

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

<b>PHARMACOLOGIC AGENTS FOR CFS/FM<sup>(1)</sup></b>				
Agent	Dose Studied	Effective	Adverse Effects	Comments
<b>Anti-depressants:</b> Amitriptyline	Initial: 10 to 25 mg/day Maximum: 75 mg/day	Yes	<ul style="list-style-type: none"> <li>■ Sedative and anticholinergic effects</li> <li>■ Cardiac toxicity</li> </ul>	<ul style="list-style-type: none"> <li>■ The agent is only effective in approximately 30% of patients.</li> <li>■ Tachyphylaxis can occur with continued treatment.</li> <li>■ Anticholinergic side effects may limit use.</li> <li>■ Not recommended for use in the elderly.</li> </ul>
Cyclobenzaprine	5 to 40 mg/day	Yes	<ul style="list-style-type: none"> <li>■ Anticholinergic and central nervous system effect</li> </ul>	<ul style="list-style-type: none"> <li>■ Side effects may limit use.</li> <li>■ Tachyphylaxis can occur with continued treatment.</li> </ul>
Fluoxetine	Initial: 10 mg/day Range: 20 to 40 mg/day Maximum: 60 mg/day	Equivocal	<ul style="list-style-type: none"> <li>■ Most commonly sexual dysfunction</li> </ul>	
Venlafaxine	37.5 to 300 mg/day	Possibly	<ul style="list-style-type: none"> <li>■ Headache</li> <li>■ Sexual dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>■ The extended release form given during the day as a single morning dose or BID dosing may be most effective.</li> </ul>
Citalopram	Initial: 20 mg/day Range: 20 to 40 mg/day Maximum: 40 mg/day, if indicated	No	<ul style="list-style-type: none"> <li>■ Sexual dysfunction</li> <li>■ Nausea</li> </ul>	
Alprazolam	0.5 to 3.0 mg/day	Unknown	<ul style="list-style-type: none"> <li>■ Sedative and hypnotic effects</li> </ul>	
<b>Analgesics:</b> Tramadol*	50 to 400 mg/day	Yes	<ul style="list-style-type: none"> <li>■ Nausea</li> <li>■ Dizziness</li> </ul>	<ul style="list-style-type: none"> <li>■ Dual mechanism of action may address altered neurotransmitters and pain signals of FM.</li> </ul>
NSAIDs	Dose range recommended by drug manufacturer	Equivocal	<ul style="list-style-type: none"> <li>■ If risk of bleeding avoid NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>■ Intolerance is common</li> <li>■ Efficacy is less than in other rheumatic conditions where inflammation is present.</li> </ul>
Opioids	Dose range recommended by drug manufacturer	Unknown	<ul style="list-style-type: none"> <li>■ Sedative effects</li> <li>■ Nausea</li> </ul>	<ul style="list-style-type: none"> <li>■ There is no clinical evidence to show efficacy.</li> <li>■ Tolerance or dependence may develop with long-term use.</li> <li>■ If used regularly, long-acting formulations are preferred.</li> </ul>
S-adenosyl-L-methionine (SAME)**	<ul style="list-style-type: none"> <li>■ 200 mg/day subq</li> <li>■ 400 mg/day IV</li> <li>■ 800 mg/day orally</li> </ul>	Possibly	<ul style="list-style-type: none"> <li>■ None documented</li> </ul>	<ul style="list-style-type: none"> <li>■ Drug is available in the United States orally, as an over-the-counter dietary supplement.</li> </ul>
<b>Sleep:</b> Melatonin**	3 to 6 mg/day	Equivocal	—	<ul style="list-style-type: none"> <li>■ May help a limited number of patients who have difficulty initiating sleep.</li> </ul>
<b>Other:</b> Magnesium and malic acid	600 to 2000 mg/day	Unknown	<ul style="list-style-type: none"> <li>■ Diarrhea</li> <li>■ Nausea</li> </ul>	

<sup>(1)</sup>Adapted from Leventhal LJ. Management of fibromyalgia. Ann Int Med 1999; 131:850-8. Other guidance regarding pharmacotherapy for CFS can be found in Reid S, et al. Chronic Fatigue Syndrome. BMJ 2000; 320(7230):292-96.

\*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.

### TREATMENT OPTIONS

R=Recommendation A=Randomized Control Trial B=Clinical Studies C=No Benefit or Harm D=Harmful

<b>FIBROMYALGIA (FM) THERAPY INTERVENTIONS</b>				
R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A		<ul style="list-style-type: none"> <li>■ Cognitive Behavioral Therapy (CBT)</li> <li>■ Graded Aerobic Exercise</li> <li>■ Antidepressant (TCA)</li> </ul>		
B		<ul style="list-style-type: none"> <li>■ Tramadol</li> <li>■ SAME</li> <li>■ SSRI (R=B/C)</li> <li>■ NSAIDs (R=B/C)</li> </ul>	<ul style="list-style-type: none"> <li>■ Acupuncture</li> <li>■ Biofeedback</li> <li>■ Trigger point injection</li> <li>■ Stretching</li> </ul>	<ul style="list-style-type: none"> <li>■ Alprazolam</li> </ul>
C		<ul style="list-style-type: none"> <li>■ Sleep education</li> <li>■ Other antidepressants (non-SSRI, non-TCA)</li> </ul>	<ul style="list-style-type: none"> <li>■ Massage therapy</li> <li>■ Relaxation therapy</li> <li>■ Myofascial release</li> <li>■ Spinal manipulation</li> <li>■ Hypnotherapy</li> <li>■ Magnesium</li> </ul>	<ul style="list-style-type: none"> <li>■ Antiviral</li> <li>■ Antifungal</li> <li>■ Antibiotics</li> </ul>
D				<ul style="list-style-type: none"> <li>■ Bed rest</li> </ul>

<b>CHRONIC FATIGUE SYNDROME (CFS) THERAPY INTERVENTIONS</b>				
R	Maximum Benefit	Some Benefit	Possible Benefit	Possibly Harmful
A		<ul style="list-style-type: none"> <li>■ Cognitive Behavioral Therapy (CBT)</li> <li>■ Graded Aerobic Exercise</li> </ul>		
B		<ul style="list-style-type: none"> <li>■ MAOI</li> <li>■ NADH</li> </ul>		
C		<ul style="list-style-type: none"> <li>■ Sleep education</li> <li>■ SSRI</li> <li>■ Other antidepressants (non-SSRI, non-TCA)</li> </ul>	<ul style="list-style-type: none"> <li>■ Relaxation</li> <li>■ Flexibility exercise</li> <li>■ Essential fatty acids</li> <li>■ Magnesium</li> <li>■ Low-dose, short term corticosteroid (R=B/C)</li> </ul>	<ul style="list-style-type: none"> <li>■ Florinef, alone</li> </ul>
D				<ul style="list-style-type: none"> <li>■ Bed rest</li> <li>■ Corticosteroid (High-dose or Replacement)</li> <li>■ Anti-viral</li> <li>■ Anti-fungal</li> <li>■ Immune therapy</li> </ul>

VA access to full guideline: <http://www.oqp.med.va.gov/cpg/cpg.htm>

DoD access to full guideline: <http://www.cs.amedd.army.mil/Qmc>

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THERAPY INTERVENTIONS FOR CFS/FM	RECOMMENDATIONS										
<b>Cognitive Behavioral Therapy (CBT)</b>	<ul style="list-style-type: none"> <li>■ Beneficial particularly if an adequate number of sessions are provided.</li> <li>■ CBT effectiveness varies across studies and may be due to the therapist's experience, number of sessions, and precise content delivered.</li> <li>■ Evidence for the efficacy of other types of psychotherapy or generic counseling is lacking.</li> </ul>										
<b>Aerobic Exercise</b>	<ul style="list-style-type: none"> <li>■ Aerobic exercise that begins at a low level and increases very slowly in intensity is effective.</li> <li>■ If pain is a significant symptom, lower impact exercises may be more beneficial.</li> <li>■ Aggressive exercise therapy is often poorly tolerated and may be harmful.</li> </ul>										
<b>Anti-Depressant Therapy</b>	<ul style="list-style-type: none"> <li>■ Tricyclic compounds, such as amitriptyline and cyclobenzaprine, have been demonstrated to be effective in treating FM and associated conditions.</li> <li>■ Tricyclic antidepressants (TCAs) may be useful for patients with CFS who have prominent pain and/or depression.</li> <li>■ Monoamine oxidase inhibitors (MAOIs) are effective for patients with CFS; however, dietary restrictions and the risk of hypertensive crisis limit their clinical utility.</li> <li>■ Selective serotonin reuptake inhibitors (SSRIs) have been found to be of potential, but variable, use in treating subpopulations of patients with FM.</li> <li>■ Co-existing depression is commonly present in patients suffering from CFS or FM. These patients may benefit from antidepressant treatment.</li> </ul>										
<b>Analgesic Therapy</b>	<ul style="list-style-type: none"> <li>■ The following classes of medications have been tried to alleviate the varied associated types of pain:                             <ul style="list-style-type: none"> <li>○ 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.</li> <li>○ 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.</li> </ul> </li> </ul>										
<b>Benzodiazepine and Non-Benzodiazepine Sedative-Hypnotics</b>	<ul style="list-style-type: none"> <li>■ In general, behavioral strategies should precede the use of pharmacologic agents for sleep disturbances.</li> <li>■ May be prescribed for short-term treatment of sleep disturbances, but are not recommended and may be harmful for treatment of chronic sleep disturbances.</li> <li>■ Are of limited utility for the cardinal symptoms of CFS/FM.</li> </ul>										
<b>Relaxation Techniques</b>	<ul style="list-style-type: none"> <li>■ Relaxation and flexibility combined with graded exercise is beneficial.</li> </ul>										
<b>Other Non-Pharmacologic Therapies</b>	<ul style="list-style-type: none"> <li>■ 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:                             <table border="0" style="width: 100%; margin-left: 20px;"> <tr> <td style="width: 50%;">○ Acupuncture</td> <td style="width: 50%;">○ Hypnosis</td> </tr> <tr> <td>○ Tender point injection</td> <td>○ Myofascial release</td> </tr> <tr> <td>○ Stretching</td> <td>○ Massage therapy</td> </tr> <tr> <td>○ Biofeedback</td> <td>○ Chiropractic manipulation</td> </tr> <tr> <td>○ Water-based exercise</td> <td>○ Yoga</td> </tr> </table> </li> </ul>	○ Acupuncture	○ Hypnosis	○ Tender point injection	○ Myofascial release	○ Stretching	○ Massage therapy	○ Biofeedback	○ Chiropractic manipulation	○ Water-based exercise	○ Yoga
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NON-RECOMMENDED/HARMFUL THERAPY INTERVENTIONS FOR CFS
<b>Bed Rest</b> <ul style="list-style-type: none"> <li>• Prolonged bed rest may be harmful in managing patients with CFS/FM.</li> </ul>
<b>Cortisol Treatment for CFS</b> <ul style="list-style-type: none"> <li>• Does not appear to be beneficial.</li> <li>• 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.                             <ul style="list-style-type: none"> <li>– While some benefit was noted in patients treated with low dose hydrocortisone, the benefit was not evident after 4 weeks.</li> <li>– No added benefit was noted in using 10 mg compared with 5 mg/day of hydrocortisone.</li> <li>– 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.</li> <li>– High dose corticosteroids do not appear to be beneficial and should be avoided.</li> </ul> </li> </ul>
<b>Immunotherapy for CFS</b> <ul style="list-style-type: none"> <li>• IVIG, dialyzable leukocyte extract (DLE) transfer factor, alpha interferon, and Poly(I) Poly (C<sub>12</sub>U) Ampligen™ cannot be recommended.</li> </ul>
<b>Anti-Viral Medication Therapy for CFS</b> <ul style="list-style-type: none"> <li>• Current data do not indicate the use of anti-viral drugs.                             <ul style="list-style-type: none"> <li>- Acyclovir and amantadine have been studied in controlled trials.</li> <li>- Other drugs (e.g., valacyclovir and ganciclovir) have been evaluated in uncontrolled and inconclusive studies.</li> </ul> </li> </ul>
POSSIBLE THERAPIES FOR CFS/FM
<b>Florinef Treatment of CFS Patients with Neurally Mediated Hypotension</b> <ul style="list-style-type: none"> <li>• Fludrocortisone is not recommended in treating CFS patients with neurally mediated hypotension.</li> <li>• 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 &amp; lightheadedness</li> </ul>
<b>Anti-Allergic Medication Therapy for CFS</b> <ul style="list-style-type: none"> <li>• Current data do not indicate the use of anti-allergic drugs.</li> <li>• If patients report allergy symptoms, non-sedating antihistamines can be tried, but data is not available for treatment of CFS/FM symptoms.</li> </ul>
<b>Magnesium Therapy for CFS/FM</b> <ul style="list-style-type: none"> <li>• 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.</li> </ul>
<b>Fatty Acid Therapy for CFS</b> <ul style="list-style-type: none"> <li>• Since clinical trial results conflict, further data are needed to clarify this issue.</li> <li>• Long-term results of EFA therapy are unknown.</li> </ul>
<b>Nicotinamide Adenine Dinucleotide (NADH) Therapy for CFS</b> <ul style="list-style-type: none"> <li>• Since this is a non-prescription drug, only limited data are available.</li> </ul>

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