A Consensus Manual for the Primary Care and Management of

Chronic Fatigue Syndrome

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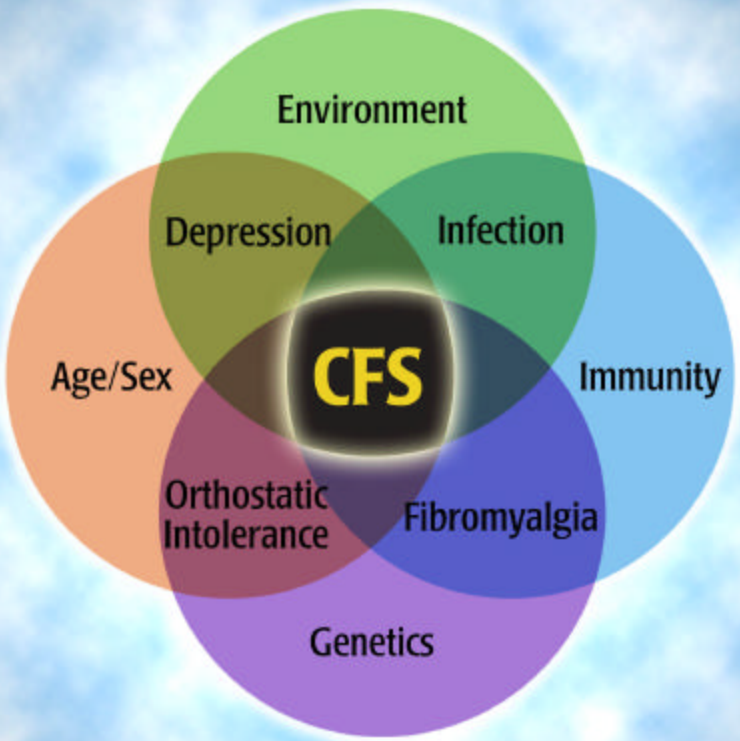

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A Consensus Manual for the Primary Care and Management of Chronic Fatigue Syndrome

Foreword

The illness called Chronic Fatigue Syndrome (CFS) plagues thousands, perhaps millions of people in the US. It is hard to think of a worse malady, one that can voraciously rob the patient of energy, cognition, sleep, immune function, and a sense of well-being. That physicians are reluctant to assume care of such challenging, distraught patients is understandable. Yet, we know that competent management of these patients can be productive and rewarding for patient and physician alike.

The genesis of this manual begins with efforts by the New Jersey Chronic Fatigue Association in conjunction with the New Jersey Department of Health and Senior Services to bring to the primary care physician a manual that could facilitate and enhance the care of patients with CFS. We have assembled a diverse group of experts in the field of CFS and asked them to focus on the symptomatology of the disease (pain, dizziness, depression, brain fog) and to deliver a product that would be helpful to the primary care physician and specialist alike.

The stigma associated with having CFS and also with caring for patients with CFS defies explanation. So, we have attempted to destigmatize the primary care of patients with CFS and to outline the range of therapies across medical disciplines that can improve the lives of these patients. These thirteen chapters are intended so that the primary care physician, and specialist alike, can appreciate the pathophysiology, differential diagnosis, and therapeutic opportunities in patients with CFS. The extensive bibliography will allow the interested caregiver to delve deeply into one of the most fascinating and complex maladies of modern medicine.

We want to thank first the State of New Jersey for its decision to support the creation of this Consensus Manual and to make it widely available. We thank the New Jersey Chronic Fatigue Syndrome Association, Inc. for its tireless support, in particular, Jon Sterling of that group, who always gives us hope and makes us better physicians. We thank the Academy of Medicine for its management of the project, in particular Sondra and Edward Moylan for going beyond the call of duty to get the project completed and, with great admiration, Lorraine Steefel for her insightful transcription of the manual.

Most of all, we thank all our patients with CFS for their faith and trust in us, that we can improve their lives now and eventually conquer this dreadful disease. To them we dedicate this manual.

Joseph F. John, Jr., MD, Editor

James M. Oleske, MD, MPH, Associate Editor

1 Pathophysiology in CFS

Kenneth J. Friedman, PhD

A successful description of the pathophysiology of CFS must explain the mechanism(s) for all of its symptoms. Based upon the current (U.S.) case definition of CFS,[1] the pathophysiology needs to account for impaired memory loss and the presence of a sore throat, tender neck (cervical) or armpit (axillary) lymph nodes, muscle pain (myalgia), headache, unrefreshing sleep, post-exertional malaise lasting more than 24 hours, and multi-joint pain (arthralgia) without swelling or redness. While all these symptoms need not be present in any one case of CFS, all are associated with the syndrome. At this time, there is no one mechanism known which can produce all the symptoms or the variability of symptoms found in patients with CFS.

This review will provide an assessment of what is currently known about the pathophysiology of CFS. Not all symptoms of CFS will be discussed, only those which have been linked to its pathophysiology. Other symptoms of CFS will be discussed in subsequent chapters.

Pathophysiologic Fatigue

To some extent, all of us have experienced fatigue: a lessened capacity to perform work, accompanied by a feeling of exhaustion and the desire to rest or sleep. It is difficult, if not impossible, to quantify the amount of fatigue that a known amount of work or degree of stress should produce in any given individual. One reason is the dependence of fatigue upon "personal factors." The well-trained athlete will experience less fatigue running a mile than a sedentary individual. A second reason is the decline of physical prowess with age. These are but two examples of personal factors that affect the magnitude of fatigue experienced subsequent to a given activity.

A number of illnesses are known to produce disproportionately large amounts of persistent fatigue, which we shall term pathophysiologic fatigue. Such illnesses include, but are not limited to, those listed in Table 1-1.

In addition, administration of certain drugs (particularly antihypertensives), cancer chemotherapy and surgery produce chronic fatigue. Recently, it has been proposed[2] that CFS and Syndrome X have "identical" clinical symptoms and may have a common pathology: abnormal ion channel function.

Since the diagnosis of CFS is one of exclusion, other known causes of pathologic fatigue should be excluded prior to the conclusion that the patient is suffering from CFS. However, symptoms of CFS overlap with other unexplained clinical conditions.[3]

Table 1-1
Conditions Associated with Profound or Chronic Fatigue

AIDS	Lyme disease
Anemia	Malnutrition
Anxiety	Myasthenia gravis
Cancer	Neuropathy
Chronic fatigue syndrome	Renal failure
Chronic obstructive pulmonary disease	Sleep disorders Multiple sclerosis
Diabetes mellitus Syndrome X	Systemic infection (bacterial or viral)
Endocrinological imbalance (e.g. adrenocortical insufficiency, hypercortisolism, hypothyroidism)	Lupus erythematosis/ Collagen vascular syndromes Mitrochondrial dysfunction
Heart failure	Valvular heart disease

Mechanism of Fatigue

The mechanism of physiological fatigue is not well understood. It is assumed to result from an imbalance at the cellular or molecular level between the need for nutrients and their actual supply and/or an imbalance between the accumulation of waste product(s) and the need for waste product removal. The lack of adequate nutrients or an excess of waste products at the cellular level leads to physiological fatigue.

The physiologist's view of fatigue

Fatigue must arise in one or more of the body's organ systems. The *perception* of fatigue is a function of the central nervous system, which usually relies upon incoming information from the neuromuscular system. Hence, a simplistic model would postulate that the perception of fatigue arises from consequences in either the neuromuscular and/or the central nervous system. Perhaps the perception of fatigue is similar to that of hunger: physiological mechanisms in the gut (and elsewhere) contribute to the perception of hunger, but over-riding emotional stress can prevent an individual from perceiving hunger.

The Site of Fatigue in Chronic Fatigue

No muscle defect found to date

It is reasonable to postulate that the muscular fatigue exhibited by patients with CFS arises from an abnormality in affected muscle. The abnormality might be a biochemical or mechanical abnormality in the contractile apparatus, the muscle's mitochondria (which supply energy for muscle contraction), the failure of impulse transmission from nerve to muscle, or hyperexcitability of sensory afferents from muscle to the central nervous system. There

have been several reports from one laboratory of altered mitochondrial morphology in the skeletal muscle of patients with CFS[4-6] and one report suggesting that CFS may be related to a carnitine deficiency.[7] (Carnitine plays a role in mitochondrial energy production). Confirming studies have been lacking.

Fatigue at the neuromuscular junction

There are few, if any, well-documented studies of fatigue in humans or other intact animal models. However, fatigue has been studied in isolated neuromuscular preparations designed to elucidate the mechanisms of synaptic transmission and the consequences of delivering rapid and repeated stimuli to a muscle fiber. Such studies provide a basic understanding of neuromuscular fatigue, but do not provide an understanding of the perception of fatigue by an intact organism.[8] Additional studies have been done on vertebrate muscles and the nerves which innervate them. Such studies reveal vertebrate muscles are composed of many motor units, and when a task requires more muscle, additional motor units within that muscle are recruited to contract and hence accomplish the task. It is not difficult to imagine that the delivery of multiple nerve stimuli or the use of additional motor units to accomplish a task would involve more metabolic energy than usual and would be perceived as fatigue.

Altered electrical activity in neural networks

The synaptic fatigue documented to occur at the neuromuscular junction is believed to occur at nerve-nerve synapses including those within the human brain. Extending the synaptic fatigue model, activities that induce greater than normal electrical activity within the brain could generate synaptic fatigue within its neural networks and possibly be the source of the fatigue that patients with CFS describe as "brain fog" and other cognitive difficulties associated with CFS. There is some evidence to suggest that greater-than-normal electrical activity (at particular sites) may be responsible for the patients' heightened perception of pain: quantitative measurements demonstrate that stimuli that are not painful in healthy subjects are perceived as painful in patients with CFS. It appears as if patients with CFS have an abnormal stimulus perception amplifier (within the CNS).

Brain scans reveal differences in metabolic activity between patients with CFS and controls suggesting brain involvement in the abnormal perceptions of patients with CFS. Magnetic Resonance Imaging (MRI) has shown differences in both the brain stem and subcortical areas of patients with CFS when compared to control subjects.[9] Single Photon Emission Computed Tomography (SPECT) studies suggest reduced blood flow in patients with CFS in the area of the hindbrain. Similar findings have been reported for both multiple sclerosis and poliomyelitis patients.[10, 11] Interestingly, both multiple sclerosis and poliomyelitis are associated with chronic fatigue suggesting a link between reduced blood flow in the hindbrain and the perception of chronic fatigue. Preliminary Positron Emission Spectroscopy (PET) studies suggest hypometabolism in the brain stem, as well as the right mediofrontal cortex.[12]

Chaudhuri[2] has put forward the suggestion that abnormal ion channel activity in excitable membranes may be responsible for CFS symptoms, since it is known that channelopathies have been found to produce an array of symptoms in several pathologic conditions. Fluctuating symptoms, inducible by physical or mental stress, are found in disorders associated with channelopathies (including hypokalemic periodic paralysis, episodic ataxia type 2, neuromyotonia, myasthenic syndromes, multiple sclerosis and inflammatory demyelinating polyneuropathies). SPECT scans of patients with CFS are similar to those seen for Syndrome X patients – a known channelopathy. Further, exposure to specific toxins known to produce abnormal sodium channels may precipitate CFS.

Pain - The Second Hallmark of CFS

Pain is another hallmark of CFS that may appear as abdominal, joint, lymph node, muscle, and/or sore throat pain, and/or headache. Many patients describe CFS as an everything hurts syndrome, and to the frustration of both patient and physician, the latter can find nothing wrong.[13]

From the physiological perspective, pain is caused by the activation of nociceptors (pain receptors) in peripheral tissues by excessive mechanical or chemical stimuli, or heat. Such stimuli depolarize the membranes of nociceptors which in turn gives rise to action potentials. These action potentials are conducted to the central nervous system along finely myelinated (A-delta) and non-myelinated (C) afferent fibers. Nociceptors have been found in cutaneous tissue, subcutaneous tissue and visceral organs. These afferents excite neurons in the spinal cord which relay the impulses to the brain. Whereas most receptors become less responsive when repeatedly activated, it has been postulated that nociceptors become sensitized by repeated noxious stimuli: subsequent innocuous stimuli may result in action potentials and pain.[14] Animal studies and recent imaging studies of the awake human brain indicate that the nociceptive afferent activity can be modified by both endogenous and exogenous factors at the level of the spinal cord and the brain.[15, 16]

One possibility of the origin of CFS pain is that old injuries may hurt anew, which suggests that the pain in CFS is associated with a condition of primary hyperalgesia. But primary hyperalgesia is associated with tissue damag, an injury, a disease, or inflammation that causes the release of one or more algesic substances into the extracellular space. Known examples of algesic substances include H^+, K^+, serotonin, histamine, one or more of the prostaglandins, bradykinin, and substance P. These sub-

stances act on the membranes of pain-sensing neurons (the nociceptors) producing primary hyperalgesia or alter microcirculation. Often accompanying primary hyperalgesia is an increase in the area sensitive to pain, a phenomenon described as secondary hyperalgesia. The mechanism of secondary hyperalgesia is believed to be similar to that of primary hyperalgesia,[17] involving the release of endogenous agents. Alterations in some of the concentrations of these substances have been found in patients with CFS, but tissue damage has not been found. Thus, while it may be attractive to postulate that the large, painful areas found in patients with CFS are due to a combination of primary and secondary hyperalgesia, it must be remembered that the abnormal and/or excessive production of algesics is a possible, but though yet unproven, mechanism of pain in CFS.

A second possibility as to the nature of CFS pain comes from the description patients with CFS give for their pain. Patients with CFS who have generalized pain and hyperalgesia describe their pain as originating in their musculature, being continuous – even at rest, and being generalized – in all four body quadrants.[18] The pain is described as diminishing with moderate exercise, but becomes worse after exercise. The hyperalgesia found in these patients is found at many locations and is chronic (overlapping the type of pain syndrome found in Fibromyalgia Syndrome, (FMS). Tender points are found on both the upper and lower body. Such symptoms suggest a nociceptive disturbance in the central nervous system, rather than in a particular muscle or particular group of muscles. However, a particular muscle or a particular group of muscles may play an essential role in generating and maintaining the central nociceptive disturbance.

This description suggests an as yet unproven possible mechanism for the chronic pain of CFS: *nociceptor sensitization*, or an increased sensitivity of nociceptors, to stimulation. While most sensory organs become fatigued with repeated stimulation, it has been shown that polymodal C fibers display enhanced sensitivity and lowered thresholds to stimulation with repeated stimulation.[17]

A third possibility is that the abnormal pain experienced by patients with CFS might be generated at sites other than the nociceptors. Other sites include the spinal cord and the brain. Nociceptor activity results in a generalized activation of myelinated A-delta and non-myelinated C fibers that project either to the dorsal horn of the spinal cord or to the medulla. In these latter two structures, other substances (such as substance P or calcitonin-gene-related peptide) and other neurotransmitters (excitatory amino acids, for example) may modulate the impulses conveying the perception of pain to the brain.

A fourth possibility is that once received in the brain, impulses conveying the perception of pain may be altered by emotions and motivation through corticofugal and subcortical descending influences. Descending inhibitory fibers cannot only influence the perception of received impulses, but can also modulate the ascending input from dorsal horn cells. In recent years, four distinct inhibitory descending systems have been identified,[17] that selectively inhibit nociceptor neurons via serotonergic and monoaminergic (nor-epinephrine releasing) mechanisms. If the serotonin in neurons of the spinal cord or medulla is depleted, the analgesic action of the central nervous system's endogenous opioids (discussed below) is blocked. Interestingly, abnormal serotonin metabolism has been found in patients with FMS, a syndrome with symptoms overlapping those of CFS.[19-21] Nor-epinephrine-containing fibers also appear necessary for opiate-induced analgesia[22, 23] and mediate dorsal horn inhibition. Both the serotonergic and monoaminergic neurons distribute widely, suggesting that these neurons have multi-target effects, which might include modulation of the response of spinal cord cells to incoming sensory information. Although unproven at this time, such pathways and mechanisms could heighten the perception of pain to incoming sensory information.

A final (fifth) possibility is the involvement of the central nervous system's (the brain's and spinal cord's) own intrinsic opioid system in the abnormal perception of pain in CFS. Three classes of opioids are currently recognized (the enkephalins, the dynorphins, and β–endorphins) as being part of this system. Each class is a distinct group of peptides, each having a distinct anatomic distribution. Enkephalins have a wide distribution throughout the central nervous system, but are found in regions believed to contribute to pain control, including dorsal horn cells of the spinal cord. Injection of dynorphin has been found to produce analgesia and dynorphin-containing cells have been found in the hypothalamus, reticular formation, and spinal and medullary dorsal horns.[24] Neurons containing the precursor of β-endorphin are concentrated in the hypothalamus and, if the hypothalamus is cut, certain forms of stress-induced analgesia are lost, which suggests that pituitary endorphins contribute to pain control.

Despite the anatomic appearance of the nervous system's being a hard-wired system, physiological studies suggest additional controls and complexities at every level of the pain perception-pain reaction pathway. A single neuron may be influenced by more than one neurotransmitter and the effect of different neurotransmitters on that neuron can be different.

Endocrine-HPA Involvement

The CFS symptoms of fatigue, myalgia, and sleep disturbances are also found in patients having adrenal insufficiency. Therefore, it is suspected that CFS has an endocrine component. While there is no evidence documenting an endocrine *origin* of CFS, there is evidence suggesting endocrine- or at least HPA-*involvement* in CFS. The components of the hypothalamic-pituitary-

adrenal (HPA) axis, consisting of the hypothalamus, anterior pituitary, and the cortex of the adrenal gland are inter-related by a series of biochemical events known to regulate the mammalian response to stress. In addition, the HPA exhibits a circadian rhythm entrained to the sleep/wake cycle.[25] In healthy individuals, physical or emotional stress "activates" the HPA, causing an increased release of cortisol and other hormones. Since many patients with CFS report that physical and/or emotional stress precipitated their illness, it is tempting to postulate that such patients become ill (at least in part) because of an inability to activate an adequate HPA response to the stressor. A reduction in HPA activity has been reported for patients with CFS.[26, 27] Reduced levels of basal evening glucocorticoids and decreased cortisol excretion were found by Demitrack.[26] These data have been interpreted as suggesting a central nervous system defect as a factor in CFS,[25] and the thesis is supported by a previous report of reduced cortisol levels (one of the biochemical markers of HPA dysfunction) in chronic and acute pain states.[28] However, the question has been raised as to whether this altered HPA activity is a consequence of the syndrome itself or of the change in sleep patterns associated with it.[25, 29]

Patients with CFS have been shown to have a reduced capacity for aerobic exercise,[30, 31] but so do healthy men after 3 weeks of bed rest.[32] Indeed, some of the parameters found abnormal in patients with CFS are similar to those found in deconditioned subjects who sleep less well than fit subjects,[33] and both patients with CFS and deconditioned subjects respond favorably to physical training.[34]

It is also known that cortisol and corticotrophin-releasing hormone (CRH) are produced during HPA activation. Both cortisol and CRH influence the immune and other body system(s). Since cortisol suppresses inflammation and cellular immune activation, it is not difficult to imagine the consequences of reduced cortisol levels. Cortisol levels are low but still within the normal range in patients with CFS. It is not known if elevation of cortisol levels as a treatment for patients with CFS would be therapeutic. Since cortisol levels are within the normal range in patients with CFS, it cannot be used as a diagnostic marker for CFS.

An additional two arguments (articulated by[25] supporting HPA involvement in CFS) are: (1) the observation of the resemblance of CFS symptoms to those of patients with glucocorticoid deficiency: debilitating fatigue, and, in response to stress, the acute onset of arthralgias, myalgias, fever, post-exertional fatigue, heightened allergic responses and disturbed mood and sleep, and (2) animal studies, which indicate that CRH induces signs of physiological and behavioral arousal. Possibly, reduced levels of CRH contribute to lethargy.

Thus, part of the challenge in determining the etiology of CFS is to distinguish between those physiological changes that are a direct *consequence* of the syndrome-precipitating factor(s) and those changes that are the body's *adaptation* to the precipitating factor(s).

Involvement of Other Organ Systems

CFS affects a number of other organ systems: the immune, cardiovascular, and gastrointestinal. In addition, cognitive function is frequently impaired. Cognitive dysfunction suggests brain (CNS) involvement in CFS. Reviews of current knowledge of the pathophysiology of these systems appear in other chapters of this manual.

- The pathophysiology of immune system dysfunction associated with CFS is discussed in Chapter 3.
- The cardiovascular pathophysiology associated with CFS is discussed in Chapter 7.
- The pathophysiology of Irritable Bowel Syndrome, the gastrointestinal disorder most often endured by patients with CFS, is discussed in Chapter 10.
- The documentation of the occurrence of cognitive dysfunction in CFS, and a discussion as to whether it is a primary symptom of CFS, or secondary to CFS-induced sleep deprivation, are presented in Chapter 5.

Epidemiology: Gender, Genetics, and the Environment

The epidemiology of CFS seems to be unclear, if not unusual, in three areas: (1) it affects mostly women, (2) the probability of exhibiting CFS may be genetically transmitted from parent(s) to child, and (3) while "outbreaks" of CFS have been documented (in which CFS has been found within communities), it infrequently seems to be passed among family members. Any proposal of a pathophysiological mechanism underlying CFS will need to account for these unusual epidemiological observations.

- The gender selectivity of known diseases and its implications for the pathophysiology of CFS are further discussed in Chapter 9 of this manual.
- The findings of inherited tendency for CFS and the occurrence of "outbreaks" of CFS raise questions of heredity vs. environment as factors in the transmission or precipitation of CFS. The implications of these findings for the pathophysiology of CFS are also presented in Chapter 3 of this manual.

Conclusion

A review of the current CFS literature indicates that CFS is associated with alterations in the physiology of many organ systems. CFS exhibits considerable overlap

with two other syndromes: FMS and Gulf War Illness. The overlap of symptoms between CFS and these other two syndromes, as well as findings of pathophysiological changes associated with the latter two syndromes, mollifies assertions that CFS is a psychological disorder.

CFS presents a unique mosaic of symptoms that cannot be explained by any single, known mechanism of disease. If CFS is caused by a single mechanism, that mechanism must be a broad-based mechanism - affecting multiple organ systems. Perhaps a cellular membrane defect, such as a channelopathy, will be found (as has been proposed by Chaudhuri[2] with the additional caveat of targeting the specific tissues affected by CFS.

As the name implies, CFS is predominantly associated with overwhelming fatigue. That fatigue is perceived as being muscular in origin. To date, no evidence of an associated pathophysiology of muscle or of the nerve-muscle junction has been found. The lack of evidence for muscle pathophysiology's being responsible for the fatigue of CFS has led investigators to explore the possibility of the fatigue's being a *perception of fatigue* within the central nervous system (CNS).

The second hallmark of CFS is pain. The pathophysiology of pain generation in patients with CFS is not understood. Hyperalgesia, the pain associated with tissue damage, does not appear to be the likely mechanism of pain in CFS, since tissue damage has not been found. Increased sensitivity of pain receptors (nociceptors) has been proposed,[17] but not shown, in patients with CFS. Such negative findings have led to the proposal of CNS and brain involvement in the generation of pain in CFS. Serotonin and monoamine pathways are suspected of being involved. In addition, the brain's own opioid system (consisting of enkephalins, dynorphins and β–endorphins) might be involved. Unfortunately, there is no definitive evidence for these mechanisms. Brain imaging techniques, however, reveal differences between normal subjects and CFS subjects. These differences might prove to be indicative of abnormal pain-perception amplification within the CNS.

Many of the symptoms endured by patients with CFS, such as fatigue, myalgia, and sleep disturbances, are found in patients having adrenal insufficiency. Therefore, the possibility of CFS having an endocrine component exists. There is no evidence documenting an endocrine *origin* to CFS,q but there is evidence to suggest endocrine *involvement* in CFS: A reduced level of hypothalamic/pituitary/adrenal (HPA) axis activity has been reported.

CFS affects a number of other organ systems and/or functions. Patients with CFS often suffer with abnormal cardiovascular reflexes, irritable bowel syndrome, and cognitive dysfunction. The pathophysiologies of these conditions, as they relate to CFS, are discussed in other chapters of this manual.

Finally, an understanding of the epidemiology of CFS should yield clues as to its pathophysiology. The similarities between the symptoms of viral infection (particularly HHV-6, EBV, CMV, and *poliomyelitis*), viral fatigue, and CFS cannot be ignored and are, therefore, addressed in Chapter 12 of this manual. Additional clues to the pathophysiology of CFS will come from better understanding of the preponderance of patients with CFS being female and the resolution of the roles genetics vs. environment have in predisposing patients to this syndrome.

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2 Initiating Care of Patients with CFS

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This chapter introduces the primary care physician to the unique, and challenging aspects of evaluating patients who present with a large array of baffling symptoms that are part of CFS, a condition whose cause is unknown and whose treatment strategies are limited. Patients greatly appreciate the provider who is knowledgeable about CFS; who takes an interest in listening to their symptoms; who treats them with respect, even without being able to offer a solution; and who can guide them in supportive care for their chronic illness.

The first interaction between patient and provider is often over the phone. The pleasant, informative receptionist who may provide a brief synopsis of the doctor's approach to treating CFS and related conditions may put the patient at ease and make him or her actually look forward to the first encounter with the physician. At this time, the receptionist should have the patient forward pertinent medical records in advance of the first visit; in addition, a standard health questionnaire, such as the SCL-90-R Symptom Checklist 90-R or the SF-36® Health Status Survey, may be forwarded to the patient to complete.

History

On arriving at the office, the patient may desire pamphlets, brochures, journals, and other reading materials relating to CFS. Announcements from support groups that discuss important issues or feature patient advocacy may also be available. While patients are completing the usual intake form listing demographic information, they may be asked to write at least three important questions prior to seeing the doctor.

At the start of the interview process, it is helpful to know something about the patient's concerns. Often, patients with CFS are seeking confirmation of their diagnosis. At other times, they may want to try certain treatments, or they may need help filling out disability forms. It is useful to focus patients on symptoms and possible ways to cope with their disorder rather than have patients spend their time completing paperwork.

After the introduction is complete, it may be easiest to begin the interview with an open-ended question or observation: "I see you have been diagnosed with CFS..." or "Tell me what this illness has been like for you...". Acting as non-judgmentally as possible from the beginning sets the tone for the entire interview.

The physician may act as a facilitator during the patient's narrative account by incorporating a checklist such as the one in Table 2-1.

Table 2-1
Symptom Checklist for Initial CFS Interview*

- Sore throat
- Painful cervical or axillary lymph nodes
- Unexplained generalized muscle weakness
- Prolonged ($\geq$24 hrs.) generalized fatigue
- Generalized headaches
- Migratory painful joints without swelling or redness
- Areas of lost or depressed vision
- Visual intolerance of light
- Forgetfulness
- Excessive irritability
- Confusion
- Difficulty thinking
- Inability to concentrate
- Depression
- Non-refreshing sleep

*Patients can grade symptoms as mild, moderate, severe, or absent.

The symptom checklist, the narrative, and the patient history may include input from the patient's companion or family member participating in the interview. Due to the extended list of symptoms in CFS, some of which are more meaningful to the patient than others, the patient may focus too long on one body system. It is important to move the interview along without seeming uncaring, while reassuring the patient that you will focus on more specific issues later or during a follow-up encounter. It is important to question the patient about the key points in the case definition for CFS, in order to obtain some sense of the patient's attitude toward these symptoms. What may begin as an information gathering session can also reveal something about the patient's ability to cope with the myriad symptoms in CFS.

Also important to note is the degree of emotional support the patient receives from friends or relatives, as in the process of the workup. As an invisible illness, CFS has its share of liabilities, since the patient looks relatively well. Therefore, the patient's symptoms may inadvertently be dismissed as trivial. From the first encounter with the pa-

tient with CFS, it is important to convey a belief in the credibility and severity of the patient's clinical complaints.

At times, it is helpful to quantify the impact of certain key symptoms, such as fatigue and muscle pain, on routine aspects of daily life, such as cooking, cleaning, and shopping. A description of a typical day or a month-long log of graded symptoms can be very illustrative for patients' physicians. Patients can also be asked to chart an overall sense of well-being on a 1-10 or 1-100 scale. (See Figure 2-1).

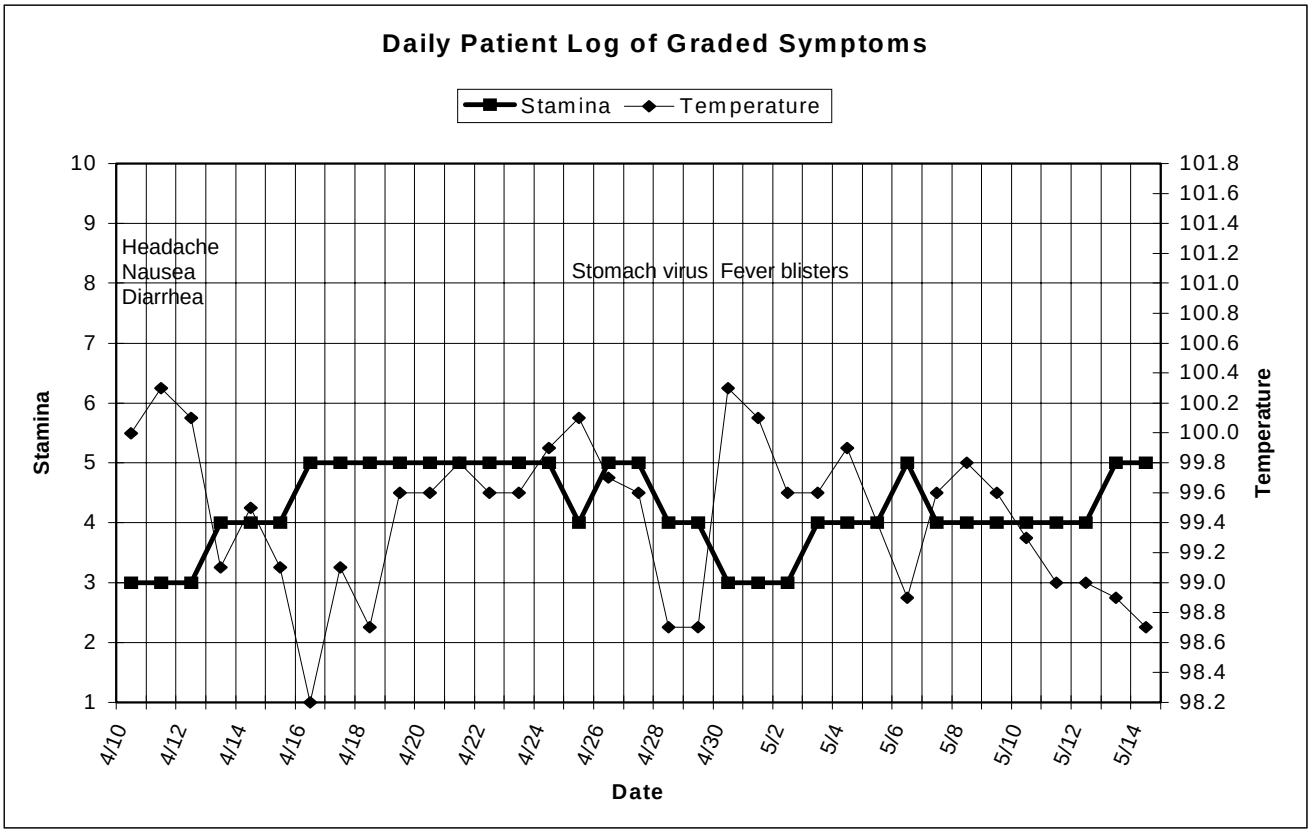
Near the end of the patient's narrative, it may be helpful to ask what therapeutic interventions, if any, have been tried and to learn what their impact has been on the underlying condition. This information helps to discern whether a patient is averse to certain treatments based on negative past experiences. The physician may want to inquire as to where the patient acquired information about his condition, i.e., through the Internet, via patient support groups, or by asking questions of other medical professionals.

Physical Examination

At the onset of the physical examination, sometimes patients who are especially ill or who have traveled a long way will ask to lie down. The nurse may perform vital signs and note them in the chart. Occasionally, if the patient reports tachycardia or a racing heart after standing for a while, proceed to ask the patient to stand still for 5 or 10 minutes while the pulse is measured. It is important to focus on the color of the pharynx, especially if the patient reports a sore throat, and to determine whether exudate is present for culture. A frequent sign in CFS is a "red crescent" formed by inflamed anterior tonsillar pillars. The physician should determine the presence of tender or enlarged lymph nodes, as often present in the anterior cervical chain, noting their size, consistency, and location (cervical, submental, and axillary).

At this junction, palpate the point of maximal impulse to assess heart size; listen to the pulse for a full minute; and try to discern a mid-systolic click characteristic of mitral valve prolapse, common in patients with CFS. If the patient has reported low grade fevers, ask that a temperature log be kept. The scalp should be palpated and examined for areas of alopecia, which can be seen in certain autoimmune disorders. The buccal mucosa should be examined for evidence of oral ulcers or canker sores, as well as the gums and general condition of the teeth. The maxillary, ethmoid, and sphenoid sinuses should be palpated to try to determine the presence of acute versus chronic sinusitis, which can be seen in patients with CFS. The thyroid gland should be carefully palpated for its size and for the presence of nodules. Many patients present with serological evidence of

Figure 2-1



autoimmune thyroiditis, but with perfectly normal thyroid function.

The chest and lung examination is conducted in the usual manner. The patient's skin should be examined for evidence of more commonplace skin conditions, such as eczema; telangiectasias and livedo reticularis, commonly found in chronic liver disease and connective tissue disorders, respectively; a bull's eye lesion characteristic of early Lyme disease pervasive in the specific geographic locations; psoriasis, which is rarely accompanied by an arthritis that affects the digits; hypopigmentation, which suggests adrenal insufficiency; and, finally, the characteristic periorbital heliotropic discoloration that may be noted in dermatomyositis, another condition that presents with fatigue and weakness. Raynaud's phenomenon can be asked about, while examining the patient's hands. Nail beds should be assessed for clubbing, which can be seen in chronic smokers or patients with obstructive lung disease, another condition associated with chronic fatigue.

The abdominal examination is also rather routine, but the physician should palpate the spleen, which can be enlarged and tender, particularly during the acute stages of mononucleosis. The liver span may be mildly enlarged in chronic active hepatitis B or in the early stages of hepatitis C infection.

The musculoskeletal examination should be conducted carefully and should focus on searching for areas of joint swelling, which can be seen in either active lupus or other connective tissue diseases; gout; and infectious arthritis, such as gonococcal or those secondary to Lyme disease, in which the skin overlying the joint may also be warm and tender. Trigger points can be checked in the typical locations, such as the occiput, the midtrapezius and lateral trochanters, but patients with CFS often have multiple tender muscle groups as seen in classic FMS. On the other hand, tenderness over proximal muscle groups in particular may be noted in polymyositis and in those patients on statins for control of hyperlipidemia. The temporal artery should be palpated gently to exclude the possibility of polymyalgia rheumatica, particularly in the elderly patient who complains of unilateral visual deficits.

The neurologic examination is also of key importance and should be performed carefully on every patient. The physician should note the patient's mental status; assess his or her expression (flat or anxious affect); quality, quantity, and organization of speech; and appropriate changes in facial expression. Cranial nerves are tested (7^{th} N. palsy noted in Lyme disease and herpes-related neuropathy). Then, a sensory examination and motor examination should follow. Cerebellar function can be limited to rapid alternating hand movements, heel-to-shin, finger-to-nose, and gait. The bulk and tone of the major muscle groups should be assessed to determine the patient's level, if any, of deconditioning. Deep tendon reflexes are next and should be intact unless there is cortical or spinal cord pathology. Mental status, which is the area most often abnormal, should be evauated last, with care including serial 7s, short-term memory, and long-term memory

Occasionally, if it is apparent that the patient is clinically depressed by his affect or by remarks that are made during the history, it is useful to perform a Beck Depression Inventory, which may form a baseline prior to embarking on treatment.

Laboratories

The following tests are important to perform at some point in the workup: CBC with differential; chemistry profile; an early morning or spot serum cortisol level; hepatitis B and C serology; TSH; ANA; RPR; and Lyme serology. If tuberculosis is suspected, a PPD should be placed along with an anergy panel. A blood test to determine the presence of an RNA low molecular weight protein, which has been reported more commonly among patients with CFS, may be ordered at the physician's discretion.

It may be helpful to question the patients about the possibility of vasovagal syncope suggested by reports of flushing, palpitations or an inability to stand for long periods of time, especially exacerbated by a warm environment. Findings from tilt table testing can support the diagnosis of CFS (See Chapter 7). Some patients may consider tilt table testing too traumatic and precipitant of symptoms. Yet, vasovagal syncope is potentially treatable and may afford the patient some relief from his fatiguing symptoms.

Imaging

Most types of brain imaging procedures performed on patients with CFS are elective and should not be ordered as part of an automatic screen. Symptoms which suggest a possible structural or functional abnormality of the brain, such as cognitive dysfunction, abnormalities noted on the neurologic examination or significant complaints of motor or sensory weakness are appropriate reasons to order an MRI of the brain to exclude infectious etiologies, such as CNS involvement with Lyme disease; cerebral vasculitis, which is rare; and demyelinating lesions associated with MS. Unidentified bright spots reported by some researchers on MRIs performed on patients with CFS are uncommon and not helpful clinically in the patient's management.[35] Arnold-Chiari malformation, which was reported by one group of researchers who examined a series of brain MRIs in patients with CFS has been dismissed after a group of radiologists failed to concur with these results in a blinded study.[36]

Similarly, SPECT scans of the brain, which measure perfusion of blood to different areas of the brain, and BEAM scans, which evaluate glucose metabolism, are research tools that have shown some abnormalities, but have

a limited clinical role until more research data is accumulated.[37-39]

Working Diagnosis

At the close of the first visit, after review of the data generated, in addition to whatever medical records the patient may have brought, it is helpful to formulate a working diagnosis. For patients who have already completed exclusionary laboratory work and possibly a psychiatric evaluation, a diagnosis may be evident. The confirmation by the physician that the patient does indeed have a real illness usually provides an immeasurable amount of relief to the patient. If a diagnosis cannot be made, however, based on the paucity of data, this fact should also be stated to the patient, with some expectation that physician and patient will work together until his or her illness is identified.

Following the completion of the history-taking and physical examination portions of the encounter, the physician should sit down with the patient and his or her family to review the findings and plans. Occasionally, at this point, a working diagnosis is formulated, especially if the patient has forwarded adequate records for review and the diagnosis of CFS has already been made by several specialists. Once the patient meets the CDC criteria for the diagnosis of CFS and has laboratory results excluding other diagnoses, future management can be discussed.

If the diagnosis of CFS remains in question, further evaluation will become necessary. More information is warranted at this time. Pamphlets or handouts about the diagnosis of CFS and how it is substantiated, in addition to a description of tests, will further educate patients. Patients appreciate monographs, since it is often difficult for them to absorb detailed information at the first meeting.

Discussion of Therapy

The physician should review a variety of therapeutic approaches, mainly those that can help with symptom relief, such as analgesics, sleep aids, and even antidepressants. Low doses of certain drugs may help considerably with sleep disturbances and have been quite useful in helping relieve some daytime fatigue (See Chapter 6).

Some patients are already quite familiar with various treatments, many of which have not been validated in placebo-controlled studies.[40] If the patient is already taking herbal or homeopathic remedies, it is vital to review each for efficacy or toxicity. Nicotinamide adenine dinucleotide (ENADA) is an example of a relatively safe over-the-counter medication being investigated in placebo-controlled trials. A six-week trial of this agent is not unreasonable, but patients should be told that they may see improvement in a narrow range of symptoms, e.g., cognition.

Ampligen is a double-stranded mismatched RNA immunemodulator with antiviral activity against a variety of agents-much like interferon. This agent is studied in a placebo-controlled clinical trial at different sites across the country. It might be well to encourage certain patients to enroll in this type of study if their diagnosis of CFS is rather certain at the conclusion of the initial interview.

Disability

If the patient is already out of work or if there are constant, debilitating symptoms, it may be well to broach the topic of disability at the first encounter. The patient should gather the necessary paperwork from the employer. Careful documentation will be necessary to file for Social Security disability, due to the elusive nature of CFS (See Chapter 13). Help from an attorney often benefits disabled patients with the documentation.

Conclusion

The patient with CFS will appreciate the physician who is not only knowledgeable about the pathophysiology of this complex illness, but who also shows empathy and understanding for the special needs of this population. Often, the first several patient encounters will cement the future relationship with the medical professional; therefore, it is important to identify any areas of concern.

Arrangements for follow-up appointments or phone contact should be made so that the patient and doctor can discuss the results of tests ordered during the first meeting, decide about disability plans and other lifestyle changes, and, finally, suggest appropriate treatment modalities. Continuity of care is extremely important for this group of patients due to the chronicity of their disorder and the need to establish a long-term working relationship with a medical provider. Many patients want and do seek information on the Internet. Though much of the public information about CFS is misleading, there are several excellent websites that patients will find useful and that they will want to discuss with their physician. The website of the New Jersey Chronic Fatigue Syndrome Association (NJCFS) can be accessed at http://www.njcfsa.org. The website of the CFIDS (Chronic Fatigue Immune Dysfunction Syndrome) Association of America, Inc., can be accessed at http://www.cfids.org.

3 Infections in CFS

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Many patients with CFS complain of fever, sore throat, and lymph node swelling and tenderness. Since these symptoms are highly suggestive of microbial disease, many physicians approach patients with CFS, at least in the initial stages, as though infection is a central mechanism or "trigger." It is clear that at least 50% of patients with CFS have an infectious episode as an initial trigger for the syndrome.[41] In some cases, the inciting event is clearly a mononucleosis-like illness, occasionally a standard EBV-associated mononucleosis. More often, it is a non-specific upper respiratory infection, a sinusitis or bronchitis, occasionally an influenza-like illness, the latter characterized by severe myalgias, high fevers, and severe malaise. Some patients may actually describe vividly an event at a specific date and time of day when they became ill, relating that after that event they never felt healthy again. Paradoxically, over time for many patients with CFS, the initial symptoms may blur and be difficult to recapture in the medical history obtained years later.

Epidemiology/Pathophysiology

Many infectious agents seem capable of inciting CFS, but few good studies provide an epidemiologic link to specific agents. One early study depicted an outbreak of disease probably associated with human herpes virus 6 (HHV-6) at Incline Village, Nevada. In this outbreak, there was evidence of depletion of B-cell lymphocytes and development of symptoms consistent with CFS.[42, 43] Older observations from Europe suggested that an illness called myalgic encephalomyelitis had occurred in clusters, which suggested an infectious/contagious basis for the outbreak.[43] Although it is tempting to attribute CFS to an unresolved infection secondary to viral infection, such as mononucleosis or influenza, it is difficult to attribute the constellation of symptoms and signs that currently define CFS as due to a single infectious agent.

There is some evidence, however, that CFS may be associated with some unresolved or persistent infectious agents. For example, most patients with CFS have persistently and, at times, markedly elevated antibodies to portions of the EBV, particularly the viral capsid, early antigen, and nuclear antigens. The same can be said, albeit less assuredly, for HHV-6. A certain percentage of patients with highly reactive HHV-6 serology will also have intermittent viremia with HHV-6, the significance of which remains unclear, since there are no studies that have been directed at eradicating HHV-6 from the vascular compartment. Recently, Belgian and French coworkers have reported that certain species of mycoplasma are associated with precipitating or perpetuating the illness.[41]

Other evidence for an infectious basis for CFS hinges on the recent observations that one of the major antiviral pathways is dysfunctional. Over the last decade, it has become clear that patients with CFS generate abnormal concentrations of an intracellular enzyme called RNase L.[41, 44, 45] Apparently, activated RNase L serves as one final arm in a more general antiviral pathway, triggered initially by extracellular interferons. Interferons, in response to foreign double-stranded DNA, stimulate the activation of 2-5 adenylate that itself activates RNase L, an enzyme capable of degrading single-stranded viral RNA or perhaps other messenger RNA.[44, 45] In a sense, this system works as a nonspecific defense mechanism before specific humoral (antibody) and other specific cellular responses take over. It appears that patients with CFS tend to fragment the functional large molecular weight RNase L (80 Kda) and produce instead a dysfunctional, low molecular weight RNase L (37 Kda).

Differential Diagnosis

Very few infectious diseases present with the panoply and diversity of symptoms seen in patients with CFS. The disease that most resembles CFS is acute and subacute EBV infection, but patients with mononucleosis tend to be younger and do not suffer with other cardinal symptoms of CFS, such as cognitive dysfunction, sleeping disorders, and allodynia. Nevertheless, the Epstein-Barr virus (EBV) was initially thought to be the cause of CFS. When serum was sampled for antibodies against two EBV-replicating enzymes in patients with CFS, abnormal titers of antibodies were found twice as often as in controls (34.1 % vs. 17.1 %). While this finding may indicate a more frequent occurrence of EBV in patients with CFS, or perhaps that EBV may precipitate CFS in a subset of patients with CFS, EBV is not the universal cause or precipitant of CFS.[46] Buchwald et al. (1996) tested 548 chronically fatigued patients, including patients with CFS, for seroprevalence and/or geometric mean titer of antibodies to 13 viruses. No consistent differences were found in patients with CFS for either of the two measured parameters. An earlier study by Mawle, et al. (1995) at the Center for Disease Control (CDC), could not find elevated titers of antibody to any herpes virus, nor evidence of exposure to enterovirus in patients with CFS.[47] Recently, workers at the CDC examined 26 patients and

52 controls for the presence of HHV-6 and HHV-7 and found no differences between patients and controls.[48] The recent report of an "outbreak" of CFS in Japan,[49] which may be affecting as much as 1/3 of the Japanese workforce may rekindle efforts to identify an infectious agent as the cause of CFS. A preliminary report suggests that this is a post-hepatitis B vaccination outbreak and may be due to a contaminating organism (De Merileir, 2000). The failure to find a single virus in all patients with CFS has led to the assertion by some that CFS is not caused by a viral agent. However, the failure to identify a causative viral agent does not preclude the possibility that CFS is caused by a yet-to-be-identified virus or co-infection with two or more viral agents or an unknown infective agent. Physicians should keep in mind that disease due to CMV can mimic CFS for a short time but usually resolves. Some patients complain of recurrent herpes-like lesions of the oral cavity that suggests regular recurrence of herpes simplex virus.

An intriguing, unifying hypothesis put forward by Lerner et al. is that CFS symptoms are caused by viral-induced channelopathies.[50] In other work, these investigators have described electrocardiographic changes explained by changes in ventricular cell membrane ion channel function.[51] These investigators believe that such changes may be caused by the presence of a virus and claim success with long-term therapy of antiviral medication. Other non-CFS literature documents the ability of viral infection to alter excitable membrane activity. Human immunodeficiency virus type 1 (HIV-1) has been shown to inhibit a large-conductance potassium channel in human glial cells,[52] while herpes simplex virus has been shown to decrease membrane excitability of nerve cells (a decrease in sodium channel activity in the plasma membrane of dorsal root ganglion cells) of adult guinea pigs.[53] Virus-induced alteration of membrane excitability, therefore, is a possible, but unproven, mechanism of CFS pathophysiology.

There is other indirect immunologic evidence for persistent viral infection. Patients with CFS often have lymphocyte depletion, including mild to moderate reductions of CD4+, as well as CD8+ lymphocytes. This type of depletion should not be confused with the CD4+ depletion seen with HIV infection. In HIV disease, the CD4+ to CD8+ ratio is usually reversed. Still, HIV antibody testing should be done on any patient with CFS who has any hint of risk factors for retroviral illness.

Bacteria, viruses, and parasites have been linked to fatiguing syndromes, including brucella, bartonella, and cyclospora.[54] Not widely known, it is reported that the cat scratch disease due to *Bartonella henselae* may present as chronically fatiguing illness.[51] In considering bartonella infection, a good history of cat exposure including being licked or sleeping with the cat, cat scratch disease serology, coupled with newer techniques to amplify bartonella DNA in blood, should help eliminate that diagnosis.

Some patients complain of recurrent oral or vaginal candidiasis. Some patients may insist that they are chronically infected with yeast, a holdover from the pseudoepidemic promulgated by some health care providers claiming that many patients with undefined disease had deep-seated, unresolved mycotic infection due to *Candida albicans*, thus the term the Yeast Connection.[55] Nevertheless, in some patients *C. albicans* can be cultured at times from the oral cavities and genital tracts of these patients, and patients report improvement of fatigue when oral azoles are used to treat the mucosal infections.

Patients with Lyme disease can have unusual presentations, but exhausting fatigue, deep bone and body pain, and cognitive dysfunction are unusual. Nevertheless, in areas of the country where Lyme disease caused by *Borrelia borgdorferi* is endemic, patients with CFS and physicians will fixate on Lyme Disease as a cause. To confound the clinical picture, Lyme disease does have its chronic form, and serology that was positive early in the disease may persist for years. Ehrlichiosis caused by agents related to the rickettsia is an emerging disease endemic in the same geographic regions as Lyme Disease. The capacity for *E. canis* to produce a chronic disease such as CFS has not been investigated.

Workers in Belgium have reported in abstract form an association of circulating peripheral blood cell-associated *Mycoplasma fermentans* with CFS. This obligate intracellular wall-less bacterium, acting either as an inciting or opportunistic pathogen, awaits more definitive studies to define its role in CFS. Mycoplasmas can have protean effects on cellular machinery, but can be interrupted by antimicrobial chemotherapy.

In this age of emerging infectious agents, including those of bioterrorism, other new microbial agents will surely arise as causes of chronic fatigue.

Diagnostic Tests

Chapters 1 and 2 outline baseline diagnostic testing for most patients with CFS. The primary care physician can obtain serology for EBV, HHV-6, CMV, toxoplasmosis, and HIV. The next level of testing may include other serologies, tests for HHV-6 viremia, RNase L determinations, and mycoplasma, rickettsial, or chlamydia DNA amplification by PCR. Thise latter tests may be difficult to obtain because of lack of third party coverage. Patients often have to secure and pay for this testing themselves by finding the most appropriate laboratory to perform the testing and to arrange third party payment, a very frustrating process for patients. Regional specialty laboratories may be very helpful to patients arranging specialized diagnostic testing. An infectious diseases physician specializing in CFS can assist the primary care physician in choosing specialized tests that may support

the diagnosis of CFS or consider other infectious diseases. Table 3-1 outlines the diagnostic tests involving infectious agents that may be considered for patients with CFS.

Therapy

There are no studies that support the routine use of anti-infectives in the therapy of CFS.[40] Nevertheless, since CFS is devastating to the individual, and since there is inferential evidence that CFS is associated with persistence of infectious agents, it is reasonable to use careful empiric trials of antivirals, antibacterials and, in certain instances, antifungal agents. Patients with early CFS and high titers of antibody to DNA viruses may benefit from a one-to-two month trial of antivirals, usually starting with an agent such as valcyclovir at doses of 500 mg twice or three times a day. If there is no response at two months, the therapy should be stopped.

Ampligen is a 50-base-pair compound consisting of double-stranded RNA (polyI-polyC_{12}U) that several studies have shown improve the Karnofsky score, a measure of well-being.[56] Preliminary evidence has also been presented to show that Ampligen will decrease the level of low molecular weight RNase L. A current clinical trial underway with Ampligen compared to placebo will determine if the product will be approved by the FDA.

Some patients will give a history of a profound response to an incidental antibacterial they had taken in the past. While there are no studies to substantiate empiric use of agents such as macrolides or quinolones, when patients are debilitated, it seems reasonable to attempt one or two month trials in selected patients who have had such beneficial responses historically. New studies are underway to determine the efficacy of antimicrobials in those patients with evidence by serology or PCR of active mycoplasma infection. Since cytokine regulation may play a role in CFS, agents to modulate cytokine pathways, such as isoprinosine, infliximab, or thalidomide, will serve as another potentially exciting area for clinical trials.[57-59]

Conclusion

Many infectious agents can cause fatigue as part of a constellation of symptoms, so they have to be considered in the differential diagnosis. There are good data to suspect that CFS itself is triggered or perpetuated by microbial agents, but classic Koch's postulates have not been demonstrated for any one agent. Newly described agents such as HHV-6 seem to reactivate as opportunistic agents and may play a role in causing persisting symptoms. Antibacterial or antiviral therapy remains empiric, but can be useful in some patients. Future research using DNA microarrays and advanced immunological technology should elucidate the role of the altered immune state in CFS and the impact of opportunistic infections.

Table 3-1
Useful Diagnostic Tests to Rule Out Infectious Causes of Chronic Fatigue Syndrome

	Diagnostic Test		
Infectious Agent	**Serology**	**Culture**	**DNA Amplification**
CMV	●	●*	
EBV	●		
HHV-6	●	●	●
Borrelia borgdorferi	●		**?**
Bartonella henslae	●		●
Brucella canis	●		
Mycoplasma fermentans			●
Tropheryma whippelii			●

* Culture of urine most useful

4 Depression in CFS*

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The CDC criteria for CFS specifically recognizes that patients can have both CFS and depression.[1] The clinician's challenge is to judge for each individual patient whether the complaint of fatigue is a primary depression, a physical illness, such as CFS, or a combination of both.

Thus, depression can mimic CFS and other physical illnesses, such as FMS. Patients with so-called atypical depression are especially likely to present to their primary care physicians complaining of feeling tired without being aware their mood is depressed. Such patients often reject the idea that their symptoms, "which feel so real," might not be physical. Of course, patients with CFS, or other chronic physical illnesses can become depressed due to that illness. The physical illness might cause depression directly by physiologic effects on the brain. Additionally, the frustration of being ill and the physical, social, and financial loss of function can trigger depression.

Fibromyalgia (FM) overlaps with CFS in terms of rates of fatigue, myalgia, sleep disturbance, and mood problems, among other criteria.[60] FM focuses more by definition, on a three month history of generalized aches and stiffness with a minimum of at least six typical and reproducible tender points,[61] there is no requirement for fatigue. Other criteria for FM are headaches, neuropsychiatric symptoms, subjective joint swelling, irritable bowel syndrome, and modulation of symptoms by activity, weather, and stress.

This chapter clearly differentiates CFS and FM, discussed as "chronic fatigue syndrome and related immune deficiency syndromes" (CFIDS), from depression in terms of physical signs and symptoms, sleep, fatigue, memory, biological parameters, brain imaging, immunology, and treatment. The focus will be on practical applications of research findings, with a further focus on future ability to show clear biologic separation and specific treatment.

Physical Signs and Symptoms

Typically, patients with major depressive disorder (MDD) have no specific signs or symptoms. Patients with CFS typically do not have the following DSM-IV criteria symptoms for major depression: anhedonia, guilt, and lack of motivation.[62] In contrast, patients with CFIDS have been reported to have multiple findings including myalgia, pharyngitis, painful lymph nodes, visual blurring, nausea, nocturia, night sweats, abnormal Romberg balance test results, hepatomegaly, and abnormal ophthalmic findings.[63, 64] Patients with CFS have been found to frequently have small adrenal glands, as determined by CT scan.[65]

Insomnia and hypersomnia are well-known symptoms of MDD,[66] and 90% of patients with CFS report a sleep abnormality[64] (See Chapter 6). Fatigue in CFS is a key criteria related to the complaint of being "tired," with an incidence of post-exertional malaise of 50% to 80%.[64] Before CFS, these patients had been physically active. At this time, although initially feeling well and energized after exercise, within 6 to 24 hours most patients notice the onset of extreme fatigue, loss of cognition, fever, and sore throats requiring retirement to bed. Muscle fiber has been found anatomically to be normal, but with reduced exercise tolerance (8.1 vs. 11.3 minutes).[67] CNS nerve exhaustion has been defined from results that indicated after exhaustion of peripheral nervous stimulation, there remained added force in the muscles of patients with CFS, as contrasted with controls (80% to 15%).[68] Increased CNS fatigue led to "…a progressive failure to fully activate the muscle during this strenuous exercise." Other correlated findings include deficiencies in carnitine, an essential regulator of mitochondrial metabolism.[69] Another report found that in terms of aerobic power, CFS patients had low fitness levels and a low range of maximal oxidative capacity.[70]

Further reports have confirmed the changes in muscle and muscle function in CFIDS that are not found in MDD. There are three levels for evaluating muscle function: gross performance, oxygen delivery, and cortical motor potentials. Recent reports have found significant reductions in maximal voluntary strength (19%, $p<.05$) and in submaximal aerobic performance scores (40%, $p<.05$) in FM patients.[71] However, fatigue loading has not always found significant differences.[72] Perhaps more important is focusing in on more specific chemical systems. For example, time constant for oxygen delivery has been found to be significantly reduced in CFS both after exercise (46.5s vs. 29s, $p=.0019$) and cuff ischemia (20s vs. 12s, $p=.03$).[73] Motor-evoked potentials as investigated by single and double magnetic stimulation revealed reduc-

* *Portions of this article were taken with permission from Jorge, C. & Goodnick, P. Chronic Fatigue Syndrome and Depression: Biological Differentiation and Treatment, Psychiatric Annals 1997; 27(5):365-371.*

tions in function in both excitatory and inhibitory pathways in FM.[74]

Memory impairment has been commonly reported both in MDD and CFS. Regarding short-term memory, consensus of research focuses on the fact that deficits are more a problem with attention than with memory storage. Patients with CFS have had particular problems, in contrast to controls, with the Stroop Color/Word test, Digit Symbol testing, and Trail Making B test.[75] One study contrasting CFS with MDD indicated paired associate learning was much worse in CFS than in MDD; results were interpreted to indicate that MDD deficits are because of reduced confidence and reaction time, whereas CFS deficits were true deficits in memory consolidation.[76] A further report showed CFS patients to have more trouble than controls sustaining attention to figural and verbal stimuli.[77] In contrast to depressed patients, who have more trouble with figures than verbal stimuli, CFS patients are equally impaired in both areas. There have been several recent studies looking at the impact of CFS and FM on memory and concentration. One study contrasting CFS and depressed patients with normal controls found that CFS patients in general had similar patterns of impairment to those with affective disorders in some tests (Stroop test for cognitive processing, and Buschke for short-term memory), but lower in others in working memory (Paced auditory serial addition task, Salthouse reading span test)[78] (See Chapter 5). The findings of slowed reaction times and reduced pre-movement-related motor potentials in CFS has been interpreted to suggest that central motor mechanisms involved in motor response preparation are impaired in this disorder.[79] Similarly, in FM, controlled studies have confirmed impairments in delayed and immediate recall, as well as sustained auditory focus; these results were correlated to pain severity and trait anxiety.[80]

Biological Findings and Diagnosis

In terms of neurochemistry, although urinary methylhydroxyphenolglycol (MHPG) levels (mg/24 hours) have been frequently found to be lower in MDD, plasma studies of MHPG in melancholia have generally found higher levels than in controls.[81, 82] However, in CFS, mean plasma MHPG has been reported as lower than in controls (8.3 vs. 10.8, p<.002).[83] With regard to serotonin, there appears to be a number of contrasts between MDD and CFIDS. Patients with MDD have been reported to have, in contrast to controls, lower plasma 5HIAA,[84] lower cerebrospinal fluid 5HIAA,[81] and lower platelet imipramine binding (IB).[85] In contrast, CFIDS patients have been reported to have greater plasma 5HIAA than controls (67.3 vs. 37.3, p=.002),[84] higher cerebrospinal fluid 5HIAA (111.1 vs. 95.1),[84] and higher platelet IB in some,[86] but not all, studies.[87] A study contrasting response in age, weight, sex, and menstrual cycle-matched samples of 10 CFS, 15 MDD, and 25 control subjects indicated that prolactin responses to the 5HT-releasing agent fenfluramine were highest in CFS patients, followed by controls, and then by MDD patients (p=.01).[27]

Further serotonin research reveals that patients with FM do not show the normal pain generally induced by IM serotonin.[88] Of interest is that patients with FM demonstrated an increase in T/C and C/C genotype of the T102C polymorphism of the 5HT2a receptor gene; however, these findings did not correlate to age of onset, duration of disease, or Beck Depression Inventory score.[89] In contrast to only 6% of blood donors, 74% of FM patients have been reported to have anti-serotonin antibodies in their sera.[90] This finding was replicated with a 77% rate of anti-5HT antibodies in FM, in contrast to only 19% with acute eosinophilia-myalgia syndrome (EMS) and 18% in controls.[91]

Melatonin levels in CFIDS are controversial: one study reported a significantly higher nocturnal melatonin plasma level for FM compared to controls, but no significant difference between CFS patients and controls.[92] However, another study reported lower levels of urine 6-sulphatoxymelatonin levels in FM patients than in controls (9.2 vs. 16.8 ug/24h, p=.06).[93] The lower urinary levels were thought to explain sleep problems found in CFIDS; consequently, the administration of 3mg melatonin nightly was found in the latter study to improve both pain and visual analogue scale for sleep.[93] Another recent parameter found to be abnormal with possible etiologic implications is nerve growth factor, which in FM has been found to be markedly increased in cerebrospinal fluid compared to controls (41.8 vs. 9.1 pg/ml).[94] This finding suggests that the painful symptoms of FM (and possibly CFS) may come from elevated substance P concentrations that, in turn, are due to faulty regulation by nerve growth factor.[94]

Among the most replicated findings in MDD are those of abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis. These include hypercortisolemia, elevated urinary free cortisol, and exaggerated cortical response to corticotropin.[81] In contrast, CFS patients have been found to have lower plasma cortisol (89 vs. 148 mmol/L, p<.01) and lower 24-hour urinary free cortisol (2.9 vs. 8.9 mmol/L, p<.04) than controls and a reduction in responsiveness to corticotropin.[95] In the first direct comparison study,[27] levels of circulating cortisol were highest in depressed patients, followed by normal controls, and, finally, in CFS patients (p=.01). Thus, it may be possible in the future to easily differentiate CFS patients from MDD patients biologically, with a simple combination of a plasma cortisol and serotonin test.

The importance in the differentiation between CFS and depression in HPA axis response has led to further studies and to a recent review that summarizes and contrasts these findings.[96] Specifically, the previous findings

of urinary free cortisol reductions in CFS but elevations in depression when contrasted to controls was replicated.[97] Dehydroepiandrosterone (DHEA) was found to be significantly lower in CFS, but not in depression, when compared to controls.[98] Impairment in DHEA response to IV adrenocorticotropin hormone (ACTH) was described (4.9 vs. 8.4 ug/L, p=.0002).[99] Impaired responses in CFS to both corticotropin-releasing hormone (CRH) and ACTH were reported.[100, 101] In agreement with these results are the findings of reduced ACTH and epinephrine to hypoglycemic challenge in FM.[102] Consistent with previous proposals of abnormal hypothalamic functioning with retained normal pituitary performance is a recent report noting a marked decrease in mean growth hormone (GH) secretion in FM when compared to controls (1.2 vs. 2.5 ug/L, p<.05) with retained normal GH responses to growth hormone-releasing hormone (GHRH).[103] In contrast, a test in CFS for GH parameters proved negative.[104]

A further area of interest has been the test of orthostatic intolerance in CFS. This test of cardiovascular response has been thought by many to be diagnostic for this disorder. In three recent studies, two in adults and one in adolescents, the rate of positive findings varied, with 28% and 40% in adults and 96% in adolescents.[105-107] Autonomic defects have been proposed, but not established, since in one of the trials, rates for controls were similar to that in CFS[107] (See Chapter 7).

Brain imaging studies have proliferated in recent years, including both positron emission tomography (PET) and single-photon emission tomography (SPECT). Frontal hypoperfusion has been reported in MDD and CFS.[35, 37] A recent study emphasized that perfusion patterns in CFS are similar, but not identical, to MDD with increased perfusion noted in right thalamus, putamen, and pallidum in both, increased perfusion noted in the left thalamus in CFS, but decreased perfusion in the left prefrontal cortex in MDD.[38] In addition to the previously reported left anterior prefrontal cortex hypoperfusion in MDD, temporal hypoperfusion has also been noted.[35] CFS patients showed significantly lower brainstem perfusion than depressed patients.[39] SPECT comparison studies have found, by degree, more severe findings in CFS than in MDD.[108] The midcerebral uptake index, an objective measurement reflecting radionuclide uptake in the brain, was found to be reduced in CFS (0.667) and in AIDS (0.650) in contrast to depression (0.731) and controls (0.716).[108] White matter abnormalities on magnetic resonance images have not been found with any regularity in CFS patients.[109] SPECT analysis of regional blood flow in FMS revealed statistically significant reduction in the right thalamus (p=.006) and in the inferior pontine tegmentum.[110] A recent PET study in FM patients reported a significant negative correlation between natural killer cell activity and posterior cingulate cortex function.[111] These imaging findings are gaining more favor as a means to demonstrate abnormalities in the brains of patients with CFS.

Although it might seem that CFS could be easily separated from MDD on the basis of laboratory indices of immune function, this is not the case. Differences are those of degree, rather than absolute. Tests of mitogen-induced lymphocyte stimulation with phytohemagglutinin (PHA) were reduced in six of 14 tests in MDD.[112] A comparison study reported PHA responsiveness to be 25% lower in CFS than in either MDD or control subjects.[113] Natural killer cell function was reduced in five of seven studies in severe MDD.[112] CFS studies have found 70% reductions in lytic units of natural killer cells, i.e., 39 for CFS versus 120 for controls.[114] The high vulnerability to infection in CFIDS (CFS and/or FM) patients previously reported was replicated in a study showing a significantly increased rate of multiple mycoplasma blood infections (52.8% or 48 of 91 patients, with double infections occurring in 30.8% and triple infections occurring in 22%).[115] In contrast, one recent report found no increased rate of HHV 6 or 7 or cytomegalovirus in civilian and Persian Gulf War veterans meeting the CDC criteria for CFS.[116] Further, anti-Epstein-Barr virus and anti-HHV6 antibody titers showed no statistical difference between CFS and control patients.[116]

Thus, diagnostic differentiation of CFS from MDD should be focused on physical signs and symptoms. A composite approach may include memory test differences (See Chapter 5), sleep EEG (See Chapter 6), serotonin function indices, and plasma cortisol testing.

Treatment

Non-psychotropic

In contrast to depressive disorders, the difference between treatment of MDD and treatment of CFS is that non-psychotropics have been used with some success in CFS. These include antivirals, immune modifiers, and ion flow treatments.[117] Antiviral agents have included acyclovir, immunoglobulins, essential fatty acids, and adenosine. Acyclovir, based on the theory of causation of CFS, failed clinically.[118] Two of three studies using immune globulin were successful;[119-121] a minimum dose of 2 g/kg/mo appeared to be important. At that dose, improvements were noted in Quality of Life visual analogue scale (41%), Hamilton Depression Rating Scale (42%), and in CD4 count (37%). An initial study of essential fatty acids (EFAs) at a dose of two capsules four times daily for 3 months led to improvement in fatigue and myalgia, rather than in depression and concentration.[122] Adenosine was beneficial in uncontrolled reports.[123]

The list of immune modifiers includes polyribonucleotide (Ampligen), LEFAC (liver extract, folic acid, and B12), Kutapressin (liver derivative extract), interferon, interleukin-2, and transfer factor. Ampligen is mismatched double-stranded RNA, which appears to

regulate expression of interferon, interleukin, and tumor necrosis factor (TNF), while activating intracellular pathways that are antiviral and enhance immune resistance. Two studies that administered up to 400 mg twice weekly for 24 weeks and a placebo-controlled study both reported improvements in overall functioning, perceived cognitive deficit, and exercise duration.[56, 124] A brief LEFAC placebo-controlled, double-blind, crossover trial did not show significant improvement; however, since CFS features may require months to improve, it is likely that this was too short a study.[125] The follow-up open label trial showed much more success. Kutapressin, a mixture of polypeptides that may be a bradykinin potentiator, has been reported to be successful in 75% of CFS patients given a mean of 33 injections at an initial rate of once weekly, followed by three times weekly.[126] A single study of oral alpha interferon at a dose greater than 1500 IU/day produced rapid relief in pain over 5 days with a much slower change in muscle tone.[127] Other case and open label studies involving interleukin-2, transfer factor, and magnesium showed initial success, but have failed in attempts at replication.

More recent non-psychotropic treatment studies for CFS and FM have addressed the potential efficacy of amantidine, L-carnitine, hydrocortisone, gamma-hydroxybutyrate (GHB), nicotinamide adenine dinucleotide (NADH) and revisited the efficacy of essential fatty acids. A well-controlled eight-week trial contrasting amantidine and L-carnitine reported significant benefit with L-carnitine, but not with amantidine.[128] Consistent with the HPA abnormalities noted with CFS (specifically, CRH-ACTH-cortisol,[100, 101]) two separate placebo-controlled trials found modest therapeutic benefits from oral low-dose hydrocortisone.[129, 130] Open-label treatment with GHB has been reported to improve fatigue and pain, as well as to reduce the alpha sleep anomaly, found in FM.[131] A double-blind trial found that 10 mg of NADH produced significant improvement over placebo in clinical outcome as determined using a rating scale based on CDC criteria ($p<.05$).[132] Unfortunately, in contrast, the positive response to EFAs previously reported could not be replicated in another three month study of high-dose Efamol Marine, with no statistical difference found between the treatment and placebo groups.[133]

An unusual treatment for CFS was based on the hypothesis that this disorder might be related to neurally mediated hypotension.[134] Abnormal responses to upright tilt testing were found in 22 of 23 patients and four of 14 control subjects ($p<.001$). Treatment was a general instruction to increase dietary salt intake by over 90% in combination with 0.1mg fludrocortisone. Of 19 patients treated for at least two weeks, nine reported subjective improvement or remission. However, a recent randomized, double-blind, placebo-controlled monotherapy trial of fludrocortisone to treat neurally mediated hypotension in CFS revealed no statistical difference in response (improvement on a global wellness scale) between fludrocortisone and placebo[135](See Chapter 7).

Psychotropic

Antidepressants continue to be used in the treatment of CFIDS. It is well known that tertiary tricyclic antidepressants, e.g., amitriptyline, produce relief of major depression generally at doses between 150 mg and 300 mg/day.[81] As previously reviewed, patients with CFIDS often improve at doses as low as 75 mg/day.[136] In contrast to MDD, there may be a differentiation in symptom response in CFS. Serotonin-based treatments may be more effective for immune, pain, and global responses; norepinephrine-based treatments may be better for the depressive symptoms associated with CFIDS. In terms of tricyclic antidepressants, imipramine failed at a dose of 75 mg/day for 12 weeks.[137] Amitriptyline has been reported to be successful in most studies, even at 50 mg/day; but the lowest study presented of 25 mg/day was not successful.[138-141] Improvement was found in morning stiffness, myalgia, fatigue, tender points, and pain tolerance. Nortriptyline, in a single A-B-A-B controlled case study, produced significant improvement in depression and overall CFS ratings.[142] Maproptyline was contrasted to clomipramine in a controlled study in FM; maproptyline was better at improving depression, whereas clomipramine was better at reducing pain.[143] Despite two further reviews that found tricyclics to be effective in CFS and FM, no further recent clinical trials have been done since 1997.[144, 145]

Monoamine oxidase inhibitors have also been reported to treat CFS.[136] Phenelzine at 15 to 30 mg/day was noted to produce good responses in 60% of patients, with 52% having prolonged improvement.[146] There are two recent clinical trials on the monoamine oxidase inhibitors selegiline and phenelzine in CFS.[147, 148] These short trials of four weeks each managed to show benefit over placebo in small sample studies by looking over a series of different ratings, with the plurality of patients showing improvement over worsening compared to placebo. However, the individual effects are not impressive clinically. The lack of greater significance most likely can be explained by a combination of two factors: a) length of active drug administration was being only four weeks while CFS patients often need as many as 12 weeks to show improvement, and b) the dose used in each study was at maximum at least 50% less than used in standard clinical practice. The most recent study done with moclobemide, a reversible inhibitor of monoamine oxidase-A, reported improvement in key symptoms experienced by patients with CFS.[149]

Bupropion, with specific effect to block reuptake of norepinephrine and dopamine, has been found to be ex-

cellent for improvement of depressive features of CFS, but not for immune indices.[150, 151]

Regarding the selective serotonin reuptake inhibitors, results are available concerning fluoxetine, sertraline, and citalopram. After initially promising case reports at a dose of 20 to 40 mg/day, fluoxetine appears, in controlled open studies for up to 12 weeks, to produce benefit for both global functioning and natural killer cell values.[152-155] However, two double-blind studies, one in FM[156] of only six weeks and one in CFS[157] of only eight weeks, did not show the same success. There are three reports available concerning sertraline; all are open studies that agree on significant improvement in fatigue, myalgia, sleep disturbances, depression, pain, and global ratings.[136, 158, 159] One of these studies clearly documented that improvement in FM symptoms was independent of the drug's efficacy as an antidepressant; thus, the biological activity of sertraline was directly responsible for its efficacy in the immune disorder.[158] Citalopram failed in one double-blind, placebo-controlled study of FM.[160] A recent 4-month trial of citalopram in FM did not reveal any statistically significant difference in the intention to treat and completer analysis between citalopram and placebo in the global judgment of improvement, though a tendency toward increased improvement in the completers was noted between the citalopram group (52.9%), compared to the placebo group (22.2%); further, significant differences in pain ratings, as measured with the Fibrositis Impact Questionnaire, were noted, as well as depressive features, as measured by the Montgomery Asberg Depression Rating Scale (MADRAS).[161]

Venlafaxine, perhaps because of its balanced effect to block reuptake of both norepinephrine and serotonin, has been reported to improve depression and pain/immune symptoms in case reports and open studies.[162-164] An initial report on nefazodone (Serzone), a serotonin receptor modulator, noted reduction in pain, with improvement in sleep, memory, and exercise tolerance during a 12 week trial.[165] In an open study of 10 patients with chronic fatigue, nefazodone treatment resulted in moderate/marked improvement in fatigue (40%), sleep (70%), mood (80%), and overall functional status (50%).[166] Further, an open study of FM treatment with tropisetron, a unique non-antidepressant 5HT3 serotonin antagonist, reported 5 of 10 patients with statistical improvement in pain score, fatigue, sleep, and number of tender points.[167]

Other reports have been presented on alprazolam and basic molecules.[136] Alprazolam at 3 mg/day maximum dose had no significant effect on any clinical measures.[168] Basic molecules have included S-adenosylmethionine (SAMe), 5-hydroxytryptophan (5HTP), and lithium. SAMe, a methyl group donor that has been used successfully in the treatment of depression, was administered at a dose of 200 mg/day intramuscularly for 21 days and led to significant reductions in both trigger points and Hamilton Depression Rating Scale.[169] 5HTP, a precursor of serotonin, given in a double-blind, placebo-controlled study and an open study for 3 months, reduced numbers of tender points and improved measures of fatigue, anxiety, pain intensity, and sleep.[170, 171] Lithium augmentation of tricyclic antidepressants at serum levels of 0.5 to 1.1 meq/L led to improvement in stiffness and pain in three cases.[172]

Psychostimulants (methylphenidate, d–amphetamine, pemoline, and modafinil) are commonly used in the treatment of medically impaired depressed patients and as adjunctive agents in the treatment of MDD.[173-176] To date, these agents have not been evaluated in CFIDS beyond a single negative case report of modafinil and FM (that may have been negative due to the briefness of the trial).[177]

Thus, in terms of treatment of CFIDS, in contrast to MDD, there is a spectrum of both non-psychotropic and psychotropic treatments. IgG may be effective, particularly in patients with depressed serum levels; Ampligen may be of universal benefit; Kutapressin may be of value. Improvements are noted from L-carnitine, GHB, and NADH. Regarding psychotropics, if the patient's focus is on chronic fatigue or depressive symptoms, bupropion and/or low dose tricyclic antidepressants may be successful. In contrast, if the CFIDS symptom picture is more of global dysfunction and immune difficulties, a serotonergic approach with sertraline may be particularly beneficial. An additional bonus to use of sertraline may be its benefits on cognitive functioning.[178] Venlafaxine and nefazodone also appear to have more global effects; however, further controlled trials for both of these promising psychotropics in the treatment of CFIDS are indicated.

It is important to remember that beyond the presentation of depressive symptoms in CFIDS, there may be a concomitant MDD that predated the CFIDS. Treatment strategies should attempt to address both illnesses if feasible. Effective interventions for a concomitant MDD does not preclude maximizing treatment specifically of the MDD; but it is important to avoid approaches that would negatively impact CFIDS secondary to psychotropic side effects.

Conclusion

When depressive symptoms exist with those of chronic fatigue syndrome, an accurate differentiation can usually be accomplished by focusing on diagnostic criteria. The presence of multiple symptoms and physical signs of CFS may be of great value. In terms of laboratory testing, a single helpful test may be measuring the plasma cortisol, which is usually high in depression and low in CFS. Future work should focus on the combination of plasma cortisol with an index of serotonin function, which is high in CFIDS and low in depression. Additional research should focus on neuroimaging and immune differ-

entiation. The combination of multiple tests should result in a significant and clinically useful separation between CFIDS and MDD.

For treatment of the patient with significant depression or MDD with CFIDS, one should think of the noradrenergic approach using bupropion or low-dose tricyclic antidepressants in combination with a selective serotonin reuptake inhibitor, especially sertraline, to aid improvement of global, pain, and immunologic parameters. Further research should focus on larger placebo-controlled, double-blind trials of these and other antidepressants, e.g., venlafaxine and nefazodone, as well as the evaluation of psychostimulants.

5 Cognitive Dysfunction in CFS

Carolyn Grace, PhD

Patients diagnosed with CFS who present for neuropsychological assessment are typically individuals who have led previously active lifestyles with minimal to no report of prior health or psychiatric disturbance. These patients frequently report a significant level of stress secondary to experiencing functional declines in physical, cognitive, social, academic and/or vocational areas. Many patients are unable to work, thus they are either on disability or in the process of applying for disability. Younger patients are often unable to attend school on a full-time basis. In addition, patients typically report questioning psychological well-being and feelings of frustration at dealing with a syndrome that does not have a definitive test for diagnosis, nor a specifically defined treatment regime. Vocational and/or educational difficulties present as attention/concentration difficulties, reduced information processing, short-term memory problems, depression, anxiety, fatigue, sleep disturbance, mood disturbance, and difficulty with initiating and completing tasks. Patients often complain of cloudy sensorium, the "brain fog" of CFS.

Neuropsychological Diagnostic Work Up

Neuropsychological assessment is helpful to establish a baseline of neurocognitive functioning, to discern the relative contribution of emotional factors in a patient's clinical presentation, to confirm the presence of cognitive symptoms consistent with CFS, and to make treatment recommendations regarding potential cognitive remediation and/or psychological interventions. A comprehensive neuropsychological evaluation includes review and assessment of the following areas: clinical interview with the patient, interview with a family member/close friend, neurocognitive assessment of general intellectual functioning (See Table 5-1), and a review of medical records, educational records, and/or vocational records. A review of past educational records and/or resume documenting employment history provides critical information for the clinician to both understand and best objectify a patient's report of symptoms.

Psychological Assessment of Mood

Psychological assessment is accomplished utilizing clinical interviews, patient observation, self-report instruments (e.g., Beck Anxiety Scale, Beck Depression Inventory II), objective testing instruments (e.g. MMPI, MCMI), and instruments assessing for malingering (e.g. Portland Digit Recognition Test, Rey 15-item test). Clinicians should be cognizant of issues of differential diagnosis.[180, 181] Certainly psychiatric syndromes may confound a patient's neurocognitive presentation. The physician can help to discern the relative contribution of psychological symptoms to the report of neurocognitive difficulties. Such decisions influence recommendations regarding the possible utility of various treatment regimes (e.g., psychopharmacologics, various psychological therapies, or cognitive remediation).

The major comorbid psychiatric diagnoses for patients with CFS include Major Depressive Episode, Panic Disorder, Generalized Anxiety Disorder, and Somatization Disorder.[182] It is possible impairment(s) that patients with CFS demonstrate on cognitive testing may be a result of primary depression.[181] In addition, ruling out malingering has benefits: validation of patient complaints, clarification for the family and other health care professionals, and the establishment of eligibility for disability/Social Security Insurance. It has also been noted that as a result of primary psychiatric illness, some patients may experience greater fatigue, which may create an additional risk factor for prolonged disability due to CFS symptoms. Conversely, the clinician must challenge psy-

Table 5-1
Neurocognitive Assessment of General Intellectual Functioning with Testing Instruments*

Instrument/Test	Measure of Test
Wechsler Adult Intelligence Scale III	General Intellectual Functioning
Wechsler Memory Scale III	Verbal Learning & Memory
California Verbal Learning Test	Verbal Learning & Memory
Benton Visual Retention Test	Visual Memory
Rey-Osterrieth Complex Figure	Visual Construction & Memory
Tapping Test,	Motor Speed & Skill
Grooved Peg Board	Motor Speed & Skill
Grip Strength	Motor Strength
Conner's Continuous Performance Test	Sustained Attention / Concentration
PASAT	Auditory Processing Speed
Controlled Oral Word Asso. Test	Verbal Fluency
Animal Naming	Verbal Fluency
Ruff Figural Fluency Test	Visual Fluency
Booklet Category Test	Nonverbal Hypothesis Testing
Wisconsin Card Sorting Test	Nonverbal Problem Solving
Hooper Visual Organizational Test	Visual Analysis & Synthesis
Writing & Oral Story Generation	Language Functioning
Aphasia Screening	Language Functioning
Boston Naming Test	Language Functioning
Stanford Diagnostic Reading Test	Reading Abilities
Wechsler Individual Achievement Test	Achievement Areas

*Adapted from Grafman, 1994[179]

chiatric diagnoses when the symptoms fit chronic fatigue, rather than a primary psychiatric disorder.[182]

Treatment

The treatment and management of the neurocognitive dysfunction in CFS includes a multidisciplinary approach to this often long-term debilitating syndrome. Aspects of treatment for consideration include psychoeducational resources, psychopharmacologic consultation, behavioral medicine, and accommodation recommendations for the academic or vocational setting.

Patients with CFS welcome the opportunity to educate themselves and family members about the biological, psychological, and environmental influences that contribute to their experience of physical, cognitive, and psychological complaints. Following neuropsychological evaluation, the typical format would be to offer a "psychoeducational meeting" to provide neuropsychological testing feedback, educational information related to biological and psychological factors contributing to symptoms (including discussion of basic principles of behavioral medicine, health psychology, and neuropsychology), and treatment recommendations.

Cognitive Behavioral Treatment (CBT)

CBT strategies are aimed at addressing aspects of cognitive schema, implementing behavior modification, introducing basic cognitive strategies for patients with cognitive complaints, and suggesting appropriate exercise programs (e.g. yoga and meditation). The literature regarding the effectiveness of such CBT with CFS is sparse, with some reports of significant improvement in symptoms and others stating no significant differences between patients receiving CBT and those without CBT.[183] Nevertheless, CBT is often a useful adjunctive treatment. Sharpe[184] has noted that cognitive-behavioral treatment is a pragmatic approach for a syndrome without any specific treatment regime. The literature regarding the effectiveness of such cognitive behavioral treatment in CFS includes reports of significant improvement in symptoms.[183, 185] The focus of such treatment is to modify the individual's perception of factors contributing to the experience of physical and psychological disability. Target areas for interventions often include physical exercise, emotional status, sleep patterns, stress level, self-esteem, social relatedness, and illness-related schema. A typical treatment format utilizes a protocol of 6-to-8 weekly treatment sessions. Patients with CFS tolerate this model, with the option to enroll in a maintenance CBT as needed. The goal of CBT is to decrease symptoms by enabling patients to develop coping skills, to recognize target areas of change, to address adjustment issues, and to modify cognitive schema and behavior patterns.

Accommodations in Academic or Vocational Settings

Many patients may benefit from accommodations that modify physical or cognitive demands of an academic or work environment. Based on neuropsychological test data, a rationale may be established for various accommodations, including, but not limited to, the following: abbreviated work or academic day, use of augmentative cognitive strategies in the classroom or work environment, reduced academic course load, staggering of examinations, etc.

Psychopharmacologic Interventions

Psychopharmacologic therapies can improve disturbances in attention/concentration, sleep-wake cycle, and the management of mood disorders. Pharmacologic intervention involves discerning aspects of normal reactive depression to a chronic illness versus endogenous/ neurobiologically based depression that may in fact benefit from medication intervention. Chapters 4 and 6 discuss some specific medications.

Conclusion

Neuropsychological assessment is a critical dimension in the management of CFS and provides assistance in the diagnosis of a complex, often debilitating syndrome. A range of specific tests of cognitive dysfunction commonly present in patients with CFS are available. In addition, neuropsychological assessment provides a means to portion out the relative contributions of potential emotional factors in the clinical presentation of CFS patients. Overall, neuropsychological assessment is designed to provide a cognitive baseline of patient abilities, assist with diagnosis, and provide recommendations for specific areas of therapeutic intervention.

6 Sleep Dysfunction in CFS

Richard N. Podell, MD, MPH

Many patients with CFS feel sleepy, as well as tired. Whether or not they have difficulty falling asleep (sleep onset insomnia) or difficulty staying asleep (sleep maintenance insomnia), most CFS patients feel that their sleep is not refreshing. They wake up in the morning feeling as if they haven't really rested.

Improving sleep is a realistic goal. As clinicians know, this is often a complex and difficult task. Even modest improvement in sleep can have important positive effects on the patient's sense of well-being.[186-191]

Pathophysiology

We only partly understand why people with CFS lack restorative sleep. For many, especially those with FMS, the EEG shows alpha wave activity inappropriately intruding into the delta waves of deep sleep. A significant minority have classic sleep disorders complicating their CFS: periodic leg movement disorder or sleep apnea. Others suffer from insomnia, hypersomnia or non-restorative sleep. The mechanisms for these aspects of CFS are not clear (See Table 6-1).

Diagnosis

When either insomnia or poor sleep is chronic, the physician should consider whether a specific, treatable sleep disorder is present. Occasionally, the diagnosis of CFS is mistaken, and a primary sleep disorder is the main cause of fatigue. More often, CFS is the diagnosis, but specific sleep disorders can complicate and exacerbate the illness. Sleep disorders can be suspected by asking patients about key symptoms, specifically about whether they snore, struggle for breath at night, or have ever been told that they stop breathing or have muscle twitching often while asleep.

Teaching a family member or friend to observe the sleeping patient for at least 30 minutes, one or several nights, can be very useful. This is the minimum that should be done for patients with chronic fatigue without a clear-cut cause. The observer should look for severe snoring, episodes of not breathing for 10 seconds or more, snorting or struggling for breath. Frequent gross or fine muscle or limb movements or twitches should be noted.

One may observe Periodic Leg Movement Disorder (PLMD) if there is a restless leg syndrome during the day or evening.[194, 195] However, lack of restless leg should not deter evaluation for PLMD. Typically, patients are not aware of nocturnal muscle twitches or limb jerks. (Having one or two twitches while falling asleep or while waking up can be normal, and does not suggest PLMD). Multiple, 30 minute observations by someone lying close to the patient in bed may detect PLMD. This condition is often missed unless a sleep study is done.

We cannot exclude a sleep disorder with a very high

Table 6-1
The Main Sleep Disorders That May Complicate CFS[192, 193]

Disorder	When to Suspect This Disorder	Comments
Obstructive Sleep Apnea	Heavy snoring or patient experiences sudden awakenings with subjective apnea or struggling for breath.	Fairly common. Bed partner may be aware, especially if they are asked to observe for typical signs.
Central Sleep Apnea	The patient does not snore, snort, or struggle but has frequent periods of apnea lasting 10 seconds or more.	Less common, but less obvious to an observer. Non-restful sleep might be the only symptom.
Periodic Leg Movement Disorder (PLMD)	Repeated episodes of twitching muscles ranging from microscopic to gross limb movements. Twitches might or might not be noticeable to bed partner.	A common syndrome that may be more common than average among patients with CFS.
Delayed Phase Sleep Disorder	Typical "night owl" pattern. Patients usually feel much better when they can keep to their preferred sleep cycle.[192, 193]	Conscientious scheduling, bright light in the AM, low dose Melatonin in the early evening, and appropriate sleeping medication can help significantly.
Alpha-Delta Sleep Disturbance	This disorder is common in patients with FMS or other chronic pain syndromes. Alpha wave intrusion is associated with reduced time in deep stage 3 and 4 delta sleep. This intrusion causes non-restful sleep.	Tricyclic antidepressants, cyclobenzaprine and trazadone tend to restore more normal sleep architecture.[190]
Narcolepsy	Profound daytime sleepiness is the hallmark, often to the point of falling asleep inadvertently.	Insufficient hours or poor quality sleep cause daytime sleepiness that can mimic narcolepsy. Recognizing narcolepsy requires the physician to maintain a high index of suspicion.
Anxiety, Depression, and/or Chronic Pain	Often complicate CFS. These tend to make the sleep disturbance worse.	Treat conditions as appropriate.

degree of confidence without professional monitoring, utilizing an overnight sleep study. We would recommend that all patients with chronic insomnia or chronically non-restorative sleep be evaluated in consultation with a sleep specialist whenever cost or third-party payment is not an issue. Therefore, clinicians should exercise judgment for each patient regarding the indications for a formal sleep evaluation. It is important to note that some patients with CFS have relatively normal overnight sleep tests. These patients also describe their sleep as not restful. The patient's subjective report should be respected as valid and be taken seriously.

Non-Pharmacologic Treatment of Sleep Problems in CFS

Trial and error may be productive. Techniques that work for one patient often fail for others. Often, long-term, rather than short-term, treatment may be needed, with all the trade-offs of potential medication side effects that that implies. Patients with CFS as a group tend to be more sensitive than average to medication side-effects.

Even modest improvements in sleep quality can make a meaningful difference in the quality of life of a patient with CFS. However, better sleep is not, by itself, a cure for CFS. Exercise intolerance and subjective fatigue typically remain problems even after sleep improves.

Sleep specialists recommend an important role for sleep hygiene and behavioral techniques. Ideally, a nurse or patient educator would spend an hour with each patient to review basic sleep hygiene and relaxation skills. Attention to these details can often make a major difference. Table 6-2 lists basic principles of sleep hygiene that should not be overlooked in patients with CFS.

Additional and more complex behavioral techniques can often help sleep problems of any kind, especially those where the overnight sleep test fails to disclose specifically treatable pathology[192, 193, 196] (See Table 6-3).

Table 6-2
Principles of Sleep Hygiene for Use in Patients with CFS

- Discuss whether medications might be disrupting sleep, e.g. decongestants, diet pills, or stimulating antidepressants. Evening caffeine or alcohol are often a problem.
- Keep your sleep schedule regular. Shifting sleep time tends to disrupt sleep. Create a habit pattern of staging down your activities throughout the evening. This process will help condition your body to expect to be able to sleep. Consider turning the TV off early. Try music or dull reading.
- Keep the bedroom dark and quiet and the mattress comfortable. Leave marital conflicts outside.
- Bed should be used only for sleep and sex. Move to a chair or couch when not engaged in either.
- Clear your mind of this day's events and the next day's worries. For example, write down your regrets and plans, then lock them in a drawer so you can go back to them tomorrow.
- Don't exercise just before bedtime. (Even relaxing meditation might make you too alert for sleep.)
- Take a hot bath in the early evening. While it initially prompts alertness, drowsiness then follows as your body temperature drops.
- Take a modest carbohydrate snack or warm milk before sleep which promotes drowsiness for some.
- Use relaxation tapes, imagery, slow diaphragmatic breathing, or meditation.
- Use ear plugs if it is too noisy. If it is too light, consider eye shades.
- Use white noise (e.g. a fan) or calm music to soothe out and block out unwanted sounds.

Table 6-3
Behavioral Techniques for Sleep Onset Insomnia

Technique	Comment
Sleep Restriction/Consolidation Therapy	Restriction of the total time in bed to 4 hours or less, whether patient actually sleeps or not. As the proportion of time sleeping increases, the time allowed in bed is extended. This technique often increases the proportion of time that one is actually asleep.
Paradoxical Intention	Trying to stay up later may help put patient to sleep
Relaxation Skills	Diaphragmatic breathing, visual imagery (e.g. counting sheep), muscle relaxation.
Cognitive Therapy	A form of brief psychotherapy that improves coping skills, e.g., not turning molehills into mountains. Several studies show that cognitive therapy can improve quality of life in CFS. Other forms, e.g., psychodynamic approaches might also be helpful, but have not been formally tested for CFS (See Chapter 5).

Pharmacologic Treatments for Insomnia or Non-Restorative Sleep

If chronic pain, sleep apnea, PLMD, anxiety or depression is a dominant problem, these symptoms should

be addressed with their standard treatments. Whether or not these disorders complicate sleep, pharmacologic regimens specifically for sleep can be very useful (See Table 6-4).

Sleep problems among many CFS patients are chronic, not intermittent. While limiting sleep medicine to intermittent use is a desirable goal, there may be good medical and psychological reasons to encourage chronic ongoing treatment. If sleep medicines are to be used regularly, it is advantageous to use those medicines, which are less likely to disrupt sleep architecture or to induce tolerance or addiction. The physician should be prepared to "test" a number of different sleep medicines. Some patients do well with a combination of sleep medicines, each at a relatively low dose. A few may benefit by rotating a different sleep medicine every night or every few nights. Patients with CFS tend to be very sensitive to medicine side effects, so it is often wise to start with new medicines with a very low dose.

For better sleep, the first choice should often be either antidepressants, such as trazadone (Desyrel) or the sedating tricyclic antidepressants, e.g., amitriptyline. chronic pain. However, because of their long action, they are often too sedating in the morning.[192, 193] When used for sleep, the tricyclics or trazadone (Desyrel) usually do best at lower doses than are needed for treating depression. The most commonly used tricyclics, listed in order of increasing sedation and increasing side effects: nortriptyline (Pamelor), doxepin (Sinequan) and imipramine (Tofranil), as well as amitriptyline (Elavil).

For the tricyclics, low doses, e.g., 10 mg, can be used at first. A few very sensitive patients might start with 1-2 mg of doxepin suspension), with stepwise increases in dosage steps toward the 20-50 mg range. If also treating depression, the increase can proceed to the usual full therapeutic doses (75-150 mg). For trazadone (Desyrel), a starting dose of 25-50 mg qhs is adequate. If necessary, one can increase in steps toward the 150 mg range. When using these antidepressant medicines, sleep benefits are often seen the first night. This result contrasts with the relatively high dose range and 3-4 weeks typically needed to see effects for depression. Yet, maximum sleep benefit probably takes several weeks.

Antidepressants can be useful sleep aids whether or not the patient is depressed. Also, some patients experience a paradoxical effect, becoming more agitated and unable to sleep. For sleep onset insomnia, consider short-acting agents, such as zafeplon (Sonata) or triazolam

Table 6-4
Commonly Used Medicines for Sleep

Classification	Medication	Prominent Side Effects	Prominent Drug Interactions	Comments
Tricyclics	Amitriptyline (Elavil) Doxepin (Sinequan) Nortriptyline (Pamelor)	Prolonged sedation; dry mouth; tachycardia; urinary obstruction; weight gain; heart arrhythmia; conversion of depression to manic phase	Drugs metabolized by P450 2D6, e.g. cimetidine; quinidine; some SSRIs; MAO inhibitors (contraindicated); anticholinergic agents	Especially useful in FMS, caution if heart arrhythmia
Antidepressant Misc. type	Trazadone (Desyrel)	Priaprism (rare); dry mouth; heart arrhythmia	Digoxin, phenytoin	Useful for sleep onset and maintenance, perhaps also FMS
Muscle relaxer	Cyclobenzaprine (Flexeril)	Dry mouth; dizziness	Similar to the tricyclics	Often used for FMS
Benzodiazepines	Clonazepam (Klonopin) Temazepam (Restoril) Lorazepam (Ativan) Estazolam (ProSom) Guazepam (Doral) Triazolam (short-acting)	Tolerance; habituation; antegrade amnesia; respiratory depression	Different drugs of this class interact adversely with specific SSRIs	Can help PLMD; duration of sedation varies with individual
Sedating antihistamines	Diphenhydramine (Benadryl)	Prolonged sedation; dry mouth; urinary obstruction	Phenothiazines; MAO inhibitors	May be useful when other medications not tolerated
Non-benzodiazapine hypnotic agent	Zolpidem(Ambien) Zafeplon (Sonata)	Dizziness, amnesia, anxiety	Sertraline, rifampin, cimetidine	May be habituating in high doses or with prolonged use. Short-acting
NSAIDs	Aspirin Ibuprofen Celecoxib (Celebrex) Rofecoxib (Vioxx)	Gastritis, gastro-intestinal bleeding, allergic reactions, renal problems, fluid retention	Coumadin, cyclosporine, (See package insert for individual agents)	May help sleep by reducing pain; A few individuals report sleep benefit even if not in pain

These medicines usually do not disrupt sleep, maintenance insomnia, or sleep architecture and may improve sleep. They can be useful for suppressing the alpha-delta sleep abnormality that is often seen with FMS or with

(Halcion). For sleep maintenance insomnia, consider zolpidem (Ambien) or one of these benzodiazepines: clonazepam (Klonopin), temazepam (Restoril), or lorazepam (Ativan). Flurazepam (Dalmane), a long-acting benzodiazepine, usually leaves patients too sedated in the morning.

Benzodiazepines have a relatively high potential for abuse, tolerance, habituation, and abuse. Ambien, a non-benzodiazepine, has less potential for tolerance and perhaps also less for habituation. However, Ambien is not entirely free from the risk of addiction. Transient amnesia has been reported for benzodiazepines as a class, especially with triazolam.

In PLMD, employ a very brief diagnostic trial of dopaminergic agonist, which is a moderately effective treatment for PLMD, e.g., Sinemet 25/100. If subjective sleep quality improves, consider PLMD as fairly likely. Do not continue to treat empirically. Confirm the diagnosis with an overnight sleep study. Lack of improvement with Sinemet does not rule out PLMD. Various antidepressants have been reported to exacerbate PLMD in some patients.

Almost all sleeping medicines should be used with caution for people who have to be alert when they first wake or throughout the day. Most hypnotics will also potentiate the sedating effects of alcohol and other sedating drugs. Use in pregnancy should be coordinated with an obstetrician (See Chapter 9).

Complementary Medicine Therapies for Sleep

There are several over-the-counter medications that patients with CFS may use as sleep adjuncts. A few are listed below:

- Melatonin is probably effective for a small minority of persons with insomnia, especially among the elderly. Little is known about potential long-term side effects or drug interactions. It is probably useful for delayed phase sleep disorder and for jet lag.[93, 197, 198]
- Valerian Root is a mediocre short-term sedative. However, at least 3 double-blind studies from Germany show benefit for sleep and for mood after 3-4 weeks of taking Valerian, 300 mg, bid. Valerian might also help anxiety. Current evidence suggests that Valerian does not usually impair mental or motor performance, although some people find it too sedating to take during the day. It does not seem to be addictive. There are no substantial long-term studies of safety or benefit.[199, 200]
- Lemon balm, hops, passion flower and skullcap are other less well-studied herbs that might have value for sleep and that are sometimes combined with Valerian.
- 5-Hydroxytryptophan (5 HTP) is available in health food stores. Tryptophan is available by prescription from compounding pharmacies. These are biochemical precursors to the neurotransmitter Serotonin (and also melatonin). They might be effective for helping sleep onset.[201] Tryptophan or 5 OHT should not be taken with SSRIs or other drugs such as MAOs that affect serotonin, since hyperserotonin syndrome has been reported. A tainted batch of tryptophan once caused an epidemic of eosinophilic myalgia syndrome, including fatalities.
- Lavender extract, used as aromatherapy, showed benefit for sleep onset insomnia and accompanying anti-anxiety effects in studies. No side effects are expected.[202]

All of these natural products can potentially interact with selected drugs or with specific nutrients or herbs. Books on this topic and computer data bases in health food stores and pharmacies are beginning to be available.[203]

Conclusion

Sleep disturbance is a major problem for patients with CFS. Sleep studies will often disclose some abnormality. Pharmacologic and non-pharmacologic measures, including cognitive therapies, can be of benefit .

Complementary medications available over-the-counter may be of help to some patients. When sleep dysfunction remains persistent and severe, a formal consultation with a sleep physiologist should be obtained.

7 Dizziness in CFS

Julian Stewart, MD, PhD

Patients with CFS classically complain of dizziness, particularly with changes in posture. Orthostatic intolerance (OI) can be defined as the development of symptoms during upright standing, relieved by recumbence. Acute orthostatic intolerance is usually manifested as syncope (fainting). Many syncopal patients have no intercurrent illness; between faints, they are well. Chronic OI also occurs; the medical history is used to determine chronicity. Defining symptoms of chronic OI include dizziness in all patients with a high incidence of altered vision (blurred, "white outs", "black-outs"), fatigue, nausea, and palpitations. A large fraction of patients also experience headache, tremulousness, difficulty breathing or swallowing, sweating, pallor, and other vasomotor symptoms.

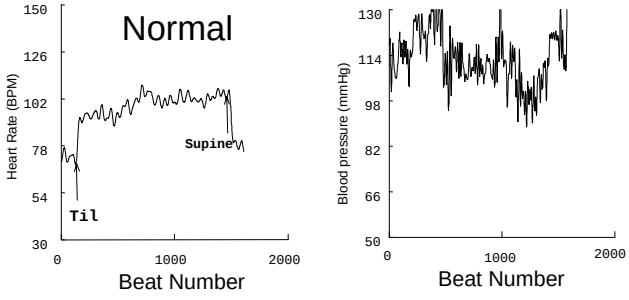
Patterns of OI are determined by an orthostatic stress test, i.e., a means by which upright gravitational stress can be imposed in a controlled fashion and the physiological response monitored in detail. While standing can be used, individual differences and patient motion may make this difficult. Therefore, the standard of orthostatic assessment is the head-up tilt table test. Head-up tilt (HUT) was used for research purposes for decades. It was first used as a clinical orthostatic stress test in 1986.[204] The device comprises a table driven by an electrical motor with a supportive footboard enabling positioning of a patient at varying angles of upright tilt. Although it would seem that an angle of 90^{o} is most physiologic, this angle usually induces too many false positives (patients with no history of OI who have intolerance induced during testing). Therefore, lesser angles, such as 60^{o} or 70^{o}, are customarily used.[205, 206] Following a resting period, the patients are placed upright. Their response over a period of tilt is assessed, usually anywhere between 30-45 minutes. At a minimum, blood pressure and continuous electrocardiography are assessed. Typically, a form of continuous blood pressure assessment, such as finger plethysmography or arterial tonometry, is used. Respirations are also assessed on a moment-to-moment basis. Other researchers have used methods to assess peripheral, thoracic (chest), and central nervous system blood flow. Many laboratories use medications, often isoproterenol, to enhance the fainting response which produces more true positive tests (and more false positives), but lacks a physiological rationale. The central purpose of a tilt table test is to reproduce symptoms of OI in a setting in which hemodynamic variables, such as blood pressure, heart rate, and blood flow, can be assessed. Most often, there is correlation with changing physiological signs, but the definition of OI requires symptoms. For example, the incidence of false positive faints during head-up tilt is high. If the complaining symptoms are not reproduced, but the patient has a simple faint, the test is judged as negative or, alternately, a false positive. It is not a sign of OI. Other patterns of hemodynamic disturbance seem invariably associated with symptoms and are more reliable indicators of chronic impairment.

The normal response to HUT is a modest increase in heart rate (See Figure 7-1), by 10-20 beats/min, without a fall in systolic blood pressure. Abnormal tilt test responses can be used to categorize patterns and physiologic types of OI. The overall patient assessment of chronicity and severity of impairment should be combined with these data to reach any conclusion concerning the nature of OI in a particular patient. In addition to the normal pattern, three typical patterns of OI are depicted in the figures, which show the systolic blood pressure and heart rate in patients during upright tilt.

Classic Simple Faint (Vasovagal Syncope)

Simple faint is a form of syncope. Syncope is defined as a sudden transient loss of consciousness with loss of postural tone and spontaneous recovery caused by impaired blood flow to the central nervous system. Impaired flow is usually, but not always, caused by low blood pressure. Syncope may occur supine or upright and under a wide variety of conditions. It may be due to medication; cardiac disease, most commonly arrhythmic disease; or severe impairment of cardiac blood flow caused by mechanical pump failure or obstruction. It may be due to transient impairment of central nervous system function, as in a transient ischemic attack (mild stroke), but this cause is less common. However, although convulsive-like movements may occur during syncope, it is distinct from

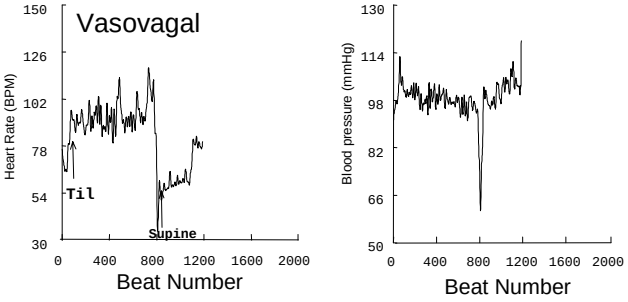
Figure 7-1
Normal Patterns of Blood Pressure Changes Seen with HUT Testing



a seizure disorder and is distinct from coma, in which loss of consciousness is not transient at all.[207] Cardiac syncope is often quite serious and should be regarded as life-threatening. Although cardiac syncope is not often closely associated with orthostasis, it may be. Causes of cardiac syncope include the long QT syndrome, arrhythmogenic right ventricular dysplasia, cardiomyopathies, left ventricular outflow obstruction, myocardial infarction, primary pulmonary hypertension, and most commonly ventricular tachycardia, bradyarrhythmias, and related arrhythmic events.[208] The first job in evaluating syncope is to evaluate the patient for possible cardiac syncope. Cardiac syncope may first manifest during exercise, which is the best and most physiologic stressor of the myocardial circulation and overall cardiac function.[209] Nevertheless, the large majority of exercise-related syncope is non-cardiogenic in origin, at least for children and adolescents. Cardiogenic syncope is not common in patients with CFS and will not be regarded further. There are numerous excellent texts on the subject.

A large fraction of syncope is either neurocardiogenic or unexplained. Often, the unexplained variety is reclassified as neurocardiogenic once tilt table testing has been performed.[210] Neurocardiogenic is the current term for fainting mediated through a combination of inappropriate vascular and heart rate control. It is rarely fatal – although it can be under certain unique circumstances (e.g. driving a car) – but it can be injurious. There is little compelling evidence for a primary role for the heart in neurocardiogenic syncope, once cardiogenic syncope has been ruled out. The term is thus somewhat misleading. Synonyms for neurocardiogenic include neurally mediated syncope and vasovagal syncope. Almost all of neurocardiogenic syncope in children can be deemed vasovagal, an appropriate descriptive designation coined by Sir Thomas Lewis[211] in which the "vaso" prefix denotes dilation of blood vessels, and the "vagal" suffix denotes slowing of the heart rate through stimulation of the vagus nerve. Vasovagal syncope almost always occurs in the upright position, which may sometimes include sitting. Therefore, it is regarded as a form of OI. Vasovagal faint is depicted in Figure 7-2. Typically, patients easily tolerate the early parts of tilt with little change in blood pressure or sensorium. Following a variable period of time, on the order of 3 to 20 minutes, patients develop orthostatic symptoms of nausea, dizziness, heat, heavy breathing, and sweatiness associated most commonly with a small, initial slow fall in blood pressure, which can be seen if the figure is inspected closely, and then an abrupt drop in blood pressure and heart rate. The early fall in blood pressure is coincident with a decrease in normal vasoconstriction. Blood pressure and heart rate may plummet precipitously, and asystole may occur. When this drop happens, there is a rapid loss of central nervous system activity and often a dysinhibition of peripheral neurologic responses resulting

Figure 7-2
Vasovagal Patterns of Blood Pressure Changes Seen with HUT Testing



in muscular movements mimicking a tonic-clonic seizure. This is denoted convulsive syncope. The absence of true seizure activity was confirmed as early as the 1950s by Gastaut and associates[212] and later reconfirmed using HUT methods by Grubb and coworkers in the 1990s[213] Such episodes, while relatively uncommon, are quite dramatic.

Mechanisms for Vasovagal Faint

The most popular proposed mechanism holds that fainting results from an errant stretch reflex from the left ventricle. The reflex is activated by an underfilled due to reduced venous return, overly contractile due to sympathetic activation, left ventricle. This results in a paradoxical reflex mediated by unmyelinated C-fiber nerves arising from the left ventricle to the nucleus tractus solitarius in the CNS and causing vagally mediated bradycardia, as well as vasodilation.[212, 214] Treatment by increasing blood volume should help relieve underfilling, while negative inotropic contractile agents should help to reduce cardiac contractility. Both hypercontractility and decreased ventricular stretch have been called into question by recent research.[212, 215] Also, patients receiving cardiac transplants retain the ability to faint, which implies that the ventricular receptor theory cannot explain all simple faints. Other theories of fainting include epinephrine or renin surges, which would rationalize the common use of isoproterenol as adjunctive provocation.[212, 216] Such surges do occur in those who faint and take some minutes to develop. However, it remains unclear whether these are the cause of the hemodynamic abnormalities or a response to decreased blood pressure during faint. A decrease in cerebral blood flow has also been shown to occur in syncopal patients and may precede a large fall in blood pressure.[212, 216] However, blood flow is similarly impaired in chronic OI in which hypotension does not usually occur.[212, 217] Other proposed mechanisms include changes in CNS neurotransmitters, such as serotonin, norepinephrine, neuropeptide Y and substance P. Causation has not been established. In summary, it is fair to say

that we still have no precise understanding of the mechanics or the mechanism of simple faint.

Dysautonomic OI

Included in this group are patients with true orthostatic hypotension defined by the American Autonomic Society to be a persistent fall in systolic blood pressure of >20 mm Hg within 3 minutes of assuming the upright position.[205] This group includes patients with autonomic failure. Autonomic failure comprises primary forms, such as primary autonomic failure and multiple system atrophy, and more common secondary forms as occur with Parkinson's disease and diabetes. Dysautonomia may also be drug-induced. Pediatric causes are rare and include familial dysautonomia as the only relatively common variant.[218] Acute forms may occur during infectious and inflammatory diseases or be related to peripheral nerve disease, e.g. Guillian-Barre syndrome. Using standard tests of circulatory autonomic function, such as timed breathing and the quantitative Valsalva maneuver, patients show signs of circulatory autonomic dysfunction. Rarely do patients with CFS have circulatory abnormalities that fulfill generalized dysautonomic criteria. However, isolated autonomic changes may occur in some patients with CFS. Findings in dysautonomia may include pupillary, gastrointestinal, and sweating abnormalities. Neurologic damage, such as occurs in cerebral palsy and trauma, may result in some autonomic dysfunction, in addition to other neurologic disability. Responses to orthostasis in such patients differ from those in truly dysautonomic patients in that compensatory mechanisms may adapt the patient to orthostasis, e.g. increased blood volume, which seldom occurs in the dysautonomic.

Dysautonomic OI is depicted in Figure 7-3. Blood pressure falls while there is usually no important change in heart rate throughout the course of the tilt. The appropriate heart rate response of the arterial baroreflex to hypotension is tachycardia, which fails to occur in these illnesses. Dysautonomic patients may be so brittle that they are hypertensive supine, hypotensive upright, and may lose consciousness due to overzealous splanchnic vasodilation, possibly due to vasoactive intestinal polypeptide, after a heavy meal.

Chronic OI and POTS

The postural tachycardia syndrome (POTS) is a disabling disease state described at least since 1940[219] and is the most common reason for referral for OI[220-225] in adults. It is an emerging form of OI in children. Patients have day-to-day disability, a feature not shared with those with simple faint. With some exception, traditional tests of autonomic function are normal in these patients. Patients are often unable to hold jobs or attend schools. Studies at the Vanderbilt autonomic laboratories have stated that this is the most common form of chronic orthostatic disability and is present in virtually every patient with sustained OI.[226] Based on published Vanderbilt data, some 30% of POTS patients fulfill criteria for CFS. However, these data originate from a select patient population. Our understanding of the pathophysiology remains incomplete. The central physical finding in POTS is upright tachycardia, although hypotension and resting tachycardia may also be present. An operational definition of the syndrome includes symptoms of OI associated with an increase in heart rate from the supine to upright position of more than 30 beats per minute or to a heart rate greater than 120 beats per minute within 10 minutes of head-up tilt (HUT). Such a response is depicted in Figure 7-4. In the case shown, the patient became immediately symptomatic following the start of HUT and required the table to be put down within a very few minutes. Although this patient was not hypotensive, hypotension may follow or occur with tachycardia. Often, it is delayed beyond the onset of the symptoms and of the tachycardia, and only shows up during the artificially sustained orthostasis enforced during HUT. Onset of symptoms often follows an infectious disease and may be related to inflammatory mediators.[227] Data from the reports of the first pediatric cases showed that POTS physiology underlies OI in the large majority of adolescents with CFS.[105, 228-230] POTS is

Figure 7-3
Dysautonomic OI Patterns of Blood Pressure Changes with HUT Testing

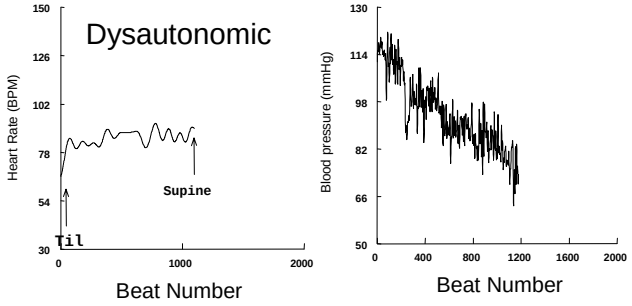
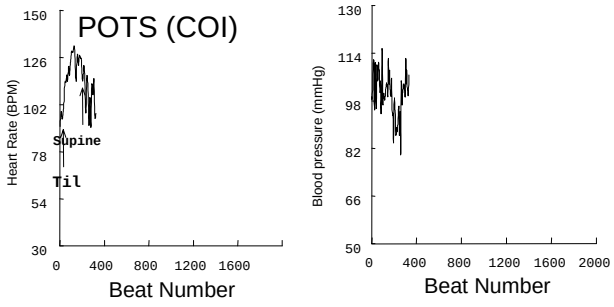


Figure 7-4
POTS (COI) Patterns of Blood Pressure Changes with HUT Testing



common, affecting an undisclosed number of patients mostly in the age range of 12 to 50 years, mostly female, approximately 80%. There is an as yet undetermined, but increasing, apparent prevalence in children and adolescents.[229] The spectrum of illness closely parallels findings in CFS.

Patients with the syndrome display an unusual amount of pooling in the lower extremities often associated with acrocyanosis. The literature contains a number of potential explanations for pooling and fluid collection in POTS, including impaired innervation of the veins or in their response to sympathetic stimulation.[221] One such explanation favors an autonomic neuropathy that predominantly affects the lower extremities.[225, 231] α^1-adrenergic denervation hypersensitivity results. A second explanation invokes decreased β^1- receptor sensitivity,[226] a third, α^1-receptor supersensitivity,[224] a fourth, altered venoconstriction,[224] while a fifth[232] suggests increased capillary filtration as an explanation. However, α^1-adrenergic control of venous filling in response to baroreflex stimulation during orthostasis is important only in skin and splanchnic circulations in humans,[233-235] while involvement of skeletal muscle β^2-receptors remain controversial.[233] α-adrenergic effects may also alter venous filling, but only indirectly through arterial vasoactivity,[233, 236] and this mechanism may be most important during exogenous β-adrenergic agonist administration, isoproterenol, or during endogenous epinephrine release later during HUT. It is uncertain how important active venoconstriction is to the orthostatic response.

Finally, venous capacitance properties in POTS could be abnormal because of altered vascular structure, altered muscle tone or both. A link with antecedent inflammatory disease is the chronic elaboration of cytokines, with potent vasoactive consequences, such as IL-1, IL-6 and TNF. Such a link seems established in CFS in which POTS and neurally mediated hypotension (actually POTS) occur with high frequency.[134, 237] Most recently, Robertson and associates have isolated an aberrant gene for the norepinephrine reuptake transporter protein, producing alternations between hypertension and hypotension in the same patient and her twin sister, dependent on norepinephrine stores.[237] This gene seems for now confined to a single family. Such results, however, highlight the likelihood of different types of inherent vascular abnormalities, resulting in a common pathway of postural tachycardia and symptoms of OI.

Preliminary data[230] suggest the hypothesis that blood pooling in patients with CFS with POTS results from a defect in arterial vasoconstriction during orthostasis, causing increased venous filling and enhanced microvascular filtration, leaking from the capillaries. This defect may be due to central nervous system dysfunction, postganglionic dysfunction, or abnormal local vasoconstrictive mechanisms. Blood is redistributed peripherally and redistribution is enhanced during orthostasis, producing increased microvascular filtration and dependent edema. Central hypovolemia causes reflex tachycardia, reduced cerebral blood flow and hypotension. POTS results in a circulation at high risk for simple fainting by virtue of a depleted thoracic vascular bed. In many ways it resembles hemorrhage or hypovolemia in that tachycardia and malperfusion are noted first, which may then proceed to hypotension or loss of consciousness or both.

OI in CFS

Much has been stated and written about OI as it applies to CFS, which has been confusing at best. Some of the confusion originates from recent appreciation of the clinical variants of OI, some from our emerging understanding that a variety of pathophysiologies underlie OI, and some from nomenclature that seems to change nonstop.

The symptoms of CFS closely match those of chronic OI, and research suggests that OI plays a role in the symptomatology of CFS. Recent investigations support the hypothesis that findings in patients with CFS result at least in part from impaired blood pressure and heart rate regulation. OI has been implicated. In their initial observations, Rowe and coworkers[134, 238] produced "neurally mediated hypotension" in twenty-one of twenty-two adult patients with CFS using HUT. These observations have led investigators to propose that there are autonomic defects in CFS.[39, 237, 239-241] In earlier work, Rowe, et. al., reported somewhat different findings in adolescents with CFS who had tachycardia often associated with hypotension during orthostasis.[238]

The reported incidence of OI in CFS from other laboratories is much more variable. A large factor has been the criteria used to diagnose OI. Rowe, for example, defined orthostatic hypotension in CFS by the presence of hypotension, which is a somewhat restrictive definition excluding many patients from consideration who otherwise would meet criteria for orthostatic hypotension.

Diagnosis of OI in CFS

The diagnosis of OI is often made on historical grounds with typical symptoms guiding the evaluation and treatment. These symptoms need to be chronic for the diagnosis. Fainting may be present, but this is seldom the case in CFS with POTS, unless patients are maintained upright for an extended and abnormal time period. Acute syndromes can represent other illnesses, which should be ruled out. Physical examination is often unrewarding, although resting tachycardia, pallor or acrocyanosis and mottling of the extremities may be important clues. Chronic sinus tachycardia may be suggestive, but other causes, such as other arrhythmias, catecholamines-secreting tumors, and hyperthyroidism need to be elimi-

nated. A standing test can be helpful. The blood pressure and heart rate should be monitored every minute and the patient needs to be immobile while standing. Also the test should be performed in garb suitable for observing both the upper and lower extremities. An excessive increase in heart rate with symptoms defines POTS. Pulse pressure is often decreased, despite maintained systolic BP in most patients. Diastolic pressure is therefore high and reflects a marked decrease in stroke volume.

Treatment of Vasovagal Faint and OI in CFS

Without a clear mechanism, there is no clear treatment. Moreover, many patients with infrequent simple faints, who do not injure themselves and who do not have convulsive syncope, may require no specific therapy, except for training in aversive maneuvers. However, there are some general maneuvers and forms of treatment that have been successfully used in syncopal patients, POTS patients, dysautonomic patients, and patients with CFS alike.

The simplest of these maneuvers is lying down. Also, leg crossing, bending at the waist, squatting and other physical maneuvers may be effective. Increased fluid and salt intake is always helpful in ameliorating the initial thoracic hypovolemia of orthostasis. Raising the head of the bed while sleeping will retain fluid overnight and decrease early morning lightheadedness. Lower body exercise, particularly isometric exercise, can be a genuine help by enhancing the muscle pump and by increasing venous tone in the lower extremities. Elastic support hose can be useful at times, but are often unacceptable to children and adults alike. Other investigators have advocated a regimen of progressively longer quiet standing as a form of orthostatic training.[225]

In terms of medication, beta-1 blockade works well in some forms of syncope possibly by blunting the release of epinephrine or renin, which are modulated by beta-1 receptors and by its central effects. Beta-1 blockade is usually unsuccessful for treating POTS in which sympathetic compensatory mechanisms may already be maximally taxed. Fludrocortisone (Florinef) in doses ranging from 0.1 to 0.4 mg/day has been a mainstay for palliative therapy of all forms of OI, although its efficacy in CFS has been recently questioned. Its primary mechanism of action is through sodium and water retention at the expense of some potassium wasting. In addition, Fludrocortisone may aid in sensitizing alpha-receptors and blocking vasodilation. Fludrocortisone has modest, if any, corticosteroid side effects. A new, direct-acting alpha-1 agonist, midodrine proamatine, given as 5-15 mg/dose (spaced 4 hours apart, three times a day) has been used to good effect in many patients with assorted forms of OI. This medication treats a deficit in norepinephrine-related vasoconstriction. Other interventions have included alpha-2 adrenergic agents, both clonidine and yohimbine, which have been used in select patients. Disopyramide has been used occasionally, but controlled studies do not support its efficacy.[228]

Recently, selective serotonin reuptake inhibitors have been used to good effect in a variety of orthostatic disabilities. These seem to interfere with hypotensive responses at a central level. Grubb and associates have demonstrated efficacy of sertraline and fluoxetine in a series of controlled studies.[242, 243] The studies were performed after careful psychiatric screening had ruled out significant depression. Personal experience bears this theory out and the SSRIs remain a useful form of therapy for many forms of OI. It remains unclear whether any treatment repairs any specific defect. Medical therapy must therefore continue to be regarded as palliative.

Effective and specific treatment for chronic OI can only be developed when a specific etiology or etiologies are discovered. It seems likely that even when there is clinically diagnosed POTS, CFS remains heterogeneous with a variety of specific etiologies, giving rise to common clinical features.

Conclusion

The evidence is clear that OI plays a key role in the pathophysiology and symptomatology of patients with CFS. Recent scientific investigations have broadened the scope of orthostatic abnormalities to include a wide range of illness in which blood flow and blood pressure regulation are impaired. Several treatment modalities may improve the symptoms resulting from POTS associated with CFS.

8 Pain in CFS

Alan Lichtbroun, MD

CFS, FMS, and multiple chemical sensitivities syndrome (MCSS) are clinical syndromes that are poorly understood in terms of cause, pathophysiology, natural history and appropriate medical management. Despite their different diagnostic labels, some data suggests that these illnesses may be similar conditions. In one major study, 70% of patients with chronic fatigue syndrome when given the appropriate physical examination met the criteria for FMS.[244]

CFS and FMS may represent a continuum of pain and fatigue in the population at large, rather than discrete diseases.[245] However, the concept of FMS and CFS as clinical syndromes has been useful both for epidemiologic and therapeutic studies.[246] In the most recent American study, the prevalence of FMS in the general population was 2%.[246] This prevalence increased with age, reaching 7% in women from ages 60-80 years. Eighty to 90% of patients have been female.

This chapter will discuss the concept of pain found in FMS and CFS, as well as discuss specifically where pain in the two disorders may have different pathophysiologies. There have been tremendous advances in the concepts of central pain mechanisms. We will discuss what causes pain amplification in FMS and by extension the cause in many cases of pain in CFS.

FMS Symptomatology

The current concept of FMS was ushered in by studies from Smythe and Modofsky in the mid-1970s.[247] They described that certain anatomical locations, termed tender points, were more tender in patients than in controls. They also reported that patients with FMS had a stage 4 sleep disturbance, and that experimental selective stage 4 disturbance produced the symptoms of muscle tenderness consistent with FMS. The diagnostic utility of tender points was verified by a series of reports in the 1980s from different observers.

A North American multicenter criteria committee determined the American College of Rheumatology 1990 criteria for the classification of FMS.[248] Two hundred ninety-three patients with FMS and 265 control patients were interviewed and examined by trained, blinded assessors. Controls were matched for age and sex. All had a rheumatic disorder that could be easily confused with FMS. The combination of widespread pain defined as bilateral, above and below the waist, and axial, and at least 11 of 18 specified tender points, yielded a sensitivity of 88.4% and a specificity of 81.1%.

Although CFS and FMS share many similar symptoms, including myalgias, sleep disturbances, decreased cognition, and neuroendocrine immune imaging study abnormalities. There are few differences between these syndromes, as well.

Pathophysiology

If pain is the sensation, nociception is the process. The three components of nociception are: the site of the body where the stimulus occurs; the spinal cord, where the signal is chemically processed; and the brain, where the pain message is interpreted for the signal location and its magnitude. In FMS, nociception mechanisms are activated and pain is chemically amplified in the spinal cord by a process known as central sensitization.

Normally, a stimulus from the peripheral tissue is transmitted to the spinal cord by the unmyelinated A-delta fibers and C fibers. During central sensitization, large myelinated fibers can be recruited to participate in nociception transmission. These neurons have contact with the spinal neurons and transmit signals much more rapidly than A-delta and C fibers. Usually, these fibers carry messages of proprioception and soft touch. During central sensitization, excitation of these fibers by relatively normal stimuli is interpreted by the cord and brain as if it were a pain signal. We will discuss later the role of substance P, as well as nerve growth factors, in mediating this switch.

Once an efferent neuroelectric signal reaches the dorsal horn area, it becomes chemically mediated. There are several chemical agents that facilitate the transmission of this message. Among them are substance P, which is a potent vasoactive peptide that also appears to be involved in pain and temperature. The C terminal peptide of substance P and other excitatory amino acids, such as glutamate, aspartate prostaglandins, and nerve growth factors stimulate the growth of neurons containing substance P. Other neurochemicals that are involved have the affect of inhibiting nociception. For example, serotonin from the raphae nucleus of the brain stem, released in the region of the dorsal horn of the spinal cord, inhibits the release of substance P, thus down-regulating nociception.

After the magnitude of the afferent pain signal has been determined, a spinal neuron is activated. The signal then crosses the spinothalamic tract on the side contralateral to the original stimulus and travels up to the brainstem to the thalamus. From there, the signal projects to the cingulate cortex or gyrus cinguli and the sensory motor cortex.

Like any other complex physiologic process, nociception can malfunction. Allodynia refers to one type of nociception dysfunction in which pain results from a stimulus that should not normally be painful. Patients with FMS experience pain from less than 4 kg per cm^2 of pressure at anatomically defined tender point sites, while healthy, normal persons would interpret that same amount of pressure as painless. Intense or chronic amplification of nociception can produce a semi-permanent change in neuro-circuitry and conductivity at several levels, causing the allodynia to spread. This semi-permanent process is then known as neuroplasticity.

To date, four independent investigations conducted in the United States and Scandinavia have shown that the cerebral spinal fluid (CSF) of persons with FMS contains markedly elevated levels of substance P, compared with normal controls.[244, 249] The average levels of substance P in the CSF of patients with FMS are 2-3 times higher than normal. This increase causes or facilitates a major increase in pain perception. If the physician were to use this information to evaluate levels of substance P in CSF as a test for FMS against normal controls, it would be 84% sensitive and 100% specific.[250]

In addition to the rewiring of peripheral nerves, where C fibers and A-beta nerve endings in the spinal cord begin to sprout and grow just like tree roots, finding each other and causing nociception, there are also pain amplifying systems within the spinal cord and brain that can influence the excitability threshold. The n-Methyl-D-aspartate (NMDA) receptors in the spinal cord are known to play a key role. Excitatory amino acids, such as aspartate and glycine (as mentioned above), activate the NMDA system, along with elevated levels of dynorphin A. A recent report from Norway indicates that dynorphin is also elevated in FMS patients.[94]

Recent research has shown that increased levels of nerve growth factor (CNGF) bathing these A-beta and C fibers that terminate in the spinal cord have been shown to lead to this sprouting and rewiring of the large myelinated fibers (A-beta fibers) into substance P, producing C fibers.

Nerve growth factors also increase fourfold in the CSF of patients with FMS, compared to healthy controls.[94] What is surprising about the research is that this fourfold increase is found only in patients who have primary FMS. If patients had a secondary condition (secondary to another inflammatory condition, such as rheumatoid arthritis or a pain condition, such as osteoarthritis and low back pain), there was no significantly elevated NGF in their spinal fluid. Thus, elevated concentration of NGF in the spine appears unique to primary FMS.

Although substance P is markedly elevated in FMS spinal fluid, all three groups, i.e., primary, secondary, as well as regional, pain disorders, had elevated concentrations of substance P that did not differ significantly. The concentration of substance P is likely increased in these patients by the availability of NGF peripherally at the actual site of inflammation or tissue injury. Knowing that injections of NGF in the spinal fluid of mice causes increased pain sensitivity, Larsen postulates that bathing the central portion of sensory fibers (spinal cord) might also sensitize them to pain and increase their pool of available substance P.

Failure of regulation by anti-nociception neurochemicals, such as serotonin, could at least partially account for this high level of substance P in FMS patients. Tryptophan, an essential amino acid, is irreversibly converted to hydroxytryptophan, which could then be converted to serotonin. The serotonin can be metabolized to five hydroxy indolacetic acid (5 HIAA), which has also been found to be low in cerebral spinal fluid of persons with FMS.[19, 251]

Platelets are the primary storage source of serotonin in the peripheral blood. A study comparing the concentration of serotonin and platelets in persons with FMS with healthy controls showed serotonin to be significantly lower in platelets of persons with FMS. Platelet serotonin in persons with FMS correlated with the average pain threshold. An assay of 24-hour urine samples demonstrated that persons with FMS also excreted less urinary 5 HIAA than did controls. (This is not the case in patients who do have CFS, but who do not also have FMS.)

It is well-established that FMS is more prevalent in woman than in men. It is interesting that normal woman synthesize approximately seven times less serotonin in their brains than normal men. This difference may be why women are at greater risk for the development of chronic pain syndromes. Under experimental conditions that reduce tryptophan levels in the blood of normal men and woman, serotonin production in the men declined by a factor of seven, while that for women declined by a factor of 42.[252]

Psychological Distress in FMS

Several lines of evidence suggest that psychological distress is central to the pain experienced and in overall morbidity in FMS.[253, 254] Although not all agree, increased psychological distress is a common characteristic of FMS. Psychological distress is strongly correlated with the number of painful tender points, not only in FMS, but also in rheumatoid arthritis. In fact, the number of painful tender points is almost linearly related to the level of distress. As noted by Wolf, "the tender point count functions as a sedimentation rate for distress, irrespective of a diagnosis of FMS".[250] High levels of anxiety and distress, together with less certainty that pain is going to resolve and a history of trauma, are predictors of who progresses from acute pain to chronic pain.

Patients who have been diagnosed with FMS can be separated by the level of psychological distress into distinct groups ranging in severity from "adaptive copers," who do well clinically, to highly dysfunctional patients,

who respond to treatment extremely poorly.[255] Consistent with the pain/psychological distress relationship developed above is the improvement that we see in measures of self-efficacy, coping, depression, and pain that accompanied the application of stress management programs. Psychological distress can also be found in CFS especially in that subgroup of patients who go on to developing FMS. Although stress comes from many sources, in CFS, both the fatigue and, possibly more importantly, the uncertain prognosis that these patients anticipate, both contribute to this distress.

Abnormalities of Muscle and Mechanical Factors

The trapezius muscles of patients with fibromylagia have significantly lower ATP, ADP, phosphocreatine and energy charge potential, and increased AMP and creatine than in normals.[256] However, when controls were matched for levels of exercise and activity, there were no significant differences either of muscle structures or metabolism. We now believe that the muscle abnormalities that are sometimes found are secondary to inactivity and pain, although a recent article by Lane, et. al., examined muscle fiber characteristics and lactate responses to exercise in 105 patients with CFS, as opposed to classic FMS.[257]

Using doppler laser flowmetry and skin temperature measurements with infrared thermometers, a recent article revealed vasoconstriction in the skin above tender points in patients with FMS, supporting the hypothesis that FMS is related to local hypoxia in the skin above tender points and reduces ATP synthesis via oxidative phosphorylation in mitochondria.[258]

A recent observation found growth hormone production is decreased by 30% in patients with FMS, especially in the early morning, possibly associated with stage IV sleep anomaly. Corticol releasing hormone (CRH) promotes the release of somatostatin, an antagonist of growth hormones. Lower levels of growth hormones also lead to decreases in DHEAs. Decreased levels also lead to impaired muscle anabolism, which makes patients with fibromylagia more susceptible to muscle trauma.

A recent report demonstrated the presence of significant metabolic abnormalities in the muscles of patients with FM, as detected by P-31 Magnetic Resolution Spectroscopy (MRS).[259] The spectroscopy camera used for measuring ATP, PCr, and inorganic phosphate (Pi) was placed directly over the quadriceps muscles.

Absolute levels of both ATP and PCr were significantly lower (15%) in muscles of the patients with FM than in the normal control subjects at rest and during exercise at 25% MV. These findings are in rather close agreement with biopsy determinations, which showed reductions in ATP and PCr of 17% and 21% respectively, in tender sites of the trapezius muscle in patients with FM, as compared with non-tender sites in the anterior tibialis or with the muscles of normal controls.[260] The reduced levels of ATP and PCr in the patients' muscles correlated inversely with clinical observations of weakness or pain, as measured on a visual analog scale (VAS) (40). Reduction of ATP in erythrocytes of patients with FM has been observed, suggesting that this may be a more general systemic phenomenon than previously thought.

Diagnosis

Both CFS and FMS patients have low levels of cortisol and CRH.[261] FMS patients have low levels of insulin-like growth factor 1 (IGF-1) and growth hormone.[262, 263] There is inconsistent data for these markers for CFS. Persons with FMS have low serum levels of serotonin[264] and low cerebral spinal fluid levels of serotonin metabolites. Persons with CFS have high plasma levels of serotonin metabolites.[251, 254] FMS is also characterized by high cerebral spinal fluid levels of two factors that promote pain: nerve growth factor and substance P,[249, 265] which has not been evaluated yet in CFS.

MRI imaging studies of brain structures suggest that persons with CFS are characterized by a high number of cortical white matter lesions, compared to healthy individuals. There are no published MRI studies of the brain structure in FMS. Resting state regional cerebral blood flow using SPECT or PET imaging has produced different results for persons with CFS and those with FMS. The patients with CFS studies generally have not produced consistent results, although two studies found evidence of brain stem hypoperfusion in patients with CFS. One recent British study found that patients with CFS show higher levels of blood flow in the thalamus, compared with healthy controls.[266] In contrast, two studies from the same laboratory reported that patients with FMS show hypoperfusion of the thalamus and/or caudate nucleus during resting conditions.[267]

Preliminary evidence from the same laboratory indicates that during exposure to painful pressure stimulation on the right side of the body, healthy individuals display significant increases in blood flow in the contralateral somatosensory cortex, thalamus, and anterior cingulate cortex.[39, 268] However, persons with FMS, as well as those with CFS who do not meet criteria for FMS, show bilateral increases in blood flow in the somatosensory cortex and cingulate cortex.[264] These findings suggest that both FMS and CFS are characterized by alterations in neural processing of sensory information.

On the other hand, neuroendocrine studies suggest that in FMS hyperexcitability of the spinal NMDA receptors increases ascending sensory transmission to the brain that enhances pain perception. Persons with CFS usually experience musculoskeletal pain, but they do not show abnormal sensitivity to pressure stimulation at multiple anatomic sites, unless they also meet the criteria for FMS. Individuals with FMS exhibit lower pain threshold levels than persons with CFS.[249, 269] They are also better than subjects with CFS and controls in discriminating

between high and low intensity stimuli that are presented in random order.

A recent abstract compares tilt table responses in chronic fatigue from FMS showing significant differences, indicating that the homeostatic response in FMS and CFS may be different.[269, 270] Lastly, immune modulation appears to be important in both disorders. CFS appears to be promoted by a TH 2 response. Activated T helper cells from patients with CFS, unlike those of FMS, produce fewer TH 1 cytokines and produce more IL-5 and TH 2 type cytokines (to preferentially stimulate cells to produce antibodies). When FMS pain arises, substance P appears to stimulate other cytokines, such as IL-8 and IL-6. Since IL-8 produces myopathic pain, IL-6 induces hyperalgesia. It is hypothesized that they play a role in modulating FMS pain syndrome in CFS patients.[254]

With the above background, we should realize that although significant differences exist between the two syndromes, many patients with CFS may have FMS. The concept of allodynia pain processing is pivotal in understanding and treating the associated pain of both disorders.

Clinical Examination

The diagnostic utility of a tender point evaluation has been objectively documented with the use of dolorimeter or algometer, pressure-loaded gauges that accurately measure force per area, and by manual palpation. Such instruments are useful in controlled studies, but in the clinic, digital palpation is usually adequate. The nine pairs of tender points are by no means inclusive, but they are representative.

On examination, patients usually appear well, with no obvious systemic illness or articular abnormalities, but complain of a diffuse deep muscle ache. Other common findings on examination include muscle "spasm" or taut bands of muscle, sometimes referred to by patients as nodules; skin sensitivity, in the form of skin roll tenderness or dermatographism or purplish mottling of the skin, especially of the legs following exposure to the cold. This condition is sometimes thought to be livedo reticularis, but more accurately represents cutis marmorata. These clinical findings are usually absent in patients with CFS who do not have FMS. As opposed to CFS, patients with fibromylagia do not present with adenopathy or fevers unless the FMS is a component of another disorder, such as SLE. (Lupus and other autoimmune diseases can be differentiated by their specific symptoms, including arthritis, i.e., warm, swollen joints, pleurisy, nephritis and more specifically positive anti-DNA antibodies as well as low complement, all of which would not be found in either CFS or FMS).

CFS also can present with arthralgias or joint pains, but usually not warm, swollen joints. These pains are often intermittent with flares and remissions, although in many cases the joint pains can be continuos.

Therapeutic Approaches

Nonmedicinal Treatments

Although widely used in the treatment of FMS, nonmedicinal therapy rarely has been studied in a controlled fashion (See **Table 8-1**). Those few treatments evaluated in controlled studies include cranial electrotherapy, cardiovascular fitness training (CFT),[271] biofeedback,[272] hypnotherapy,[273] and cognitive behavioral therapy.[274] Forty-two patients with fibromylagia were randomly assigned to a 20-week program of CFT or a flexibility exercise program. Eighty-three percent of those patients assigned to the CFT program improved their physical fitness by incremental stationary bicycle riding. There was significant improvement in tender point pain threshold and in patient and physician global assessment in the CFT group, but no significant differences in pain intensity or sleep disturbances in the two groups.

Table 8-1
Nonmedicinal Therapeutic Treatments for Pain in CFS

Efficacy Shown In Controlled Therapeutic Trials
- Cardiovascular Fitness Training
- Aqua Therapy
- EMG-Biofeedback
- Electroacupuncture
- Cranial-electrotherapy Stimulation
- Hypnotherapy
- Cognitive Behavioral Therapy

Anecdotal Efficacy Show In Uncontrolled Trials
- Transcutaneous Nerve Stimulation
- Local Injection
- Multidisciplinary Therapy
- Resonance Biofeedback
- Reiki
- Feldenkrais
- Neuromuscular Therapies (including)
  Tai Chi
  Yoga
  Myofacial Release Technique
  Cranial Sacral Therapy
  Alexander Technique
  Stain Counter Strain Therapy

Efficacy Lacking in Uncontrolled Trials
- Ultrasound

The possible ameliorative effects of CFT on FMS may involve mechanisms as diverse as improved muscle blood flow or CNS-induced hypoalgesia, felt to be related to activation of endogenous opioids. Vigorous exercise also induces increases in adrenocorticotropic hormone (ACTH) and cortisol, which may also promote analgesia.

The only controlled report of EMG biofeedback training randomized 12 patients with fibromylagia to EMG biofeedback or sham biofeedback.[273] The EMG biofeedback group had a significant improvement in pain, morning stiffness and tender points. Hypnotherapy was found to be better than physical therapy in 40 patients with refractory FMS. The hypnotherapy group demonstrated better outcome in pain, fatigue, sleep and global assessment, but not in tender points.[274] Goldenberg has found that a mindfulness meditation-based relaxation response program is helpful in FMS. Other less well-studied non-medical treatments include transcutaneous electrical nerve stimulation (TENS), acupuncture, laser treatment, and tender point injections. A new modality called cranial electrotherapy has recently been proposed as a treatment for FMS.[275] It has been found to improve quality of life and sleep, as well as to decrease anxiety as much as 100% in a double-blind controlled trial. Its benefit in alleviating pain, however, has been less dramatic, but beneficial.

A recent article described the effectiveness of electroacupuncture in relieving symptoms of FMS, including pain threshold, pain on visual analog scale, and sleep quality in a randomized trial comparing a sham procedure on 70 patients.[276]

Medicinal Treatments

Despite the fact that there is no evidence of tissue inflammation in FMS or CFS, anti-inflammatory medications are often utilized and have been studied in controlled trials.[60] Therapeutic doses of naproxen (Naprosyn) and ibuprofen (Motrin, Advil, Nuprin) and 20mg daily of prednisone were not significantly better than placebo in clinical trials. Nonsteroidal anti-inflammatory drugs (NSAIDs) may have a synergistic effect when combined with central nervous system (CNS) active medications, but they may be no more effective than simple analgesics.[140] Anti-inflammatory medications are better utilized in chronic fatigue where there are arthralgias and myalgias rather than FMS complaints (See Table 8-2).

In contrast, certain CNS active medications, most notably the tricyclics, amitriptyline, and cyclobenzaprine, have been consistently found to be better than placebo in controlled trials. The doses of amitriptyline studied have been 25-50mg, usually given as a single dose at bedtime.[139] In one report, amitriptyline was associated with significant improvement, compared with placebo or naproxen in pain, sleep, fatigue, patient and physician global assessment, and the manual tender point score. Cyclobenzaprine, 10-40mg in divided doses, also improved pain, fatigue, sleep, and tender point count.[277, 278] Clinically meaningful improvement with the tricyclic medications has occurred in only 25-45% of patients, and the efficacy of these medications may level off over time.

Other tricyclics and different classes of CNS active medications, including venlafaxine (Effexor)[163], alprazolam (Xanax),[279] temazepam (Restoril),[168] and fluoxetine (Prozac),[280] as well as 5-hydroxytryptophan[281] and an analgesic containing carisoprodol (Soma)[282] and acetaminophen (paracetamol),[169] have been found to be somewhat effective in preliminary studies.

Bennett assessed the efficacy of recombinant human growth hormone in the treatment of 50 women with FMS and low IGF-1.[258] In a randomized double-blind, placebo-controlled study, women with FMS and low IGF-1 levels experienced an improvement in their overall symptoms and number of tender points after nine months of daily growth hormone therapy. This author has used growth hormone releasing factors (amino acids) ornithine, glutamine and arginine with some dramatic results in a few patients (unpublished).

Table 8-2
Pharmacologic Agents Used to treat CFS Patients with Musculoskeletal Pain

Classification	Medication	Adverse Effects
Anticonvulsant	gabapentin (Neurontin) clonazepam (Klonopin)	Somnolence, Dizziness, Ataxia
Antidepressants	Tricyclics: amitriptyline (Elavil)[1] desipramine (Norpramin) doxepin (Adapin, Sinequan) nortriptyline (Pamelor)	Drowsiness, Dizziness, Dry mouth, Constipation
	SSRIs: fluoxetine (Prozac)[1] paroxetine (Paxil)[1] nefazodone (Serzone)[1] sertraline (Zoloft)[1]	Nausea, Headache, Insomnia
	Miscellaneous: trazodone (Desyrel)	Drowsiness, Dry Mouth, Dizziness, Lightheadedness
	venlafaxine (Effexor)[1]	Nausea, Dizziness, Somnolence, Insomnia
Centrally Acting Sympathetic Agonist	tizanidine HCL (Zanaflex)	Dry Mouth, Somnolence, Insomnia
Hormonal Agents	somatatropin (Nutropin, Serostim)	Headache, Muscle Pain or Weakness, Mild Symptoms of Hyperglycemia
	Growth Hormone[1]	Possible Acceleration of Cancer Growth
	GH Releasers (amino acids)	Possible Acceleration of Cancer Growth
	oxytocin	Lactation, Short-term Facial Flushing, Tingling
	DHEA	Acne, Menstrual Irregularities
Mild CNS Stimulants	methylphenidate (Ritalin) mogafinil (Provigil)	Nervousness, Insomnia
Monoamine Oxidase Inhibitors	phenelzine (Nardil)	Dizziness, Headache, Drowsiness
Muscle Relaxants	carisoprodol (Soma)[1]	Drowsiness, Dizziness, Vertigo
	cyclobenzaprine (Flexaril)[1]	Drowsiness, Dry Mouth, Dizziness
	metaxalone (Skelaxin)	Nausea, Vomiting, GI Upset
	methocarbamol (Robaxin)	Lightheadedness, Dizziness, Drowsiness
	orphenadrine (Norflex)	Dry Mouth, Tachycardia, Palpitation
Nonnarcotic Analgesic	tramadol (Ultram)[1]	Dizziness, Drowsiness, Headache
Nonsteroidal Anti-inflammatory	naproxen (Aleve, Naprosyn[2])	Dizziness, Headache, Nausea, Flatulence, Diarrhea, Constipation, GI Upset and Pain
	Cyclooxygenase-2 Inhibitors: celecoxib (Celebrex)	Flatulence, Diarrhea, Dizziness, Headache, GI Upset, Pain
	rofecoxib (Vioxx)[2]	Dizziness, Mild Fatigue, Weakness, Diarrhea, GI Upset, Pain
Opioids	codeine morphine (MS Contin) oxycodone (Oxycontin)	Abuse Potential, Sedation, Confusion, Nausea, Vomiting, Decreased Appetite
Opioids and Combination Opioids	oxycodone and acetaminophen (Percocet) oxycodone and aspirin (Percodan) acetamenophen (Tylenol #3 & #4)	Abuse Potential, Dizziness, Drowsiness, Nausea, Vomiting
Opioid Agonists/Antagonists	nalbuphine (Nubain)	Abuse Potential, Drowsiness, Sleepiness, Confusion
Opioid Extenders/Antiemetics	hydroxyzine (Vistaril)	Dizziness, Drowsiness, Sleepiness, Confusion
Over-the Counter	acetaminophen (Tylenol, Anacin-3, Panadol, Phenaphen, Valadol)	Lightheadedness
	aspirin	Heartburn, Indigestion, Tinnitus
	ibuprofen (Advil, Motrin, Nuprin)	Dizziness, Headache, Nausea, Flatulence, Diarrhea
	SAMe[1]	None
	5 HTP	None
	malic acid[1]	None
	magnesium[1]	Diarrhea, Nausea
Detoxifier (alleged)	guaifenesin	Increased Mucous, Increased Pain
5 HT 3 Receptor Antagonists	tropisetron (Experimental use in US)	Unknown
Anesthetics	lidocaine	Cardiac Arrhythmia with Parenteral Infusion
Substance P Antagonists	capsaisin[1]	Burning, Eye Burning on Contact
NMDA Receptor Antagonists	Ketamine dextromethorphan	Abuse Potential

1 Efficacy shown in placebo-controlled trials
2 Annecdotally successful

A benzodiazepine, such as clonazepam (Klonopin), 0.5 to 1 mg at bedtime, promotes improved sleep, relaxes the muscles and helps restless leg syndrome. Psychometric tests showed significant improvements in depression and anxiety state scores, while functional symptoms improved with extended tropisetron treatment. Patients with elevated dopamine and/or reduced plasma 5-HT concentrations tended to show a higher response rate.[283, 284]

Adenosyl methionine, a methyl donor in many methylation reactions in the brain, has an antidepressant action. Placebo treatment did not cause any significant improvement. Other studies using venlafaxine (Effexor) in an open eight-week trial of 11 patients, 55% experienced 50% or more reduction of FMS symptoms. The presence of lifetime psychiatric disorders, particularly depression and anxiety disorders, predicted a positive response to venlafaxine.[163]

As mentioned above, C fibers activated by noxious stimuli promote the release of amino acids, such as aspartic acid, which activate NMDA receptors and produce painful signals. The anesthetic ketamine, a noncompetitive antagonist to NMDA, decreases FMS pain levels better than lidocaine or opiates.

Tramadol (Ultram) is a weak opioid that also inhibits norepinephrine and serotonin at the level of the spinal cord, thereby augmenting the descending inhibitory pain pathways. Results of a recent multicenter study showed tramadol to have a very good safety and efficacy profile.[285] In that study, approximately 90% of patients considered tramadol useful for managing FMS pain.

Finally, in rare instances, a small number of patients will need stronger pain medications. There is a place for narcotics in carefully selected patients with FMS.[286] This area, however, continues to be controversial. When they are used, the author requires a narcotic contract to be written, which the patient signs and agrees to close follow-up. The author uses longer acting narcotics, which may have less risk of addiction. Physicians should also understand terms such as drug dependence, tolerance, and pseudo-addiction (a pattern of drug-seeking behavior in patients who have adequate pain relief, but the patient is drug-seeking to address this need for pain relief. This behavior is often mistaken for addiction).

There have been few longitudinal studies of FMS. These have demonstrated persistent pain and significant impact on function. Thirty-nine patients were surveyed for three consecutive years and, although more than 80% of patients continued to take medications for FMS, 67% reported feeling poor or fair and had moderate to severe pain, with no significant change in symptoms over the three years.[287, 288] Factors associated with improved outcome were a younger age and lower global and pain scores at the time of the initial survey. A recent follow-up of the majority of those patients eight years later found that although all still have FMS symptoms, 65% felt better than they were when initially diagnosed.

Conclusion

Pain symptoms are commonly found in CFS, be they arthralgias, myalgias, or the lower pain threshold found in FMS. There is often an overlap of pain syndromes in chronic fatigue syndrome and FMS. The concepts of allodynia, central pain processing, and nocioceptive dysfunction in FMS may play a role in pain in CFS. A large group of patients with CFS also have arthralgias and myalgias, which differ from the classic tender points and decreased pain threshold found in FMS. Multiple nonpharmocologic and medicative approaches are palliative for both disorders.

9 Women's Health in CFS

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The incidence of CFS in women is twice that of men.[289] Patients with CFS can suffer from the entire spectrum of gynecological illnesses, but diagnostic confusion can occur because some symptoms are common to both CFS and some gynecological conditions, such as premenstrual syndrome (PMS) or menopause. In many women, these common gynecological conditions may also cause an exacerbation of existing CFS symptoms. Although scientific studies are few, a number of gynecological conditions are found to occur more frequently in women with CFS. These conditions are usually associated with abnormal reproductive hormone levels, immune dysfunction, or pain. Some of these conditions may even predate the onset of CFS.[290, 291] It appears that endocrine and/or immunological changes may be present in patients with CFS before the full blown syndrome becomes manifest.

Gynecological Symptoms in CFS

Gynecological symptoms in women with CFS should be properly evaluated and not assumed to be merely part of the CFS symptomatology. In principle, a full gynecological history should be taken. Examination of the breasts, abdomen, and a pelvic examination should be carried out; the latter with appropriate cultures and a Pap smear, including specific laboratory tests. Any further investigation will depend on abnormalities found. Referral to a gynecologist sensitive to patients with CFS may be useful if further assessment is needed to make a correct diagnosis. In this chapter, we will discuss or outline a number of specific symptoms and related problems that are found more commonly in female patients with CFS than in otherwise healthy women and suggest appropriate therapies.

Low Estrogen States, Menopause, and Osteoporosis

Many premenopausal patients with CFS have scanty, irregular periods, intermenstrual bleeding, and sometimes, periods of amenorrhea. These symptoms can predate the onset of CFS, are typical of anovulatory or oligo-ovulatory cycles and are associated with a low estrogen state. Hirsutism may be associated with oligomenorrhea. Researchers have found that ovarian hormone (estradiol) levels were low in some 25% of a small group of pre-menopausal women with CFS, who had normal follicle stimulating hormone (FSH) levels.[292] The normal FSH levels distinguish this condition from menopause, where FSH levels are raised. The researchers suggested that a chronic estrogen deficiency state is present in a subgroup of women with CFS.[292] There are a number of central nervous system symptoms that are associated with the low estrogen state: tiredness, headaches, dizziness, lack of concentration, insomnia, depression, and anxiety. These can overlap the symptoms of CFS.

At menopause, heavy irregular periods, scanty periods, or amenorrhea can occur. FSH levels are raised and are associated with vasomotor instability, causing night sweats, frequently feeling hot, and flushing of the face. All of these symptoms may be due either to reproductive hormone changes, to CFS, or a combination of both. One point of difference is that vaginal dryness is usually present if estrogen levels are low and less likely to be present if the symptoms are due to CFS. Many women with CFS find that the symptoms of CFS worsen at menopause.

In a younger premenopausal woman, the presence of a low estrogen state can be confirmed by measurement of blood estradiol levels (low) and FSH levels (not raised). In perimenopausal women between the ages of 40 and 50, FSH levels may fluctuate, making serial measurements helpful. In a woman over the age of 50, menopause is more likely, and the blood FSH is characteristically raised.

In premenopausal patients with CFS, treatment just to regularize the periods is not necessary, but if estrogen levels are low, the co-existing CNS symptoms may be much improved by hormone replacement therapy, although it will not cure symptoms due to CFS. In one uncontrolled trial, it was found that symptoms improved in 80% of patients with CFS with low estrogen levels, following hormone treatment of estradiol patches and cyclical progesterone therapy.[292] Hormone replacement therapy can also be helpful in menopausal patients. For example, insomnia associated with CFS is much improved if a menopausal patient is no longer awakened several times each night by hot sweats.

Women with CFS who may have had a low estrogen state for some years are particularly at risk for osteoporosis. When osteoporosis is severe, it leads to loss of height and bone fractures. A small study found that five of seven hypoestrogenic, premenopausal women with CFS had a low bone density.[292] Other factors in patients with CFS contributing to osteoporosis are exercise intolerance because exercise exacerbates CFS symptoms and lack of vitamin D, due to inability to go outside in the sunlight, as

a result of weakness and photophobia. Vitamin D is needed for calcium absorption. Calcium intake may also be low, if the patient avoids milk due to lactose intolerance, which is common in CFS. The diagnosis of osteoporosis can be confirmed by bone density measurement.

Hormone replacement therapy; calcium, magnesium, and vitamin D supplementation; and weight-bearing exercise, if tolerated, help to prevent and treat osteoporosis. If the condition is severe, there are several pharmacologic agents approved for the prevention and treatment of osteoporosis, which can reduce the incidence of fractures. With the exception of hormone replacement therapy (HRT), their potential effect on patients with CFS has not been studied.

Premenstrual Syndrome

Premenstrual Syndrome (PMS) occurs widely in the general population, but seems to be more common in patients with CFS, occurring in over 50%.[290] PMS can predate the onset of CFS; however, it seems to be less common before the onset of CFS than in normal control women.[290] The symptoms of PMS start in the luteal phase of the menstrual cycle and rapidly improve within a day or two of the period. The most common symptoms include mood swings, irritability, depression, headache, insomnia, carbohydrate cravings, breast pain and tenderness, fluid retention and abdominal bloating. A patient may incur a weight gain of two or more pounds at this time. In addition, in women with CFS, the CFS symptoms frequently worsen premenstrually.

There is some dispute about the cause of PMS. It is thought to be hormonal in that it usually occurs in association with ovulatory cycles. In one study group of women using gonadotropin-releasing hormone agonists, when ovulation was abolished and estradiol levels fell, PMS symptoms were relieved.[293] Some recent research has found that the condition is linked to a deficiency in serotoninergic activity in the brain.[294] In PMS, treatments have been many and various, but until recently few have been very satisfactory. In several placebo-controlled trials, serotoninergic antidepressants (SSRIs), such as fluoxetine (Prozac), 20 mg either daily or on days 14 to 28 during the woman's menstrual cycle, were found to be successful, relieving PMS symptoms in up to 90% of patients.[295] However, there are no specific studies in patients with CFS. Side effects of treatment tended to improve with time. Some different approaches used in the past have been found to be no better than a placebo. These include the use of progestogens, estrogens, vitamin B6, and evening primrose oil.[296]

Endometriosis

Endometriosis is reported to occur in up to 20% of women with CFS. It can predate the onset of the CFS.[290] There may be no symptoms of the disease and the condition may be discovered only during surgery for another condition, such as infertility. Dysmenorrhea is the most frequent problem, and it can be out of all proportion to the severity of the condition. Pain can also occur before the onset of the menstrual period. Dyspareunia, intermittent pelvic pains, and pain related to the bladder or the bowel can also occur. Endometriosis is often associated with infertility.

In endometriosis, the endometrial cells that line the uterus are found also in the pelvic cavity and to a lesser extent in the abdominal cavity. Rarely are they present elsewhere. This condition is thought to be due to retrograde transport of endometrial fragments along the fallopian tubes and occurs in many normal menstruating women, most of whom have no sign of endometriosis. These endometrial cells are most likely disposed of by the scavenger cells of the immune system. In women with immune abnormalities, such as CFS, the scavenging cells may be overwhelmed. With each menstrual cycle, the ectopic endometrial cells are shed. This process can result in localized bleeding, which can be painful and may lead to inflammation and scarring in the affected area.

A physical examination may show no abnormality, but there may be thickening and lack of mobility of the uterus due to scarring or cystic enlargement in the ovaries. An ultrasound scan may demonstrate enlarged cystic ovaries. If symptoms are severe, the only certain way to confirm the diagnosis, and exclude other conditions is by laparoscopy and biopsy. Sometimes in spite of having all the painful symptoms of endometriosis, no abnormality is seen on laparoscopy. Then, the diagnosis should be reviewed because CFS is characterized by many different painful syndromes.

The current treatment of endometriosis is by analgesics, such as nonsteroidal anti-inflammatories (NSAIDS), oral contraceptive pills (OCPs), or progestational agents. Also used are an anti-estrogen with some immune modulating effects, such as danocrine (Danazol), or the GnRH agonist, leuprolide acetate (Lupron). Caution is advised in the prescription of these treatments, as they all have side effects that may not be tolerated in patients with CFS. For the treatment of infertility, there is no proof that treatment of mild endometriosis by hormones is any better than no treatment. Women with endometriosis who become pregnant are often much improved following delivery of the child. If severe pain caused by endometriosis does not respond to hormone treatment, surgery may be required as a last resort. It is very important to distinguish pain from endometriosis from pain from other CFS problems before embarking on any surgery. Otherwise, a traumatic procedure will fail to relieve the pain.

Dysuria

Twenty percent of patients with CFS have dysuria.[290] Some patients with CFS have severe symptoms of

pain, frequency and urgency of urination occurring both during the day and night. A urine culture may show a bacterial infection, which can be treated with antibiotics. Frequently, in spite of careful investigation, the urine is sterile. The patient should be referred to a urologist or urogynecologist for further investigation, as symptoms may be due to interstitial cystitis, detruser instability, urethral syndrome, or endometriosis. Interstitial cystitis is thought to be associated with some immune system abnormalities. An informal survey of some patients with interstitial cystitis found that 13.8% also suffered from CFS.[297]

Vaginal Problems

Twenty-nine percent of a series of CFS patients complained of vaginal discharge.[298] There are many causes of vaginal discharge. A thick creamy vaginal discharge associated with vaginal irritation may denote a vaginal infection with *Candida albicans*. The yeast organism is present vaginally in many symptomless women, but overgrowth leading to symptoms is likely to occur in patients with abnormal immune function or more likely in patients who have had repeated courses of antibiotics, are pregnant, or who have diabetes. Some doctors and their patients believe that many women with CFS suffer from a chronic multi-system yeast infection, which exacerbates CFS symptoms, but this theory is unproven. Certainly, positive cultures of oral swabs for yeast are unusual. There is disagreement as to whether recurrent or persistent vaginal candidiasis is more common in women with CFS. In all cases of vaginal discharge, a swab should be obtained for diagnosis.

In culture-proven cases, there are a number of effective vaginal anti-fungal preparations that can be used. A short course of treatment is often adequate, but treatment may need to be extended to two weeks if clearance of yeast is slow. Vaginal yeast infection is normally a very localized condition so that only local treatment is indicated. If recurrence is persistent, reinfection from the gastrointestinal tract should be considered.

Sexual Dysfunction

Sexual dysfunction is present in up to 20% of patients with CFS.[13] Decreased libido is a common cause and dyspareunia can also occur. Loss of libido can be associated with low reproductive hormone levels, or be due to the severe fatigue, malaise and pain that are so prominent in CFS. Dyspareunia may be present due to vaginal dryness from low estrogen levels or the presence of a local pelvic cause, such as endometriosis or vulvodynia. For low estrogen syndromes, use of a vaginal estrogen cream locally or administration of hormone replacement therapy to the patient may be helpful. Sexual problems can put a severe strain on both a patient and her partner. They may need counseling to help them save their relationship. They both need to understand the causes of the problem and find ways to adjust to the situation.

Galactorrhea

Leakage of milk from the breasts not associated with pregnancy has been reported to occur more commonly in patients with CFS than in control women. It can predate the onset of CFS.[290] Serum prolactin levels should be checked. If elevated, and especially if the patient has associated headaches or visual complaints, an MRI of the sella tursica should be undertaken. Although there is no evidence of any increase in its incidence, breast cancer must also be excluded by examination and mammography, especially if leakage is unilateral and no other cause is found. The patient should be referred to a specialist.

Fibroids and Ovarian Cysts

A history of ovarian cysts, including polycystic ovaries, and uterine fibroids were found to be more common in patients with CFS. These conditions have also been found to predate the onset of CFS more often than is found in control women.[290] There is no reported evidence of any increase in ovarian cancer in CFS. Referral to a gynecologist may be indicated if either condition warrants surgical intervention.

Pelvic Inflammatory Disease

A history of pelvic inflammatory disease, and of sexually transmitted disease was reported in a retrospective survey to be more common in women prior to their CFS.[290] No studies have investigated the presence of any specific infective agents. Pelvic inflammatory disease may have stemmed from endometriosis, rather than from a pelvic infection, or the symptoms and signs could have been elicited from the presence of fibroids or ovarian cysts in some CFS patients with pelvic pain.

Dysmenorrhea

About 15% of normal women suffer from dysmenorrhea, but at least 30% of patients with CFS are said to suffer from it.[299] Severe dysmenorrhea may occur on its own or it can be a symptom of a number of gynecological conditions, which are more common in patients with CFS than in the general population. These are endometriosis, fibroids, pelvic inflammatory disease, and ovarian cysts. In all these conditions, menses may be heavy. If there is any abnormality found on examination, such as a pelvic mass, further gynecological investigation is indicated.

Mild dysmenorrhea usually responds to analgesics, such as aspirin or acetaminophen (Tylenol), but NSAIDS, such as ibuprofen may work better. Severe pain can be treated by suppressing ovulation with cyclical hormone treatment, such as OCPs.

Hysterectomy

Patients with CFS are significantly more likely than controls to have had a hysterectomy.[291] The reasons for the excess of this surgery in patients with CFS is not known, but may be associated with the increased numbers of patients with endometriosis, fibroids, or ovarian cysts.

Gynecological Surgery in Patients with CFS

Surgery in women with CFS can be associated with various problems that are rarely found in healthy women. Many patients with CFS are found to require a much smaller dose for their weight than normal women of anesthetic agents given either for an epidural or for a general anesthetic, or drugs used for pain relief.[300] Some patients with CFS suffer from orthostatic intolerance. Because many anesthetic agents cause vasodilatation,[301] efforts need to be made to ensure that blood volume and blood pressure are maintained in these patients. A general anesthetic can also aggravate CFS symptoms, and may be associated with delayed recovery in patients with CFS.[300] When a general anesthetic is necessary, potentially hepatotoxic gases should be avoided.[300]

Pregnancy in Women with CFS

CFS commonly affects women in the peak childbearing years. Some may seek information about possible risks of pregnancy from their healthcare provider, who needs to be able to give them preconception counseling. Because there is almost no peer-reviewed research, the healthcare provider must base advice on these risks mainly on anecdotal information.

Preconception Counseling

Because people with CFS vary greatly regarding severity of symptoms, they must make their own decisions about whether to have children, depending upon their own circumstances and on information about pregnancy in other people with CFS. Both parents should be in agreement because the baby's father will almost certainly have to do a great deal more for both mother and child than in families where the mother is healthy. The following factors should be discussed with both potential parents:

- Possible transmission of CFS to the child
- Effects of pregnancy on CFS
- Effects of CFS on pregnancy, labor, delivery, and the puerperium
- CFS and breastfeeding
- Coping with childrearing

Possible Transmission of CFS to the Child

The majority of women with CFS have normal healthy children. Most children with CFS have healthy parents; however, CFS in both mother and child does occur, although the incidence has not been established. Genes certainly influence the occurrence of CFS because twin studies have shown that monozygotic twins are almost three times as likely to both have CFS, compared with dizygotic twins.[302] An affected child usually initially develops CFS later in childhood or adult life. The possibility of the baby's developing CFS in infancy has not been investigated.

Effects of Pregnancy on CFS

During pregnancy, many women with CFS feel better, especially after the first trimester. Others remain the same, while some feel worse. Opinions vary as to how many improve. Immediately after delivery, some mothers remain better, while others relapse. Within weeks of delivery, most mothers' symptoms return to their pre-pregnancy condition. Improvement during pregnancy is thought to be due to the effect of hormones. Even if they feel better, mothers with CFS will need much more rest during pregnancy than healthy mothers.

Effects of CFS on Pregnancy

Many patients with CFS use a variety of both over-the-counter and prescribed medications to relieve symptoms. Some vitamins, such as folic acid, are known to be beneficial both before and during pregnancy. Patients should be advised to take a daily dose of folic acid before becoming pregnant because it has been shown to reduce the incidence of neural tube defects. However, some medications can damage a growing fetus, especially in the early stages of pregnancy. The effects of most herbal preparations on the fetus is unknown. For this reason, the patient should discuss with her healthcare provider which potentially dangerous treatments should be stopped before pregnancy. The patient will then find out whether she can cope if her CFS symptoms worsen as a result of stopping the medications.

Pregnancy is not recommended in the early stages of CFS.[303] This may be a time when a woman is very ill, the diagnosis may be uncertain, and a possible infective agent that might cause the disease may be actively multiplying. Women known to have active viral replication with a virus such as HHV-6 need to discuss the risk of pregnancy with an expert.

Infertility occurs in about 10% to 20% of normal couples. It is possibly higher in patients with CFS because many have problems that can cause infertility, such as endometriosis or sexual problems, such as lack of libido.[303]

First trimester miscarriage occurs in 10% to 20% of normal pregnancies. The miscarriage rate was reported to be higher than normal (27%) in a group of women with CFS.[304] Patients with CFS may have to overcome the frustration of becoming pregnant only to miscarry.

The most common symptom of early pregnancy is morning sickness, which usually improves after the first trimester. In women with CFS, this symptom may be more severe, lasting throughout the day and even persisting into the later months of pregnancy.[299] The extreme form of sickness, hyperemesis gravidarum, is also more common than in normal women. It is probably associated with the impaired activity of the HPA axis seen in CFS[26] because studies have shown that hyperemesis can be completely alleviated by adequate doses of corticosteroids.[305] For morning sickness, bed-rest and pharmacologic agents, such as promethazine hydrochloride (Phenergan) or ondansetron hydrochloride (Zofran), may be used. Also, complementary therapies, such as fresh ginger or Sea-bands worn around the wrists, may be helpful.

In mothers with CFS, there is some anecdotal evidence that slow growth of the baby before birth appears to be much more common than in normal women.[306] The baby may well be diagnosed as being dysmature.

The incidence of premature birth is unknown, as well as whether any other complications of pregnancy are more or less common in mothers with CFS. There is no evidence that the fetal abnormality rate is any different from that which occurs in normal pregnancies.

Good prenatal care should start early in pregnancy. An ultrasound scan should be done in the first trimester to confirm the age of the fetus and the date of delivery, and to reassure the parents of the presence of a fetal heart beat. A dysmature baby also requires close monitoring in pregnancy.

Effect of CFS on Delivery of the Baby

A mother with CFS is likely to tire more quickly than others in labor. In order to avoid this situation, adequate pain relief should be given. An epidural anesthetic can be useful. Prolonged labor can be avoided and the baby delivered before exhaustion occurs by using C-Section in the first stage or forceps in the second stage of labor. A C-Section before labor may be recommended. C-Sections require an epidural or a general anesthetic. Many women with CFS require a much smaller dose than normal of both drugs given for pain relief in labor and drugs used for epidural and general anesthetics.[300]

CFS and the Puerperium

Many women with CFS are exhausted by childbirth and require a longer stay in the hospital afterward. The fact that these are days of early discharge from the hospital after delivery should be taken into consideration and arrangements made prior to delivery.

Postpartum depression is much more common in women with CFS.[292] The new mother may respond to supplemental hormones,[307] as well as to antidepressants. After delivery, contraception should be discussed. One of the progesterone-only pills can be used while breast feeding or a standard oral contraceptive pill (OCP) used if bottle feeding. The intra-uterine contraceptive device is not advised because of a possible risk of infection[303] that may lead to pelvic inflammatory disease.

CFS and Breastfeeding

A mother with CFS should consider several factors before deciding whether to breastfeed her infant. While there is no evidence that an infectious agent that might be the cause of CFS could be passed to the baby in breast milk and could remain dormant in the child and active later in life, such a scenario remains a theoretical possibility. Women should weigh the well-known benefits of breastfeeding with theoretical, unproven risks of postnatal exposure.

Many women feel less fatigue during pregnancy, but frequently relapse after their baby is born. If so, previously successful CFS medications may be beneficial. Bottle feeding is recommended if these medications pass into the breast milk and could adversely affect the child. Information on CFS medications and lactation should be obtained.[308]

Many mothers with CFS successfully breastfeed their babies, and some mothers feel better while they are breastfeeding. However, if a new mother with CFS finds nursing her baby overwhelming, the baby can easily be bottle fed.

Coping with Childrearing

During childrearing, CFS really takes its toll. Both parents will suffer frustration and difficulties that other families do not have to face. In the majority of cases, the happiness brought to the family by the child make the effort more than worthwhile. New mothers who have severe CFS may have difficulty walking or lifting their baby. They will need to remain within their own limits, while spending their scarce resources of energy on their child. Most mothers find that it is necessary to organize help from their husbands, relatives, and friends. Advice on how to cope can be obtained from other mothers in a local support group.

Medical Termination of Pregnancy

When an unwanted pregnancy occurs, patients with CFS may seek advice on a medical termination of pregnancy. Dealing with the problem of an unwanted pregnancy and therapeutic abortion may well cause a relapse of CFS symptoms.[309] However, pregnancy complications in CFS patients rarely constitute medical justification for termination of pregnancy.

Conclusion

There are many gynecologic and obstetrical problems experienced by women with CFS. The incidence of infertility, miscarriage, vomiting in pregnancy, exhaustion in

labor, and puerperal depression is higher than in normal women. Pregnancy, however, is usually uncomplicated for the majority of these women. In fact, CFS symptoms may improve in some patients after the first trimester. At times, surgical delivery of the child may be necessary to avoid exhaustion in labor. Before delivery, the advantages and and disadvantages of breast feeding should be discussed.

Compared to the normal incidence, children of women with CFS may have an increased likelihood of developing CFS during their lifetime. Childrearing is often the biggest challenge for mothers with CFS.

Some common gynecological conditions, such as menopause and PMS, make CFS symptoms worse and are themselves made worse by CFS. Symptoms of other conditions that are more common in women with CFS may predate the onset of CFS. These conditions are usually associated with either abnormal reproductive hormone levels, immune dysfunction, or pain.

The conditions with abnormal reproductive hormone levels include anovulatory and oligo-ovulatory cycles, with low estrogen levels leading to a multitude of CNS symptoms, loss of libido, and, in later years, osteoporosis. Hirsutism may or may not also be present. Abnormal prolactin levels may be associated with galactorrhea. Endometriosis and interstitial cystitis may be associated with immune abnormalities. Painful conditions include endometriosis, pelvic inflammatory disease, dysmenorrhea, dysuria, and dyspareunia. Ovarian cysts and fibroids are also found more frequently in patients with CFS, as is a history of having had a hysterectomy. Gynecological symptoms should not be assumed to be merely part of the CFS symptomatology. Their investigation and treatment in patients with CFS should follow standard gynecological practice, and patients will benefit from relief of symptoms.

10 Gastrointestinal Symptoms in CFS

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Patients with chronic fatigue syndrome often suffer from overlapping conditions, including FMS and gastrointestinal (GI) disorders, particularly irritable bowel syndrome (IBS). The diagnosis of IBS in this group of patients may often be missed and go untreated, adding to the already significant morbidity of CFS.

All clinicians involved with patients with CFS must be aware that IBS often occurs as a coexistent condition. IBS is defined as a functional disorder of the gastrointestinal tract characterized by abdominal pain and discomfort, accompanied by an alteration of bowel function. Patients may experience diarrhea, constipation, or a combination of both, often with bloating and urgency. In our experience, some patients with chronic fatigue syndrome may have abdominal complaints that do not clearly fit the criteria of IBS; this subgroup may be best defined as nonulcer dyspepsia. These patients experience bouts of postprandial upper abdominal pain, early satiety, nausea, abdominal distention, and bloating in the absence of organic disease. Thus, the clinician caring for the patient with CFS should have a clear understanding of the interaction of IBS and CFS.

Pathophysiology

Many patients who have CFS suffer episodes of IBS. Although the pathophysiology of IBS is not fully understood, the nature of the precipitating factors most commonly include dietary factors and stress. Recently, bacterial overgrowth has been implicated as a precipitating factor in some patients.[310] In addition, disregulation of the intestinal motor and sensory, as well as central nervous system, functions have been identified as key factors.[311, 312] Serotonin receptors are believed to play an important role in pain perception and gastrointestinal motility.

Even if the precipitating factors of IBS are uncertain, the symptoms of diarrhea and constipation involve an alteration in the permeability of the intestinal cells or the permeability between cells, as has been argued for inflammatory bowel disease.[313, 314] To the extent that cytokines are involved in regulating endothelial cell adhesion molecules and producing reactive oxygen metabolites,[314]episodes of IBS may reflect increasing levels of specific cytokines associated with altered states of immune function. The finding of bacterial overgrowth of the small intestine's being associated with IBS symptoms also implies an immune system dysfunction, which permits the overgrowth to occur.

CFS and IBS have properties in common: IBS is characterized as a functional gastrointestinal disease, whose symptoms are controlled (at least in part) by serotonin (5-HT).[315] Thus, alterations in 5-HT levels may play a role in IBS, as has central nervous system 5-HT levels been implicated as a mechanism for CFS. Both CFS and IBS may have sensory dysfunction components,[316] and both are found to occur predominantly in women with possible variations in severity associated with the menstrual cycle.[317, 318]

Diagnosis

The task of the physician caring for the patient with CFS is not only to be aware of the common GI complaint often associated with CFS, but also to be vigilant for GI disorders that could masquerade as chronic fatigue syndrome. The diagnosis of CFS does not afford protection from later development of an unrelated gastrointestinal problem. It is imperative that the clinician recognize that specific signs and symptoms, such as blood in the stool, anemia, fever, weight loss, and nocturnal symptoms are not usually attributable to chronic fatigue syndrome and would require further radiologic or endoscopic evaluation to rule out underlying malignancy or inflammatory bowel disease. Infectious diseases, such as giardiasis and cyclosporidiosis may masquerade as an irritable bowel syndrome and should be excluded by careful analysis for fecal ova and parasites. Finally, the diagnosis of ulcer disease and erosive gastritis must be considered, particularly in patients with CFS and FMS who use aspirin or nonsteroidal anti-inflammatory drugs. Gastric infection with *Helicobacter pylori* usually can be eradicated with a two- to three-week course of antimicrobials and may protect the patient from eventual helicobacter-associated cancer. Celiac sprue should be ruled out in those patients with CFS and gluten sensitivity. Diagnosis can be suggested by the presence of anti-gluten antibodies.

Treatment

The management of IBS in patients with CFS revolves around the establishment of a firm diagnosis and reassurance to the patient that he or she can be helped. Treatment modalities are primarily empiric and include dietary modification and pharmacologic therapies, as well as patient education about IBS. Dietary management often involves eliminating offending items such as caffeine, alcohol, fatty foods, and large meals. Increased fiber intake may be necessary, particularly in the setting of con-

stipation. If a patient depends on caffeine for treating fatigue, a risk-to-benefit ratio needs to be done. Obesity itself can be a long term problem for the CFS patient, due to forced inactivity and altered eating habits and patterns.

At times, lactose and sorbitol may need to be eliminated. Patients with sprue or gluten sensitivity need not eliminate all wheat-based products from the diet. After a medical evaluation that which may include endoscopy, ultrasound, and colonoscopy, patients with CFS may benefit by a nutritional consult by a registered dietitian (See Chapter 10).

GI medication can often help patients with CFS (See Chapter 10). Dicyclomine, hyoscyamine sulfate, or clidinium bromide are some examples of medications that may provide symptomatic relief from abdominal pain or cramps. Pharmacologic measures may also include antidiarrheals, such as loperamide, or in more severe cases, tricyclic type antidepressant therapy could be considered. Recently, newer therapies have been based on the finding that serotonin plays a key role in IBS, but currently there are no selective 5-HT3 receptor antagonists on the market.

Alosetron hydrochloride (Lotronex), which is a selective 5-HT3 receptor antagonist, has been shown to be effective in alleviating pain and diarrhea in female patients with diarrhea-predominant IBS. Tegaserod maleate (Zelnorrn), a serotonin receptor partial agonist, is being investigated for treatment of IBS associated with constipation. Unfortunately, alosetron, which was removed from the market due to adverse side effects, and tegaserod, are not currently clinically available. This class of compounds will hopefully lead to improved therapies for IBS.

Conclusion

Intestinal symptoms in patients with CFS are very common and resemble those of patients with IBS. Other diagnoses to be considered in selected patients with CFS who have GI symptoms include cancer and infectious diseases. Therapy is empiric and symptomatic but can be very helpful in reducing symptoms and improving quality of life for patients who have a multitude of problems in other organ systems.

11 CFS in Children and Adolescents

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Like adults, children and adolescents can develop CFS. Typical symptoms are of significant severity and duration that they lead to age-specific dropout, school failure, loss of friends, inability to participate in after-school activities, and family disharmony.[319-321] Children and adolescents with CFS (CACFS) have more generalized complaints, such as vague abdominal pain, alternating constipation and diarrhea, rashes, fevers, and atopic symptoms, including food intolerances.[319, 322-324] The neurologic symptoms in children may be more difficult to evaluate, due to language, cognitive ability and developmental stage. In addition, there is the recent appreciation that there may be a continuum of developmental conditions, such as autism and CFS, that are linked by common neuro-immuno- and endocrine abnormalities. As confusing as the individual symptoms are to the physician, so are the usual lack of collaborating physical findings and non-diagnostic laboratory studies. Until recently, the evaluating physician had little available literature on which to base a specific diagnosis.[325, 326] Since 1988, there has been an increasing number of studies examining the epidemiology, natural history, and etiopathogenesis of CFS, which have helped define the parameters of this syndrome in adults.[327-330]

The literature for CACFS is more limited than that on adults. The diagnosis of CFS in the pediatric population is complicated by the unique and changing developmental, physical, and emotional characteristics of children compared to adults.[331, 332] The long term impact of the cognitive abnormalities with CFS is more pervasive in the child, due to disease onset during a period of rapid intellectual development. Frustration and secondary depression are frequent components for the youth and families trying to cope with a child having an undiagnosed illness, who is always tired and unable to keep up with peers. Many physician encounters with such patients are characterized by an all too brief history, curtailed physical examination and limited laboratory evaluation. The diagnostic outcome is predictable: the patient's illness is diagnosed as depression, a psychosomatic illness, and malingering or school phobia. The outcome for the individual and family members is also predictable: conflict, confusion, and the search for a diagnosis and cure from anyone, regardless of cost or competency.

Pathogenesis of CFS in Children and Adolescents

Pediatric patients with symptoms of CFS usually present after the age of eight and frequently at the onset of puberty. The adolescent patient is more likely to have signs and symptoms similar to adults. As many as 15% of CACFS have a history of another family member with CFS, suggesting a genetic predisposition.[333, 334] The pediatrician has to differentiate a number of illnesses and syndromes, both congenital and acquired, that can have fatigue as the major presenting complaint. Many of these conditions that have fatigue as a major component will be diagnosed by standard evaluations for known medical or psychological disorders. Some of these disorders include cystic fibrosis, inflammatory bowel disease, atopic conditions, complex seizure and other neurologic diseases, and juvenile onset diabetes. While youths with unexplained persistent fatigue of greater than six months meet the same criteria that have been described in adults, pediatric patients are more likely to have their illness associated with viral infections, immune dysfunction, and persistent inflammatory reactions that may cause the complex and multiple symptoms of CFS.[335-338]

The human DNA Herpes viruses, with their ability to maintain a latent life-long infection with periods of reactivation, are candidates for being one of the infectious causes of CFS. The similarities between the prolonged fatigue-like illness that can complicate acute infectious mononucleosis (IM) due to Epstein-Barr Virus (EBV) in the older child or adolescent and CFS described in adults, led to the initial suspicion that EBV was a candidate as the etiological agent of CFS. The findings in early studies of patients with CFS demonstrating a distinctive EBV serological response supported this assumption. Subsequent studies of larger numbers of adult patients with CFS, however, did not consistently demonstrate this unique serological response. Other viral illnesses associated with chronic fatigue include cytomegalovirus (CMV), Human Herpes Virus-6 (HHV-6) infection, and Parvovirus B-19. A subset of patients with CFS may represent the interaction of more than one latent viral infection and subsequent abnormal immune responses.[339-345]

Like adults, CACFS patients may have the etiology of their illness based on other organ system abnormalities. The possibility of orthostatic intolerance should be considered in the child with chronic fatigue who has a problem with dizziness or changes in position or in maintain-

ing upright posture. Endocrine abnormalities including hypothyroidism, diabetes, and sex hormone dysfunction should be suspected in the child with obesity and maturation problems, which are complicated by onset of puberty.[346-348]

Evaluating CFS Patients

The physician presented with a child or adolescent with complaints of chronic fatigue should consider the following the medical evaluation: (1) Allow enough time for an adequate history (at least ½ hour) and, prior to the initial patient visit, make every attempt to obtain previous medical records. (2) Many patients with CFS have seen multiple health care providers and specialists. (3) The initial encounters with the physician for the patient with CFS should be devoted to differential diagnosis to ensure that the suspected CFS patient's multiple complaints are not due to other causes. This work-up of exclusion needs to include selected laboratory studies guided by a thorough history and careful physical examination.

Clinical Evaluations

There are several similarities between adults meeting the diagnostic criteria of CFS and adolescents and older children diagnosed with IM and other post-infectious fatigue illnesses. CFS and post-infectious fatigue cause significant fatigue, persisting for greater than six months and can be associated with other symptoms. Older children with acute IM present with one or more signs and symptoms, including exudative tonsillitis, enlarged lymph glands, hepatosplenomegaly, encephalitis, carditis, dermatitis, hemolytic anemia, thrombocytopenia, jaundice, fever, and fatigue. This acute viral infection with EBV is well characterized, but there remains, however, a general lack of appreciation as to how severe and prolonged a bout of acute EBV mononucleosis can be for the older child and youth. Adolescent patients may experience periodic flare-ups of sore throat, cervical adenopathy, and fatigue two years after the initial bout of acute IM and have persistence of symptoms, especially fatigue, for three to five years after a severe bout of acute EBV infection. In general, however, older children and adolescents with post-infectious related fatigue frequently recover and do not progress into adulthood with CFS. Only a longer period of observation of such patients will answer the question of the relationship between the severity of acute IM, treatments given and the development of CFS later in life.

In children with noninfectious background for their CFS, there is no standard duration of their illness, but most children outgrow it over four years. The course of recovery varies greatly from patient to patient. There is frequent exacerbation of symptoms, during which patients feel they are again as sick as at disease onset. However, when patients more objectively evaluate their symptoms, it is recognized that there has been a slow, but gradual, recovery over time from CFS for many patients. There can be fluctuation in symptoms over the course of pediatric CFS, with episodes lasting from one to six weeks, interspersed with periods of improvement. Frequently, some patients are made worse by intercurrent illnesses, emotional or physical stress, and are unable to perform daily activities of living. It has been recommended that a more formal mental status examination by a neuropsychologist be included as part of the evaluation of CFS that includes both subjective and performance aspects of fatigue level and overall functional performance. Some of these instruments may not be appropriate for young adolescents and children, and physicians may need to collaborate with a clinical psychologist. Due to the chronicity of CFS, periodic measurement of quality of life should also be part of the overall clinical evaluation, such as the one proposed by Gortmacher.[349-353]

Laboratory Evaluations

As a baseline, children and adolescents with suspected CFS should have a CBC differential and platelet count, sedimentation rate, multiple blood chemistry, thyroid functions, ANA, and a urine analysis. If there are episodes of fever, patients should also have several blood cultures taken. A more aggressive FUO evaluation will need to be considered in patients with persistent episodes of fever. Patients with predominant CNS symptomatology suggesting a chronic encephalopathy (confusion, episodes of lack of concentration, headache, depression, and insomnia) may benefit from a more detailed neurologic evaluation by a consultant neurologist that may include neuroimaging of the brain. Examination of spinal fluid is usually reserved for patients with CFS suspected to have multiple sclerosis or other significant CNS abnormalities.

A more intensive laboratory evaluation that would be performed as part of a research protocol or by a specialist on selected patients may include: serological assays (IgM and IgG antibodies) or PCR assays for suspected infectious process (HHV-6, CMV, EBV, Paravirus B-19, mycoplasma/chlamydia). Lymphocyte subsets can reflect the degree of immunosuppression or immune stimulation. Some patients with CFS have evidence of Common Variable Immunodeficiency Syndrome (CVID) that has an associated humoral immune dysfunction. Selected patients with unexplained fatigue associated with fevers and a past history of recurrent infections should have quantitative immunoglobulin (IgG,A,M,E) and IgG subclass levels measured. If these humoral immune studies are abnormal, referral to an immunologist is appropriate for further immune system evaluation. If there is evidence of orthostatic intolerance, referral to a cardiac center with experience with diagnosis and management of this condition is appropriate. Other subspecialist referrals may be indicated.[105, 228, 354]

Treatment for CFS in Children and Adolescents

Just like adults, there is no specific therapy for CACFS patients, but many agents may relieve symptoms. It should be remembered that children with CFS may have unusual sensitivity to medications and lower dosages should be started with gradual increases in dosages. In the few published natural history studies of pediatric CFS, 8-27% of children recovered, 28-46% improved, while 12-30% did not improve during the study period. Antiviral drug trials with acyclovir (directed against EBV, CMV, HHV-6) have no demonstrated efficacy and may be toxic. Long-term antibiotic therapy including many patients diagnosed with chronic Lyme disease as the bases of their CFS, is currently under further study and is not generally recommended.

Children with CFS suffer many negative feelings (See Table 11-1). Symptomatic care and emotional support are important in improving the quality of life and general well-being of an individual with CFS. The best individual to coordinate this program would be a non-judgmental and committed pediatrician who has experience with children with a chronic illness. CACFS patients usually do poorly when they receive fragmented care from a number of specialists. Any patient with a chronic illness needs emotional support to manage the stress of the illness. Pediatric patients with CFS frequently have multiple emotional/psychological symptoms during the course of their illness that interfere with their ability to fully participate in social and educational settings.[355-359] Many CACFS patients benefit from the techniques available through an experienced mental health professional.

Table 11-1
Negative Feelings Many CACFS Experience

Fear	Loss	Resentment	Decreased Self-Esteem
Anxiety	Sadness	Anger	Confusion and Worry
Stress	Shame	Self-blame	Family Discord / Conflicts
Depression	Isolation	Guilt	Relationship Problems

Good nutrition is important in the management of CFS, although it is not proven *per se* to be associated with a specific vitamin/mineral deficiency. A daily vitamin/mineral supplement to include antioxidants is a reasonable recommendation, but high doses or intravenous administered vitamins are not recommended. Patients may benefit from limited exercise (therapeutic strengthening/breathing exercise, yoga) that gives a psychological lift, but that is not so strenuous that it results in a relapse of more severe fatigue. CACFS patients appear at greater risk of having exacerbation or onset of typical allergic diseases during the course of their CFS. Children experiencing asthma, rhinitis, sinusitis, conjunctivitis, and other inhalant allergic symptoms should receive appropriate allergic care, which may include the use of non-sedation antihistamines. Such antihistamines do not cross the blood brain barrier and, therefore, do not exacerbate the fatigue, as is the tendency of other classes of antihistamines. Additional allergic-based therapies and evaluations may be helpful, depending on the individual's specific symptoms.[360]

Many patients with CFS have insomnia or poor sleep habits despite feeling exhausted. Such patients may benefit from taking a low dose antidepressant before bedtime. When headache is a major manifestation of a CFS patient, acetazolamide (Diamox Sequels, 500 mg), taken prior to bedtime, acts as a mild diuretic and possibly lowers cerebral spinal fluid pressure. Some patients complain of tingling in their hands with this drug and it should not be used if there is a history of kidney stones. Patients treated with acetazolamide may improve after two weeks and can be maintained on a reduced dose schedule thereafter.[186]

The joint symptoms and generalized aches and pains that many patients with CFS experience will frequently be improved with a nonsteroidal anti-inflammatory agent. Selected patients may require more intensive treatment for chronic pain that may include opioids. The use of steroids in CFS is controversial, and the serious side effects and toxicity of these hormones must always be considered. Only infrequently would the risks of using steroids be outweighed by possible benefits in a specific patient. There are indications for steroids in acute EBV IM syndrome (impending upper airway obstruction, impending rupture of the spleen, cardiomyopathy, encephalitis, and severe thrombocytopenia or hemolytic anemia). The patient with acute IM treated with steroids often has dramatic improvement, including a feeling of well-being and a lessening of fatigue. However, the long-term risk of using steroids with a known latent viral agent (EBV) having oncogenic potential is a major therapeutic decision requiring careful evaluation of benefit and risk. In addition to prednisone, ACTH, and the cortisol metabolic intermediate, dehydroepiandrosterone (DHEA) have been suggested as possible therapies for adults with CFS, but these medications in children and adolescents have not been studied.

When a child or adolescent with CFS is identified to have dysgammaglobulinemia, major or subclass deficiency, or poor function of subclass antibody, replacement therapy with intravenous gammaglobulin (IVIG) may be helpful. This group of patients, when treated with monthly IVIG (400 mg/kg/per dose), has symptomatic improvement usually beginning after the third dose with less fatigue, less cervical adenopathy, and fewer sore throats. The cost of IVIG is significant, and this limits its use to those patients with defined antibody deficiency associated with their CFS.[361-363]

Patients with CFS may benefit by referral to recognized CFS experts, who may also have access to clinical

treatment trials that include study of physical therapy, antidepressants, acetazolamide, IVIG, anti-inflammatory agents, DHEA, treatment of orthostatic intolerance, and other modalities, including complimentary therapies. Children and adolescents with CFS should be incorporated into National Centers of Excellence for CFS.

Psychological Issues

CACFS patients may benefit from psychotherapy (counseling from a trained professional, preferably one who is knowledgeable about and sensitive to issues related to chronic illness) both for support and to achieve the ability to better cope and manage the emotional/psychological and physical symptoms of CFS. Counseling can also assist CACFS patients to work through the stages of emotional conflict they experience, which are similar to those experienced after the death of a loved one: shock, denial, anger/depression, bargaining, and acceptance. In CACSF patients, this process can be described by four phases, as well: shock, defensive retreat, acknowledgement, and adaptation. The stages/phases are not always clear-cut and vary considerably from one person to another. There exists a broad range of how CFS affects each individual child. The more severely afflicted, like other children with severe handicaps, will tend to become isolated, while the less severely afflicted might be able to interact quite normally with peers.[321, 364-366] In general, CACFS patients may exhibit the following behaviors:

- Denial–They do not want to be considered sick. They want to be like everyone else. They may especially be in denial when they have good days and tend to greatly overdo on those days.
- Isolation–They often feel isolated from peers because they cannot keep up socially. They may also feel greatly misunderstood when friends or schoolmates challenge their disability, especially when peers interpret a "good day" as a fair barometer of their health status.
- Depression/Anxiety–They may become depressed/ anxious in reaction to being sick, to not being what they once were, to the realization that some of their dreams or aspirations may have to be deferred or even remain unfulfilled.
- Resiliency–They will often show great courage, resourcefulness, and determination in the face of physical disability, cognitive impairment, and social adversity.

One psychological reaction will usually be mixed with another, and they do not usually occur in an orderly sequence. As one CACFS patient explains, "You deny it, acknowledge it, resent it, and finally accept it as an obstacle, or stumbling block, not as something that has sealed your fate."

A range of mental health programs are available for CACFS patients,[367-369] as shown in the following table (Table 11-2).

Table 11-2
Mental Health Programs Available for CACFS

Program	Comments
Psychoeducational Psychotherapy	Provides necessary information regarding chronic illness, as well as a clear and critical understanding of the emotional impact of the illness. It can also aid in reducing self-blame and de-stigmatize the CACFS patients' experience.
Cognitive and Behavioral Psychotherapy	In cases of any chronic illness, cognitive-behavioral interventions can assist individuals in challenging and changing faulty perceptions and beliefs regarding CFS that underlie the emotional stress for CACFS patients. Therapists well-trained in Cognitive and Behavioral Therapy may be difficult to find.
Individual Psychotherapy	May aid the student in enhancing self-esteem, relieving depressive and anxious feelings, as well as helping to develop more adequate coping strategies.
Family Psychotherapy	May be recommended to assist CACFS patients and their families in coping with the impact of CFS. Families of CACFS patients are directly affected by this illness, and relationships are often under a great deal of stress. Family psychotherapy can have a positive affect on interpersonal relationships and improve communication among all involved family members.
Support Groups	May be therapeutic for CFS patients, as well as for the families. They can promote "relief in hearing similar experiences" that alleviate shame, as well as provide validation in discovering "they are not the only ones."
Group Psychotherapy	Provides similar gains, as do support groups, with the difference that psychotherapy groups are facilitated by a professional trained in guiding and promoting specific and greater emotional healing, as well as coping skills and strategies.

Pediatricians and other physicians providing primary care for CACFS patients should advise their patients and their families to seek counseling services and make necessary referrals.

The Role of Schools in Accommodating Students with CFS

The majority of children with CFS cases (up to 94%) experience worsening of their school performance, due to the physical and cognitive symptoms and 20 to 44% of CACFS may be home-schooled because they are too ill to attend classes. CACFS who cannot attend school miss out on important social development opportunities and social functioning may be impaired in more than half of all CACFS patients.[370, 371]

Given the physical limitations and cognitive deficits often associated with CFS, children and adolescents with this syndrome may qualify for Special Services under the Individuals with Disabilities Education Act (IDEA). The IDEA provides additional federal funding for educating students with one or more of 13 listed conditions and students with CFS often qualify under other health impaired: "having limited strength, vitality, or alertness due to chronic or acute health problems… which adversely affect a child's educational performance." Eligible students receive an Individualized Education Plan (IEP) written by a multi-disciplined IEP team.

Superintendents, principals, supervisors of special education, guidance counselors, school social workers, and psychologists are very much involved in IDEA eligibility evaluations; yet, often the role of the school nurse as a bridge between the medical and school communities has been overlooked. Both in the eligibility evaluations and in the IEP meetings, the school nurse's medical knowledge could be invaluable in successfully planning a program that would meet the educational needs of children with CFS.

It is important that a multidisciplinary approach addresses the needs of the student and families and ensures that the student's teachers participate. The process should also allow for parent/student involvement. Consultations with the student's physician(s) should be periodic, in light of the relapsing/remitting nature of the syndrome.

As many as 40% of students with CFS are too ill to attend school full-time and home tutorial services should be provided. Where students can attend school for all or part of the day, multiple accommodations (See Table 11-3) have proved successful in helping schools provide appropriate educational settings for students with CFS.

Table 11-3
Accommodations Schools Can Provide for CACFS

- Less rigid attendance and tardiness policies
- Extra time for tests and assignments
- Classroom committees and copies of lecture notes
- Make-up work
- Flexibility in scheduling with classes and assignment deadlines
- Provision of a syllabus or schedule of upcoming assignments, so the student can keep up with the class when unable to attend school
- Access to the school elevator
- Tutor(s) for class work assistance and/or Home Instructor(s) for classes taken at home
- Extra sets of textbooks for home to eliminate the burden of carrying heavy textbooks to and from school
- Transportation to and from school
- Flexibility with course requirements, e.g. omitting physical education
- Permission to graduate from high school in more than four years and/or decreasing the required number of credits to graduate

The Role of Primary Care Providers in Care of Patients with CFS

While recognizing that the physician must evaluate and suspect emotional/psychological illness and make appropriate referrals, many patients with CFS are suffering from a poorly understood organic syndrome. Many of these patients' emotional distresses and depressions are reactive and related to their chronic organic illnesses and the frequent disbelief and frustration of physicians, friends, and family. It is the role of a primary care provider to evaluate, to offer appropriate supportive care, and to help their patient avoid victimization by "health" providers offering often expensive, but unproven, therapies. Constant referrals to multiple specialists are usually not helpful to the patient. There are, however, appropriate subspecialties that may be helpful in evaluation of the individual patient, including neurology, psychology, cardiology, gastroenterology, rheumatology, rehabilitation, allergy/immunology, and infectious diseases. In children and adolescents, pediatric-trained specialists are preferable.

There are specific syndromes that are often confused with CFS, in which referrals to specialists are especially appropriate, such as Fibromyalgia rheumatica, which should be diagnosed and managed in collaboration with a rheumatologist. In selected areas of the United States, Lyme disease is frequently misdiagnosed as CFS, especially when associated with arthralgia-like symptoms, despite the lack of any confirmatory laboratory studies. Without the help of an experienced infectious disease specialist, patients misdiagnosed with Lyme disease are frequently given prolonged courses of unnecessary antibiotics before an appropriate diagnosis of CFS is made.[372-374]

Conclusion

Children and adolescent patients presenting with prolonged fatigue require a careful, thorough evaluation. They deserve to have a physician who will provide compassionate care, appropriate advice and referral, while maintaining patient contact and advocacy.[319, 320, 375, 376] The pediatrician should help patients with CFS negotiate the difficult problems they will encounter with entitlement programs, schools, and managed care organizations. Those patients who are disabled and unable to work or go to school need to have their physician provide support documentation to the Social Security Administration.

12 Behavioral Rehabilitation for CFS

Richard L. Bruno, MD, PhD
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Over the past 19 years, we have studied the cause and treatment of disabling fatigue in adults who had polio 40 years ago. Our clinical findings and laboratory studies have shown that late-onset post-polio fatigue is associated with impaired attention and information processing speed, blood glucose negatively correlated with attention, a blunted ACTH response to fasting, plasma prolactin correlated with fatigue, lesions on MRI in the brain's activating system and brain wave slowing–findings often identical to those in patients with CFS.[340, 377] These findings led to the formulation of the Brain Fatigue Generator (BFG) Model of post-viral fatigue syndromes and our study and treatment of people with chronic fatigue from other causes.[340, 378-382]

Symptomatology

As in polio survivors, we have found that fatigue severity in patients with CFS is associated with difficulty staying awake during the day, trouble concentrating, relatively mild deficits on neuropsychologic tests of attention, and symptoms that are triggered by physical overexertion, emotional stress, and cold exposure. Symptoms of sleep-disordered breathing and nocturnal myoclonus/periodic movements in sleep are reported in half to nearly three-quarters of patients with CFS, as frequently as they are reported in polio survivors. The similarities between the pathophysiology, signs and symptoms of post-polio fatigue and CFS prompted us to apply the multidisciplinary evaluation and treatment program we developed to treat post-polio fatigue to those with chronic fatigue.[378, 379]

Diagnostic Approach

The Fatigue Management Program (FMP) evaluation consists of psychologic and physical medicine evaluations to document the nature and severity of psychologic, cognitive and physical symptoms, functional limitations and patients' abilities to cope with their symptoms and decreased ability to function.

Psychologic Evaluation

The psychological evaluation begins by asking patients to list their treatment goals and to complete a Fatigue Symptom Questionnaire that documents subjective symptoms and functional limitations. Any psychiatric diagnoses that could cause fatigue, cognitive impairment and functional limitations, including major depressive episode, somatoform, personality, and factitious disorders, are documented. Similar to polio survivors, 11% percent of patients with CFS have depressive disorders. Unlike polio survivors, our research has found that 16% of those with chronic fatigue have personality disorders or factitious disorders. A higher percentage of patients with these psychiatric diagnoses report moderate to severe muscle weakness, difficulty with mind wandering and muscle pain. Patients with factitious disorders had severe deficits or inconsistent performance on neuropsychologic testing, impairments that would have made impossible the patients' documented levels of daily functioning and academic achievement. They also had very low scores on the Sensitivity to Criticism and Failure scale of the Reinforcement Motivation Survey, suggesting a diagnosis of schizoid personality disorder.[381] It was not surprising that this small subgroup of patients neither fully participated in treatment for their fatigue, nor did their symptoms or level of functioning improve. Psychiatric disorders must be ruled out before CFS is diagnosed or treated.

Patients with a co-morbid major depressive episode are considered for an activating antidepressant medication. However, medication is only prescribed if symptoms are severe or interfere with participating in treatment, or if patients have had several weeks of psychotherapy as part of the FMP and symptoms have not improved.

Physical Medicine Evaluation

Medical records from and tests ordered by specialists in infectious diseases, neurology, cardiology, and rheumatology are reviewed to insure that there are no other medical causes for fatigue symptoms. Supine and standing blood pressure is taken to document postural tachycardia syndrome (POTS) or neurally mediated hypotension (NMH) which, if present, is treated by a consulting cardiologist. Patients' medications are also reviewed. If patients or patients' family members report patient snoring, sleep apnea, or muscle twitching, patients are referred for a sleep study.

When alternative causes for fatigue have been ruled out, patients are diagnosed with idiopathic fatigue or CFS, depending on whether they meet the 1994 CDC criteria. All patients with fatigue are offered the opportunity to participate in the program, regardless of whether or not they meet CFS diagnostic criteria or have been fatigued for less than six months. Regardless of the diagnosis, it is vital to treat patients as soon as they realize that they have unremitting fatigue that is impairing their ability to function.

Therapeutic Approach

All physicians can adopt the FMP approach to some degree within their own practice. The purpose of the FMP is not curing CFS, but managing symptoms–preventing increases in symptoms; reducing symptoms, if possible; and slowly, but consistently, increasing function without increasing symptoms. The heart of the program is teaching patients to listen to their bodies by keeping daily symptom and activity logs and to pace activities, to conserve energy, and to stop activities before symptoms occur or increase. This protocol ends the roller-coaster cycle of activity-exhaustion-rest-activity that prevents symptoms from improving.

Treatment Protocol

The treatment of fatigue is approached from a behavioral perspective by all members of the treatment team, which includes a physician, behavioral psychotherapist, nutritionist, occupational and physical therapists. Therapy begins by asking patients to keep a daily log of steps (as measured by a pedometer), activities, perceived exertion, fatigue, muscle weakness, pain, diet, emotional stress, thoughts, and emotions (Figure 12-1). Such a log is used to relate physical and emotional symptoms to activities, exertion, stressors, thoughts, and feelings. Logs are reviewed with patients by each therapist and evaluation results are used by the treatment team to formulate a behavioral plan to modify activities that trigger and perpetuate symptoms to initiate self-care activities and symptom management strategies. Patients are seen once a week by each therapist. The roles of each type of therapist are:

- *Occupational therapists* assess how patients use their energy in doing daily activities, including self-care,

Figure 12-1
DAILY LOG FORM

Name: Day: Date:

Time	Activities & Steps	Perceived Exertion Rating	Specific Muscle Weakness	Overall Fatigue	Pain Mood	Activities that Produced Symptoms & Modifications
			Rate as mild – moderate – severe			
Up	Food? Sleep Quality?					Activity:
Break						Symptom:
						How did you do the activity & how were you positioned?
Noon	Food?					How could you modify?
Break						Activity:
						Symptom:
						How did you do the activity & how were you positioned?
6 PM	Food?					How could you modify?
Bed						
	Total Steps:					

Perceived Exertion Rating Scale:	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	Very, Very Light			Very Light		Fairly Light			Somewhat Hard		Hard		Very Hard		Very Very Hard

dressing, household, and work activities. British infectious disease specialist Melvin Ramsay, who first began treating chronic fatigue in 1955, concluded, "The fundamental tenet of the management of a case of CFS is REST with graduated activity well within the limitations which the disease imposes."[383] A British survey of over 2,000 CFS patients and recent clinical studies have found that pacing activities reduced symptoms in over 80%.[384]

Therefore, patients are helped to listen to their bodies and to use the daily logs to identify the causes of symptoms and to learn to stop activities before symptoms increase. The occupational therapist identifies ways to simplify work, pace activities, and include mid-morning and mid-afternoon rest breaks to conserve energy and decrease fatigue. Also addressed are patients' sleep/wake cycles. Patients often shift their hour of sleep to early morning and hour of waking to late morning. Some even reverse the cycle, staying awake all night and sleeping all day. Other patients nap frequently throughout the day. Patients are helped to shift their hour of sleep, in half-hour increments, to between 11 PM and 12 PM. They are also encouraged to limit the duration of a once-daily nap to 90 minutes or less, to nap only in the afternoon, and not to nap after 5 PM.

- *Nutritionists* assess protein and calorie intake to help maintain or decrease weight and to decrease fatigue. A study of polio survivors has shown that eating a balanced diet that includes about 16 grams of protein (0.5 grams of protein/pound) at each meal–especially at breakfast–and small, 8 gram protein snacks during the twice-daily rest breaks limits portion sizes, decreases daytime fatigue, and promotes weight reduction.
- *Physical therapists* assess muscle weakness and pain, while evaluating posture and gait. Postural changes and frequent stretching during the day is recommended to decrease muscle pain. Only as fatigue comes under control through energy conservation is any *non-fatiguing* exercise considered. The CFS patient survey and recent clinical studies have found that exercise increased symptoms in 50% of CFS patients.[384, 385]
- *Behavioral psychotherapists* monitor the behavioral plan and patients' ability to promote self-care by either decreasing fatigue-producing activities or slowly increasing activity without increasing fatigue. Behavior modification techniques are used to decrease and eliminate hyperactivity, which is often thought by patients to be necessary to be accepted by family, friends and employers, or decrease and eliminate inactivity, which is thought by patients to protect against increased fatigue and pain.

As therapy progresses, patients are weaned from medications that have been prescribed to treat specific symptoms, e.g. stimulants for fatigue, sleeping medications for insomnia, and pain medications. When patients have consistently applied the behavioral plan and incorporated symptoms management techniques, nonsteroidal anti-inflammatory drugs may be prescribed for residual muscle or joint pain. Patients are not prescribed stimulants, sleeping medications, narcotics, or muscle relaxants.

Team and Family Meeting

In the fifth week of treatment, the FMP team meets with patients and their family members to explain the putative pathophysiology of CFS, why patients need to modify behavior to manage fatigue, and how family members, co-workers and friends can provide appropriate assistance with housekeeping and work activities.

The treatment program lasts from eight to twelve weeks. Patients graduate when their symptoms have been reduced or do not increase from day to day and their function has improved. They leave with a home program of stretching, while they continue to keep daily logs until their first follow-up visit with their treatment team at one month post graduation. If symptoms are well-controlled at that point, a non-fatiguing exercise program is prescribed.

Non-Compliance with Self-Care Issues

Non-compliance is the principle cause of patients' symptoms and functional ability not improving. Compliance problems arise with the daily logs and the behavioral plan. Patients invariably have difficulty keeping logs because they interfere with the performance of their scheduled activities, require too much energy to complete, or force patients to recognize the severity and pervasiveness of their symptoms.

Invariably, patients have difficulty in complying with the behavioral plan. They "forget" to alter their schedules, to eat breakfast, and often refuse lifestyle modifications. Many patients report a fear of increased symptoms or fear of criticism and a sense of failure when they merely contemplate lifestyle changes, even though without necessary changes, symptoms persist. Studies of patients with CFS, chronic pain, and PPS find that patents' ability to change their behaviors and decrease symptoms is directly related to their ability to challenge long-held beliefs about what they believe they should achieve and do for others in order to survive, to face fears concerning their worthiness in spite of their decreased activity or productivity, and to tolerate the emergence of some increase in fatigue or pain, as their activity level increases.[340, 378-380]

There are two types of non-compliers, *hyperactive* and *passive. Hyperactive* non-compliers are those who will not decrease activity in order to control fatigue and pain, or who become excessively active again as soon as their symptoms begin to decrease. Predictors of hyperactive non-compliance are: 1) a history of refusal to rest or pace activities, 2) an elevated Type-A behavior score

above 50, or 3) an elevated Sensitivity to Criticism and Failure score above 60.

The early identification of hyperactive non-compliers is important, since hyperactive behavior is often overlooked or even welcomed, since therapists are pleased when a patient becomes active again and is apparently "extremely well motivated for therapy." Hyperactive non-compliance should immediately be discussed with the patient, and its persistence should be addressed by requiring the patient to sign a behavioral contract stating that the program will be followed and hyperactivity will be reduced.

Passive non-compliers are those who will not keep treatment appointments, refuse to complete daily logs, to slowly increase activity, or to include stretching in their daily routines because of fear that their symptoms will increase. Predictors of passive non-compliance are: 1) a history of refusal to increase activity, 2) a low Type A behavior score below 30, or 3) a low Sensitivity to Criticism and Failure score below 50. As with hyperactivity, the occurrence of passive non-compliance should immediately be discussed with the patient and should be addressed with a behavioral contract. This contract should make clear that continued treatment is contingent on slowly, progressively and consistently increasing activity, attending all therapy sessions, and fully complying with prescribed therapies. Again, passive non-compliance should trigger a referral to a behavioral psychotherapist.

Passive non-compliance is much more common in patients with chronic fatigue and pain. In young people with fatigue, an extremely low Type-A score (below 25) was found to be associated with malingering, while a low Sensitivity to Criticism and Failure score (below 40) was associate with a schizoid personality disorder.[340] These patients appeared to be insensitive to suggestions from the treatment team and the needs of and impact of their disability on others and refused to continue treatment. Patients who are passively non-compliant and have been found to have marked cognitive deficits should be evaluated by a clinical psychologist to rule out malingering, factitious, and personality disorders that would be a primary cause for reports of fatigue and functional disability and would make treatment in a behavioral program impossible.

Follow Up

As fatigue and pain decrease, patients commonly increase activity and find that their symptoms also increase. To help prevent this result, patients are asked to strictly adhere to the modified daily schedule, as set forth in their behavioral plan after they graduate from the program and to keep daily logs until they are seen for the follow-up meeting with the treatment team at one month post-discharge. To promote continued self-care, patients are seen at three-, six- and twelve-months post-graduation and are encouraged to call their therapists at any time with questions or for support.

Conclusion

Chronic fatigue has been a recognized clinical entity since the first documented outbreak in 1934, which sickened 150 doctors and nurses at the Los Angeles County General Hospital who were caring for polio survivors.[386] It is inexplicable that a condition whose epidemics have been described in the medical literature for over 65 years should have recently become one where patients are being blamed for their symptoms, symptoms considered to be a "variant of depression," psychosomatic or the result of deconditioning, in spite of research findings to the contrary.[385]

For nearly a decade, the behavioral rehabilitation approach described above has helped patients in the US and Britain to manage their symptoms, increase their ability to function and take back their lives. We encourage clinicians to think about CFS from the brain up, instead of from the mind down, so that patients can receive treatment for their symptoms, instead of being blamed for them.

13 Disability in CFS

Barbara B. Comerford, Esq.

Patients who seek treatment for CFS often suffer such extreme functional limitations that they are unable to work and must apply for disability benefits from the Social Security Administration and/or private long-term disability insurance companies. Children may also present with the same debilitating symptoms that affect their ability to perform activities of daily living, including limitations on school attendance. (See Chapter 11). Under certain circumstances, a child may be eligible to receive Social Security benefits.

All treating physicians are expected to provide medical support for both private and government disability applications. In the context of a patient suffering from CFS, medical support for functional limitations is critical. This chapter provides an understanding of what medical information is required from the treating physician to support an application for disability benefits in the context of a patient with CFS.

Material Selection

The functional and medical requirements necessary to establish disability discussed in this article are derived both from state and federal laws. Those dealing with private long-term disability insurance policies arise as a result of federal legislation, known commonly as ERISA, where the coverage is purchased by or through the employer,[387] and under state law when the insurance policy is obtained privately by an individual.

The Social Security Administration has promulgated numerous regulations and rulings that govern accepted medical evidence in the disability context, and specifically in Chronic Fatigue Syndrome cases.[388-391]

Medical/Legal Requirements To Establish Disability In CFS Cases

A patient presenting with CFS frequently suffers such debilitating physical and cognitive limitations that activities of daily living are substantially restricted, frequently precluding the patient from performing activities of daily living, such as household chores, work, school, and in some cases, basic hygiene. Indeed, many patients spend substantial periods of time virtually bedridden. When such a patient requests assistance from her physician in the disability application process, the doctor may be confused, irritated and without direction. Providing medical information in the disability process, whether at the behest of the Social Security Administration or the disability insurance company requires time that is often in short supply following the advent of managed care.

To assist a patient in the disability process, the physician must produce all records and complete reports requested by the government or the private disability insurance carrier. Unfortunately, many of the forms sent are not adequate to depict the limitations or restrictions of the CFS patient. Therefore, medical narratives are often required to explain special facts about the patient's condition. A common problem in CFS cases is functional capacity evaluations in so far as patients experience good days and bad days. A CFS patient who is well enough to complete a functional capacity evaluation over one or two days almost certainly rested for days in advance to do so. The results of the evaluation will then reflect only the level of function on good days. CFS patients experience extremely low levels of function on bad days, and therefore, cannot be tested on those days. This condition must be explained to the source requesting information so that the actual extent of limitation is understood. The role of the CFS-treating physician is to provide guidance and understanding to the party requesting medical information.

While the Social Security Administration requires proof that the patient is totally disabled, private long-term disability insurance companies may only require proof that the patient is incapable of performing the material and substantial duties of her own occupation. However, the same insurance policy might require proof of total disability after 24 months. (See Table 13-1).

Toward that end, many insurance companies and the Social Security Administration supply long forms that require the physician to check boxes regarding the patient's functional abilities. Typically, the categories include limitations listed in Table 13-2.

Table 13-1
Items of Importance in Disability Determination

- Area of specialty – board certifications (if any) & degree
- Patient history (onset of CFS symptoms)
- The date treatment began
- The frequency of treatment
- The date the patient was last seen
- The complaints, signs and symptoms presented by the patient (e.g. with clinical documentation for six consecutive months palpably swollen or tender lymph nodes; nonexudative pharyngitis; persistent reproducible muscle tenderness on repeat exams; or other medically accepted CFS medical signs)
- All laboratory findings, other diagnostic test results or objective findings (e.g. an elevated antibody titer to Epstein Barr virus capsid antigen equal to or greater than 1:5120, or early antigen equal to or greater than 1:640; an abnormal MRI brain scan; neurally mediated hypotension by clinically accepted form of testing; or any other laboratory findings consistent with medically accepted clinical practice)
- A list of other disease processes excluded
- All functional limitations (see Table 13-2)
- Restrictions
- Treatment rendered and patient response
- Response and side effects of all medications
- Prognosis for recovery
- The opinion of the physician on the issue of total disability
- Whether patient satisfies CDC requirements and why

Table 13-2
Functional Limitations Categories

Bending	Fine Manipulation	Simple Grasp
Climbing Stairs	Lifting	Sitting
Cognitive Activity	Pushing/Pulling	Standing
Concentrating	Power Grip (Bilateral)	Walking
Dexterity	Reaching	
Difficulty with Verbal Retrieval	Remembering	

Forms are often misleading, however, particularly in the context of a chronic fatigue syndrome case, as was noted above. The patient often presents with functional limitations that ebb and flow, resulting in "good days" and "bad days." Frequently, patients report that on a "good day," they function somewhat normally, followed by "bad days" of being bedridden and completely fatigued. Therefore, when an Attending Physician Form requires the physician to provide a vocational classification from sedentary to heavy work, he is often confused because of the good day/bad day manifestation of the illness. On "bad days," the patient is often incapable of even sedentary work, in that she may be so fatigued she spends most of the day resting, and most forms do not provide a "less than sedentary" classification. Nevertheless, on "good days," a patient may indeed have sedentary abilities or more. Add to that the unpredictability of when a patient experiences a good day, then the inadequacy of the forms becomes even more apparent (See Table 13-3). Therefore, if a patient were to respond "sedentary," the answer would not be accurate. So, if a patient has more bad days than good, an accurate response might well be "less than sedentary." It is also important to note that many individuals suffering from CFS are under the age of 50. As such, Social Security regulations identify them as "younger individuals." If a younger individual can perform sedentary work, the regulations require a finding of "not disabled." Therefore, a younger individual must be classified as "less than sedentary" to be found disabled under the Social Security Act.

Table 13-3
Activities Level Defined

Sedentary:	10 lbs maximum lifting or carrying articles. Walking/standing on occasion. Sitting 6/8 hours.
Light:	20 lbs maximum lifting. Carrying 10 lb articles frequently. Most jobs involving standing with a degree of pushing and pulling.
Medium:	50 lbs maximum lifting with frequent lifting/carrying of up to 25 lbs. Frequent standing and walking.
Heavy:	100 lbs maximum lifting. Frequent lifting/carrying of up to 50 lbs. Frequent standing/walking.

The CDC definition should be used as a checklist and whether or not it is satisfied should be indicated within the body of the report; remember, the longitudinal clinical requirements must also be met.

Therefore, if a disability form does not allow for accurate representation of the limitations, those details should be included in a letter annexed to the form. This addition is recommended in all CFS cases, due to the inherent problems presented.

All the information that both Social Security and most long-term disability insurance companies require from the treating physician is found in Table 13-1. The Social Security Administration has incorporated the standards for determining eligibility for disability benefits in a ruling, SSR 99 (2)(P). The ruling can be referenced at the Social Security Administration web site (http://www.ssa.gov).

Documentation

Listing functional limitations presents the most difficulty for physicians, due to the ebb and flow of CFS symptoms. Toward that end, the physician should request from each patient a weekly diary during the period of disability. That log can be incorporated into the patient's chart to chronicle the extent of limitation. It can be appended to the physician report, in response to the limitation inquiry by either the Social Security Administration and/or the disability insurance company. The physician must be sure to instruct the patient to provide accurate information, including "bad days," during which the diary

could not be done, due to fatigue and cognitive difficulties. This step is crucial because insurance claims representatives frequently remark that CFS claimants allege cognitive impairments, but then write extensive cogent letters that seemingly undermine that claim. The diary, therefore, serves to memorialize the actual ebb and flow of cognitive abilities on the part of the patient. Both the Social Security Administration and the insurance industry invest a substantial portion of revenue to investigate fraud. Therefore, it is crucial that the information accurately reflect (without minimizing complaints, either) the extent of daily limitations.

Both the Social Security Administration and the long-term disability insurance companies require that the treating physician support a finding of disability. Most long-term disability insurance companies require not only completion of attending physician reports, but also records of treating sources, including objective findings and other information contained in the patient chart.

With respect to cases involving children who apply for SSI Childhood benefits, it is important to note that only indigent (welfare eligible) children are qualified, and that the standard for disability is somewhat different from adults. However, the pediatrician must also comply with the above checklist (See Table 13-1), keeping in mind the importance of clinical support with objective findings concerning the extent of CFS impairment (See Chapter 1).

Conclusion

Disability evaluation in CFS can be made less arduous for the treating physician. The most important source of medical information is the patient's treating CFS physician. In Social Security cases, deference is given to the treating physician by most fact finders where accurate information is documented. On the other hand, disability insurance companies are not required to give such deference. However, the more demonstrated knowledge in CFS the physician has, the more persuasive the patient or her attorney can be in advocating the claim. By providing the information set forth here, the physician will assist the patient in the disability process and will provide a strong basis for appeal in the event of denial.

Glossary of Selected Acronyms

ACTH	Adrenocorticotropic Hormone
CACSF	Children and Adolescents with Chronic Fatigue Syndrome
CFIDS	Chronic Fatigue Immunodeficiency Syndrome
CFS	Chronic Fatigue Syndrome
CMV	Cytomegalovirus
CRH	Corticotropin Releasing Hormone
CVID	Chronic Variable Immunodeficiency Syndrome
DHEA	Dihydroepieudorterone
EBV	Epstein Barr Virus
FM	Fibromyalgia
FMS	Fibromyalgia Syndrome
GH	Growth Hormone
HHV-6	Human Herpes Virus-6
HIAA	Hydroxyindole Acetic Acid
HIV	Human Immunodeficiency Virus
IGF-1	Insulin-like Growth Factor
IL-1	Interleukin-1
IVIG	Intravenous Immunoglobin
LE	Lupus Erythematosis
MMPI	Minnesota Multiphasic Personality Inventory
MS	Multiple Sclerosis
NADH	Nicotinamide Adenine Dinucleotide
NGF	Nerve Growth Factor
NSAIDS	Nonsteroidal Antiinflammatory Drug
OI	Orthostatic Intolerance
PCR	Polymerase Chain Reaction
PHA	Phytohemagglutinim
POTS	Portural Orthostasis Syndrome

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