional malaise and fatigue, and cognitive, cardiac and immune dysfunction than in FMS. Pain is the most prominent feature in FMS, which is often triggered by physical trauma. Many ME/CFS patients also meet the criteria for FMS. The research test³ for deregulation of an antiviral defense pathway can distinguish ME/CFS from FMS. Patients meeting both criteria test the same as ME/CFS patients.

Differences Between ME/CFS and Psychiatric Disorders

ME/CFS is not synonymous with psychiatric disorder. Pay careful attention to the characteristics, dynamics of progression, and correlation of symptoms.

- **Depression:** Reactions to exercise (see chart on page 4) are helpful in distinguishing ME/CFS from depression. ME/CFS patients have symptoms such as joint and muscle pain, severe headaches, recurrent sore throats and upper respiratory infections, tender lymph

nodes, cardiopulmonary symptoms, COI, tachycardia, and a cluster of cognitive impairments, which are not commonly seen in depression. Some ME/CFS patients may suffer from reactive depression due to their pathophysiological impairments and reduced quality of life, but many objective indices can differentiate ME/CFS from primary depression.

- **Somatoform Disorder:** There is some symptom overlap between somatoform disorders and ME/CFS. However, somatoform disorder patients often have a long history of complaints starting before thirty years of age. In order to diagnose any type of somatoform disorder, the symptoms cannot be "fully explained by any demonstrable general medical condition, by the direct effects of a substance, or by another mental disorder". Many objective biophysiological findings have been demonstrated to underlie the symptoms of ME/CFS. Patients meeting the criteria of ME/CFS must be excluded from the diagnosis of Somatoform Disorder. Member countries of the World Health Organization (WHO) are obliged to adhere to the regulations of the WHO's

International Classification of Diseases (ICD) and use their ICD classification. In a letter dated January 23, 2004, Andre l'Hours of WHO headquarters clarified that "it is not permitted for the same condition to be classified to more than one rubric as this would mean that the individual categories and subcategories were no

longer mutually exclusive". **Thus, ME (and CFS), classified as a neurological disease in the WHO ICD, cannot also be classified as somatoform disorder, which is classified as a mental or behaviour disorder.**

TREATMENT GUIDELINES

Goals

Early intervention can minimize the effects of ME/CFS in some patients.

- 1. Top priorities are patient support and well-being:** Reduce the patient's confusion with a positive diagnosis, reassure continuing care, and give realistic hope. A climate of illness disbelief may lead to risk of suicide. It is essential for the patient's physiological and psychological well-being that s/he is able to maintain autonomy concerning the pacing and complexity of activities and programs.
- 2. Patient empowerment:** Respect the patient's knowledge of his/her body and experiences.
- 3. Optimizing functional ability:** Assist the patient in setting personal, emotional, and activity boundaries in which s/he can be as active as possible without aggravating symptoms, and then encourage him/her to gradually extend boundaries at his/her **own pace, and as able.**

Guidelines

- 1. The treating physician knows the patient best** and should direct and coordinate treatment and rehabilitative efforts.

- 2. All rehabilitative personnel must be knowledgeable about ME/CFS.**

- 3. The biological pathophysiology of ME/CFS is a reality that must be respected and reflected in all treatment and rehabilitative programs.** Total illness burden, impairments, low endurance, overload phenomena, and fluctuation of symptom severity and activity boundaries must be respected. Focus on reducing symptomatology and maintaining function. It is essential that the patient does not exceed his/her endurance limitations or activity boundaries too often or too deeply because this can cause a severe, long-term relapse.

- 4. Involve the patient in setting realistic goals and developing an individualized, flexible program conducive to healing.** The patient must have autonomy concerning the complexity and pacing of activities, and incorporate rest periods as needed. Begin the program at a level that will ensure success, assist the patient in recognizing early warning signs, and plan alternate strategies for low-energy days. The goal is for the patient to be as active as possible without exacerbating symptoms. Patients can explore ways to increase activity boundaries if and when able.

Self-Help Strategies (SHS)

A hypothesis underlying the use of Cognitive Behaviour Therapy (CBT) for ME/CFS is based on the premise that the patient's impairments are learned due to wrong thinking and "considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behaviour, and emotional processes. The patient merely has to change their thinking and their symptoms will be gone. According to this model, CBT should not only improve the quality of the patient's life, but could be potentially curative"⁴⁶. Supporters suggest that "ideally general practitioners should diagnose CFS and refer patients to psychotherapists for CBT without detours to medical specialists as in other functional somatic syndromes"⁴⁷. Proponents ignore the documented pathophysiology of ME/CFS, disregard the

reality of the patients' symptoms, blame them for their illness, and withhold medical treatment. Their studies have often included patients who have chronic fatigue but excluded more severe cases as well as those who have other symptoms that are part of the clinical criteria of ME/CFS. Further, their studies fail to cure or improve physiological impairments such as OI, sore throat, IBS, etc. Dr. A. Komaroff⁴⁸, a Harvard based world authority, stated that the evidence of biological process "is inconsistent with the hypothesis that (the syndrome) involves symptoms that are only imagined or amplified because of underlying psychiatric distress. It is time to put that hypothesis to rest". Some physicians, who are cognizant of the biological pathophysiology of ME/CFS, teach patients coping skills but call them "CBT". We urge such doctors to use the term "Self-Help Strategies" and avoid using the terms "Cognitive Behaviour Therapy" and "Cognitive Retraining Therapy".

Self-help Strategies (SHS) assist patients in coping with their chronic illness by conserving energy, minimizing symptom flare-ups, and maximizing coping skills and functionality.

1. Patient Education:

- Meet with the patient and her/his meaningful others as soon as possible after diagnosis to discuss the illness, what to expect, develop SHS, and provide educational information.
- Assist patients in recognizing aggravators and early warning signs so they can stop before exceeding their activity boundaries and prevent crashes. Encourage patients to take their temperature before and after an activity. If their temperature drops after an activity, they may have done too much.
- Provide information on relaxation and stress reduction techniques.
- Provide information regarding energy conservation techniques and environmental modifications.
- Encourage avoidance of known aggravators as much as possible in order to prevent flare-ups.

2. Self-Development: Encourage patients to

- trust their feelings and experiences
- set aside a time to rest and do something they enjoy
- set personal and activity boundaries and find their optimal activity rhythms
- gradually extend boundaries, if and when able, but not exceed activity boundaries

3. Maximizing Sleep: Patients should be encouraged to

- conserve energy by pacing daytime activities
- listen to their body signals and incorporate rest periods into their day as needed. (Sleep dysfunction and low energy reserves

are prime concerns. Over-exhaustion may increase insomnia.)

- establish a regular bedtime and do quiet activities, or use relaxation tapes before bedtime
- have a warm bath before bed to relax their body and keep their body warm at night
- reserve bed for sleep and sex
- give their body proper postural support e.g. use a contoured pillow
- keep the bedroom as a "worry-free sanctuary"
- do calming and slowing meditations if sleep is impossible

4. Balanced Diet and Nutritional

Considerations: Encourage patients to

- eat a balanced, nutritious diet and eat meals at regular times
- keep well hydrated
- take a multi-enzyme tablet with meals if indicated or if they have IBS
- take nutritional supplements as needed. (The biochemistry and needs of each patient is unique. Chronically ill patients require nutritional support for healing. If practical, a vitamin and mineral profile can assist in assuring that the patient is receiving adequate nutrients and indicate specific deficiencies. Start with a one-a-day vitamin/mineral supplement, replenish electrolytes, and add supplements as required.)

5. Body Movement and Fitness: Encourage patients to

- use good body mechanics and use techniques and practices, such as yoga, to improve balance
- stay active within their limitations; avoid activities and work which takes them beyond their capacity

Self-Powered Exercise

It is most disturbing that even though post-exertional malaise/fatigue is a hallmark feature and a criterion of ME/CFS, patients are often prescribed exercise unwisely. Research studies confirm that ME/CFS patients have different physiological responses to exercise than those who are healthy or depressed, as indicated in the chart on page 4. While not all patients exhibit all of these abnormal reactions, most exhibit some of them. Traditional exercise programs can provoke relapses.

As much care must be taken in prescribing exercise as prescribing medication to ME/CFS patients⁴⁹. Exercise must be individualized, entered into cautiously, and monitored diligently. Exercise programs should adhere to the previously stated goals and guidelines and the following principles:

1. **Initial Patient Evaluation:** A thorough history and examination, **with particular attention to cardiac vascular responses to activity**, must be completed before considering any exercise program. The reality of the unique medical issues, biological dysfunctions and limitations, risk factors, and pain generators must be identified and addressed.
2. **Medical Management** must be optimized before introducing exercise. Patients with less severe symptoms that are under control may benefit from very gentle exercise to maintain functionality. Some patients may only be able to exercise in bed, but exercise is **not** recommended for all patients.
3. **Principles of Treatment:** Exercise should be done under the guidance of a well qualified exercise physiologist or physical therapist, who is knowledgeable about ME/CFS.

- **Minimize relapses:** Exercise should be individualized, based on the patient's abilities/limitation, accommodate energy fluctuations, and focus on improving function. Exercises must be very gentle and carefully paced. Incorporate frequent rest breaks to ensure complete recovery. Often it may be appropriate to begin with two minute exercise periods three times weekly. The patient should be well hydrated before exercising.
- **Accommodate circulatory and cardiac impairments:** Many patients have reduced maximum heart rates and must not be pushed towards standardized age-predicted target heart rates. Significantly impaired oxygen consumption levels suggest there may be an abnormal reliance on anaerobic energy pathways during exercise in patients with ME/CFS, thus exercises that would be aerobic for healthy individuals may be anaerobic for patients. Any graded exercise expansion may be inappropriate for some.
- **Maximize self-efficacy:** Involve patients in planning. It is imperative for them to maintain autonomy over the intensity and pacing of exercise and activities.

Cautions: There are potential dangers if ME/CFS patients are pushed to increase their heart rate to age-predicted target heart rates. As indicated in the chart on page 4, research studies suggest that their hearts may be functioning at a suboptimal level and many have autonomic disturbances; thus they may not be able to accommodate the normal target heart rate. Externally paced "Graded Exercise Programs" or programs based on the premise that patients are misperceiving their activity limits or illness **must be avoided**.

Symptom Management & Treatment

The Consensus Document (pages 49-67) provides guidelines, dosage, effects and level of evidence for commonly used pharmaceuticals, and are ranked in order of the preference of the members of the Consensus Panel. Many patients are hypersensitive to medication so begin dosage at a lower level than recommended. Start low, go slow. Warn patients about possible side effects. No pharmaceutical is universally effective. Keep regime as simple, safe, effective, and inexpensive as possible.

1. **Sleep Disturbance:** Sleep quality and quantity must be taken into consideration.
 - a. **Physical remedies:** See "Maximizing Sleep" in the previous section on Self-Help Strategies. Patients need to incorporate rest periods into their day as required. Associated sleep dysfunctions should be treated, such as upper airway resistance syndrome, and a positive pressure mask can be prescribed for sleep apnea.

A Clinical Case Definition and Guidelines for Medical Practitioners

- b. Other remedies:** melatonin, valerian, calcium and magnesium salts, aroma therapy
 - c. Pharmaceuticals:** Low dose tricyclic antidepressants (short-term at low dose but side effects can be severe, and patients must be warned about possible weight gain), zopiclone, clonazepam, and L-tryptophan may be helpful. SSRI's, such as Prozac, may worsen sleep fragmentation.
- 2. Pain**
 - a. Physical remedies:** Avoid known pain exacerbators such as prolonged sitting, standing, writing, computer work, and any bend over work posture; and heavy lifting, housework, and gardening. Relaxation techniques, local heat, a warm bath and gentle stretching of muscles, mobilization of joints, magnetic pulsers, and Bio-Resonance therapy may assist in alleviating pain. Gentle massage therapy, physiotherapy, chiropractic treatments, acupuncture, EMG biofeedback, spray and stretch if tolerated, myofascial release techniques including needling to release taut muscles, ultrasound and electronic muscle and nerve stimulation may be helpful in some cases. Synaptic Electronic Activation Technology (SEA Tech®) has shown promising longer term pain relief. SEA Tech® is contraindicated in pregnancy and if pacemakers are present.
 - b. Pharmaceuticals:** Use acetaminophen as a baseline analgesic. Short-term use of low dose tricyclic antidepressants, NSAID analgesics, gabapentin, and baclofen may be useful.
- 3. Fatigue:** Treat sleep disturbance before attempting to treat fatigue.
 - a. Physical remedies:** Self-Help Strategies including setting priorities and boundaries, balancing activities with rest periods, simplifying tasks and using adaptive devices are important. Breathing exercises, restorative resting postures, massage therapy, craniosacral therapy, and aromatherapy for those without chemical sensitivities may be helpful.
 - b. Pharmaceuticals:** methylphenidate, oral cyanocobalamin, modafinil, amantadine, dextroamphetamine. Most fatigue killers have short term effects and may not help overall endurance and work capacity; they may not extend crash points.
- c. B12/Cyanocobalamin:** Anecdotal reports and studies suggest some ME/CFS patients with normal blood counts improve in energy level, cognitive ability, weakness, and mood with mega dose B12 injections, possibly due to a reduced ability in transporting B12 into the cells or low CNS B12 levels.
- 4. Cognitive Manifestations**
 - a. Physical remedies:** Some patients are able to think better in a semi-reclined position or lying down. Speech therapy may be helpful in treating problems with word-finding, information processing and memory. Mindful meditation, mental exercises, reading within one's ability and then learning new information or skills, as one is able, may be of assistance.
 - b. Pharmaceuticals:** try methylphenidate, modafinil, nimodipine, dextroamphetamine, cyanocobalamin (3c) and cautions under 3b.
- 5. Autonomic Manifestations**
 - Orthostatic Intolerance and Dizziness***
 - a. Physical remedies:** If dizziness is caused by proprioceptive disturbances in the neck, instruct the patient to avoid extension or quick rotation of the neck. If caused by orthostatic intolerance, patients should get up slowly while holding on to something and avoid standing for extended periods of time. Use of support stockings, avoiding large meals and dehydration, and pumping legs intermittently when sitting may be helpful. Immediately lying down at the first signs of dizziness usually relieves the symptoms caused by neurally mediated hypotension (NMH) and postural orthostatic tachycardia syndrome (POTS).
 - b. Pharmaceuticals:** Before starting any pharmaceutical treatment for NMH or POTS, these conditions should be confirmed by a tilt-table test. A combination of therapies usually has the best result. Begin by increasing salt intake if the patient is not hypertensive; then either add a beta blocker (e.g. atenolol), or an alpha 1 agonist (e.g. midodrine). Midodrine is usually more effective than floriene for chronic orthostatic tachycardia. If increased salt intake helps initially but loses its effect, consider fludrocortisone. If these therapies are not effective, consider paroxetine. Vertigo requires an anti-nauseant such as meclizine,

but no treatment is particularly effective. Meditative techniques may help mild cases.

Irritable Bowel Syndrome (IBS): Adjust diet and conduct food elimination trials to determine food intolerance. Use antispasmodics and anti-diarrheal agents judiciously.

6. Neuroendocrine Manifestations

Anxiety States

a. Physical remedies: Self-help strategies (SHS) assist in developing coping skills. Relaxation techniques such as slow deep breathing, listening to soothing music, a warm relaxing bath, massage therapy, and if the patient is able, gentle aquacise, swimming or walking can reduce tension. Herbs such as lavender and thyme may be helpful in some cases. Some patients may benefit from supportive counseling.

b. Pharmaceuticals: Benzodiazepines and buspirone are commonly used.

Depression

a. Physical remedies: Reactive depression may result from living with a poorly understood chronic illness which has the complex symptom set of ME/CFS and the greatly reduced functionality associated with it. SHS, massage, and bright light therapy may be helpful. Patients who are severely depressed should be referred for supportive counseling.

b. Pharmaceuticals: SSRIs are the first line choice but usually are ineffective in treating fatigue and may interfere with sleep. Newer antidepressants such as venlafaxine, nefazodone or bupropion may be of assistance. Most ME/CFS patients cannot tolerate a high enough dosage of tricyclic antidepressants to be effective in depression, but low doses may be effective for pain and sleep, if tolerated.

c. Herbal and mineral remedies: Patients with low red blood cell magnesium have improved with intramuscular magnesium sulphate in some cases. St. John's Wart may be effective in mild depression but should not be used for marked depression or taken with other antidepressants.

Hypothalamic-Pituitary-Adrenal (HPA)

Axis Abnormalities

Pharmaceuticals: fludrocortisone, (DHEA) dehydroepiandrosterone

Hypoglycemia: food low on the glycemic index may be beneficial

7. Immune Manifestations

a. Immune stimulator and viral modulator: amplitigen. Essential fatty acids (EFA) have been used for their antiviral effect.

b. Antiviral therapies: Valacyclovir may be helpful for confirmed herpes infection. Herbal remedies such as wild oregano and olive leaf extract may have antiviral effects.

c. Antibiotic treatment for mycoplasma and chlamydia: Suggested antibiotic treatments for confirmed mycoplasma or chlamydia infections include doxycycline, clarithromycin, ciprofloxacin, azithromycin and bioxin. Use with caution and accompany treatment with probiotics and immune boosters.

Blood Donations: Donating blood is not recommended because it may exacerbate symptoms due to low circulating blood volume. It is possible that some patients carry infectious agents in their blood.⁵⁰

Immunization: Live vaccine immunization is generally not recommended because of the risk of worsening symptoms and triggering relapses. Research has confirmed a frequent dysfunction of the 2-5A synthetase/ribonuclease L antiviral defense pathway in many patients³. Because of these risks, decisions regarding vaccinations must remain with the treating physician and the patient. If immunization is done, it is generally recommended that injections be administered by the treating physician and the dose be divided into three or four mini doses, each given a full month apart to ensure there are no delayed reactions.

Great strides have been made in the knowledge about ME/CFS in the last decade. Now it is time for an intensive research program in order to bring a greater understanding and successful treatment of patients. It would be helpful to establish patient subgroups, such as those who are in the acute or chronic stage, mild or severe cases, and viral or other onset. The establishment of a Centre of Excellence where the same patients are used in numerous studies and the research findings shared amongst researchers may clarify information and assist in the efficient use of treatment for the different subsets of patients.

Appendix 1: SYMPTOM SEVERITY AND SEVERITY HIERARCHY PROFILE

NAME _____ DATE _____

1. Rank your symptoms in order of severity (1 being your most severe symptom) in the left column.
2. Rate severity of symptoms by putting a check mark in appropriate column to the right of symptoms.

Symptom Severity and Severity Hierarchy Profile					
RANK	SYMPTOM	Absent (0)	Mild (1)	Moderate (2)	Severe (3)
	Post-exertional fatigue: loss of physical and mental stamina, fatigue made worse by physical exertion				
	Long recovery period from exertion: takes more than 24 hours to recover to pre-exertion activity level				
	Fatigue: persistent, marked fatigue that substantially reduces activity level				
	Sleep Disturbance: non-restorative sleep, insomnia, hypersomnia				
	Pain: in muscles, joints, headaches				
	Memory disturbance: poor short term memory				
	Confusion and difficulty concentrating				
	Difficulty retrieving words or saying the wrong word				
	Gastrointestinal disturbance: diarrhea, IBS				
	Recurrent sore throat				
	Recurrent flu-like symptoms				
	Dizziness or weakness upon standing				
	Change in body temperature, erratic body temperature, cold hand and feet				
	Heat / cold intolerance				
	Hot flushes, sweating episodes				
	Marked weight change				
	Breathless with exertion				
	Tender lymph nodes: especially at sides of neck and under arms				
	Sensitive to light, noise, or odours				
	Muscle weakness				
	New sensitivities to food / medications / chemicals				
	Total Check Marks in Column	x 0	x 1	x 2	x 3
	Column Total				

Total Score: _____ **Overall symptom severity:** _____ mild, _____ moderate, _____ severe
(Mild – occurring at rest, moderate – symptoms that occur at rest become severe with effort, unable to work, and severe – often housebound or bed-bound.)

Other symptoms _____

Aggravators _____

Change in symptoms _____

How good is your sleep on a scale of 1-5? (5 – good restorative sleep, 1 – no sleep) _____

How do you feel today on a scale of 1 – 10? (10 – terrific, 1 – totally bedridden) _____

Carruthers BM, Jain AK, De Meirleir K, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols – A Consensus Document. Journal of Chronic Fatigue Syndrome 11(1):7-116, 2003. © Copyright 2003 Haworth Press. Document available at 1-800-HAWORTH, docdelivery@haworthpres.com, www.HaworthPress.com. Reprinted slightly modified and condensed with permission.

Appendix 2: SLEEP AND PAIN PROFILE

Name _____ Date _____ to _____

Please complete chart for the week before your next appointment.

Day	Awakening time	Temp. a.m.	Time Slept	Sleep Quality	Pain a.m.	Pain p.m.	Temp. p.m.	Energy level	Bed Time	Min. to fall asleep
Week Avg.										

Temp a.m.: Take your temperature as soon as you awaken, while you are still lying down. Also indicate if you feel cold (C), had cold feet (CF), or cold hands (CH), and if you were stiff (S).

Time Slept: Indicate approximate number of hours and minutes you slept.

Sleep Quality: Good, fair, or poor. Also indicate the number of times you woke during the night including waking up much too early, e.g. if you woke up twice (W2). Indicate if you know why you woke up – e.g. to urinate, muscle cramps, nasal congestion, etc.

Pain: 0 to 10. 0 being no pain, 10 being the worst pain you have experienced.

Energy Level: Indicate your average energy level for the day - 0 being bedridden, 10 full of energy.

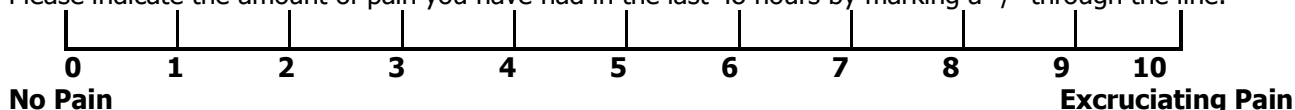
Temp p.m.: Take your temperature before going to bed. Indicate if you feel cold.

Min. to Fall Asleep: Indicate as best you can how many minutes it took you to fall asleep.

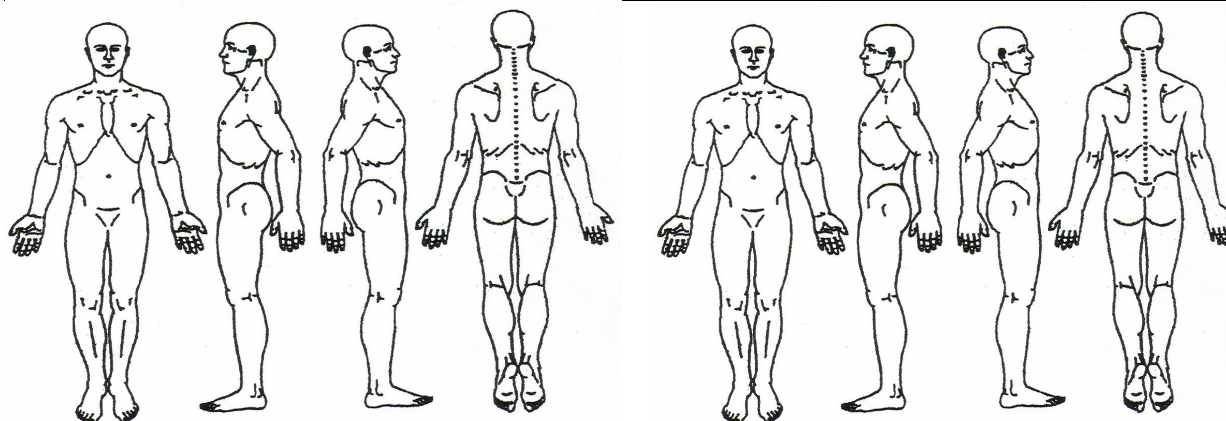
Was anything in particular bothering you this week, e.g. family crisis? _____

Pain Visual Analog Scale (Pain VAS), Body Pain Diagram

Please indicate the amount of pain you have had in the last 48 hours by marking a "/" through the line.



On the following diagrams, please indicate your areas of: Aching: ===== Burning Pain: xxxxx
 Stabbing Pain: ///// Pins & Needles: ooooo Other Pain: ppppp Describe: _____



Pain on Day 1

Pain on Day 7

Jain AK, Carruthers BM, van de Sande MI, et al. Fibromyalgia Syndrome: Canadian Clinical Working Case Definition, Diagnostic and Treatment Protocols – A Consensus Document. *Journal of Musculoskeletal Pain* 11(4):3-107, 2003. Co-published simultaneously as "The Fibromyalgia Syndrome: A Clinical Case Definition for Practitioners. Russell IJ - Editor. © Copyright 2004 Haworth Press Inc.. Copies available from Document Delivery Service: 1-800-HAWORTH, docdelivery@haworthpres.com, www.HaworthPress.com. Reprinted slightly condensed and modified with permission from Haworth Press.

Appendix 3: ASSESSING OCCUPATIONAL DISABILITY

A. Requirements of the Occupational Disability Assessment

1. **Assess symptoms of a patient's disability:** Check the wording for entitlement of the specific disability carrier. Give comprehensive explanations about how the patient's symptoms/condition impose(s) particular functional limitation on the person's ability to engage in the duties of his/her specific job, or any job for which the patient is reasonably qualified by way of education, training and experience, and which would enable the person to earn an income commensurate with that of their present job. *Clinical notes should contain such assessments on a regular basis.*
2. **Assess prognosis:** Care must be taken not to set definite deadlines in anticipating recovery and future employability, because inability to meet these deadlines may be interpreted as malingering.
3. **Assess rehabilitative potential:** The treating physician is responsible for the patient's care and is in the best position to assess the patient's condition, treatment and recovery potential. The treating physician should direct all rehabilitative efforts and his/her opinion and advice should never be supplanted by the opinions and proposals of other rehabilitative personnel.
4. **Provide medical opinion:** Give a comprehensive opinion, substantiated by detailed subjective/ objective evidence, regarding the impact of the patient's functional limitations, the impact of disability, and whether or not the patient's condition necessitates him/her to remain off work to prevent further deterioration.

B. Medical Documentation

It is essential that documentation of severity of symptoms and disability is done on an ongoing basis.

1. **Medical history:** Document total illness burden, not just primary diagnosis. History should include assessment by a family physician or specialist conversant with ME/CFS, diagnosis, abnormal laboratory findings, objective physiological findings such as OI, severity of symptoms and impact on the patient's functional abilities, duration of illness, and response to treatments.
2. **Questionnaires, patient diaries, scales, etc:** Have the patient complete scales on initial visit and then every six months or so. These scales help monitor the patient's status, and assess effectiveness of treatment, general function and activities of daily living, and prognosis. Periodic, structured interviews are useful in assessing symptom severity, interaction, impact and cumulative effects. Discussion of patient's diary, questionnaires, Dr. David Bell's CFS Disability Scale, the American Medical Association's criteria for permanent impairment using peak oxygen consumption levels, heart rate and blood pressure responses during exercise tests, and the Medical Outcomes Study Short-Form Profile (SF-36) may be helpful.
3. **Further Documentation:** Documentation of any objective findings should be included.
4. **Functional Limitations:** Indicate how functional limitations affect ability to do ADL, IADL, rehabilitative programs, and work activities. Consider physical, cognitive, and emotional functional limitations, effects of chronic symptoms, lack of endurance, impaired neurocognitive functions, unpredictability and fluctuation of symptom dynamics (even from hour to hour), and cumulative fatigue effects.
5. **Assessment by vocational providers:** Certified occupational therapists knowledgeable about ME/CFS, can provide information regarding the patient's level of function in the home with consideration to a 24-hour work day. Workplace assessments should be conducted on the job site when possible with attention to physical mental, emotional, social and environmental demands and workplace aggravators.
6. **Assess Prognosis:** In a review of prognostic studies⁷, a 9-year study reported 12% and the other 5 studies indicated between 0% and 6% of patients return to their premorbid state of functioning. Generally, patients with severe acute onset symptoms and those with comorbid fibromyalgia have greater symptom severity. The more stringent the criteria are, the poorer is the prognosis. Since it is not possible to determine the prognosis of an individual case with certainty, prognosis remains a clinical estimate.
7. **Provide medical opinion** as to whether the patient is ready to return to work or is disabled.

Workplace Aggravators: (Adapted from⁵¹) The following may cause pain, and physical and cognitive fatigue:

- prolonged sitting, writing, deskwork, handwork, telephone use, bending over workspace, standing, stairs, driving, and walking more than a tolerated distance
- unsupported extension of arms and reaching overhead; heavy lifting, carrying, housecleaning, gardening, etc
- computer work, numerical calculations, multi-tasking, tasks requiring remembering or recent events-time sequences; fast-paced and complex work surroundings, tight deadlines, sensory overload
- change in or long work hours, shift work; environmental factors: cold, heat, air pollutants, chemicals; stress

Tests for Abnormalities in ME/CFS (See www.mefmaction.net for sources of some specialized tests)

While there is not one definite test for ME/CFS, many tests may indicate abnormalities. The standard battery of tests may be inadequate to reveal abnormalities in ME/CFS patients. Many of the following tests are not available in general medical laboratories but may be available in research facilities or more generally available in the future:

- **Virology, etc:** viral antibodies, including Coxsackie B; bacteria, including HHV6; mycoplasma, etc.
- **37-kDa 2-5A RNase L immunoassay:** protein, activity, PKR cleavage, & elastase activity assays
- **Other immunological markers:** NK cell levels and function *per cell* for low NK cell cytotoxicity; CD4-CD8 ratio; ANA; activated immune complexes – IgG sub-fractions including IgG1 and IgG3, circulating immune complexes IL2 & IL4; Th1 –Th2 response to mitogen stimulation (high levels of Th2 indicate autoimmunity), flow cytometry for activated/elevated lymphocytes; antilamin antibodies may indicate autoimmunity and brain cell damage (lamin B antibodies are evidence of autoimmunity); humoral autoimmunity for polypeptides of the nuclear envelope (NE); antibodies in neuronal cells MAP2 (kinase regulators)
- **Urinary markers:** 24-hour urine free cortisol; elevated amino-hydroxy-N-methyl-pyrrolidine correlate with quantity of symptoms; IAG – tryptophan metabolite, is usually positive and indicates a leaky gut, which in turn is indicative of a leaky blood brain barrier; urinary creatine & other muscle metabolites
- **Endocrine testing:** CT scans may show reduced adrenal gland size; thyroid hormone levels with attention to bioavailability of T3 & those with reduced level should be checked for selenium as it regulates conversion of T4 to T3; reduced HPA function
- Increased 5HT neurotransmission
- **Chronic orthostatic intolerance:** Use tilt-table test or monitor the pulse and blood pressure while standing. Note: This monitoring must be done with caution and someone standing beside the patient.
- **Cardiac Dysfunction:** 24-hour Holter monitoring - Specifically ask to either view the results yourself or to report repetitive oscillating T-wave inversion and T-wave flats. This pattern is typical of many ME/CFS patients but may not be reported.
- **Cardiopulmonary Exercise Testing:** AMA Guide for Evaluation of Permanent Impairment. Lower cardiovascular and ventilatory values at peak exercise help determine functional capacity, and peak oxygen consumption levels determine disability categories.
- **Computer Science and Application (CSA™)** Actigraph is a small device that measures frequency and intensity of activity in one minute intervals for up to 22 days. Typically, less intense and shorter activity peaks followed by longer rest periods are identified. It is helpful to have the patient keep a daily diary of activities during this period and/or wear a speedometer.
- **CNS, ANS:** Romberg test; nystagmus test (may fluctuate from positive & negative throughout the day); altered sympathetic modulations; subnormal and/or fluctuating diurnal body temperature
- **Cognitive performance:** decreased processing speed, working memory, information learning, etc.
- **SPECT scans** may reveal significantly lower cortical/cerebellar regional cerebral blood flow frequently in the frontal, parietal, temporal, occipital, brain stem and throughout the cerebral cortex.
- **PET scans** may reveal decreased glucose metabolism in the right mediofrontal cortex, and significant hypoperfusion and hypometabolism in the brain stem.
- **MRI brain scans:** Elevated numbers of punctuate lesions, particularly in the frontal lobes and subcortical areas, suggest demyelination or edema. Do spinal MRI for disc herniation and minor stenosis.
- **qEEG brain topography:** Elevated EEG activity in theta and beta frequencies and increased intracerebral electrical sources in left frontal region delta and beta frequencies in eyes closed condition may be identified. Reduced sources in right hemisphere (beta) may be noted during verbal cognitive processing.
- **Hypercoagulability:** flow cytometry - fibrinogen, thrombin/anti-thrombin complexes, etc.
- **Positive tests for fibromyalgia syndrome and myofascial pain syndrome** should be noted.
- **Skin conductivity and skin temperature:** The combination of a lower ability of the skin to conduct electrical current in response to visual and auditory stimuli, and a higher skin temperature of fingers indicate a down-regulation of autonomic sympathetic tone.
- **Sleep studies** may indicate that there is insufficient time spent in the deeper stages of sleep, and alpha wave intrusion into delta waves within non-REM sleep.
- **Ocular test:** slowed and marked jerkiness of saccades; difficulty with and slowed changing of visual fixation, constricted peripheral fields; low and/or incomplete blinking; small pupils; light hypersensitivity, tear film abnormalities such as low tear break-up time, inadequate production of the oil or mucus layer in tears, rose Bengal corneal staining; visual midline shift
- **Allergies or sensitivities; Lung function testing; Liver function:** CPK and liver function

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This short Overview only provides highlights from:

Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner AM, Bested AC, Flor-Henry P, Pradip Joshi, Powles ACP, Sherkey JA, van de Sande MI. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. A Consensus Document. *Journal of Chronic Fatigue Syndrome* 11(1):7-115, 2003. The full Consensus Document is highly recommended as an informative resource book for medical practitioners.

The Canadian Consensus Document on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

This is a **VITAL DOCUMENT** that gives a new focus and new direction to all involved with ME-CFS. It makes available the clinical experience and understanding of physicians who are pre-eminent in the field and encapsulates thousands of hours of clinical investigations that are important to sufferers from ME-CFS and all who are concerned for their care, support, and the understanding of this multi-faceted organic illness.

It offers-

HOPE - for patients whose multiple symptoms have so often been dismissed as psychiatric or of biopsychosocial origin with consequent loss of benefits and support when they are most needed.

CLARITY - for physicians by providing an abundance of clinical procedures and protocols that provide objective evidence of organic multi-system and multi-organ disorders associated with the neuroendocrine and immune systems. It is in agreement with the long established international classification of ME-CFS as a neurological disorder, ICD-10 G.93.3.

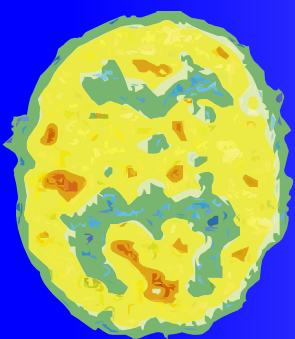
DIRECTION - for clinical treatments and research programmes especially the most recent ones concerning the need for sub-types in addressing ME-CFS and the deeper understanding of, changes in gene expression, mitochondrial dysfunction, and of pathologic changes in the endothelium with concomitant vascular damage. Mitochondrial dysfunction offers an explanation of the debilitating fatigue that is one of the defining features of ME-CFS and is consistent with chronic heart failure recently described in a cohort of ME-CFS patients.

UNDERSTANDING - of the complexity and perplexity of ME-CFS as a multi-symptom, multi-organ and multi-system illness that is increasingly recognised as an archetype of other related illnesses such as Gulf War Syndrome, multiple chemical sensitivity, MCS, and Fibromyalgia syndrome, FMS.

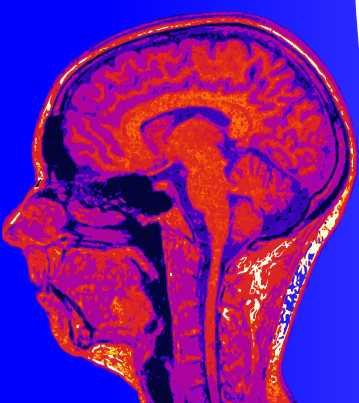
Dr. Malcolm Hooper
Emeritus Professor of Medicinal Chemistry
Department of Life Sciences
University of Sunderland
United Kingdom

Reviews and Commentaries of

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A Consensus Document**

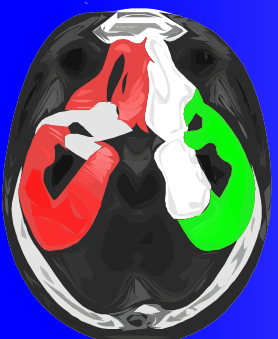


Myalgic Encephalomyelitis / Chronic Fatigue Syndrome is a complex illness that can cause life-long disability, yet has languished for years without clear recognition by the medical community. The paradox of the illness is that it can cause severe discomfort and markedly limit daily activity, yet persons with the illness may look, to the casual observer, relatively well. Because of this paradox, many in the medical profession have ignored the seriousness of ME/CFS.



In the past few years, science has made extraordinary strides in understanding the basic mechanisms of ME/CFS. Yet, because of its complexity, little of this science has reached medical practitioners to be used in relieving the suffering of patients affected with the illness. It is now possible to define abnormalities in the neurological, immune, autonomic, and neuroendocrine systems in a concise way that can paint a portrait of this disabling illness. The Canadian consensus definition of ME/CFS is a concise summary of these advances and permits a clear diagnosis for patients. The Canadian Consensus Document should be read and studied by every medical provider.

David S. Bell, MD, FAAP
Past Chairman: Chronic Fatigue Syndrome Advisory Committee,
US Department of Health and Human Services



While the primary goal was to establish a clinical case definition for ME/CFS, the ME/CFS Consensus Document is a comprehensive overview of ME/CFS, including pathophysiology, symptoms, physical findings, and treatments. This Consensus Document is clearly the most comprehensive review of ME/CFS to date. It records the experience of many long time practitioners, which provides an insight into signs and symptoms that has never been recorded elsewhere. Never before has there been a consensus on treatment. This paper considers not only pharmacotherapy, but also makes recommendations for patient education, energy conservation, pacing, stress reduction techniques, diet, and exercise. One of the most important aspects of the ME/CFS Consensus Document is that it indicates the level of proof for various recommendations.

This is *THE MANUAL* for diagnosing and treating ME/CFS. Perhaps every office that treats patients with ME/CFS should be using this document as the diagnosis and treatment blueprint.



Charles W. Lapp, MD
Director: HUNTER-HOPKINS CENTER, Charlotte, North Carolina
Advisory Committee for CFS: US Department of Health & Human Services
Board of Directors: American Association for Chronic Fatigue Syndrome

