Definition for CFS (Chronic Fatigue Syndrome):
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.

Four or more of the following symptoms that persist or recur 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
- Unrefreshing sleep (i.e., waking up feeling unrefreshed)
- Post-exertional malaise lasting > 24 hours

Neurocognitive difficulties common in CFS/FM
- Forgetfulness
- Memory disturbance
- Problems with concentration

Sleep disturbances common in CFS
- Unrefreshing sleep that is characterized by:
  - Difficultly falling asleep
  - Frequent awakenings
  - Abnormal limb movements (e.g., myoclonus)
  - Sleep Apnea (CFS present if sleep apnea treatment does not remedy fatigue)

patient with medically unexplained symptoms (MUS):
- Has unexplained symptoms after an appropriate assessment.
- May have been given one or more diagnoses that lack a well-defined disease explanation (e.g., idiopathic chronic fatigue, burning semen syndrome, diffuse pain syndrome, dysautonomia, hypoglycemia, multiple chemical sensitivities).

How to Characterize Symptoms

<table>
<thead>
<tr>
<th>SYMPTOM ATTRIBUTES</th>
<th>QUESTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Has the symptom existed for days, weeks, or months?</td>
</tr>
<tr>
<td></td>
<td>Has the symptom occurred only intermittently?</td>
</tr>
<tr>
<td></td>
<td>Particularly with regard to pain and fatigue, can the patient define if these symptoms occurred only two or three days per month or constantly?</td>
</tr>
<tr>
<td></td>
<td>Is the symptom seasonal?</td>
</tr>
<tr>
<td></td>
<td>Are there times of the day when the symptom is worse?</td>
</tr>
<tr>
<td>Onset</td>
<td>Can the patient recall exactly how the symptom began?</td>
</tr>
<tr>
<td></td>
<td>Were there triggering events, either physical or emotional?</td>
</tr>
<tr>
<td></td>
<td>Was the onset subtle and gradual, or dramatic and sudden?</td>
</tr>
<tr>
<td></td>
<td>Have the triggering events tended to be the same over time or are there changing patterns?</td>
</tr>
<tr>
<td>Location</td>
<td>Is the symptom localized or diffuse?</td>
</tr>
<tr>
<td></td>
<td>Can the patient localize the symptom by pointing to it?</td>
</tr>
<tr>
<td></td>
<td>If the pain is diffuse, does it involve more than one body quadrant?</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>Does the patient have any diagnosed co-existing illnesses?</td>
</tr>
<tr>
<td></td>
<td>What is the time relationship between the onset and severity of the co-existing illnesses and the symptoms of fatigue and/or pain?</td>
</tr>
<tr>
<td></td>
<td>What are the other symptoms than pain and/or fatigue?</td>
</tr>
<tr>
<td></td>
<td>Are there co-morbid diagnoses?</td>
</tr>
<tr>
<td></td>
<td>Are there changes in the patient’s weight, mood, or diet?</td>
</tr>
<tr>
<td>Previous episodes</td>
<td>If the symptoms are episodic, what is the pattern in regard to timing, intensity, triggering events, and response to any prior treatment?</td>
</tr>
<tr>
<td>Intensity and impact</td>
<td>How severe are the symptoms (use the 1 to 10 Numerical Rating Scale [NRS])?</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>Post-exertional malaise lasting &gt; 24 hours</td>
</tr>
<tr>
<td>Previous treatment and medications</td>
<td>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 changed the patient’s quality of sleep.</td>
</tr>
<tr>
<td>Past medical, surgical and psychological history</td>
<td>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.</td>
</tr>
<tr>
<td>Patient perception of symptoms</td>
<td>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 moods and fears.</td>
</tr>
</tbody>
</table>

Assessment and Diagnosis

- Determine the full guideline for appropriate assessment.
- Use past medical and surgical history to determine the presence of CFS or other conditions.
- Evaluate psychological and social factors.
- Consider initiating symptom-based treatment modalities.
- Follow up as indicated:
  - Summarize patient’s condition
  - Develop a treatment plan
  - Initiate/continue treatment
  - Consider symptomatic treatment
  - Provide patient and family education
  - Follow up with scheduled visits at frequent intervals
  - Reassess symptoms severity

Unexplained Symptoms (MUS)

VA/DOD Clinical Practice Guideline Management of Medically Unexplained Symptoms (MUS): Chronic Pain and Fatigue Pocket Guide

VA/DoD access to full guideline: http://www.healthechoices.va.gov/clinicalpractice/UnexplainedSymptomsPocketGuide.pdf

May 2002

VA/DoD Clinical Practice Guideline Management of Medically Unexplained Symptoms (MUS): Chronic Pain and Fatigue Pocket Guide

VA/DoD access to full guideline: http://www.healthechoices.va.gov/clinicalpractice/UnexplainedSymptomsPocketGuide.pdf

May 2002
Criteria for Fibromyalgia (ACR) Both criteria must be present for diagnosis:
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 (cervical 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 lower segment pain.
2. Pain in 11 of 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 point of insertion of the sternocleidomastoid muscle.
- Second rib: bilateral, at the costochondral junctions, just lateral to the costosternal joint on the upper surface.
- Lateral epicondyle: bilateral, 2 cm distal to the epicondyle.
- 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 provider would ask:
- For pain: "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?"
- 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, school or social activities, 0 being does not interfere at all and 10 being completely interferes?"

ASSOCIATED SOMATIC SYMPTOMS

<table>
<thead>
<tr>
<th>Cardiovascular System</th>
<th>Endocrine System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>Generalized fatigue</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Excessive sweating, localized or generalized</td>
</tr>
<tr>
<td>Eyes, Ears, Nose &amp; Throat</td>
<td>Hypoglycemia (e.g., sudden severe hunger, headache, sudden anxiety, tremulousness/shakiness, sweating, confusion, and unconsciousness/coma)</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>Dry skin</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
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</tbody>
</table>

Respiratory System
- Asthma
- Dyspnea
- Cough

Dietary System
- Dry mouth
- Dysphagia (e.g., "lump" in the throat, difficulty swallowing, and sore throat)
- Dyspepsia
- Irritable bowel (diarrhea or constipation)

Gastrointestinal System
- Irregular menstrual cycles
- Dysemenorrhea
- Irritable bladder (urgency of urination)

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
- Tinnitus
- Double vision
- Balance problems and dizziness
- Dry eyes or excessive tearing

BATHE TECHNIQUE
Provides a time-efficient way to address the impact of patients' symptoms on their level of function.
- Background: "What is going on in your life?"
- Affect: "How do you feel about it?"
- Trouble: "What troubles you the most about the situation?"
- Handle: "What helps you handle that?"
- Empathy: "This is a tough situation to be in. Anybody would feel (down, stressed, etc.). Your reaction makes sense to me."

For management of MUS, see Treatment Options Pocket Guide
PHARMACOLOGIC AGENTS FOR CFS/FM(1)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose Studied</th>
<th>Effective</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amitriptyline</td>
<td>Initial: 50 to 250 mg/day, maximum: 75 mg/day</td>
<td>Yes</td>
<td>Sedative and anticholinergic effects, cardiac toxicity</td>
<td>The agent is only effective in approximately 30% of patients.</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Tachyphylaxis may occur with continued treatment.</td>
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<tr>
<td>Cyclobenzaprine</td>
<td>5 to 40 mg/day</td>
<td>Yes</td>
<td>Anticholinergic and central nervous system effects</td>
<td>Tachyphylaxis may occur with continued treatment.</td>
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<tr>
<td>Fluoxetine</td>
<td>Initial: 10 mg/day, range: 20 to 40 mg/day, maximum: 60 mg/day</td>
<td>Equivocal</td>
<td>Most commonly sedative dysfunction</td>
<td></td>
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<tr>
<td>Venlafaxine</td>
<td>37.5 to 300 mg/day</td>
<td>Possibly</td>
<td>Headache, sexual dysfunction</td>
<td>The extended release form given during the day as a single morning dose or BID dosing may be more effective.</td>
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<tr>
<td>Citalopram</td>
<td>Initial: 20 mg/day, range: 20 to 40 mg/day, maximum: 60 mg/day, if indicated</td>
<td>No</td>
<td>Sexual dysfunction, nausea</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5 to 3 mg/day</td>
<td>Unknown</td>
<td>Sedative and hypnotic effects</td>
<td></td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Analgesics:</td>
<td>Tramadol**</td>
<td>50 to 800 mg/day</td>
<td>Nausea, dizziness</td>
<td>Dual mechanism of action may address altered neurotransmitters and pain signals of FM.</td>
</tr>
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<tr>
<td>NSAIDs</td>
<td>Dose range recommended by drug manufacturer</td>
<td>Equivocal</td>
<td>If risk of bleeding avoid NSAIDs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>Efficacy is less than in other rheumatic conditions where inflammation is present.</td>
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<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>Dose range recommended by drug manufacturer</td>
<td>Unknown</td>
<td>Sedative effects, nausea</td>
<td></td>
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<td></td>
<td>Tolerance or dependence may develop with long-term use.</td>
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<td></td>
<td>If used regularly, long-acting formulations are preferred.</td>
</tr>
<tr>
<td>S-adenosyl-L-</td>
<td>200 mg/day (sub), 400 mg/day (IV), 800 mg/day (oral)</td>
<td>Possibly</td>
<td>None documented</td>
<td>Drug is available in the United States orally, as an over-the-counter dietary supplement.</td>
</tr>
<tr>
<td>methionine (SAMe)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep:</td>
<td>Melatonin**</td>
<td>3 to 6 mg/day</td>
<td>Equivocal</td>
<td>May help a limited number of patients who have difficulty initiating sleep.</td>
</tr>
<tr>
<td>Other:</td>
<td>Magnesium and malic acid</td>
<td>600 to 2000 mg/day</td>
<td>Diarrhea, nausea</td>
<td></td>
</tr>
</tbody>
</table>


**Tramadol - Non-formulary medication. Available by physician request using the non-formulary process. 
**SAMe and Melatonin are nutritional supplements that VA does not provide. Are available as over the counter products.
### THERAPY INTERVENTIONS FOR CFS/FM

<table>
<thead>
<tr>
<th>Therapy Interventions</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| **Cognitive Behavioral Therapy (CBT)** | - Beneficial particularly if an adequate number of sessions are provided.  
- CBT effectiveness varies across studies and may be due to the therapist’s experience, number of sessions, and precise content delivered. 
- Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking. |
| **Aerobic Exercise** | - Aerobic exercise that begins at a low level and increases very slowly in intensity is effective. 
- If pain is a significant symptom, lower impact exercises may be more beneficial. 
- Aggressive exercise therapy is often poorly tolerated and may be harmful. |
| **Anti-Depressant Therapy** | - 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. |
| **Analgesic Therapy** | - The following classes of medications have been tried to alleviate the varied associated types of pain: 
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) and tramadol may be useful for treating certain associated pain symptoms (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. |
| **Benzodiazepine and Non-Benzodiazepine Sedative-Hypnotics** | - In general, behavioral strategies should precede the use of pharmacologic agents for sleep disturbances. 
- May be prescribed for short-term treatment of sleep disturbances, but are not recommended and may be harmful for treatment of chronic sleep disturbances. 
- Are of limited utility for the cardinal symptoms of CFS/FM. |
| **Relaxation Techniques** | - Relaxation and flexibility combined with graded exercise is beneficial. |
| **Other Non-Pharmacologic Therapies** | - The following types of non-pharmacologic therapies are 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 
  - Water-based exercise  
- Hypnosis 
- Myofascial release 
- Massage therapy 
- Chiropractic manipulation 
- Yoga |

### NON-RECOMMENDED/HARMFUL THERAPY INTERVENTIONS FOR CFS

- Prolonged bed rest may be harmful in managing patients with CFS/FM.
- Does not appear to be beneficial. Studies have been performed to examine the role of low dose (5 to 10 mg/day of hydrocortisone), replacement (20 to 35 mg/day of hydrocortisone), and high dose corticosteroids in reducing the symptoms: 
  - 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 10 mg compared with 5 mg/day of hydrocortisone. 
  - Replacement 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.

### POSSIBLE THERAPIES FOR CFS/FM

- **Fluorinef Treatment of CFS Patients with Neurally Mediated Hypotension** 
  - Florinef (fludrocortisone) is not recommended in treating CFS patients with neurally mediated hypotension. 
  - Uncontrolled studies have shown that use of salt loading with or without beta-blockers may be beneficial in producing short term improvement in symptoms of fatigue & lightheadedness. 
  - The possible benefits of intramuscular magnesium sulfate injections must be confirmed since the only follow-up evaluation of this treatment was at six weeks. 
  - Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking.

- **Anti-Allergic Medication Therapy for CFS** 
  - Current data do not indicate the use of anti-allergic drugs. 
  - If patients report allergy symptoms, non-sedating antihistamines can be tried, but data on added benefit was not noted in using 10 mg compared with 5 mg/day of hydrocortisone.

- **Immunotherapy for CFS** 
  - IVIG, dialyzable leukocyte extract (DLE) transfer factor, alpha interferon, and Poly(I) Poly(C) “Ampligen” cannot be recommended.

- **Magnesium Therapy for CFS/FM** 
  - The following types of non-pharmacologic therapies are 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: 
  - Aggressive exercise therapy is often poorly tolerated and may be harmful. 
  - Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking. 
  - The benefit was not evident after 4 weeks. 
  - No added benefit was noted in using 10 mg compared with 5 mg/day of hydrocortisone. 
  - Replacement 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.

- **Anti-Viral Medication Therapy for CFS** 
  - Current data do not indicate the use of anti-viral drugs. 
  - Other drugs (e.g., valacyclovir and ganciclovir) have been evaluated in uncontrolled and inconclusive studies.

- **Mineralocorticoids for CFS/FM** 
  - The following types of non-pharmacologic therapies are 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: 
  - Aggressive exercise therapy is often poorly tolerated and may be harmful. 
  - Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking.

- **Fludrocortisone Treatment of CFS Patients with Neurally Mediated Hypotension** 
  - Fluorinef (fludrocortisone) is not recommended in treating CFS patients with neurally mediated hypotension.

- **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.**

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- **Co-existing depression is commonly present in patients suffering from CFS or FM. These patients may benefit from antidepressant treatment.**

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) and tramadol may be useful for treating certain associated pain symptoms (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.**

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- **Are of limited utility for the cardinal symptoms of CFS/FM.**

- **Relaxation and flexibility combined with graded exercise is beneficial.**

- **The following types of non-pharmacologic therapies are 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**

- **Water-based exercise**

- **Hypnosis**

- **Myofascial release**

- **Massage therapy**

- **Chiropractic manipulation**

- **Yoga**

- **IVIG, dialyzable leukocyte extract (DLE) transfer factor, alpha interferon, and Poly(I) Poly(C) “Ampligen” cannot be recommended.**

For assessment and diagnosis of MUS, see Assessment & Diagnosis Pocket Guide.