VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

Veterans Health Administration
Department of Defense

Version 1.0

Prepared by:

THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**
Working Group

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TABLE OF CONTENTS

Version 1.0

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE

TABLE OF CONTENTS

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INTRODUCTION

Version 1.0

INTRODUCTION

Medically unexplained symptoms (MUS) such as chronic pain and fatigue are a critical public health issue for the Veterans Health Administration (VHA) and TheDepartment of Defense (DoD) On a broader level, physical symptoms account for more than half of all outpatient visits each year in the United States—an estimated 400 million visits. The data collected from general population surveys help to clarify the types and frequency of physical symptoms experienced in the general population:

Table 1. Prevalence of Physical Symptoms

Physical Symptoms	Prevalence in the General Population	Prevalence Among Survey Respondents
Fatigue	22%	58%
Joint pain	26%	59%
Headaches	21%	37%
Sleep Difficulties	15%	35%
Dyspnea	14%	32%
Abdominal Pain	11%	24%

[Kroenke, & Mangelsdorf, 1989; Kroenke et al., 1990, Kroenke & Price, 1993, Kroenke et al., 1994]

The National Ambulatory Medical Care Survey (NAMCS) data of 1989 similarly found that patient concerns of fatigue, headaches, joint pains, and skin rashes resulted in an estimated 47.6 million outpatient visits. The estimated number of outpatient visits for fatigue was 7 million; for headaches, 9.6 million; for joint pains, 17 million; and for skin rashes, 14 million. In addition, it was found that many patients experienced more than one symptom.

Other studies have shown that MUS are often treatment refractory and associated with a high proportion of population-wide disability and health care utilization (Escobar et al., 1998; Katon et al., 1991b).

For military personnel, veterans, and their families, MUS take on even greater importance. Concerns of a "Gulf War Syndrome," putatively caused by wartime exposures, have served as a stark reminder of the challenges that medically unexplained physical symptoms will pose for clinicians, response organizations, and scientists in the event of future military action, terrorist threat, or technological disaster.

Fortunately, there were relatively few combat-related injuries and diseases during the Gulf War conflict; however, up to 45 percent of deployed veterans (as compared to 15 percent of non-deployed veterans) developed a constellation of symptoms and syndromes including muscle and joint pain, fatigue, memory problems, headaches, and gastrointestinal complaints (Fukuda et al., 1999). This experience was not unique to U.S. troops. Veterans of this conflict from the United Kingdom experienced a similar increase in this spectrum of illness (Unwin et al., 1999).

This experience was also not unique to the Gulf War. For example, after World War I many returning veterans described chronic, debilitating physical symptoms that they attributed to chemical exposures incurred during months of trench warfare (Straus, 1999); after Vietnam, hundreds of thousands of veterans sought evaluation for concerns related to agent-orange (dioxin) exposure (IOM, 1999); and the concerns of a "Balkan War Syndrome" [Rogers, 2000] after the peacekeeping in Croatia [National Defense, 2000]. These experiences reinforce the importance that those of us who care for military personnel, veterans, and their families must become skilled at caring for MUS and sometimes engage in the public health debate that accompanies them—debate that often heightens the level of concern and exacerbates the degree of suffering and disability associated with them.

Several expert panels have been convened to examine these illnesses. There is some agreement that this is not a single illness, but rather a constellation of symptoms similar in form to fibromyalgia (FM) and Chronic Fatigue Syndrome (CFS) [Aaron et al., 2001].

Medically Unexplained Symptoms (MUS): Solution to a Confusing Nomenclature

A major obstacle to understanding MUS is the confusing terminology sometimes applied to them. Clinicians, scientists, symptomatic individuals, the media, employers, and other groups frequently apply labels to unexplained symptoms for different purposes. These labels may communicate an implied pathogenesis, such as Chronic Fatigue Syndrome (infectious), certain low-level chemical sensitivities (allergic), somatoform disorders (psychiatric), and Fibromyalgia (rheumatologic). This VHA/DoD guideline will rely on the more generic terms "medically unexplained symptoms" or "unexplained symptoms" to describe physical symptoms that provoke care-seeking, but have no clinically determined pathogenesis after an appropriately thorough diagnostic evaluation (i.e., signs found on examination or laboratory findings) (Engel and Katon, 1999).

A General Approach to CFS, FM, and MUS Management

At present, the treatment of MUS, CFS, FM, and related syndromes is as much an art as it is a science. While it is difficult to reduce the management of MUS to a simple paradigm or single algorithm, there is increasing agreement that treatment strategies have many common elements. Often, differences in treatment approaches may be due to differing traditions and theoretical perspectives across clinical disciplines, rather than to scientific research. In keeping with these observations and the need to recommend effective therapies for military personnel and veterans with MUS, the VHA and DoD have partnered in an effort to develop a clinical practice guideline (CPG) for unexplained chronic pain and fatigue.

The VHA/DoD Working Group did not assume that a single algorithm was possible for all MUS. Instead, the Working Group first developed separate algorithms for CFS and FM. Then the two algorithms were juxtaposed and similarities and differences were identified. In the therapy intervention section of the guideline, the evidence for the two conditions was separated into evidence tables, allowing the reader to quickly identify recommendations that are common for both conditions and those restricted to only one condition. The strength of the treatment recommendations and the supporting evidence supporting remains separated for the two conditions, so that readers may reconstruct and evaluate the thought processes underlying the recommendations.

There is wide appreciation within the Working Group that CFS/FM is part of a continuum of syndromes that providers in different clinical specialties see in their daily practice. Although evidence is often lacking regarding how best to manage different segments along the continuum, CFS/FM offers an excellent starting place for formulating tentative management recommendations. Therefore, the existing evidence for and against various therapies in CFS/FM was used to suggest potentially effective approaches for the rest of the continuum. In a few places, evidence gleaned from clinical trials examining therapies for similar “overlapping” symptom syndromes (e.g., irritable bowel syndrome, mechanical low back pain, somatization disorder, and other chronic pain conditions) was used to formulate treatment recommendations in the absence of more relevant evidence.

Goals of the Guideline

The VHA/DoD Clinical Practice Guideline on the Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue is intended to assist medical care providers in all aspects of patient care. The system-wide goal of evidence-based guidelines is to improve the patient’s outcome. The overall expected outcome of successful implementation of this guideline is to:

- Formulate an efficient and effective assessment of the patient's complaints.
- Optimize the use of therapy to control symptoms.
- Minimize preventable complications and morbidity.
- Achieve satisfaction and positive attitudes regarding the management of chronic unexplained illness

The current guideline represents a significant step toward achieving these goals for patients in the VHA and DoD. However, as with other CPGs, remaining challenges involve developing effective strategies for guideline implementation and evaluating the effect of guideline adherence on clinical outcomes.

The guideline is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advances and patterns evolve. The guideline is based on information available at the date of publication, and is intended to provide a general guide to best practice. However, it should be emphasized that evidence-based clinical practice involves using of the best available research evidence, but also exercising of the practitioner's clinical judgment, to take into account individual patient preferences. The guideline can assist care providers, but the use of a CPG must always be considered as a recommendation, within the context of a provider's clinical judgment, in the care for an individual patient.

For the Future

Patients with MUS are sometimes considered "difficult." In large part, this is because clinicians are unable to make the patients feel better and their demands exceed the capabilities of conventional medical care. When combined with loss of function, loss of control and support, and high levels of disability, this illness is among the most frustrating, both for patients and providers. The implementation of this guideline will lead to better care, earlier recognition, better patient education, and effective multi-modal management. If this is accomplished, patients with CFS/FM can still lead a relatively rewarding life.

The VHA and DoD are developing a variety of clinical tools for implementing this guideline and a set of indicators to measure their impact on the quality of the related care. Modifications to the guideline will undoubtedly be necessary, as a result of lessons learned and findings from new clinical research are disseminated. The developers believe that this guideline should always be considered "a work in progress."

Key Points

1. Establish that the patient has MUS.
2. Obtain a thorough medical history, physical examination, and medical record review.
3. Minimize low yield diagnostic testing.
4. Identify treatable cause (conditions) for the patient's symptoms.
5. Determine if the patient can be classified as Chronic Multi-Symptom Illness (CMI) (i.e., has two or more symptoms clusters: pain, fatigue, cognitive dysfunction, or sleep disturbance).
6. Negotiate treatment options and establish collaboration with the patient.
7. Provide appropriate patient and family education.
8. Maximize the use of non-pharmacologic therapies:
    - Graded aerobic exercise with close monitoring
    - Cognitive behavioral therapy (CBT)
9. Empower patients to take an active role in their recovery.

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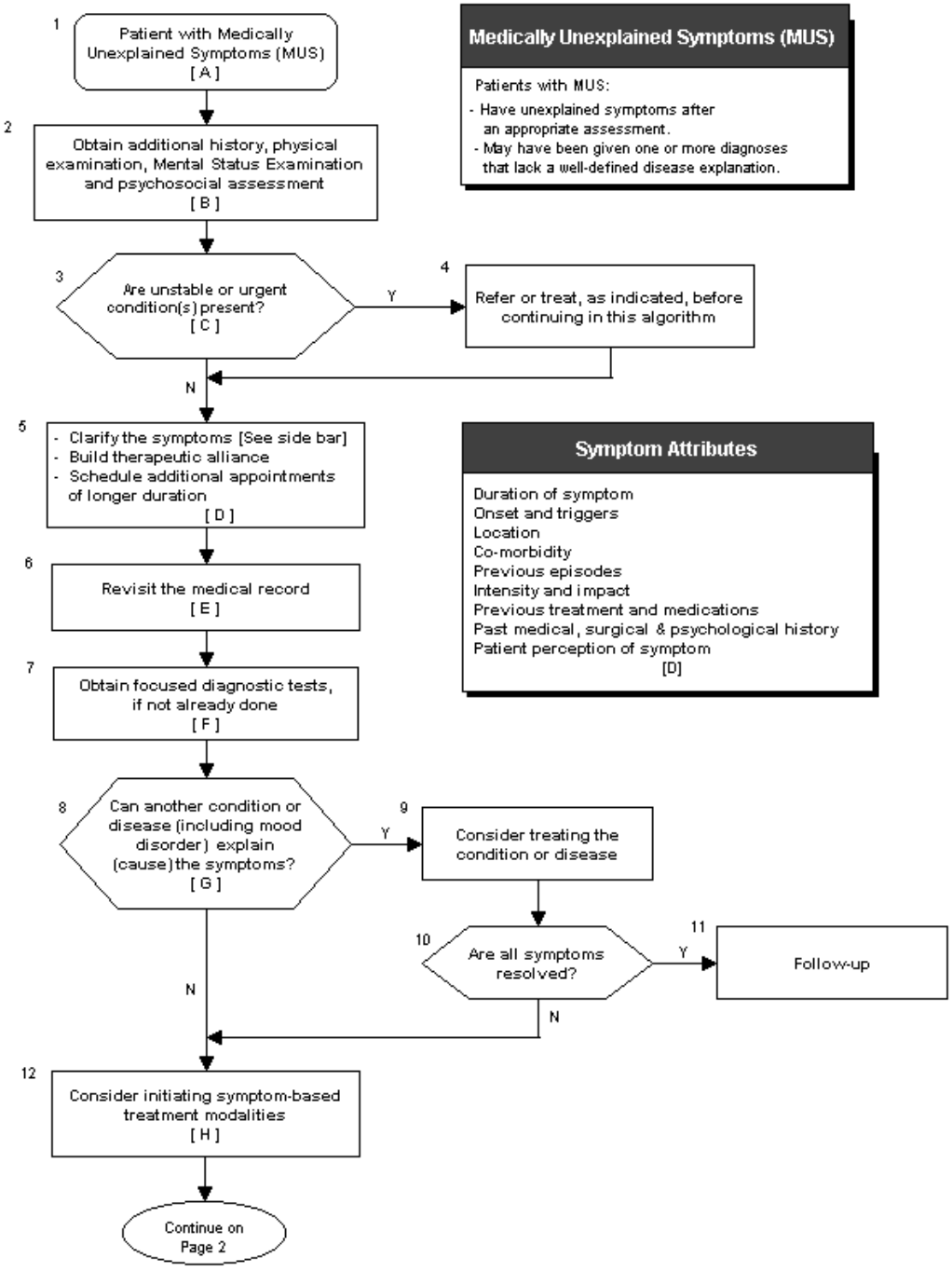
SECTION A: ALGORITHMS AND ANNOTATIONS

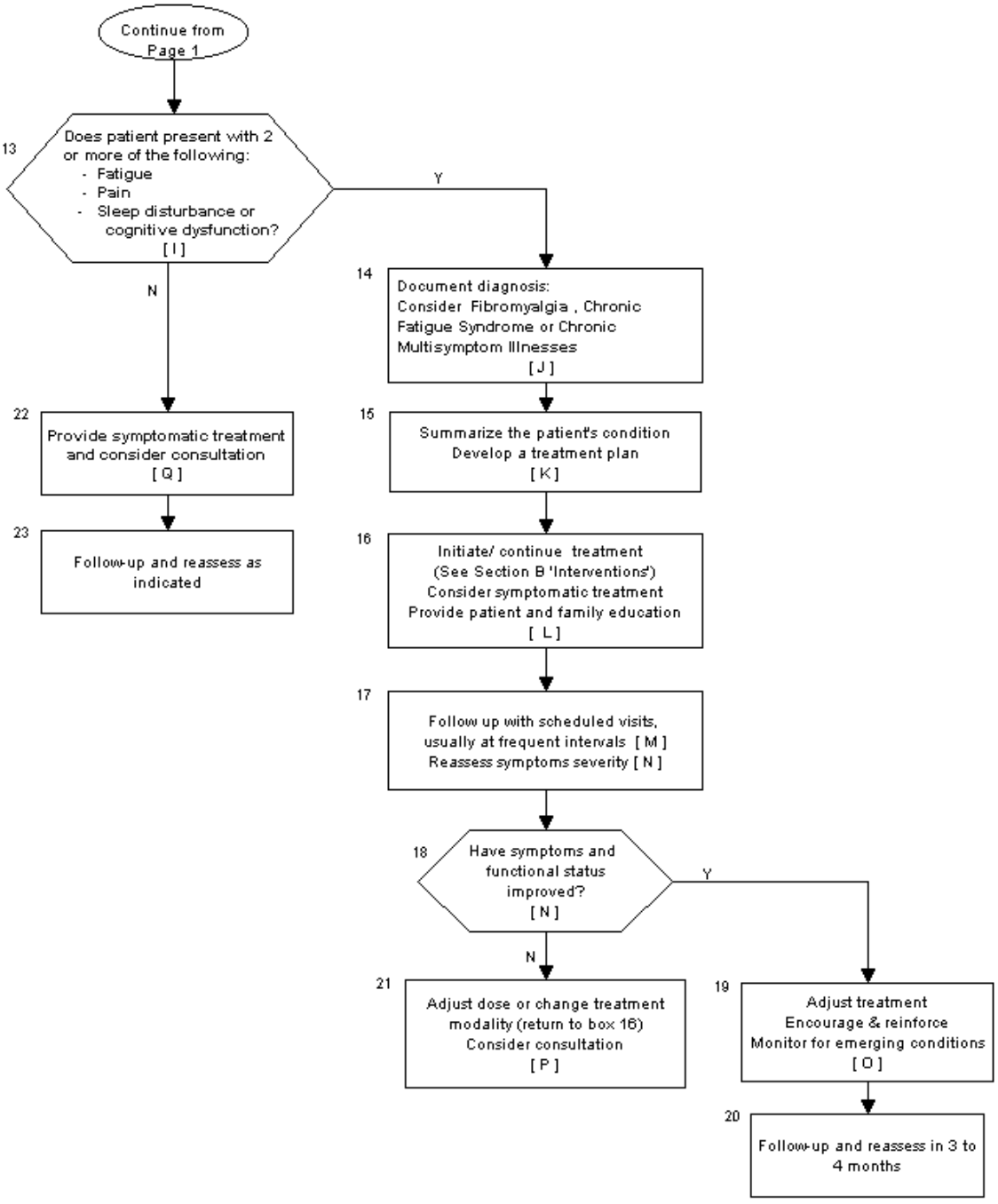
Version 1.0

Clinical Practice Guideline for Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue



Clinical Practice Guideline for Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue

Page 2



ANNOTATIONS

A. Patient with Medically Unexplained Symptoms (MUS)

OBJECTIVE

Identify patients with persistent symptoms not explained by a known medical etiology.

ANNOTATION

Patients managed by this guideline have symptoms that remain relatively unexplained after an appropriate medical assessment that includes focused diagnostic testing (Kroenke et al., 1990; Kroenke & Price, 1993; Kroenke & Mangelsdorf, 1989). Patients are often given multiple labels that lack a well-defined disease explanation. Usual clinical features include a relative lack of objective signs and a chronic symptom course often marked by exacerbations, remissions, and recurrences. Therefore, clinical management must be based largely upon patient report, rather than specific findings on clinical examination or diagnostic testing (Engel & Katon, 1999a). A compassionate approach to patients with medically unexplained symptoms (MUS) is essential (Engel & Katon, 1999b).

B. Obtain Additional History, Physical Examination, Mental Status Examination (MSE), and Psychosocial Assessment

OBJECTIVE

Obtain comprehensive patient data to rule out alternative explanations for unexplained symptoms.

ANNOTATION

A thorough and early review of all sources of information can help in validating the patient's health concerns, while communicating care and understanding—the necessary building blocks to an effective patient-clinician partnership. Sources of information include the following:

- All medical records
- Medical history and psychosocial assessment
- Review of systems
- Physical examination and mental status examination (MSE)
- Routine test results
- Standard health assessments

Additional medical history

In obtaining a medical history, the clinician should focus on key symptoms that may suggest a well-defined disease explanation.

Physical examination

Patients with unexplained symptoms have often been examined several times in the past. However, important details may have been overlooked due to time constraints or the frequency that clinicians encounter such complaints in the absence of objective findings. Setting aside time for a detailed and thorough examination is critical for the assessment and may also help in building an alliance with the patient, who in many cases was seen by several clinicians.

Mental Status Examination (MSE)

A careful MSE should be performed, including assessment of appearance, behavior, mood and affect, cognition, thought content and processes, and insight and judgment. A useful screen for cognitive impairment in elderly patients consists of four questions from the Mini-Mental State Examination (MMSE) (Koenig, 1996) (i.e., orientation to time, orientation to place, memorizing and repeating three non-related items, and spelling "world" backwards).

Psychosocial Assessment

A psychosocial assessment is critical in evaluating the patient with unexplained symptoms and should include a screening for suicidal ideation and substance use disorders.

The Patient Health Questionnaire (PHQ) is an excellent screening tool for assessing the presence of the most common psychiatric conditions associated with complaints of fatigue: depression, symptoms, and anxiety (Spitzer et al., 1999; Spitzer et al., 1994).

C. Are Unstable or Urgent Condition(s) Present?

OBJECTIVE

Identify patients that are unstable and need immediate treatment.

ANNOTATION

Unstable or urgent conditions represent situations that mandate immediate attention. A complete discussion of diagnosis and management of the entire range of possible urgent conditions is beyond the scope of this guideline. These conditions are generally recognized and managed by the astute primary care clinician.

Some potentially unstable or urgent conditions include (but are not limited to) the following:

- Suicidal ideation or psychosis
- Objective evidence of joint swelling
- Fever (over 101.1 degrees F/38.4 degrees C)
- Significant weight loss
- Focal findings on neurological examination
- Severe anemia or elevated white blood cells

D. Clarify the Symptoms; Build Therapeutic Alliance; Schedule Additional Appointments of Longer Duration

OBJECTIVE

Obtain detailed information on the patient's symptoms and health concerns, allowing adequate time to enhance the patient's trust and faith in the clinician.

ANNOTATION

Clarify The Symptoms

Patients who present with unexplained pain or fatigue often carry a cluster of symptoms that must be understood as accurately as possible. Taking an accurate history is an essential part of the diagnostic work-up. Questions that may prompt patients to provide important attributes of their symptoms are summarized in the following table.

Table 1. Clarification of Symptoms

Symptom Attributes	Questions
Duration	Has the symptom existed for days, weeks, or months? Has the symptom occurred only intermittently? Particularly with regard to pain and fatigue, can the patient define if these symptoms occurred only two or three days per month or constantly? Is the symptom seasonal? Are there times of the day when the symptom is worse?
Onset	Can the patient recall exactly how the symptom began? Were there triggering events, either physical or emotional? Was the onset subtle and gradual, or dramatic and sudden? Have the triggering events tended to be the same over time or are there changing patterns?
Location	Is the symptom localized or diffuse? Can the patient localize the symptom by pointing to it? If the pain is diffuse, does it involve more than one body quadrant?
Co-morbidity	Does the patient have any diagnosed co-existing illnesses? What is the time relationship between the onset and severity of the co-existing illnesses and the symptoms of fatigue and/or pain? What are the symptoms other than pain and/or fatigue? Are there co-morbid diagnoses? Are there changes in the patient's weight, mood, or diet?
Previous episodes	If the symptoms are episodic, what is the pattern in regard to timing, intensity, triggering events, and response to any prior treatment?
Intensity and impact	How severe are the symptoms (use the 1 to 10 Numerical Rating Scale (NRS))? Ask the patient to describe any new limitations they have experienced compared to their usual life-style, including limitations in physical endurance or strength (e.g., climbing stairs, shopping, and amount or quality of their sleep).
Previous treatment and medications	Exploring this aspect of the history may be complicated and require obtaining prior medical records, or having an authorized telephone conversation with the prior treating clinician. Ask the patient to bring in their medication bottles on a subsequent visit and document the exact names of the medications. Find out which medications have/have not been helpful.
Past medical, surgical and psychological history	This area includes chronic and major acute illnesses and injuries, allergies, surgical procedures, and hospitalizations. The psychological history may take several visits to clarify, depending upon the ease with which the patient can articulate their emotional status and past and present issues. Explore stressors such as occupational and family issues.
Patient perception of symptoms	Often omitted from the history-taking are questions designed to gain some understanding of what the patient believes is happening. Ask the patient about their hunches and fears.

DISCUSSION

Duration

The duration of the symptoms until time of presentation is variable and patients may have spent years seeing numerous clinicians and undergoing extensive evaluations without ever obtaining a diagnosis. Many patients may relate the onset of their symptoms to a significant event (e.g., severe illness, trauma, military mobilization, and viral illness). Some patients may present with symptoms after sustaining central/axial skeletal trauma, such as a motor vehicle accident with resultant whiplash.

Exploring the history and clarifying the details may require several visits. However, the more the clinician can create an atmosphere of calmness and interest in the details, the more likely it is that important aspects of the history will be elicited. Details that may not seem important to the patient to mention in a hurried history may emerge in a subsequent or follow-up visit and provide important clues in determining a diagnosis.

Location

Pain location is important as it may provide useful information to help guide further assessment and treatment. Asking patients to indicate on their bodies where they feel pain can help to assess the distribution (location) of pain. It is also useful to employ a standard pain drawing, consisting of a line drawing outline of the front and back of a human body (see Section C).

Co-morbidity

Other chronic illnesses may occur as co-morbid conditions, including:

- Thyroid disease
- Rheumatic disease
- Sleep apnea
- Neurological disease
- Depression

Irritable bowel syndrome, migraine headaches, and multiple-chemical sensitivity occur more frequently in patients with Chronic Fatigue Syndrome/Fibromyalgia (CFS/FM). The elderly individual also has a higher risk for the presence of malignancy, which should be kept in mind during the evaluation. It is important not to ignore co-morbidities that may represent a true underlying condition that will require treatment.

Previous episodes

The patient may have had prior episodes of similar symptoms in the past, as well as prior treatments.

Patient perception of symptoms

Patients should be given the opportunity to relate their experiences and complaints, at each visit, in their own way. Although time-consuming and likely to include much seemingly irrelevant information, this has the advantage of providing considerable information concerning the patient's intelligence, emotional make-up, and attitudes about their complaints. This also provides patients with the satisfaction that they have been "heard-out" by the clinician, rather than merely being asked a few questions and exposed to a series of laboratory tests based on "high technology."

As the patient relates the history, important nonverbal clues are often provided. The clinician should observe the patient's attitude, reactions, and gestures while being questioned, as well as his or her choice of words or emphasis. The impact from the symptoms may range from annoying to totally disabling and patient perceptions regarding the cause and impact are important to understand in managing the disorder. Stressors such as occupational and family issues should also be explored.

The BATHE technique (Servan-Schreiber et al., 2000) provides a time-efficient way to address the impact of patients' symptoms on their level of function. The BATHE technique addresses the following topics:

- **B**ackground: "What is going on in your life?"
- **A**ffect: "How do you feel about it?"
- **T**rouble: "What troubles you the most about the situation?
- **H**andle: "What helps you handle that?"
- **E**mpathy: "This is a tough situation to be in. Anybody would feel (down, stressed, etc.). Your reaction makes sense to me."

Build Therapeutic Alliance

The lack of diagnosis or effective treatment can make the management of patients with unexplained symptoms challenging. It may also cause frustration for both the patient and the provider. A high level of patient trust and faith in the clinician is required in order to maintain continuity of care and continue patient management through regular follow-up appointments. The initial evaluation helps establish a special partnership between the patient and clinician. To strengthen the partnership with the patient, the clinician should (Stuart & Lieberman, 1993):

- Acknowledge and indicate commitment to understand the patient's concerns and symptoms.
- Encourage an open and honest transfer of information that will provide a more comprehensive picture of the patient's concerns and medical history.
- Indicate commitment to allocate sufficient time and resources to resolving the patient's concerns.
- Avoid open skepticism or disapproving comments in discussing the patient's concerns.

At each patient visit, the clinician should consider the following:

- Ask if there are unaddressed or unresolved concerns.
- Summarize and explain all test results.
- Schedule follow-up visits in a timely manner.
- Explain that outstanding or interim test results and consultations will be reviewed during the follow-up visits.
- Offer to include the concerned family member or significant other in the follow-up visit.

DISCUSSION

Patients have certain common hopes and expectations when they see a clinician (Marple et al., 1997). Patients want to be listened to, be able to fully express their fears and concerns, and share their burden. They want the clinician to be interested in them as fellow human beings, in a compassionate but nonjudgmental fashion. They expect professional competence and to receive the best in medical science and technology. They want to be reasonably informed as to the probable cause of their concerns and what the future is likely to hold.

Schedule Additional Appointments of Longer Duration

The clinician's initial evaluation helps establish a high level of trust by demonstrating that the patient's symptoms will be taken seriously. Continuity of care is also essential for building a trusting therapeutic alliance and rapport. Continuity is achieved through regularly scheduled follow-up appointments that encompass:

- Several appointments
- Extended visits
- Setting aside time to review the medical record and laboratory results

E. Revisit the Medical Record

OBJECTIVE

Clarify the history of the MUS.

ANNOTATION

Review the patient's medical record for co-morbidities, prior episodes, occurrences of other unexplained symptoms, prior evaluations, and the nature and extent of prior therapy.

The review should include the following:

- Complete medical history
- Family and social history
- Occupational and deployment history
- Exposure to possible risks, hazards, and toxic agents
- Prescription history, including over-the-counter medications and herbs
- Clinical notes
- Other documented history and physical examinations
- Radiological, laboratory, and other ancillary test results
- Effectiveness of previous therapies and reasons for past treatment failures or successes

F. Obtain Focused Diagnostic Tests, If Not Already Done

OBJECTIVE

Identify objective findings that may suggest the diagnosis.

ANNOTATION

After a complete history and physical examination, there are several Australia routine laboratory tests that will assist in completing the patient assessment (CFS Guideline, Medical Journal of Australia, 1997):

- Complete blood count
- Electrolytes
- Blood urea nitrogen
- Creatinine
- Glucose
- Calcium
- Phosphate
- Liver function tests
- Total protein
- Thyroid-stimulating hormone
- Erythrocyte sedimentation rate
- Urinalysis

The clinician also should ensure that health care maintenance is up to date.

The following tests should only be ordered if the history or physical examination results strongly suggest the need (CDC, 1999):

- Serological tests for:
  - Epstein-Barr virus
  - Lyme disease (in the absence of polyarthritis, history of tick bite, or erythema chronicum migrans)
  - Immunologic function testing
- Neuroimaging

G. Can Another Condition or Disease (Including Mood, Anxiety, and Substance Use Disorders) Explain (or Cause) the Symptoms?

OBJECTIVE

Identify patients for whom treatment of cause may resolve the symptoms.

ANNOTATION

After obtaining a detailed history, completing a thorough physical examination, obtaining laboratory test results, and using a screening tool (e.g., the PHQ) the clinician should determine whether an explanatory or causal condition can be diagnosed or whether the symptoms remain medically unexplained.

The following examples of the patient's description may indicate a related diagnosis. In most instances, the symptoms of CFS can be distinguished from the closely related phenomena of somnolence, muscle weakness, neuromuscular fatigability, depressed mood, or anhedonia.

Table 2. Patient's Description of Fatigue or "Tiredness"

Patient's Description	Clinician's Interpretation
Reduced muscle power at rest Difficulty walking or lifting weights	Muscle weakness (e.g., myopathy or polymyositis)
Loss of muscle power over time with activity	Neuromuscular fatigability (e.g., myasthenia gravis)
Physical and mental fatigue at rest	Central fatigue (e.g., multiple sclerosis)
Lack of motivation to commence tasks Lack of pleasure from tasks undertaken	Anhedonia (e.g., major depression)
Daytime sleepiness Short sleep latency	Somnolence (e.g., sleep apnea or narcolepsy)
Breathlessness at rest or on exercise	Dyspnea Weakness (e.g., airflow limitation, cardiac failure, or anemia)
Muscle or joint pain Fever or malaise	Inflammation (e.g., systemic lupus erythematosus) Infection (e.g., influenza)

Chronic Fatigue Syndrome CPG Working Group Royal Australian College of Physicians, 1997.

When considering depression, the clinician should assess whether the symptoms are causing the depression or the depression is resulting in physical complaints. Physical illness may cause psychosocial distress through a direct biological link, such as through neurotransmitters involved in both pain and mental disorders. Physical symptoms may cause emotional distress by overwhelming an individual's ability to cope. Distress may increase unhealthy behaviors that increase the risk of such symptoms. The disordered sleep and changes in autonomic

nervous system functioning associated with stress may cause these symptoms. Finally, both mental disorders and MUS may be found together in some people, simply by chance.

DISCUSSION

Studies of patients with MUS indicate high rates of major depression and panic disorder (Goldenberg, 1987; Katon et al., 1985; Katon et al., 1991a; Black et al., 1990; Simon et al., 1990; Hudson et al., 1992; Clauw & Chrousos, 1997). Several mechanisms might account for this correlation (Engel & Katon, 1999b).

Studies indicate that increasing numbers of physical symptoms are accompanied by an increasing likelihood of experiencing anxiety and depressive disorders (Katon & Russo, 1992; Kroenke et al., 1994; Russo et al., 1994; Kisely et al., 1997). For example, in a study using self-reports from a sample of more than 1,000 health maintenance organization enrollees, increasing numbers of pain complaints were strongly associated with elevated levels of anxiety, depression, and physical symptoms that did not cause pain (Dworkin et al., 1990). In a separate study, the percentages of people with anxiety and depressive disorders increased with increasing numbers of physical symptoms (both medically explained and unexplained from the perspective of the interviewer) (Kroenke et al., 1994). Depression and anxiety are consistently associated with MUS across many studies that used several different methods and cross-sectional (Simon & VonKorff, 1991), case-control (Katon, 1988; Katon, 1991b; Sullivan et al., 1988; Walker et al., 1988; Walker et al., 1990), and longitudinal designs (Leino & Magni, 1993; Von-Korff et al., 1993). Katon and colleagues have found that the relationship of physical symptoms to common anxiety and depressive disorders is linear. As the number of anxiety and depressive symptoms or lifetime episodes of these disorders increases, the prevalence and number of MUS also increases (Katon, 1991b).

These data suggest that medically unexplained physical symptoms may sometimes be a marker of psychosocial distress. In occupational medicine settings such as the military, with a younger and medically healthier population than the general population, this effect is probably amplified. With a lower base rate of most diseases, there is a higher likelihood that unexplained symptoms are due, at least in part, to more common and less easily recognized psychiatric disorders, such as anxiety and depressive disorders (Engel & Katon, 1999b).

H. Consider Initiating Symptom-Based Treatment Modalities

OBJECTIVE

Reduce symptoms and promote functioning and well-being.

ANNOTATION

Although the criteria for CFS require six months duration of symptoms prior to making the diagnosis, the initiation of appropriate treatments for unexplained symptoms and for myalgias may be considered earlier.

There is a point in the course of the diagnostic work-up and clinical monitoring at which the symptoms may appear to be "unexplained." The time that elapses in reaching this point varies.

- Early interventions should include restoration of sleep and management of pain.
- The clinician must maintain an ongoing vigilance to the possibility of emerging diagnosable conditions.

DISCUSSION

Clinical medicine typically involves a process of using symptoms, physical findings, and test results to establish a specific disease diagnosis for which a disease-specific treatment intervention will be prescribed (Engel et al., 1998). The clinician should keep in mind, however, that in a significant number of clinical encounters, such a specific diagnosis will not be established (Kroenke & Mangelsdorf, 1989; Schappert, 1992).

In situations involving unexplained symptoms, early intervention may improve prognosis (Working Group consensus) (QE=III). In light of this possibility, and despite the fact that the criteria for making the diagnosis of CFS require the presence of symptoms for at least six months, the clinician should consider that the symptoms may ultimately fall into the category of unexplained symptoms; appropriate interventions may be initiated within the first three months following presentation. This is also true for myalgias and conditions, such as FM (Buchwald & Garrity, 1994). A meta analysis of 26 studies revealed that among patients in primary care with fatigue lasting <6 months, at least 40 percent of patients improved. As the definition becomes more stringent the prognosis appears to worsen. Consistently reported risk factors for poor prognosis are older age, more chronic illness, a co-existing comorbid psychiatric disorder, and holding a belief that the illness is due to physical causes (Joyce et al., 1997). Similar to the recommended treatments for FM and CFS, early interventions should address restoring sleep, managing pain, and possibly providing cognitive behavioral therapy (CBT). The approach is oriented toward symptom management and optimization of physical and psychosocial functioning in all realms (Walker et al., 1998).

EVIDENCE

Recommendations	**Source**	**R**
Early intervention may improve prognosis.	Working Group consensus	B

QE= Quality of Evidence; R = Recommendation (See Appendix 1)

I. Does Patient Present With 2 or More of the Following: Fatigue, Pain, Sleep Disturbance, or Cognitive Dysfunction?

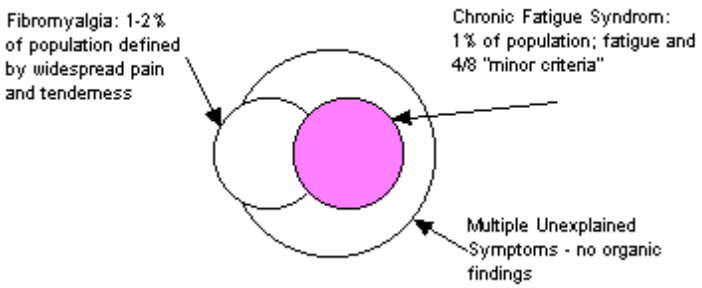
OBJECTIVE

Identify and describe signs and symptoms for classification of CFS/FM.

ANNOTATION

Chronic unexplained symptoms are very common in the general population. In many instances, these symptoms occur in isolation (e.g., fatigue and headaches). However, it is also common for these symptoms to aggregate in individuals, leading to hypothesized "syndromes" that have been given a variety of terms, such as CFS, FM, and somatoform disorders (see Figure 1). There are substantial data suggesting that overlapping illnesses have common mechanisms and respond to similar types of interventions. Careful assessment of fatigue, pain, cognitive difficulties, sleep disturbance, and associated physical symptoms, considering their impact on the patient in isolation and aggregate, will allow the clinician to reach an appropriate diagnosis.

Figure 1. Overlapping Chronic Multi-Symptom Illnesses



Fatigue

Persistent fatigue is the primary manifestation of CFS and is present in over 90 percent of FM patients, as well. Patients may describe their fatigue in various ways. It is also present in otherwise healthy patients and in a wide array of other illnesses (see Table 4). Fatigue should be differentiated from transient tiredness. Patients report a diminished ability to perform mental and physical tasks because of fatigue, and that those tasks increase their fatigue. Fatigue is not substantially improved by rest, including sleep, naps, or cessation of activities. The patient may also describe sleep disturbance—unrefreshing sleep that may be characterized by difficulty falling asleep, frequent awakening, abnormal limb movements (such as myoclonus), or sleep apnea.

Pain

Pain is the primary manifestation in FM and is very common in CFS. Patients complain of muscle and joint pain, but are usually unable to differentiate between muscle and joint area pain. Pain usually becomes widespread (typically bilateral and above and below the waist) and is poorly localizable (meaning it occurs "all over"). Occasionally patients will complain only of unilateral body pain. The characteristic of widespread pain indicates a central nervous system etiology.

"Widespread pain" is defined as occurring in at least three quadrants: above and below waist, right and left side of the body, and axial. The pain-drawing methodology may be helpful because it allows the patient to indicate the location of their pain on a line drawing of the human body (Margolis et al., 1986). This method permits a systematic and standard method to assess pain location and determine whether the patient meets the "widespread pain" criteria (see Section C).

On examination there is increased tenderness, often very marked, to palpation in characteristic locations, defined as "tender points" (TPs)—pain on digital palpation. Although there is controversy regarding the assessment and usefulness of evaluating TPs, three options have been offered:

1. Simple count of the number of TPs, following the procedure as described in the original American College of Rheumatology (ACR) paper (Wolfe et al., 1990) may be misleading unless a carefully standardized assessment is followed.

2. Myalgic scores (Baumstark & Buckelew, 1992; Tunks et al., 1995), which use a dolorimeter for patients to rate the amount of pressure required for each point to become painful. The "myalgic score" is the sum of the amount of pressure for all aggregated TPs. The average myalgic score can be determined by dividing the summed score by 18. The advantage of using this approach is that there is a greater range of scores, and although the number of positive TPs may not change over time or as a result of treatment, the myalgic score may be responsive to time and treatment.

3. Manual Tender Point Survey (MTPS) (Starz et al., 1997; Okifuji et al., 1997) have the following advantages: a) it follows a standard protocol and has an instructional booklet and tape, b) it does not require a dolorimeter, and c) it provides a range of scores similar to the myalgic score, while at the same time it permits determination of the absolute number of TPs so that the ACR criteria can be used.

Headache and sore throat are common complaints in patients with CFS. The headache should be of a new type, different from that previously experienced, with a new pattern or severity. Patients often complain of a myriad of other vague pain, unexplained by clinical evaluation, either at the same time or over time (e.g., urethral symptoms, pelvic pain, tension, or migraine). However, these complaints are not included in the definition of CFS/FM.

Cognitive Difficulties

Neurocognitive difficulties are common in CFS/FM and may include the following:

- Forgetfulness
- Memory disturbance
- Problems with concentration

Sleep Disturbance

Poor sleep is a frequent complaint in FM, and some patients have objective abnormalities noted in sleep studies. But even though disturbed sleep likely plays a significant role in symptom expression in some patients, and may contribute to some of the physiologic abnormalities (e.g., low IGF-1), the aggregate data do not support the notion that disturbed sleep alone is causing this illness.

Sleep disturbances, common in CFS, may include unrefreshing sleep (i.e., waking up feeling unrefreshed) that may be characterized by difficulty falling asleep, frequent awakening, abnormal limb movements (e.g., myoclonus), or sleep apnea. A shift from regular night-time sleep to day-time naps and a late-night to late-morning sleep cycle is sometimes noted. It is known that chronic disruption of the normal sleep pattern can induce symptoms in healthy volunteers, including fatigue, musculoskeletal pains, irritability and concentration impairment.

Associated Physical Symptoms

While the recognized criteria for CFS/FM emphasize the presence of chronic pain and fatigue, it is nonetheless important to note that patients suffering from CFS/FM generally present a number of physical symptoms that complicate the approach to diagnosis. The clinician who is alert to the possibility of MUS will find it easier to make the diagnosis and not become unduly alarmed. The subjective symptoms associated most frequently with CFS/FM are included in the following table.

Table 4. Associated Somatic Symptoms

Cardiovascular system Palpitations Raynaud's phenomenon	**Endocrine system** Generalized fatigue Excessive sweating, localized or generalized Hypoglycemia (e.g., sudden severe hunger, headache, sudden anxiety, tremulousness/shakiness, sweating, confusion, and unconsciousness/coma) Dry skin Hair loss
Eyes, Ears, Nose & Throat Dry eyes Dry mouth Sore throat Sinusitis Rhinorrhea	
Respiratory system Asthma Dyspnea Cough	**Musculoskeletal system** Costochondritis Temporo-mandibular dysfunction Muscle spasms (including nocturnal myoclonia) Coccydynia
Digestive system Dry mouth Dysphagia (e.g., "lump" in the throat, difficulty swallowing, and sore throat) Dyspepsia Irritable bowel (diarrhea or constipation)	**Central Nervous system** Disturbance of mood Chronic headaches, migraines Generalized dysesthesia (e.g., burning sensation, heat, numbness, chills, pins and needles, subjective sensation of swelling) Hypersensitivity to noise, odors and air conditioning Insomnia Tendency to drop things Tinnitis Double vision Balance problems and dizziness Dry eyes or excessive tearing
Genitourinary system Irregular menstrual cycles Dysmenorrhea Irritable bladder (urgency of urination)	

J. Document the Diagnosis: Consider Anxiety, Sleep Apnea, Upper Airway Resistance Syndrome, Fibromyalgia (FM), Chronic Fatigue Syndrome (CFS), or Chronic Multisymptom Illnesses (CMI)

OBJECTIVE

Assign specific diagnostic labels that may have implications in the clinical course of treatment for patients with MUS.

ANNOTATION

Chronic Fatigue Syndrome

CFS is the current term used to describe a syndrome involving a set of defined (yet in many ways, non-specific) symptoms and behaviors that include, as a defining element, severe disabling fatigue and a combination of associated symptoms including cognitive impairments (memory and concentration), sleep disturbances and musculoskeletal pain. The condition has been described for centuries using a variety of nomenclatures (e.g., febricula, nervous exhaustion, neurasthenia, epidemic neuromyasthenia, benign myalgic encephalomyelitis, royal free disease, and chronic mononucleosis) (Shafran, 1991; Demitrack, 1998). To date, no clear pathophysiology or etiologies have been established, and current evidence points to a heterogeneous and multi-causal pathogenesis (Wilson et al., 1994; Schwartz, 1988; Demitrack & Greden, 1991; Demitrack, 1997). In 1994, an international study group coordinated by the Centers for Disease Control (CDC) established the most widely accepted criteria for case definition of CFS (Fukuda et al., 1994).

A case of chronic fatigue syndrome is defined by the presence of:

> Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.
>
> *and*
>
> Four or more of the following symptoms that persist or reoccur during six or more consecutive months of illness and do not predate the fatigue:

- Self-reported impairment in short term memory or concentration
- Sore throat
- Tender cervical or axillary nodes
- Muscle pain
- Multi-joint pain without redness or swelling
- Headaches of a new pattern or severity
- Unrefreshed sleep
- Post-exertional malaise lasting >24 hours

Fibromyalgia

FM is the current term used to describe a syndrome involving a set of defined (yet in many ways, non-specific) symptoms and behaviors that include, as a defining element, widespread musculoskeletal pain and tenderness. The condition has been described for centuries using a variety of nomenclatures (e.g., muscular rheumatism, fibrositis, fibromyositis, and psychogenic rheumatism). To date, no clear pathophysiology or etiologies have been established. In 1990, a committee of the ACR established the most widely accepted criteria for case definition of FM (Wolfe et al., 1990). The ACR criteria include the following:

1. History of widespread pain of at least 3 months duration.
   Definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cerival spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lowere segment pain.

2. Pain in 11 or 18 tender point sites on digital palpation (performed with an approximate force of 9 lb/4 kg).
   Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 sites:

   - Occiput: bilateral, at the suboccipital muscle insertions.
   - Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
   - Trapezius: bilateral, at the midpoint of the upper border.
   - Supraspinatus: bilateral, at origins above the scapula spine near the medial border.
   - Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
   - Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
   - Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
   - Greater trochanter: bilateral, posterior to the trochanteric prominence.
   - Knee: bilateral, at the medial fat pad proximal to the joint line.

For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered 'painful'."

The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Concurrent symptomatology is nearly universal and includes fatigue, headaches (both migraine and musculoskeletal), paresthesias, hearing/ocular/vestibular complaints, cognitive difficulties (memory and concentration), "allergic" and chemical sensitivity symptoms, non-cardiac chest pain, palpitations, dyspepsia, irritable bowel syndrome and affective/somatoform disorders (Clauw, 1995).

Labeling

There is insufficient evidence to allow clinicians to predict the impact that diagnostic labels such as FM syndrome, CFS, multi-chemical sensitivity (MCS), CMI, or Gulf War Illness (GWI) will have on the clinical course of patients with these symptoms. There is evidence, however, to suggest that the clinician should consider the following potential impacts:

- Assigning specific diagnostic labels may have implications in the clinical course for a particular individual with MUS.
- There may also be negative effects of labeling. A diagnostic label may sometimes unnecessarily cause a patient to define him or herself as ill, an effect that could be especially problematic in occupational health care settings.
- The potential risks and benefits of applying a particular diagnostic label to unexplained symptom clusters should be weighed by the clinician and discussed with the patient prior to applying such a diagnostic label.
- The clinician should consider generic approaches to managing MUS; such approaches may be useful, without having to rely on specific diagnostic labels.

K. Summarize the Patient's Condition; Develop a Treatment Plan

OBJECTIVE

Identify the patient's problems and potential treatment options.

ANNOTATION

Assure that the patient understands the meaning and impact of CFS/FM syndrome on their life and the potential improvement a recommended treatment may offer. A final acceptable treatment plan should be negotiated with the patient and documented in the medical record.

- Prepare a summary of the problems and potential treatment plans prior to meeting the patient.
  - – Develop a problem list with an assessment of problem severity and urgency for treatment.
  - – Develop treatment options for discussion with the patient.
- Educate the patient.
  - – Discuss the general concept of MUS and how problems associated with this diagnosis apply to the patient.
  - – Evaluate the patient's understanding.
  - – Describe treatment options and the associated risks and benefits.
  - – Describe the prognosis of the illness.
- Collaborate with the patient and determine the patient's preferences.
  - – Determine the patient's goals for recovery.
  - – Explore and discuss the patient's beliefs regarding his or her illness.
  - – Determine if the patient agrees with the priority and severity of the problems and urgency for treatment.

– Determine the level of the patient's agreement with the recommended treatment or one of the alternative options.
– Determine the patient's motivation to begin treatment and identify barriers to treatment.
– Obtain the patient's consent to the treatment plan.

- Empower the patient for self-management.

  – Move the responsibility of patient improvement from the treatment team to the patient.
  – Encourage a change in life-style, including exercise, diet, sleep hygiene, stress reduction, relaxation training, leisure activity schedule, and pacing.

- Implement the treatment plan.

  – Coordinate treatment plan activities.
  – Establish a referral and interdisciplinary team approach, if indicated.

- Follow-up.

  – Monitor treatment progress and patient improvement.
  – Establish a regular follow-up schedule throughout and after treatment.

Role of the Primary Care Manager (PCM)

In the course of the assessment, the primary care provider should also serve as the primary care manage (PCM) and develop a problem list that summarizes the findings of specialty consultations and diagnostic procedures related to the diagnosis of CFS/FM or CMI. The PCM should determine the severity of each identified problem and the impact it will have on the patient's functional ability and quality of life, so that a baseline can be established against which improvements can be assessed. The PCM should also identify problems for which treatment is most urgently recommended. The most urgent treatments may be defined as those treatments expected to result in the greatest improvement when addressing the most severe problems.

Role of Consultants

The PCM is not expected to directly provide treatment, but is expected to serve as the focal point for a multi-disciplinary approach to treatment that may span the continuum of care, beginning with self-management. The treatment team may include those from whom prior consults have been obtained, such as physical therapy, nutrition, social work, psychology, rheumatology, and significant others within the patient's social network. The PCM, with patient consent, may find it useful to involve the patient's employer/supervisor, spouse, and friends in the defined treatment team.

Mental health professionals should provide input into implementing psychotherapies and psychopharmacology in outpatient or partial hospitalization settings. Social workers should help build family and social support networks, or recommend changes in the patient's living situation, in order to create a positive support network. Within the most intensive treatment setting within the continuum of care, residential treatment may be required to assure the presence of a support network.

Continuum of Care

A continuum of care should cover a range of levels of intensity, including self-care in the home through outpatient treatment, partial hospitalization, residential treatment, and hospitalization. Patients may be encouraged to use wellness centers and gyms as part of the plan to improve physical conditioning, diet, and stress management. In outpatient settings, the patient may be willing to keep a diary of symptoms, events, and diet that can be reviewed by the outpatient provider.

Substance use disorders commonly occur in all patient populations, but are commonly missed in comprehensive medical assessments. The PCM should be sensitive to the harmful and potentially addictive use of alcohol, medication, and illicit drugs that transcend all three areas. Treatment programs that comprehensively address

addiction recovery have high success rates and should be expected to significantly improve the patient's quality of life and functional level.

L. Initiate/Continue Treatment

ANNOTATION

CFS/FM has significant negative impact on the patient's physical, mental and social well-being. Multi-disciplinary treatment should cover these three main areas. Interventions expected to improve physical well-being include a graduated exercise regimen (monitored through physical therapy, exercise trainers, and social supports), improved sleep habits, and medication (monitored by the physician). Mental well-being may be improved through individual or group therapy, medication, and creating a supportive social network. Social well-being may be improved through resolving legal, financial, occupational, or recreational problems.

The expected outcome of intervention should be to significantly alter the patient's lifestyle and improve the identified problem areas, rather than discover a disease etiology or "cure."

THERAPY INTERVENTIONS

- With early recognition, patient education, and effective multi-modal management, most patients with CFS/FM condition can lead a fairly normal life.
- The optimal intervention for FM would include non-pharmacologic treatments, specifically graded aerobic exercise, and cognitive-behavioral therapy, in addition to appropriate medication management, as needed for sleep and pain symptoms.
- The optimal interventions for CFS would include non-pharmacologic treatments, cognitive-behavioral therapy and moderate aerobic exercise, in addition to appropriate medication management as needed for associated depression, insomnia or myalgia, and sleep hygiene.

Tables 5 and 6 summarize the therapies for CFS and FM and the potential benefit or harm of these interventions based on evidence from randomized controlled trials. The significance of the results of the research is indicated using the "Recommendation" (R) grading system described in Appendix 1 (e.g., R = A indicates significant benefits that are based on good clinical trails). For detailed recommendations on the treatment interventions, see Section B: Therapy Interventions for CFS/FM.

Table 5. Therapy Interventions for FM

R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A		Cognitive Behavioral Therapy Graded Aerobic Exercise Antidepressant (TCA)		
B		• Tramadol * • SAMe ** • SSRI (R = B/C) • NSAIDs (R = B/C)	• Acupuncture • Biofeedback • Trigger point injection • Stretching	• **Xanax**
C		• Sleep education • Other antidepressants (non-SSRI, non-TCA)	• Massage therapy • Relaxation therapy • Myofascial release • Spinal manipulation • Hypnotherapy • Magnesium	• **Antiviral** • **Antifungal** • **Antibiotics**
D				• **Bed rest**

R = Recommendation(See Appendix 1)

* ***Tramadol non formulary medication. Available by physician request using the non-formulary process.***

** S***ame and melatonin are nutritional supplements not provided by the VA and are available as over the counter product.***

Table 6. Therapy Interventions for CFS

R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A	Cognitive behavioral threrapy Graded aerobic exercise			
B		MAOI NADH		
C		• Sleep education • SSRI Other anti-depressants (non-SSRI, non-TCA)	• Relaxation • Flexibility exercise • Essential fatty acids • Magnesium • Low-dose, short term corticosteroid (R = B/C)	• Florinef, alone
D				• Bed rest • Corticosteroid **High-dose or Replacement** • Anti-viral • Anti-fungal • Immune therapy

R = Recommendation (See Appendix 1)

Sleep Hygiene

In patients with CFS, behavioral approaches to sleep-wake cycle disturbances are likely to be more successful than pharmacologic approaches, as the latter do not induce normal sleep. Cognitive and educational management approaches should be aimed at promoting an understanding of the role of disordered sleep, and dispelling any irrational fears or inappropriate beliefs about sleep. Relaxation training and stress management may be useful for some patients.

The aim of sleep management is to establish a regular, normalized sleep-wake pattern. Patients should be encouraged to:

- Restrict the night-time sleep period to about eight hours.
- Avoid going to bed too early in the evening.
- Avoid stimulants during the evening period.
- Wake at a regular time in the morning (e.g., 7 am).
- Arise from bed at a regular time in the morning (e.g., by 8 am).
- Reduce (to less than 30 minutes) or abolish daytime naps.
- Engage in daytime physical and mental activities (within the limits of the individual's functional capacity).

If a patient with CFS has a concurrent *primary* sleep disorder (e.g., sleep apnea, restless leg syndrome, or narcolepsy) specific intervention is required. The goals of sleep management should be to establish a regular, unbroken, night-time sleep pattern and to improve perceptions of the quality of sleep.

Brief Introduction to Cognitive Behavioral Therapy

CBT has been found to be particularly beneficial for patients with CFS/FM (See Section B: Therapy Interventions for CFS/FM). If CBT is not available to your patients or they are not interested in seeing a mental health provider, the clinician may wish to consider utilizing some aspects of CBT in their clinic-based management. The following measures may help to empower patients and prevent them from dwelling on their symptoms:

- Work with patients to find more effective coping mechanisms.
- Help patients understand how avoiding activity and staying in bed may exacerbate their symptoms, rather than improving them.
- Encourage patients to maintain diaries, initially recording such items as weight, diet, sleep, and other objective elements.
- Later, guide patients toward writing more about life events and feelings and emotions; help them to see connections between life events and emotions, and in turn, physical symptoms.
- Help patients understand how expressing their feelings, either verbally or in writing, may help to prevent manifestation as somatic symptoms.
- For creative or artistic patients, encourage creative writing, which has been shown to improve the health status of patients with asthma and rheumatoid arthritis (Smyth et al., 1999), or artwork.

Patient and Family Education

Some patients want only to be told that their condition is non-progressive and not causing damage or inflammation to their body. These patients generally have milder symptoms that have been present for some time and possess adequate strategies for improving symptoms and maintaining function. Education may be the only necessary treatment for these patients.

Patient education is of paramount importance for ALL patients with CFS/FM. The clinician should describe the condition in terms comfortable to them, and then refer the patient to reputable sources for additional information. Several national patient support organizations (e.g., American Fibromyalgia Syndrome of America, National Fibromyalgia Research Association, and Fibromyalgia Alliance of America) produce excellent materials to help patients with FM learn more about their illness. Patients should be warned about getting information from less reputable sources, particularly on the Internet, where there is a great deal of misinformation.

Internet-savvy patients may be interested in learning more from some of the sites listed in Section D (Information Sources). Patients should be warned about the lack of evidence for, and potential harm from, some suggested "cures" that may be espoused by Web sites or other sources (e.g., Internet Chat/Support Groups). The high rate of placebo responses in conditions such as CFS/FM allows some poorly controlled studies to indicate benefits when there are no true benefits and possibly harmful effects.

Helping patients to gain a clear understanding of the nature of their illness is an important element of care management. For example, some patients harbor fears that an infection or environmental pollutants may be causing irreversible damage. Others may have been led to believe that any physical activity at all could be harmful. Unwarranted concerns of this kind may lead to maladaptive attitudes and behaviors that may increase the disability and retard recovery.

Psychosocial Support

As with other chronic illnesses, managing patients with CFS/FM requires consideration of the psychological and social impacts of the illness. Patients may be unable to continue full-time work, so financial difficulties may rapidly develop.

A successful return to work or school after a prolonged illness with CFS/FM often requires a rehabilitation program that incorporates medical treatments, psychological support, and occupational therapy. The clinician may need to coordinate the help of other health care and educational professionals to implement the appropriate program for the patient.

Consideration should also be given to the impact that the illness may be having on the patient's family. In some circumstances, it may be useful for the spouse or partner to accompany the patient with CFS/FM to a consultation, to help them better understand the illness and provide an opportunity to discuss any coping difficulties.

Joining a patient support group may be valuable for some patients. Support groups can offer individual and group support, education, and advice (e.g., how to gain access to social welfare agencies). Patients may also benefit from the opportunity to exchange coping strategies for dealing with day-to-day difficulties common to those living with debilitating conditions. However, the quality of advice can vary and it is therefore useful for the clinician to be knowledgeable about the activities and attitudes of local support groups.

With early recognition, patient education, and effective multi-modal management, most patients with CFS/FM can lead a fairly normal life. Clinicians should be prepared to act as advocates for their patients in negotiations with employers, educational institutions, and social welfare organizations. For instance, the patient may need assistance in arranging part-time work or school alternatives or securing disability allowances.

The clinician should refocus the attention from symptoms to improving patient functioning. Potentially modifiable psychosocial barriers to patient functioning could include the following:

- Living environment—Homelessness can perpetuate chronic illness as the result of environmental exposure and virtually non-existent personal hygiene.
- Support systems—Negative support on the part of the spouse, family, or significant other can impair and even worsen functionality.
- Job—Work place factors have been associated with illness-related behavior.
- Finances—Disability compensation can perpetuate illness by requiring continuing symptoms and disability for the worker to be eligible for benefits.

M. Follow-Up with Scheduled Visits, Usually at Frequent Intervals

OBJECTIVE

Promote adherence to therapy and monitoring of clinical status.

ANNOTATION

- The goal of follow-up visits is to monitor the severity of symptoms, impact of the symptoms on activities, effects of treatments, and presence of adverse effects to treatments, and assess patients for new symptoms suggestive of other diagnoses.
- Scheduled visits are preferred over as-needed (PRN) revisits.
- The amount of time between visits will vary depending on a number of factors, including the following:
  - Quality of the provider/patient relationship (i.e., new or established patient)
  - Distress of the patient
  - Need for refinement of the treatment plan
  - Presence or absence of psychosocial stressors
- If symptoms remit, the interval between follow-up visits may gradually lengthen.

– Initially, a revisit at two to three weeks would be appropriate.
– As soon as the patient is doing well, then revisits every 3 to 4 months would be recommended.
– Visits at one to two-month intervals may be needed for patients on a graded exercise program or weight loss program to reinforce compliance.

- Continually re-evaluate the patient for worsening of chronic symptoms or presence of new symptoms suggestive of other diagnoses.

DISCUSSION

Regularly scheduled, brief follow-up visits are appropriate and have been shown to be associated with improved physical functioning and greater cost-effectiveness without impacting patient satisfaction with care (Smith et al., 1986; Smith et al., 1995; Servan-Schreiber et al., 2000). Visits of 15 to 20 minutes at perhaps two to three week intervals are initially appropriate; as the patient improves gradually lengthen the intervals; for patients with new symptoms or worsening of chronic symptoms decrease the intervals, if needed. This allows patients to receive care without having to develop new symptoms.

N. Reassess Symptoms Severity

OBJECTIVE

Track the patient's clinical response to treatment.

ANNOTATION

The primary reason for assessing current symptom status is to compare to the baseline status and estimate the response to active treatment strategies. With the lack of objective findings, treatment response must be monitored using subjective patient reports of symptoms and their impact on functional status. Though the symptoms are subjective, it is possible, using standardized questioning, to obtain reproducible measurements of the patient's clinical status. The following standardized assessments are recommended:

For pain: "On a 0 to 10 scale, 0 being no pain and 10 being pain as bad as you can imagine, what number would you say your pain has been over the past week?"

For symptoms other than pain: "On a 0 to 10 scale, 0 being no (insert SYMPTOM) and 10 being (insert SYMPTOM) as bad as you can imagine, what number would you say your (insert SYMPTOM) has been over the past week?"

For symptom impact: "During the past week, how much have your symptoms interfered with your usual work or activities, 0 being does not interfere at all and 10 being completely interferes?"

The clinician should initiate a complete initial symptom assessment (e.g., symptom duration, onset, triggers, and severity for new symptoms not previously assessed) (see Annotation D).

O. Adjust Treatment; Encourage, Reinforce, and Monitor for Emerging Conditions

OBJECTIVE

Provide appropriate, effective follow-up, reassurance, and patient education for patients with CFS/FM.

ANNOTATION

With patient consent, the clinician should become less involved as the patient is able to sustain lifestyle changes that have positive impact on functional ability and quality of life.

- Assure the patient that you believe their symptoms are real.
- Assess progress towards negotiated goals.
- Reevaluate the patient, with special concern for new symptoms or worsening chronic symptoms.
- Respond to the patient's desire to change the treatment plan or behavior that indicates a need to re-evaluate the treatment plan.
- Assess the patient's adherence to treatment and address any barriers to treatment.
- Assist the patient to take an active role in their recovery.

DISCUSSION

It is essential to establish a good rapport with patients on their initial visit in order to establish long term relationships in caring for their chronic condition. Many patients may have had, from their perspective, a less than satisfactory encounter with medical care providers. It should be made clear to patients that you realize the symptoms are real, that they will be thoroughly evaluated, and that there are treatments that can help them. Do not say that, "There's nothing serious;" do not suggest that, "It's all in your head;" and do not dismiss them with, "There really is nothing I can do for you." Such statements are harmful to the patient and destructive for the clinician/patient relationship.

A management plan should be negotiated with each patient, giving the patient an active role in managing his/her illness. Both pharmacologic and non-pharmacologic measures (psychotherapies such as CBT, sleep hygiene, diet/nutrition, exercise, activities, and hobbies) should be considered. The physical examination may be a particularly important part of the visits early in the patient-clinician relationship to ensure that other medical problems are not missed and to reassure the patient. Over time, the physical examination may be more limited, and replaced by attention to life stressors and coping mechanisms. Helping patients to shift their focus away from rumination on the potential etiology of their symptoms or the symptoms themselves and to living well with their symptoms, is especially helpful. However, any new symptoms should be carefully assessed and not assumed to be manifestations of CFS/FM.

Regularly scheduled, brief follow-up visits are appropriate, and have been shown to be associated with improved physical functioning and greater cost-effectiveness (Smith et al., 1986; Smith et al., 1995). Visits of 15 to 20 minutes at perhaps two to three week intervals are initially appropriate; gradually lengthen the intervals as the patient improves; decrease the intervals, if needed, for patients with new symptoms or worsening of chronic symptoms. Other factors determining the frequency of visits include, but are not limited to the patient's anxiety level, need for medication adjustments, and compliance with exercise or nutrition programs.

It is essential to maintain regular clinical contact with the patient, which includes diligent monitoring for changes in symptomatology or physical status that might warrant additional diagnostic assessments and treatment.

P. Consider Consultation

OBJECTIVE

Provide the clinician advice and guidance in treating CFS/FM.

ANNOTATION

The PCM is not expected to directly provide treatment, but is expected to serve as the focal point for a multi-disciplinary approach to treatment that may span the continuum of care, beginning with self-management. The treatment team may include those from whom prior consults have been obtained, such as physical therapy, nutrition, social work, psychology, rheumatology, and significant others within the patient's social network. The PCM, with patient consent, may find it useful to involve the patient's employer/supervisor, spouse, and friends in the defined treatment team.

Mental health professionals should provide input into implementing psychotherapies and psychopharmacology in outpatient or partial hospitalization settings. Social workers should help build family and social support networks, or recommend changes in the patient's living situation, in order to create a positive support network. Within the most intensive treatment setting within the continuum of care, residential treatment may be required to assure the presence of a support network.

Q. Provide Symptomatic Treatment and Consider Consultation

OBJECTIVE

Provide appropriate treatment and follow-up.

ANNOTATION

For unexplained symptoms that are not CFS or FM:

- Continue time-contingent follow-up.
- Emphasize efforts to improve functioning.
- Monitor for treatable disease explanations for symptoms (including psychiatric disorders).
- Use rehabilitative psychosocial strategies (e.g., CBT, and gradual physical reactivation/exercise) and symptom-based pharmacologic therapies, as appropriate (see Annotation L).
- Reassess target symptoms and clinical status at each visit.

DISCUSSION

Individuals who have one or more MUS, but who do not meet criteria for CFS/FM, may nonetheless benefit from treatment. Although there is little data to support this, the same principles that are advocated for the management of CFS/FM (in Annotations K through M) may be effective in these patients. Initiating treatment early in this subset of patients may help to prevent the development of more symptoms (Working Group consensus). In patients who are less symptomatic, it may be reasonable to begin by using education and non-pharmacologic therapies before moving toward the use of symptom-based pharmacologic therapy.

Algorithms and Annotations
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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

SECTION B: THERAPY INTERVENTIONS FOR CHRONIC FATIGUE SYNDROME/FIBROMYALGIA

Version 1.0
Pending Approval

SECTION B: THERAPY INTERVENTIONS FOR CHRONIC FATIGUE SYNDROME (CFS) AND FIBROMYALGIA (FM)

Page

THERAPY INTERVENTIONS FOR CHRONIC FATIGUE SYNDROME (CFS) AND FIBROMYALGIA (FM)

SUMMARY

- In clinical practice, non-pharmacologic therapies are frequently under-utilized in treating patients with CFS and FM, even though there is an abundance of data suggesting these modalities are beneficial.

- Given the absence of curative care, multi-modal approaches that combine the use of non-pharmacologic and pharmacologic therapies may address the spectrum of symptoms and disabilities often present in CFS and FM (Working Group consensus).

- It may be helpful to add therapies using a stepped care approach, even though supporting evidence does not exist. For example, patients with more severe pain who are treated with analgesics may be able to exercise more.

Iatrogenic harm is an important source of morbidity in CFS and FM. **The clinician should** a**void medications with serious side effects and unknown benefits.**

- High-dose and replacement-dose corticosteroids, mineralocorticoids, anti-viral, antifungal, immunotherapy (Cytokine), immune globulin (IVIG), and anti-allergic therapy interventions were studied and shown to have no benefit for CFS; potential harm outweighs possible benefits.
- Low-dose short-term corticosteroids (1 mg/d prednisone) may help some patients with CFS, but have small clinical relevance for chronic conditions.
- Some vitamins and nutritional supplements are safe and may offer small benefits for some patients.
- The choice to use nutritional supplements should be guided by patient preference.
- Examples of nutritional supplements are: essential fatty acids, magnesium, NADH, SAMe (S-adenosylmethionine), herbs, vitamin B-12, and folic acid.

NON-PHARMACOLOGIC THERAPIES – MAXIMUM BENEFIT

Graded Aerobic Exercise

- Aerobic exercise that begins at a low level and increases very slowly in intensity is effective in helping CFS and FM patients.
- If pain is a significant symptom, lower impact exercises may be more beneficial for CFS and FM patients.
- Aggressive exercise therapy is often poorly tolerated and may be harmful.

CFS	FM
• Graded exercise is beneficial [McCully et al., 1996] *(QE=I).* • Aggressive exercise therapy is often poorly tolerated and may be harmful. *Progressive exercise program: see Section D.*	• Aerobic exercise that increases very slowly in intensity is effective. • The patient's choice of exercise is very important because it should be an activity easily performed every day. Daily aerobic exercise should be the patient's goal. *Progressive exercise program: see Section D.*
The beneficial effects of exercise persist after the treatment is discontinued. • In one randomized controlled trial of graded exercises for 12 weeks, 55% of patients with CFS were better in terms of reduced fatigue and increased functional capacity after completing the program. At a one-year follow-up evaluation, 74% of patients rated themselves as "better" [Fulcher & White, 1997] *(QE=I).* • In another trial of graded exercise, patients that completed the six months exercise program had an improved health perception and reduced fatigue [Wearden et al., 1998] *(QE=I);* however, the drop out rate was higher for those in the exercise group than the non-exercise group. • There is considerable indirect evidence suggesting that prolonged bed rest may be harmful [Reid, et al., 2000] *(QE=III).*	Several studies show that exercise, especially aerobic exercise that increases very slowly in intensity, is effective in helping FM patients. • Aerobic exercise should begin extremely slowly and progress in very small increments. The patient's choice of exercise is very important because it should be an activity easily performed every day. Daily aerobic exercise should be the patient's goal [Wigers et al., 1996; Clark, 1994] *(QE=I).* • Aquatic exercise in a warm pool (96 to 100 degrees Fahrenheit) is one of the mildest forms of exercise and minimizes strain on the spine and upper extremity soft tissues. Other types of exercise that have been shown to be useful include walking and using a treadmill [Mannerkorpi et al., 2000; Wolfe, 1994; Wigers et al., 1996, Buckelew et al., 1998] *(QE=I).* • Stretching exercises are an intervention to improve posture and control of proximal and peripheral joints and muscle groups. The basic rule is to avoid maximum stretching and to stretch very slowly and gently [Clark, 1994; Fulcher & White, 1997; Gowans et al., 1999; Nichols & Glenn, 1994] *(QE=I).*

Therapy	R
Graded exercise is beneficial.	A
Bed rest may be harmful.	D

Therapy	R
Graded exercise is beneficial.	A

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

NON-PHARMACOLOGIC THERAPIES – MAXIMUM BENEFIT

Cognitive Behavioral Therapy (CBT)

- CBT is beneficial in patients with CFS or FM, particularly if an adequate number of sessions are provided.
- The effectiveness of CBT varies across studies. This may be due to the experience of the therapist, number of sessions, and precise content delivered.
- Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking.

CFS	FM
• A critical review of controlled clinical trials [Kroenke & Swindle, 2000] examined the efficacy of CBT for unexplained symptoms and symptom syndromes *(QE=I).* • The Cochrane systematic review identifies the same three randomized controlled trials, finding CBT to be effective for CFS patients (NNT=2) [Price & Cooper, 1998] *(QE=I).* • There is evidence demonstrating the benefits of CBT for the treatment of frequently associated symptoms (e.g., back pain, other pain syndromes, and irritable bowel syndrome) [Kroenke & Swindle, 2000] *(QE=I).* • Well-designed trials involving over 200 patients: – Two studies demonstrated the efficacy of CBT [Sharpe et al., 1996] [Deale et al., 1997] *(QE=I)*, and one study found no benefit [Lloyd et al., 1993] *(QE=I).* – Two positive studies involved more CBT sessions (13 to 16), whereas the one negative study involved only 6 sessions. – The interventions were usually weekly or twice weekly, with the follow-up length ranging from 3 to 12 months.	• There is evidence demonstrating the benefits of CBT for the treatment of frequently associated symptoms (e.g., back pain, other pain syndromes, and irritable bowel syndrome) [Kroenke & Swindle, 2000] *(QE=I).* • Benefits of CBT for the treatment of FM have also been demonstrated in several trials [Vlaeyen et al., 1996; Nicassio et al., 1997; Nielson et al., 1992; Walco & Ilowite, 1992; White & Nielson, 1995] *(QE=I).*

Therapy	**R**
CBT is beneficial for CFS and FM.	A
CBT is beneficial for the treatment of back pain, other pain syndromes, and irritable bowel syndrome.	A

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

NON-PHARMACOLOGIC THERAPIES– POSSIBLE BENEFIT

Relaxation Techniques

- Relaxation and flexibility therapy have been studied in conjunction with other non-pharmacologic interventions.

CFS	FM
• There are many resources for relaxation techniques in the psychology, counseling, physical therapy, and occupational therapy professions. Buckelew shows that relaxation techniques combined with a gradual aerobic exercise program provide better results [Buckelew et al., 1998] *QE=I.* • Exercise and the CBT approach have been shown to be more effective at improving aerobic capacity, symptomatic status, and functional performance than relaxation and flexibility therapy [Fulcher & White, 1997] *(QE=I).* In the Deale trial, the group that received relaxation therapy demonstrated modest improvement, but far less than was shown for the CBT group [Deale et al., 1997] *(QE=I).* *Sample programs for relaxation techniques: see Section D.*	• Flexibility programs are useful in conjunction with a graded aerobic exercise program [Gowans, et al., 1999] *(QE=III).* • Patients with marked levels of pain and/or a high level of deconditioning may benefit from an exercise program that includes gentle flexibility work for the first few days, before progressing to walking or pool therapy. *Recommended flexibility exercises for CFS and FM: see Section D.*

Therapy	R
Relaxation combined with exercise is beneficial.	A
Exercise and CBT are more effective than relaxation and flexibility therapy.	A
Relaxation is less effective than CBT.	C

Therapy	R
Flexibility programs combined with aerobic exercise programs are beneficial.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

NON-PHARMACOLOGIC THERAPIES– POSSIBLE BENEFIT

Massage Therapy

- There are no specific studies about the effects of massage on patients with CFS or FM.
- Given the lack of evidence and lack of consensus among experts, no specific recommendations can be made.

CFS	FM
The effects of massage on low back pain, myofascial trigger points, post-exercise muscle damage, and long-term neurological patients have been studied. *There are no specific studies about the effects of massage on patients with CFS.*	One randomized controlled trial (RCT) looked at the treatment of myofascial trigger points with ultrasound, massage, and exercise in one group; sham-ultrasound, massage and exercise in the second group; and a control group. • It was concluded that ultrasound provided no pain reduction, but massage and exercise reduced the number and intensity of trigger points. • The impact of this reduction on neck and shoulder pain is weak [Gam et al., 1998] *(QE=III).*
The clinician may want to prescribe a trial of gentle massage on a case-by-case basis to evaluate its benefits to patients. Massage, in this case, would be part of a comprehensive treatment program.	

Therapy	**R**
Massage may be of modest benefit for CFS and FM.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

NON-PHARMACOLOGIC THERAPIES– POSSIBLE BENEFIT

Other Non-Pharmacologic Therapies

The following types of non-pharmacologic therapies have been shown to be of some possible benefit, especially in FM, and may be reserved for individuals who fail to respond to symptom-based pharmacologic therapy, exercise, and cognitive-behavioral approaches:

- Acupuncture
- Tender point injection
- Stretching
- Biofeedback
- Hypnosis
- Myofascial release/massage therapy
- Chiropractic manipulation

In many cases, the choice to use these therapies will be guided by patient preference or issues such as reimbursement by third-party payers.

CFS/FM

There are no studies that suggest which of these therapies would work best in a given patient, although anecdotal experience suggests that patients with regional pain may respond best to therapies such as acupuncture, tender point injections, and chiropractic manipulation.

- Acupuncture has been shown to be of benefit in many chronic pain conditions [NIH, 1997]. There are several studies likewise suggesting that it is of benefit in FM, although all of these studies suffer from methodological flaws [Waylonis, 1977; Deluze et al., 1992].

- Tender or trigger point injection has likewise been shown to reduce pain, although this may be more effective in individuals with regional, rather than widespread pain, and dry needling may be just as effective as injection with lidocaine or corticosteroids [Hong & Hsueh, 1996].

- Chiropractic manipulation, myofascial release or massage therapy, and stretching exercises have all been shown to be of benefit in at least one controlled trial, although these studies have methodological problems that limit their extrapolation.

- Both hypnosis and biofeedback have been shown to be of benefit in randomized controlled trials, and in many cases are integrated into CBT programs [Ferraccioli et al., 1987].

NON-PHARMACOLOGIC THERAPIES – POSSIBLY HARMFUL

Bed Rest

CFS	FM
• There is no evidence that bed rest is an effective treatment for CFS [Working Group consensus] *(QE=III).* • There is considerable indirect evidence suggesting that prolonged bed rest may be harmful [Reid et al., 2000] *(QE=III).*	• Although there are no data for FM, in other chronic pain conditions bed rest has been shown to be detrimental, and should be discouraged.

Therapy	R
Bed rest is harmful in managing patients with CFS.	D
Prolonged bed rest may be ineffective or harmful in CFS.	E

Therapy	R
Bed rest and aggressive exercise therapy are harmful in managing patients with FM.	D

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES – SOME BENEFIT(1)

Antidepressant Therapy

Antidepressant drugs may provide symptomatic relief of pain, sleep disturbances, and depressed mood in people with CFS.

- Tricyclic compounds, such as amitriptyline and cyclobenzaprine, have been demonstrated to be effective in treating FM and associated conditions.
- Tricyclic antidepressants (TCAs) may be useful for patients with CFS who have prominent pain and/or depression.
- Monoamine oxidase inhibitors (MAOIs) are effective for patients with CFS; however, dietary restrictions and the risk of hypertensive crisis limit their clinical utility.
- Selective serotonin reuptake inhibitors (SSRIs) have been found to be of potential, but variable, use in treating subpopulations of patients with FM.
- Co-existing depression is commonly present in patients suffering from CFS or FM. These patients may benefit from antidepressant treatment.

CFS	FM
TCA • There are no randomized controlled trials for patients with CFS. Evidence from studies of TCA in FM patients suggests that fatigue is less responsive to TCAs than pain. **MAOI** • Trials using MAOIs (e.g., phenelzine and moclobemide) showed improvement in the treatment of multiple symptoms, illness severity, and mood [Natelson et al., 1996; Hickie et al., 2000] *(QE=I).* • Long-term benefits are uncertain, and safety considerations (e.g., hypertension and dietary restrictions) may necessitate consultation with a mental health professional before initiating MAOI therapy.	**TCA** • Two meta-analyses of controlled trials demonstrated the efficacy of antidepressants over placebo in treating the symptoms of FM (for all symptoms, including pain, sleep, fatigue, the number of trigger points, and overall well-being) [O'Malley et al., 2000] *(QE=I)* [Arnold et al., 2000] *(QE=I).* • TCAs found to be effective include amitriptyline and cyclobenzaprine (Flexeril®). • To increase the tolerance of cyclobenzaprine and amitriptyline start with low dosages and slowly increase. These compounds should be administered several hours before bedtime, begun at low doses (10 mg or less), and increased slowly (10 mg every 1 to 2 weeks) until the patient reaches the maximally beneficial dose. • Controlled trial evidence demonstrates the benefits of antidepressants for a range of chronic pain conditions (e.g., chronic headache, FM, irritable bowel syndrome, and idiopathic pain). • Moderate improvement has been demonstrated in global assessment, pain, and sleep; less improvement has been demonstrated in fatigue. • Many studies have been short-term trials; sustained benefits in long-term follow-up need to be better established. • The optimal dose of these compounds varies tremendously across groups of patients. Blinded research trials do not allow evaluation of highly individualized dosing regimens that can be used in clinical practice, making generalization of the results difficult.

Antidepressant Therapy (Continued)

CFS	FM
SSRI • Fluoxetine showed no benefit for depression or fatigue in patients with CFS [Vercoulen et al., 1996] *(QE=I).* • Fluoxetine improved depression, but not functional capacity or fatigue, in a study that compared exercise and fluxetine in a 2x2 factorial study [Wearden et al., 1998) *(QE=I).*	**SSRI** • SSRI side effects appear to be somewhat better tolerated than tricyclic compounds. • Studies show conflicting results regarding the efficacy of fluoxetine (Prozac®) in FM. One trial showed a beneficial effect (either alone or with amitriptyline), while another trial demonstrated no advantage over the placebo. • Citalopram (Celexa®) was not beneficial in a single trial, and venlafaxine (Effexor®) (a dual-acting agent that works on both serotonin and noradrenergic pathways) was possibly beneficial in a single, open-label trial. • More studies are required to examine the relative efficacy of SSRI agents and newer antidepressants, such as venlafaxine.

Medication	**R**
TCA	C
SSRI	C
MAOI	B

Medication	**R**
TCA	A
SSRI	B
MAOI	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES – SOME BENEFIT

Analgesic Therapy

Various classes of medications have been tried in patients with CFS or FM to alleviate the varied associated types of pain.

- Nonsteroidal anti-inflammatory drugs (NSAIDs) and tramadol may be useful for treating certain pain symptoms associated with CFS and FM (e.g., migraine and tension headaches, non-cardiac chest pain, irritable bowel syndrome, and a variety of chronic pain conditions) though they do not necessarily lead to a global beneficial effect.
- Neither benzodiazepine nor opioids have been studied as isolated drugs in clinical studies. These drugs should not be used as first line therapy, but may be of benefit for selected patients who fail to respond to other better-studied drugs, and should be used cautiously (Working Group consensus).

CFS	FM
• There are no studies looking at the treatment of pain associated specifically with CFS. • There are no studies looking at the effectiveness of tramadol in CFS. • There are no data or studies to suggest that usual principles of analgesic therapy are not applicable to CFS [Working Group consensus] *(QE=III).*	**NSAIDs** • NSAIDs are often part of the pharmacologic treatment of FM, however, an inflammatory process has not been identified as a cause or consequence of this syndrome. • Ibuprofen showed no benefit over placebo for pain, sleep disturbance, duration of stiffness, or fatigue [Yunus et al., 1989; Russel et al., 1991] *(QE=I).* • Naproxen showed no significant effect on any outcome parameters (e.g., patient and physician global assessments, patient pain, sleep difficulties, fatigue, and tender points) when compared to placebo [Goldenberg et al., 1986) *(QE=I).* • When used in addition to the agent amitriptyline, there was an additive effect [Goldenberg et al., 1986] *(QE=I).* **Tramadol (Ultram)*** • Tramadol was noted to decrease the pain on a visual analogue scale by 20%; placebo increased the pain level by 20% [Biasi, 1998] *(QE=I).* •

Medication	R
NSAIDS	B
Tramadol	B

Medication	R
NSAIDS	B
Tramadol	B

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

* Tramadol non-formulary medication. Available by physician request using the non-formulary process.

PHARMACOLOGIC THERAPIES – SOME BENEFIT

Benzodiazepine and Non-Benzodiazepine Sedative-Hypnotics

Some patients with FM have objective abnormalities noted in sleep studies. But even though disturbed sleep likely plays a significant role in symptom expression in some patients, and may contribute to some of the physiologic abnormalities, the aggregate data do not support the notion that disturbed sleep alone is causing this illness.

In patients with CFS, behavioral approaches to sleep disturbance are likely to be more successful than pharmacologic approaches, as the latter do not induce normal sleep.

- In general, behavioral strategies should proceed the use of pharmacologic agents for sleep disturbances.
- Benzodiazepine and non-benzodiazepine sedative-hypnotics may be prescribed for short-term treatment of sleep disturbances in patients with CFS or FM, but are not recommended and may be harmful for treatment of chronic sleep disturbances.
- Benzodiazepines and non-benzodiazepine sedative-hypnotics are of limited utility for the cardinal symptoms of CFS and FM (Drewes et al., 1991)

CFS	FM
• No specific studies for CFS have been published. In the absence of evidence suggesting safety or efficacy, benzodiazepine and non-benzodiazepine sedative-hypnotics cannot be recommended for CFS and may be harmful [Working Group consensus] *(QE=III).*	• Two RCTs of benzodiazepine sedative-hypnotics for the treatment of FM have shown no benefit over placebo (Russell, 1991; Quijada-Carrera et al., 1996) *(QE=I).* • Two RCTs for non-benzodiazepine sedative hypnotics for the treatment of FM have shown no benefit over placebo (Gronblad, 1993; Muldofsky, 1996) *(QE=I).*

Medication	**R**
Sleep hygiene	A

Medication	**R**
Benzodiazepine sedative hypnotics	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT/POSSIBLY HARMFUL

Cortisol Treatment for CFS

Therapeutic studies of corticosteroids were initiated based on the observation that some patients with CFS or FM manifested a slight decrease in urinary cortisol levels.

- Corticosteroids do not appear to be beneficial in treating patients with CFS.
- Studies have been performed to examine the role of low dose (5 to 10mg/day of hydrocortisone), replacement (20 to 35mg/day of hydrocortisone), and high dose corticosteroids in reducing the symptoms of patients with CFS.
  - While some benefit was noted in patients treated with low dose hydrocortisone, the benefit was not evident after 4 weeks.
  - No added benefit was noted in using 10mg compared with 5mg/day of hydrocortisone.
  - **lacement doses of hydrocortisone had some benefit at 12 weeks, but adrenal suppression occurred; replacement doses of hydrocortisone may be harmful and should be avoided.**
  - High dose corticosteroids do not appear to be beneficial and should be avoided.

CFS	FM
• Low dose hydrocortisone (5mg to 10mg/day) was more effective than placebo in reducing fatigue in adults with CFS, but the beneficial effect diminished after one month. Adrenal function was not suppressed by low dose hydrocortisone [Cleare et al., 1999] *(QE=I).* • Replacement doses of hydrocortisone (25 to 35mg/day) given for 12 weeks was associated with slight and not statistically significant improvement compared with placebo. Adrenal suppression occurred after 12 weeks [McKenzie et al., 1998] *(QE=I).*	• Uncontrolled studies using high dose corticosteroids have yielded no benefit and can be harmful [Clark et al., 1985] *(QE=I).* • No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, corticosteroids cannot be recommended for FM and may be harmful [Working Group consensus] *(QE=III).*

Treatment	**R**
Coricosteroids are not recommended in low, replacement, or high doses for patients with CFS or FM and can be harmful.	E

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT/POSSIBLY HARMFUL

Immunotherapy for CFS

Various immunologic abnormalities have been described in patients with CFS, such as depressed natural killer cells, an increase in activated circulating lymphocytes, and an increase in immune complexes. None are specific for CFS or abnormal in all CFS patients.

- Of the immunologic treatment currently investigated, IVIG, dialyzable leukocyte extract (DLE) transfer factor, alpha interferon, and Poly (I)·Poly (C_{12}U) Ampligen™ cannot be recommended for patients with CFS.

CFS	FM
• **Immunoglobulin** (1 g/kg of intravenous monthly infusion for 6 months) found no difference in response rates compared to placebo (N=28)[Peterson et al., 1990] *(QE=I).* • **Immunoglobulin** (2 g/kg for 3 months) showed an improvement in symptoms compared to placebo. Symptoms and disability returned 6 months after the end of the therapy (N=49). Adverse effects included phlebitis (55%) and constitutional symptoms (82%), such as headaches, fatigue, and diminished concentration [Lloyd et al., 1990] *(QE=I).* • **Intravenous immunoglobulin** showed no benefit in a large RCT (N=96) [Vollmer-Conna et al., 1997] *(QE=I).* • **Dialyzable leukocyte extract (DLE**), also known as transfer factor, showed no beneficial effects in a double-blind placebo controlled trial [Lloyd et al., 1993] *(QE=I).* • **Alpha interferon** showed no beneficial effects over placebo in a small study [See & Tilles, 1996] *(QE=I).* • **Poly (I)·Poly (C_{12}U) (Ampligen™)** given **intravenously** twice weekly for 6 months was associated with an enhanced capacity to perform activities of daily living and an improvement in memory. Adverse effects included hepatic toxicity [Strayer et al., 1994] *(QE=I).*	• No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, immunologic therapy cannot be recommended for FM (Working Group consensus) *(QE=III).*

Treatment	R
Immunoglobulin IV	D
Alpha interferon	D
DLE	C
Ampligen®	D

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT/POSSIBLY HARMFUL

Anti-Viral Medication Therapy for CFS

CFS often begins abruptly following a 'flu'-type illness, leading to the hypothesis that anti-viral therapy may be beneficial for patients with CFS.

- Current data do not indicate the use of anti-viral drugs.
- Acyclovir and amantadine have been studied in controlled trials. Other drugs (e.g., Valacyclovir and Ganciclovir) have been evaluated in uncontrolled and inconclusive studies.

CFS	FM
• **Acyclovir** was no better than placebo in relieving symptoms; however, 12% of the Acyclovir-treated patients developed reversible renal failure [Straus et al., 1988] *(Q=I).* • **Amantadine** is an anti-viral drug used to treat influenza A, and is also effective for treating fatigue in patients with multiple sclerosis. In one trial of patients with CFS, Amantadine was not effective in relieving symptoms and was poorly tolerated when given for 8 weeks [Plioplys AV & Plioplys S, 1997] *(QE=I).*	• No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, anti-viral therapy cannot be recommended for FM (Working Group consensus) *(QE=III).*

Medication	**R**
Acyclovir	E
Amantadine	D

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT

Florinef Treatment of CFS Patients with Neurally Mediated Hypotension

Neurally mediated hypotension, manifested by fatigue and lightheadedness, occurs in a subset of patients with CFS. About one-third of CFS patients have positive tilt table tests.

• Fludrocortisone (Florinef) does not appear to be beneficial in treating neurally mediated hypotension in patients with CFS.	
CFS	FM
• Uncontrolled studies have shown that use of **salt loading plus** pharmacologic therapies alone or in combination may be beneficial [Bou-Holaigah et al., 1995] *(QE=II).* • **Fludrocortisone** in a dose of 0.1mg/day given for 6 weeks was no more effective than placebo [Peterson et al., 1998], in a small controlled study of CFS patients with neurally mediated hypotension *(QE=II).* • A larger study using **fludrocortisone** in a dose of 0.1 mg/day found no benefit of drug versus placebo [Rowe et al., 2001] *(QE=I).*	*Not applicable.*

Treatment	R
Fludrocortisone versus placebo.	C
Salt loading, with or without beta-blockers, improves symptoms of fatigue and lightheadedness.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT

Anti-Allergic Medication Therapy for CFS

Patients with CFS often report environment and food sensitivities and have a high incidence of positive allergy history (83 to 90 percent) and/or positive immediate skin test reactivity to various allergies (50 percent). No data on the frequency of atopy is available for patients with FM.

CFS patients commonly report new allergies or exacerbation of old allergies.

- Current data do not indicate the use of anti-allergic drugs.
- If patients report allergy symptoms, non-sedating antihistamines can be tried, but data is not available for treatment of CFS or FM symptoms.

CFS	FM
• A double-blind placebo controlled trial using terfenadine, a non-sedating antihistamine that is off the market, found no clinical benefit with this drug in the treatment of CFS symptoms [Steinberg et al., 1996] *(QE=I).*	• No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, anti-allergy medications cannot be recommended for FM (Working Group consensus) *(QE=III).*

Medication	**R**
Anti-allergic medication.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT

Magnesium Therapy

Investigators in England noted that patients with CFS had diminished red blood cell magnesium levels [Cox et al., 1991]; however, this was not confirmed by other studies [Clague et al., 1992; Hinds et al., 1994; Swanink et al., 1995].

- The possible benefits of intramuscular magnesium sulfate injections must be confirmed since the only follow-up evaluation of this treatment was at six weeks. Further studies are needed before this therapy can be recommended.

CFS	FM
• Intramuscular injections of **magnesium sulfate** (1gm in 2 ml) weekly for 6 weeks showed benefits when compared with placebo and no adverse effects [Cox et al., 1991] *(QE=I).* • Other researchers have failed to confirm this finding [Gantz, 1991] *(QE=III).*	• **Oral magnesium** (at approximately 1000 mg/day) has shown no clear treatment effect compared to placebo [Russell et al., 1995] *(QE=I).* • Reduction in the severity of the pain measures was demonstrated in the open label trial with dose escalation and a longer duration of treatment.

Therapy	R
Intramuscular magnesium sulfate.	C

Therapy	R
Oral magnesium in FM.	C
Malic acid and magnesium in the treatment in FM.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT

Fatty Acid Therapy for CFS

One hypothesis suggests that an increase in the various cytokines may produce many of the symptoms of CFS. Essential fatty acids (EFA) may decrease the production of cytokine.

- Since clinical trial results conflict, further data are needed to clarify this issue.
- Long-term results of EFA therapy are unknown.

CFS	FM
• **Essential fatty acids** (4 g/day of a mixture of oil of evening primrose and fish oil) showed improvement in symptoms over placebo at three months [Behan PO & Behan WM, 1990] *(QE=I).* • No significant difference between EFA and placebo was found in the Warren et al. study (1999) *(QE=I).*	• No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, fatty acids therapy cannot be recommended for FM (Working Group consensus) *(QE=III).*

Therapy	**R**
Essential fatty acids for improving symptoms.	C

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC THERAPIES - NO BENEFIT

Nicotinamide Adenine Dinucleotide (NADH) Therapy for CFS

NADH (ENADA®) is an over-the-counter drug that facilitates generation of Adenosine Triphosphate, which may be depleted in CFS patients.

• Since this is a non-prescription drug, only limited data are available.	
CFS	FM
• There are no systematic reviews. • **NADH** (10 mg/day for 4 weeks) reduced fatigue in a small clinical trial (N=26) compared with placebo (31% versus 8%); long-term benefits are unknown [Forsyth et al., 1999] *(QE=II).* • Adverse effects were not noted. • A cost of $40 to $50 per month is the only adverse effect.	• No specific studies for FM have been published. In the absence of evidence suggesting safety or efficacy, NADH therapy cannot be recommended for FM (Working Group consensus) *(QE=III).*

Therapy	**R**
NADH for reducing fatigue in CFS patients.	B

QE = Quality of Evidence; R = Recommendation (See Appendix 1)

PHARMACOLOGIC AGENTS FOR CFS/FM

Agent (Reference)	Dose Studied	Effective	Adverse Effects	Comments
Amitriptyline	Initial: 10 to 25 mg/day Maximum: 75 mg/day	Yes	• Sedative and anticholinergic effects • Cardiac toxicity	• The agent is only effective in approximately 30% of patients. • Tachyphylaxis can occur with continued treatment. • Anticholinergic side effects may limit use. • Not recommended for use in the elderly
Cyclobenzaprine	5 to 40 mg/day	Yes	• Anticholinergic and central nervous system effect	• Side effects may limit use. • Tachyphylaxis can occur with continued treatment.
Fluoxetine	Initial: 10 mg/day Range: 20 to 40 mg/day Maximum: 60 mg/day	Equivocal	• Most commonly sexual dysfunction	
Venlafaxine	37.5 to 300 mg/day	Possibly	• Headache • Sexual dysfunction	
Citalopram	Initial: 20 mg/day Range: 20 to 40 mg/day Maximum: 40 mg/day, if indicated	No	• Sexual dysfunction • Nausea	
Alprazolam	0.5 to 3.0 mg/day	Unknown	• Sedative and hypnotic effects	
Analgesics				
Tramadol *	50 to 400 mg/day	Yes	• Nausea • Dizziness	• Dual mechanism of action may address altered neurotransmitters and pain signals of FM.
NSAIDs	Dose range recommended by drug manufacturer	Equivocal	• If risk of bleeding avoid NSAIDs	• Intolerance is common • Efficacy is less than in other rheumatic conditions where inflammation is present.
Prednisone	15 mg/day	No	• Numerous well recognized long term side effects	
Lidocaineinjections	0.5 to 1.0 Ml of 0.5% solution	Possibly	• Allergic reactions	• Benefits may be due to mechanical effects of needling

PHARMACOLOGIC AGENTS FOR CFS/FM (continued)

Agent (Reference)	Dose Studied	Effective**	Adverse Effects	Comments
Opioids	Dose range recommended by drug manufacturer	Unknown	• Sedative effects • Nausea	• There is no clinical evidence to show efficacy. • Tolerance or dependence may develop with long-term use. • If used regularly, long-acting formulations are preferred.
S-adenosyl-L-methionine (SAMe)**	• 200 mg/day subq • 400 mg/day IV • 800 mg/day orally	Possibly	• None documented	• Drug is available in the United States orally, as an over-the-counter dietary supplement.
Growth hormone	Treat to insulin-like growth factor-1 target	Possibly	• Carpal tunnel symptoms	• Agent has been evaluated in only one study, in individuals with low IGF-1 levels. • Insulin-like growth factor target for therapy is 250 ng/mL. • Expense may be prohibitive.
Sleep				
Melatonin**	3 to 6 mg/day	Equivocal	—	• May help a limited number of patients who have difficulty initiating sleep.
Other				
Magnesium and malic acid	600 to 2000 mg/day	Unknown	• Diarrhea • Nausea	
g-Hydroxy-butyrate	2.25 g injection at bedtime and 4 hours later	Unknown	• Rebound alertness	• Nighttime dosing and rebound alertness may limit clinical usefulness. • Agent is available only as an oral solution in the United States for use in narcolepsy.

Adapted from Leventhal, 1999. Other guidance regarding pharmacotherapy for CFS can be found in Reid et al., 2000.

* Tramadol – non-formulary agent. Available by physician request using the non-formulary process

** SAMe and melatonin are nutritional supplements that the VA does not provide. Are available as over-the-counter products.

Therapy Interventions for CFS/FM
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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

SECTION C: PAIN ASSESSMENT

Version 1.0

PAIN ASSESSMENT

Assessment of pain should include the following domains:

A. Pain description
B. Behavioral manifestations of pain
C. Impact of pain
D. Current and past treatments for pain
E. Patients' expectations for pain relief

It is desirable, during initial assessment, to inquire and record patients' descriptions of their pain, aggravating and alleviating factors, perceptions of the impact of pain, current and past treatment(s) for pain, and patients' ratings of acceptable pain relief. Routine pain screening should include observation and documentation of pain intensity, onset, duration, and location. The patient's behavior should also be observed and recorded.

Time permitting, the assessment should be repeated at regularly planned intervals, when a new pain is reported, and when any new interventions to control pain are initiated. The use of standard methods on a routine basis is highly desirable, time permitting.

A. Pain Description

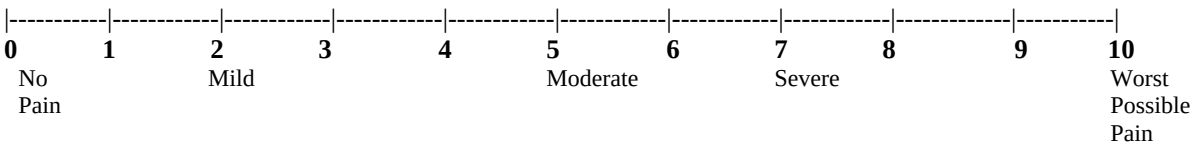
Pain Intensity

Assessment and documentation of pain scores in a systematic and consistent manner is an important mechanism for promoting identification of unrelieved pain at the individual patient care level. Availability of pain scores will provide an important index for monitoring improvement in the pain management.

Patients are asked to rate the intensity of their pain using the 0 to 10 Numeric Rating Scale (NRS) on which 0 equals no pain and 10 represents the worst possible pain (see Figure 1). The number reported by each patient is the pain score and should be documented in the medical record. The NRS may be used either verbally or visually. Pain intensity levels are measured at the initial visit, following treatment, and periodically, as guidelines dictate.

When using the NRS for pain the provider would ask, "On a scale of zero to ten, where zero means no pain and ten equals the worst possible pain, what is your current pain level?"

Figure 1. Numeric Rating Scale (NRS)



An individual often experiences pain in more than one site in his or her body. In these situations, patients may be confused about what site to emphasize in reporting their experience of pain, using the NRS. Practitioners should encourage the patient to provide a single, global estimate of pain intensity.

Self-report measures of pain intensity may not be appropriate for patients with problems communicating verbally (e.g., patients with strokes). In these instances, the clinician should rely on behavioral observations (e.g., wincing or grimacing) and physiological indices (e.g., increase in respiratory rate or significant increases in heart rate or blood pressure).

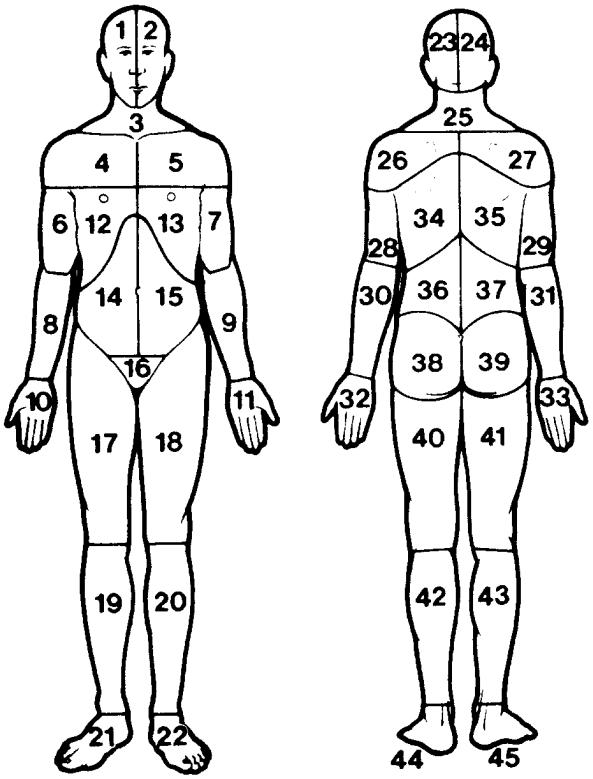
Onset and Duration of Pain

Onset and duration of pain should be determined by patient self-report or by someone who is familiar with the patient and his or her condition.

Pain Location

Pain location is important as it may provide useful information to help guide further assessment and treatment. Asking patients to indicate on their bodies where they feel pain can help to assess the distribution (location) of the pain. It is also useful to employ a standard pain drawing, consisting of a line drawing outline of the front and back of a human body (see Figure 2). Patients/significant others should be asked to indicate the location of their pain on the drawing by marking or shading in the areas of the figure. Pain drawings may be more appropriate during the initial pain assessment, time permitting, when pain persists, or when a new pain develops, rather than on a routine basis.

Figure 2: Pain Drawing [Margolis et al., 1986]



A coding system based on a grid of regions has been established [Margolis et al., 1986]. This system may be useful in detecting changes in multiple areas over time.

Pain Description

Patients should be asked to describe their pain. When time permits, the use of a standard form, such as the short form of the McGill Pain Questionnaire (SF-MPQ) [Melzack, 1987], may be helpful as it provides patients with a list of frequently endorsed pain descriptors. The short form consists of 15 representative adjectival descriptors selected from the longer SF-MPQ [Melzack, 1975]. Patients/significant others should rate each term on a 4-point intensity dimension. The descriptors were selected on the basis of their frequency of endorsements by patients with a variety of acute, intermittent, and chronic pain syndromes (see Table 1). Descriptors 1 through 11 represent the sensory dimension of pain and 12 through 15 represent the affective dimension.

Table 1: McGill Pain Questionnaire (SF-MPQ) [Melzack, 1987]

	Description	NONE	MILD	MODERATE	SEVERE
	Score	**0**	**1**	**2**	**3**
1	Throbbing				
2	Shooting				
3	Stabbing				
4	Sharp				
5	Cramping				
6	Gnawing				
7	Hot/Burning				
8	Aching				
9	Heavy				
10	Tender				
11	Splitting				
12	Tiring- Exhausting				
13	Sickening				
14	Fearful				
15	Punishing- Cruel				

Scoring:

- Each item should be scored: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
- Mean score of "sensory pain"=sum of scores for items 1 to 11, divided by 11.
- Mean score for "affective pain"=sum of scores for items 12 to 15, divided by 4.
- Mean overall pain score obtained by the sum of scores for all 15 items, divided by 15.

Factors That Alleviate/Exacerbate Pain

Patients/significant others should be asked to list factors that alleviate their pain ("What kinds of things make your pain feel better, e.g., heat, medicine, or rest?") and what factors exacerbate their pain (What kinds of things make your pain worse, e.g., coughing, walking, or sitting?"). Checklists are available and may be used to assist patients, time permitting.

B. Behavioral Manifestations of Pain

The healthcare professional should not only ask for patients' self-reports, but also observe their behaviors for an indication of the severity of the pain and pain impact. The general areas to observe include the following:

- Facial/audible expression of distress (e.g., grimaces, moans, or crying)
- Ambulation and posture (e.g., movement in a protective or guarded fashion; limping, and frequent shifting of position; frequent stops when ambulating; and lying in fetal position)
- Avoidance of activities (e.g., frequent lying down), avoidance of specific movements and other behaviors believed to indicate pain, distress, or suffering (e.g., wringing hands, using a cane, or wearing a cervical collar)

The nature, number, and frequency of these behaviors should be recorded, when possible.

C. Impact of Pain

The 0 to 10 NRS can be used to assess the impact of the pain with the appropriate anchors (0=does not interfere; 10=completely interferes). Patients/significant others can be asked to rate how much pain affects or interferes with their general activity, sleep, ability to walk, interactions with other people, and personal care (e.g., washing and dressing).

The 0 to 10 NRS can also be adapted to assess the patient's moods. The two most important areas are anxiety and depression and may be assessed by using the appropriate anchor terms: 0=extremely worried/anxious/upset; 10=not at all worried/anxious/upset; 0=extremely depressed; 10=not at all depressed. There are a number of other measures available to assess patients' moods [Bradley & McKendree-Smith, 2000].

D. Current and Past Treatments for Pain

Patients/significant others (if a patient is unable to communicate) should be asked what pain management methods (e.g., pharmacologic or non-pharamcologic) have been used to treat their current and past pain and how effective these were for each pain event, using the 0 to 10 NRS.

E. Patient's Expectations for Pain Relief

When possible, the patient's/significant other's goal for, or acceptability of, pain control should be rated using the 0 to 10 NRS, defining the anchors as: 0=absolutely no pain; and 10=worst pain I can imagine.

Satisfaction with pain control should be assessed by asking patients/significant others to rate their satisfaction with their current and past pain control. The 0 to 10 NRS can be used to assess patient satisfaction, defining the anchors as: 0=completely unsatisfied; and 10=completely satisfied.

DISCUSSION

For pain evaluation, the patient should be asked about A through C and E above and observed for any pain-related behaviors (B above). Many clinicians and investigators have recommended the use of visual analog scales (VAS) to assess pain intensity. Several studies have reported that patients (especially older patients) have difficulty understanding the appropriate use of these scales [Jensen et al., 1986; Jensen et al., 1989; Jensen et al., 1992]. The advantage of the VAS scale is the almost infinite number of intensity ratings. Such a large range will permit identification of very small changes. This may be important for research; however, it is not essential in the clinical situation. In addition to the difficulty patients have in using the VAS, it is cumbersome for clinical use as it requires someone to measure the very small units using a ruler. There are several devices available that can be used to assist the evaluator in measuring VAS scores; however, there does not seem to be sufficient need to use VAS in the clinical context. The numeric rating scale is easy to administer and to score, demonstrates high compliance rates, and has been shown to have good consistency over time (test-retest reliability).

Self-report measures of pain intensity may not be appropriate for patients with problems communicating verbally (e.g., patients with strokes or coma). Other methods are available to assess pain in these patients [Hadjistavropoulos et al., 2000].

The presence of pain affects multiple areas of patients' functioning and is not always directly correlated with pain intensity. It is important to assess not only pain description and ratings of pain intensity, but also patients' perceptions of how pain affects important areas of physical functioning, including the ability to engage in routine daily activities, sleep, interactions with others, and mood [Turk & Okifuji, 1999].

There are a number of measures designed to assess the impact of pain on functional activities; however, many of these are specific to the location of the pain (e.g., back pain). Some general measures also exist, most notably the SF-36 [Ware & Sherbourne, 1992]. However, these measures tend to be quite long and may place too heavy a burden on patients in the preoperative setting. Brief measures of functional activities have been shown to be useful and proxy measures for more extensive and more specific activity measures [Daut & Cleeland, 1982].

Although there are a large number of extensive self-reports and interviews designed to assess the role of emotional factors and the present mood state of patients [Bradley & McKendree-Smith, 2000 in press], such extensive measures may not be appropriate as an initial assessment. Self-report on a relatively few items assessing mood have been shown to be highly correlated with more extensive questionnaires [Daut & Cleeland, 1982; Kerns et al., 1985]. These relatively brief measures of patient mood have been shown to have good reliability (i.e., internal consistency, stability), validity, and sensitivity to change.

Pain Assessment
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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

SECTION D: THERAPY PROGRAMS

Version 1.0
PENDING APPROVAL

Graded Exercise Options for Fibromyalgia

The following table shows a progressive exercise program for fibromyalgia, from mildest to most intensive.

Recommended Exercises	Frequency/ Duration	Suggested Exercise Program Progression	Not Recommended
Lower extremity range of motion in a warm pool	• 5 to 10 minutes • 2 to 3 days/week**	• If tolerated well, add 3 to 5 minutes each week and 1 day every 2 weeks.	• Swimming • Walking in the pool • Exercising in a cool swimming pool.
Upper extremity range of motion in a warm pool	• 5 to 10 minutes • 2 to 3 days/week**	• If tolerated well, add 3 to 5 minutes each week and 1 day every 2 weeks.	• Resistive exercise • Swimming • Exercising in a cool swimming pool.
Gentle lower extremity stretching	• 5 to 10 minutes • 2 to 3 days/week*** • Reassess the technique the patient is using to stretch.	• If tolerated well, add 1 day every week until the patient is stretching 7 days/week. • Stretch before and after aerobic exercise.	• No stretching to the end range of motion. • No stretching both joints of two joint muscles, such as gastrocnemius or quadriceps.
Gentle upper extremity stretching	• 5 to 10 minutes • 2 to 3 days/week*** • Reassess the technique the patient is using to stretch.	• If tolerated well, add 1 day every week until the patient is stretching 7 days/week. • Stretch before and after aerobic exercise.	• No stretching both joints of two joint muscles, such as biceps. • No stretching to the end range of motion.
Aerobic exercise with the lower extremities **(e. g., very slow treadmill beginning at 1 mph or less, as tolerated; exercise bike; or walking)**	• 5 minutes • 3 days/week*** • The goal is to achieve a heart rate of 85% of the target heart rate for adults.	• Increase the duration to 1 to 2 minutes/week. • Add 1 day every other week with a goal of 20 to 30 minutes of aerobic exercise 4 to 5 days/week. • Very poorly conditioned patients may begin at 40% of the target heart rate. To calculate this use the formula (220-age) x .40 and gradually progress to (220- age) x .85, as tolerated.	• No jarring (i.e., high impact) forces should be felt in the lower extremities. • Wear shoes that have very good cushioning and are made for walking. • Avoid hyperextending the knees.

** *If pain increases reduce frequency or duration.*
*** *If pain increases after stretching reduce frequency or duration and/or reduce the number of joints being stretched or put on hold.*

Relaxation Techniques for Chronic Fatigue Syndrome and Fibromyalgia

Sample Relaxation Techniques	Frequency/ Duration	Suggested Program Progression	Not Recommended
Accompany this technique with an audiotape on guided videotape. Initially: Gently tighten one hand and then gradually let go. Breathe in while tightening the muscles and breathe out while letting go. *Progression:* Tighten around the elbow and let go. Tighten around the shoulders and let go. Tighten facial muscles and let go. Tighten stomach muscles and let go. Tighten buttocks and let go. Tighten thigh muscles and let go. Tighten calf and foot muscles and let go.	• Daily • 15 minutes/day with upper body only.	• Progress to 30 minutes/day for the entire program.	• Do not tighten muscles to the point of joint or muscle pain. • • Do not hold breath while tightening muscles.
Another program may involve just breathing techniques, using an audiotape. – Inhale and let your belly button rise; exhale and let it fall. – Keep shoulders low and chest quiet. – Breath slowly and gently.	• Daily • 5 minutes	• Work up to 20 minutes.	• Do not tighten the muscles around the neck, chest, and shoulders.

Flexibility Programs for Patients with Chronic Fatigue Syndrome and Fibromyalgia

- This type of program is best overseen by a physical therapist or occupational therapist.
- Flexibility exercises may be part of a comprehensive exercise program, in which case, stretching should be done preceding and following a graded aerobic exercise program.
- Flexibility programs combined with a graded aerobic exercise program are more beneficial.
- Complete the following neck and upper extremity flexibility exercises in a warm pool (i.e., 94 to 96 degrees) or warm shower, if possible.

Recommended Exercises	Frequency/ Duration	Suggested Progression	Not Recommended
1. Stand in front of a mirror. – Bring your chin slowly towards your chest. – Bring your head back, looking up to the ceiling. – Turn your head gently to the left, bringing your chin towards your left shoulder. – Do the same to the right side. – Bring your left ear down towards your left shoulder, bending your head to the left. – Do the same to the right side. 2. Hold a cane, mop handle, or stick in both hands. Lie on your back and do each of these exercises separately. – Lift the cane up overhead with both hands and move it horizontally to the left and right. – Bend and straighten your elbows while holding the cane and bring your wrists forward and backward. 3. Lie on your back and bend your knees up with feet flat on the bed or floor. – Slowly rock your knees to the left and then the right. – Slowly bring your right knee to your chest and then back. – Do the same with the left knee. – Lie on your back with knees bent and feet flat on floor. Position your feet pointing to a wall. – Slowly straighten out one leg so that it is positioned with your knee straight and leg stretched up along the wall. And hold for a few minutes. – Repeat with the other leg. 4. Stand with your hands supporting you against a wall. – Place one leg behind you with the knee straight and the heel on the floor. – Gently lean forward, bending your other knee to stretch the ankle and calf muscles. – Repeat with the other leg.	• 3 times/week or as tolerated well, without soreness or pain.	• Build up to daily. • Move slowly and gently. • Begin with a low number of repetitions, which result in no feeling of stretching, pulling, or pain.	• Do not stretch to the end of range of motion since this may lead to increased soreness and pain. • Do not bounce near end of range of motion.

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE

MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

SECTION E: INFORMATION SOURCES

Version 1.0

Information Sources

1. **Centers for Disease Control and Prevention (CDC)** http://www.cdc.gov/ncidod/diseases/cfs/

   - CFS Home Page
   - CFS Information
   1. - Treatment
   - Publications
   - Support Groups
   - CFS Definition
   - Research

2. **The Georgetown University Chronic Pain and Fatigue Research Center**
   http://www.dml.georgetown.edu/depts/pharmacology/fmscfs/

   1. Education: Fibromyalgia; Chronic Fatigue
      http://www.dml.georgetown.edu/depts/pharmacology/fmscfs/education.htm
   2. Illness Management: Evidenced-Based Treatment; Patient Care; Self-Management 101
      http://www.dml.georgetown.edu/depts/pharmacology/fmscfs/illness.htm
   3. Links http://www.dml.georgetown.edu/depts/pharmacology/fmscfs/links.htm

3. **National Institute of Allergy and Infectious Diseases**

   National Institutes of Health (NIH)

   Chronic Fatigue Syndrome: Fact Sheets and Brochures http://www.niaid.nih.gov/publications/cfs.htm

   - Chronic Fatigue Syndrome
   - CFS: NIH Consultation Report
   - Chronic Fatigue Syndrome State of the Science Conference Report, dated October 23-24, 2000
   - Chronic Fatigue Syndrome Resources for Patient

4. **Royal Australasian College of Physicians'** Clinical Practice Guidelines on the Evaluation of Prolonged Fatigue and the Diagnosis and Management of Chronic Fatigue Syndrome:
   http://www.mja.com.au/public/guides/cfs/cfs1.html

5. **American Association for Chronic Fatigue Syndrome** http://www.aacfs.org/ is a non-profit organization of research scientists, physicians, licensed medical healthcare professionals, and other individuals and institutions interested in promoting the stimulation, coordination, and exchange of ideas for CFS research and patient care, as well as periodic reviews of current clinical, research, and treatment ideas on CFS for the benefit of CFS patients and others.

6. **Fibromyalgia Network** http://www.fmnetnews.com/pages/criteria.html

   - Definitions of FM and chronic fatigue
   - Coping tips for patients

7. **National Fibromyalgia Partnership, Inc. (NFP)** http://www.fmpartnership.org/FMPartnership.htm

   The National Fibromyalgia Partnership (NFP), has been in existence since June 1992. Originally known as the Fibromyalgia Association of Northern Virginia, Inc. (FMANV) and then the Fibromyalgia Association of Greater Washington, Inc. (FMAGW), the organization has quickly evolved into a large non-profit association offering a wide array of services and activities to patients and professionals.
   Its best known publications are its *FM Monograph* and its quarterly journal, *Fibromyalgia Frontiers.*

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF **MEDICALLY UNEXPLAINED SYPMTOMS: CHRONIC PAIN AND FATIGUE**

APPENDIX 1: GUIDELINE DEVELOPMENT PROCESS

Version 1.0

Guideline Development Process

This guideline for the management of medically unexplained symptoms (MUS) of chronic pain and fatigue is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VHA, DoD and academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group that included rheumatologists, internists, nurses, family practitioners, psychologists, psychiatrists, specialists in infectious disease, epidemiology, immunology, and occupational health, as well as consultants in the field of guideline and algorithm development. Policy makers and civilian practitioners joined this group of experts from the VHA and DoD.

This guideline is a novel effort. There are very limited published guidelines for this topic. Several published articles focus on a single episode (symptom) of care or a single situation (e.g., management of low back pain). The guideline was designed to cover a broad spectrum of symptoms, and thereby provides an overview of treatment options, as well as discussion about general clinical approaches to patients with MUS.

This document will complement other existing evidence-based clinical based guidelines (CPGs) that address stress-related conditions such as depression, anxiety, tension headache, and musculoskeletal disorders. Work also continues within the VHA and the DoD to develop CPGs for management of related illnesses among armed forces personnel and veterans (i.e., Post-Deployment Health Evaluation and Management, and Post Traumatic Stress Disorder).

Development Process

The process of developing this guideline was evidence-based whenever possible. Evidence-based practice integrates clinical expertise with the best available clinical evidence derived from systematic research. Where evidence is ambiguous or conflicting, or where scientific data are lacking, the clinical experience of the multidisciplinary Working Group was used to guide the development of consensus-based recommendations. The developers incorporated the evidence and recommendations into a format that would maximally facilitate clinical decision-making (Woolf, 1992).

The search for evidence that is used to develop a guideline should be directed by well-defined clinical questions/key terms. This is an essential step, because only well-focused questions and search terms will lead to a successful search (AHCPR 1996). The review of the literature and the identification of evidence for this guideline included several steps. These steps have been defined and improved over the past three years as part of the External Peer Review Program (EPRP) clinical practice guideline development project, and are based on the experience of the VHA/DoD in developing several other clinical practice guidelines. This process followed the EPRP "Priority Model."

The process includes the following steps:

1. Four experts (members of the Working Group) each developed a summary of key practice issues, based on evidence, for the management of CFS and FM. The four drafts were then consolidated into one suggested summary of evidence by an editor.

2. Researchable questions were developed, based on the summary. The questions specified:

    - Population - characteristics of the target population
    - Intervention - diagnostic, screening, therapy, and assessment
    - Control - the type of control used for comparison
    - Outcome - the outcome measure for this intervention (morbidity, mortality, patient satisfaction, and cost)

3. A systematic and reproducible search of the literature was conducted. It focused on the best available evidence to address each key question, and ensured maximum coverage of studies at the top of the hierarchy of study types: evidence-based guidelines, meta analyses, and systematic reviews (Cochrane, EBM, EPC reports). These sources may yield a definitive answer to some questions.

   The search continued using well-known and widely available databases that were appropriate for the clinical subject. Limits on language (English), time (1997 through June 2000) and type of research (Randomized Controlled Trials (RCT)) were applied. The search included Medline and additional specialty databases, depending on the topic.

   The search strategy did not cast a wide net. Once definitive clinical studies that provided valid relevant answers to the question were identified, the search stopped. It was extended to studies/reports of lower quality (observational studies) only if there were no high quality studies.

4. The results of the search were organized and reported in tables using a reference manager and spreadsheet software. The reports included the research question, the source, study type, measures, and conclusions. At this point, additional exclusion criteria were applied. Typical exclusions were studies with physiological endpoints, or studies of populations that were not comparable to the population of interest (e.g., studies dealing with children and adolescents were excluded).

5. The assembled experts suggested numerous additional references. Copies of specific articles were provided to participants on an as-needed basis. This document includes references through June 2000. During the final editing stages, important review documents were incorporated into the document and added to the reference list.

6. The clinical experts evaluated the studies according to criteria proposed for judging the internal validity of randomized controlled trials (AHCPR, 1996) and developed evidence tables.

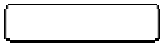
7. The evidence tables, generated by the systematic process, were then compared to the summary developed in Step 1 of the process. The summary was modified to reflect the evidence. The evidence tables and the summary guided the development of the algorithm and annotation for this guideline.

Algorithms

The guideline is presented in an algorithmic format. There are indications that this format improves data collection and clinical decision-making and helps to change patterns of resource use. A clinical algorithm is a set of rules for solving a clinical problem in a finite number of steps. It allows the clinician to follow a linear approach to critical clinical information needed at the major decision points in the disease management process, and evaluation and management strategies that include the following:

- Ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (SMDMC, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.



Rounded rectangles represent a clinical state or condition.

Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.

Rectangles represent an action in the process of care.

Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. The reference list at the end of each section includes all the sources used—directly or indirectly—in the development of the annotation text. A complete bibliography is provided at the end of the document.

The clinical experts subjected all decision points in the algorithms to simulation exercises. The algorithm was applied to hypothetical "patients" to test whether it was likely to work in a real clinical situation. Based on these tests, the necessary changes were made to ensure accurate clinical logic. Treatment must always reflect the unique clinical issues in an individual patient-clinician situation. Due to the nature of the algorithmic format, the specific assessment and treatments actions are presented in separate boxes. It is recognized, however, that clinical practice often requires a nonlinear approach and concurrent processes.

Rating the Evidence

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group reviewed the articles for relevance and graded the evidence using the rating scheme published in the U. S. Preventive Service Task Force Guide to Clinical Preventive Services, Second Edition (U.S. PSTF, 1996), displayed in Table 1. The experts themselves, after an orientation and tutorial on the evidence grading process, formulated Quality of Evidence (QE) ratings. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal health care system. The QE rating is based on experimental design and overall quality. Randomized controlled trials (RCTs) received the highest ratings (QE=I), while other well-designed studies received a lower score (QE=II-1, II-2, or II-3). Quality, consistency, reproducibility, and relevance of the studies are also considered.

Table 1. Quality of Evidence Rating Scheme (U.S. PSTF, 1996)

Quality of Evidence (QE)	
Grade	**Description**
I	Evidence is obtained from at least one properly randomized controlled trial (RCT).
II-1	Evidence is obtained from well-designed controlled trials without randomization.
II-2	Evidence is obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one center or research group.
II-3	Evidence is obtained from multiple time series, with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence.
III	Opinions of respected authorities are based on clinical experience, descriptive studies and case reports, or reports of expert committees.

The U.S. PSTF grading process suggests assigning a second grade that reflects the strength of the recommendation (SR) for each appraised study. The "Strength of Recommendation" score (i.e., the SR) reflects the effectiveness and potential harm of the recommendation as indicated by the scientific studies. Often, the most basic patient management questions and well-accepted care strategies have not been tested through RCTs (i.e., QE = I), especially when experimental design puts patients at risk. For example, no RCTs have been conducted to quantify the value of administering supplemental oxygen to a patient who presents with chest pain.

The recommendation rating (R) was formulated, using a rating scale from A to E. The specific language used to formulate each recommendation conveys the Working Group's opinion of both the clinical importance attributed to the topic and the available strength of evidence. When appropriate and necessary, expert opinion was formally derived from the Working Group to supplement or balance the conclusions reached from the scientific evidence review. Thus, the rating of R (displayed in Table 2) combines the significance of the scientific evidence and the considerations of standards of care and potential harm.

Table 2. Recommendation Rating Scheme

Recommendation (R)	
Grade	**Description**
A	A strong recommendation, based on evidence or general agreement, that a given procedure or treatment is useful/effective, always acceptable, and usually indicated.
B	A recommendation, based on evidence or general agreement, that a given procedure or treatment may be considered useful/effective.
C	A recommendation that is not well established, or for which there is conflicting evidence regarding usefulness or efficacy, but which may be made on other grounds.
D	A recommendation, based on evidence or general agreement, that a given procedure or treatment may be considered not useful/effective.
E	A strong recommendation, based on evidence or general agreement, that a given procedure or treatment is not useful/effective, or in some cases may be harmful, and should be excluded from consideration.

The members of the Working Group participated in two workshops in Washington, DC to reach a consensus about the guideline recommendations. The draft was revised by the experts through numerous conference calls to incorporate the best evidence into the final guideline. This guideline is a work in progress, and will be updated periodically or when significant new evidence is published.

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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

APPENDIX 2: ACRONYM LIST

Version 1.0

ACRONYM LIST

ACR	American College of Rheumatology
AHCPR	Agency for Health Care Policy and Research
ATP	Adenosine Triphosphate
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFS	Chronic Fatigue Syndrome
CMI	Chronic Multi-Symptom Illnesses
CPG	Clinical Practice Guideline
DLE	Dialyzable Leukocyte Extract
DoD	Department of Defense
EFA	Essential Fatty Acids
EPRP	External Peer Review Program
FM	Fibromyalgia
FMAGW	Fibromyalgia Association of Greater Washington, Inc.
FMANV	Fibromyalgia Association of Northern Virginia, Inc.
GWI	Gulf War Illness
IVIG	Immune Globulin
MAOI	Monoamine Oxidase Inhibitor
MCS	Multi-Chemical Sensitivity
MMSE	Mini-Mental State Examination
MPQ	McGill Pain Questionnaire
MSE	Mental Status Examination
MTPS	Manual Tender Point Survey
MUS	Medically Unexplained Symptoms
NADH	Nicotinamide Adenine Dinucleotide
NAMCS	National Ambulatory Medical Care Survey
NFP	National Fibromyalgia Partnership
NIH	National Institutes of Health
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OT	Occupational Therapy
PCM	Primary Care Manager
PHQ	Patient Health Questionnaire
PRN	As Needed
PT	Physical Therapy
QE	Quality of Evidence
RCT	Randomized Controlled Trial
SAMe	S-adenosylmethionine
SF	Standard Form
SMDMC	Society for Medical Decision Making Committee
R	Recommendation
SNRI	Serotonin Noradrenergic Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TP	Tender Point
U.S. PSTF	United States Preventive Services Task Force
VAS	Visual Analog Scale
VHA	Veterans Health Administration

VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

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Version 1.0

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VHA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF **MEDICALLY UNEXPLAINED SYMPTOMS: CHRONIC PAIN AND FATIGUE**

APPENDIX 4: BIBLIOGRAPHY

Version 1.0

Appendix 4:

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