VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC MULTISYMPTOM ILLNESS

Department of Veterans Affairs

Department of Defense

Clinician Summary

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendations.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil or by contacting your regional TRICARE Managed Care Support Contractor.

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Introduction

Chronic multisymptom illness (CMI) and medically unexplained symptoms are a critical health care issue for the Veterans Health Administration (VHA) and the Department of Defense (DoD). CMI imposes a significant burden of illness, disability, and decreased quality of life on a number of military Service Members, families, and Veterans. Therefore, diagnosis and effective therapy and related management of CMI have great importance for Veterans Affairs (VA) and DoD. After every modern military combat deployment, some Service Members have reported illnesses characterized by multiple chronic symptoms upon their return. [3] Systematic studies have demonstrated that CMI is similar to many historical postwar illnesses. [4] Among these, population-based studies have consistently demonstrated a higher prevalence and severity of symptom reporting in Gulf War Veterans than in non-deployed Veterans or other control groups. [5-7] While these symptom-based illnesses have been described after military deployments, the experience of CMI is not unique to those who served in the military, to any specific combat era, or to those who were deployed to either combat or non-combat environments.

Although the character of medically unexplained symptoms appears similar after modern wars, at this time there is insufficient evidence to determine if the excess symptoms reported after these deployments share a common precipitating factor or pathophysiology. The authors of this CPG defined a working case definition of chronic multisymptom illness with the goal of enhancing the health care and ultimately improving the health status for all the populations cared for in VA and DoD.

In developing this VA/DoD clinical practice guideline (CPG), the Work Group reviewed randomized clinical trials (RCTs) and systematic reviews on treatments for the symptoms commonly associated with CMI, including studies on related conditions with overlapping symptoms such as fibromyalgia, CFS, and IBS. It is likely that treatments found to be effective for one of these related or comorbid conditions are beneficial for some patients experiencing CMI; however, the generalizability of the findings of the studies of these conditions to CMI has not been definitely established.

While other chronic conditions were not specifically included in the literature review during the development of this CPG, the CMI guideline may be relevant to chronic conditions that manifest with multiple chronic symptoms and functional limitations. Chronic overlapping physical and cognitive symptoms are sometimes attributed to specific events or conditions such as mild traumatic brain injury (mTBI) or post-traumatic stress disorder (PTSD), when instead they may reflect contributions from multiple factors, and thus may be amenable to the recommendations contained in this CPG. Though not specifically studied, this CPG is likely to be a helpful adjunct to the current VA/DoD guidelines for mTBI, PTSD, and major depressive disorder (MDD), especially when patients report multiple chronic symptoms not readily explained by these or other health conditions.

This CPG is intended to provide primary care clinicians with a framework by which to evaluate the individual needs and preferences of patients who may be experiencing chronic multisymptom illness or

medically unexplained symptoms, leading to improved clinical outcomes. It is also likely to be used by other health care professionals, including specialty care providers.

The overall expected outcome of successful implementation of this guideline is to:

- Formulate an efficient and effective assessment of the patient's condition
- Optimize the use of therapy to reduce symptoms and enhance functionality
- Minimize preventable complications and morbidity
- Emphasize the use of personalized, proactive, patient-driven care

Working Definition of Chronic Multisymptom Illness

Chronic multisymptom illness (CMI) is a label given to a diverse set of disorders including, but not limited to, chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS). CMI encompasses military-specific medically unexplained illnesses, such as Gulf War Illness, Gulf War Syndrome, or post-deployment syndrome. The definition of CMI also includes patients without accepted labels, defined by generally accepted criteria, who exhibit persistent or frequently recurring symptoms negatively impacting daily function for a minimum of six months duration from two or more of the following six categories: fatigue, mood and cognition, musculoskeletal (including pain), respiratory, gastrointestinal and neurologic (including headache). Patients with symptoms lasting less than six months, or who experience only one of the listed symptoms, or with a clearly organic-based disease that explains all/most of their symptoms were not covered in this report. Further consideration for inclusion should be given to symptoms affecting the following systems: genitourinary, cardiopulmonary, and sleep.

Scope of this CPG

Individuals who meet the above descriptive criteria and also meet established criteria for specific symptom-based syndromes (e.g., fibromyalgia, IBS, CFS) may derive benefit from this CPG. The CPG provides information on potential risk factors for CMI, diagnostic technologies that may be used for screening and assessment of CMI, management of CMI, and pharmacologic and non-pharmacologic therapies for the treatment of CMI. Risk factors that may be associated with predisposing, precipitating, and perpetuating CMI include medical (e.g., obesity), psychological (e.g., abuse history), and occupational/environmental (e.g., chemical exposure). The categories of diagnostic technologies considered under this CPG include biomarkers (biological markers and neuroimaging studies), neuropsychological test batteries, and sleep studies.

Some of the management approaches considered include team-based approaches, core competencies of the treatment team, patient-provider communication styles, the role of occupational and other rehabilitative services, behavioral health services, and patient follow-up practices.

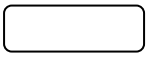
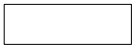
Pharmacologic therapies include, among others, antibiotics, antidepressants, and pain medications, while non-pharmacologic therapies included psychological (i.e., hypnosis), physiological (i.e., exercise) and complementary and alternative treatments (i.e., acupuncture, biofeedback, and nutritional supplements).

Algorithm Format

This clinical practice guideline includes an algorithm, which is designed to maximally facilitate clinical decision-making for the management CMI. The use of the algorithm format was chosen based on the understanding that such a format can inform diagnostic and therapeutic decision-making, and has the potential to change patterns of resource use. It allows the provider to follow a systematic approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Decisions to be considered
- Actions to be taken

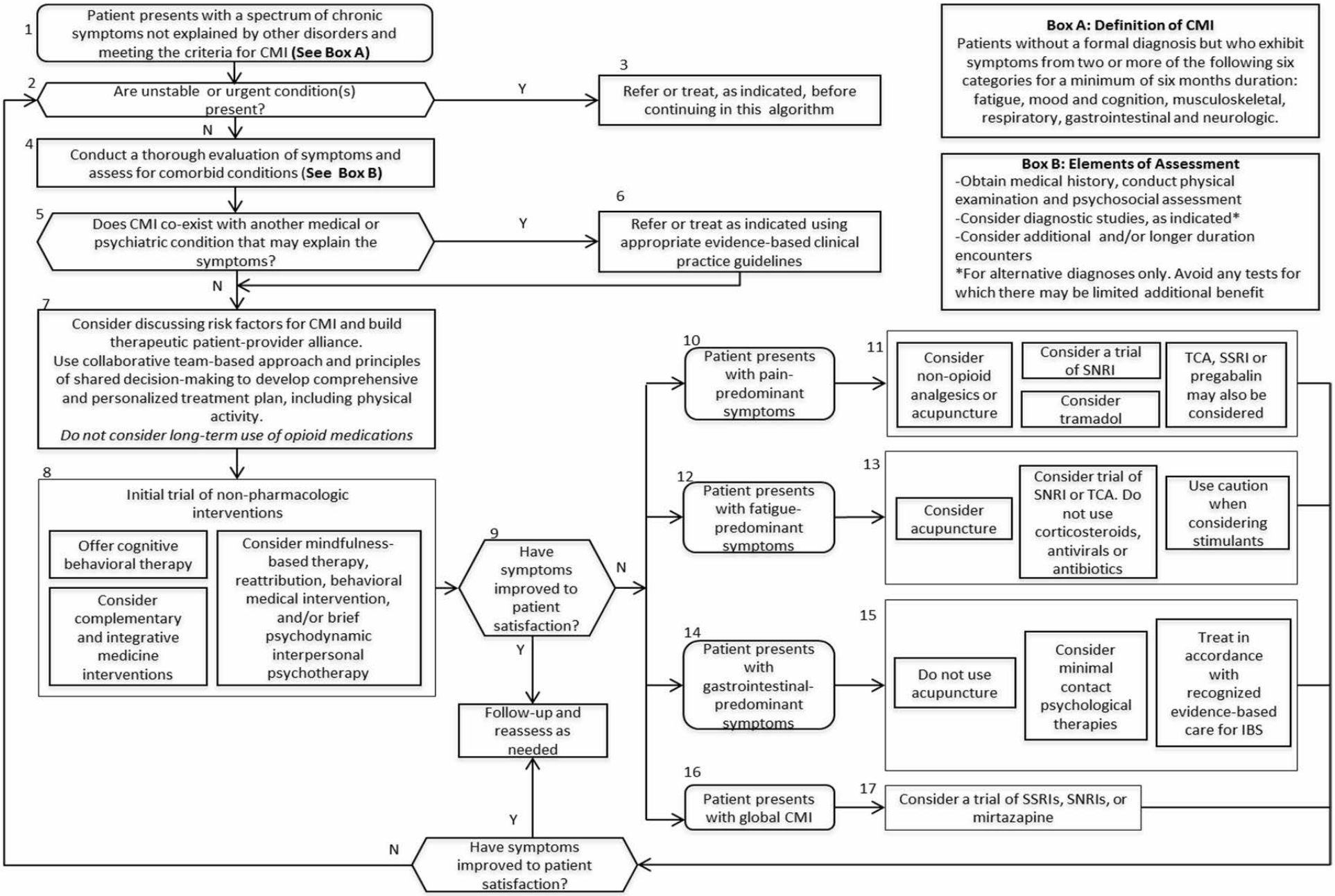
A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm, and arrows connect the numbered boxes indicating the order in which the steps should be followed. [10]

	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.
	Rectangles represent an action in the process of care.
	Ovals represent a link to another section within the guideline.

This CPG 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. This CPG is based on information available at the date of

publication, and is intended to provide a general guide to best practices. 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 of an individual patient.

Algorithm



Recommendations

#	Recommendation	Strength of Recommendation
	Diagnosis and Evaluation	
1	The guideline panel recommends that all patients receive a thorough evaluation of symptoms based on clinical judgment.	Strong For
2	This guideline panel recommends against the use of any test for which there may be limited additional benefit to confirm the diagnosis of CMI. Testing for rare exposures or biologic effects should only be done in the presence of supportive history or physical findings.	Strong Against
3	This guideline panel suggests discussing risk factors using principles of health risk communication within a therapeutic patient-provider alliance for those patients who wish to further understand factors that could contribute to their condition.	Weak For
	Management Strategies	
4	The guideline panel recommends using a collaborative, team-based approach, including a behavioral health specialist, for the primary care management of patients with CMI.	Strong For
5	The guideline panel recommends that the healthcare team use shared-decision making principles to develop a comprehensive and personalized treatment plan in the care and management of patients with CMI.	Strong For
6	The guideline panel suggests that all providers involved in the care of patients with CMI enhance their knowledge of the following critical domains: a. Communication skills (e.g., active listening, risk communication/perception) b. Empathy skills c. Working with interdisciplinary teams d. The biopsychosocial model e. Risk factors for CMI and analogous conditions f. Military cultural competency g. Deployment related exposures	Weak For
	Therapeutic Interventions for Global CMI	
7	The guideline panel suggests incorporating appropriate elements of physical activity as part of a comprehensive and integrated treatment plan for patients with CMI.	Strong For
8	The guideline panel recommends offering cognitive behavioral therapy, delivered by trained professionals, for patients with CMI.	Strong For
9	The guideline panel recommends considering mindfulness-based therapy, reattribution, behavioral medical intervention, and/or brief psychodynamic interpersonal psychotherapy, delivered by trained professionals, for patients with CMI.	Weak For
10	The guideline panel recommends considering complementary and integrated medicine interventions as a component of personalized, proactive patient-driven care in the management of patients with CMI.	Weak For
11	The guideline panel suggests considering a trial of selective serotonin reuptake inhibitor (SSRI), serotonin–norepinephrine reuptake inhibitor (SNRI), or mirtazapine for the treatment of clinical symptoms of CMI.	Weak For
12	The guideline panel suggests against the use of doxycycline for the treatment of patients with clinical symptoms of CMI.	Weak Against
13	The guideline panel recommends against the long-term use of opioid medications for	Strong Against

#	Recommendation	Strength of Recommendation
	the management of patients with CMI	
	Therapeutic Interventions for Pain-Predominant CMI	
14	The guideline panel suggests considering acupuncture as part of the management of patients with pain-predominant symptoms of CMI.	Weak For
15	The guideline panel suggests considering non-steroidal anti-inflammatory drugs (NSAID) for treating certain peripheral pain symptoms associated with CMI, though they do not necessarily lead to global beneficial effect.	Weak For
16	The guideline panel suggests considering tramadol for treating certain pain symptoms associated with CMI that fail to respond to other non-opioid analgesic medications or non-pharmacologic approaches.	Weak For
17	The guideline panel suggests a trial of serotonin–norepinephrine reuptake inhibitor (SNRI) for the treatment of patients with clinical symptoms of pain-predominant CMI.	Weak For
18	The guideline panel suggests considering a trial of tricyclic antidepressants (TCA), selective serotonin reuptake inhibitor (SSRI), or pregabalin (PGB) for the treatment of patients with clinical symptoms of pain-predominant CMI.	Weak For
	Therapeutic Interventions for Fatigue-Predominant CMI	
19	The guideline panel recommends considering acupuncture as part of the management of patients with fatigue-predominant symptoms of CMI.	Weak For
20	The guideline panel suggests considering a trial of SNRI or tricyclic antidepressants (TCA) for patients with clinical symptoms of fatigue-predominant CMI.	Weak For
21	The guideline panel suggests against the use of pharmacologic agents for sleep disturbances in CMI.	Weak Against
22	The guideline panel suggests against the use of stimulants for the treatment of fatigue-predominant CMI.	Weak Against
23	The guideline panel recommends against the empiric use of antivirals or antibiotics for the treatment of fatigue-predominant CMI.	Strong Against
24	The guideline panel recommends against the use of corticosteroids for the treatment of fatigue-predominant CMI.	Strong Against
25	The guideline panel recommends against the use of immunotherapy for the treatment of the symptoms of fatigue predominant CMI.	Strong Against
	Therapeutic Interventions for Gastrointestinal-Predominant CMI	
26	The guideline panel suggests treating patients with CMI and predominantly gastrointestinal symptoms, in accordance with recognized evidence-based care for IBS.	Weak For
27	The guideline panel recommends considering minimal contact psychological therapies for treatment of gastrointestinal-predominant CMI.	Weak For
28	The guideline panel suggests against the use of acupuncture for treatment of patients with gastrointestinal-predominant symptoms of CMI.	Weak Against

Pharmacologic Agents for Chronic Multisymptom Illness

Refer to current Product Information for additional prescribing information.

Note: References below refer to the full evidence-based clinical practice guideline for management of CMI, which can be found at: http://www.healthquality.va.gov/

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Escitalopram [1]	10–20 mg/d; titrate up from 10 mg/d to 20 mg/d after 1 month. Adequate Trial: 12 weeks	Global	• Headache • Nausea • Nasopharyngitis • Insomnia • Sexual dysfunction • Suicidal ideation • QTc prolongation • Serotonin syndrome	• Improved somatic symptom severity, depression, pain, anxiety. • Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Citalopram (20–40 mg/d) may be a reasonable substitute for escitalopram.
Fluoxetine [2-6]	10–80 mg/d; titrate up from 10 mg/d by 10 mg/d at intervals of at least 1 week. Adequate trial: 6-12 weeks Hepatic impairment: Use lower doses or less frequent dosing	Global* Pain	• Nausea • Headache • Insomnia • Nervousness • Anxiety • Somnolence • Asthenia • Diarrhea • Anorexia • Suicidal ideation • Serotonin syndrome • QTc prolongation	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated within 5 weeks of discontinuing fluoxetine • Contraindicated with pimozide or thioridazine; avoid with other QTc prolonging drugs • Consider long elimination half-life during dosage titration and drug discontinuation
Sertraline [2]	25–350 mg/d; titrate up from 25 mg/d by 50 mg/d at intervals of at least 1 week Adequate Trial: 12 weeks	Global*	• Nausea • Somnolence • Dry mouth • Constipation • Dizziness • Sexual dysfunction • Suicidal ideation • Serotonin syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Conditional risk of QTc prolongation†

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Venlafaxine [7] Venlafaxine Extended-release [8]	37.5–225 mg/d; titrate up from 37.5 mg/d by 37.5–75 mg/d at intervals of at least 1 week Adequate Trial: 12 weeks 75–225 mg/d; titrate up by 75 mg/d at intervals of at least 1 week Adequate Trial: 12 weeks	Global*	• Nausea • Headache • Fatigue • Dizziness • Constipation • Tremor • Dry mouth • Increased blood pressure • Sexual dysfunction • Suicidal ideation • Serotonin syndrome • QTc prolongation • Discontinuation syndrome	• Improved pain, anxiety, quality of life but not somatic symptom severity • Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Taper dose slowly when discontinuing therapy to avoid withdrawal symptoms
Mirtazapine [7]	15–60 mg/d; titrate up from 15 mg/d by 15 mg/d at intervals of at least 1–2 weeks Maximum: 60 mg/d Adequate Trial: 12 weeks	Global*	• Somnolence • Dizziness • Dry mouth • Increased appetite • Weight gain • Constipation • Increased cholesterol • Neutropenia • Suicidal ideation • Serotonin syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • High incidence of somnolence (>50%) • Low doses may be useful for insomnia • Conditional risk of QTc prolongation† • Infrequent sexual dysfunction
Duloxetine [9]	60–120 mg/d; titrate up from 20–30 mg by 20–30 mg/d over 2 weeks Adequate trial: 12 weeks Do not ordinarily use in patients with hepatic insufficiency. Not recommended in patients with severe renal impairment (CrCl <30 ml/min)	Pain Fatigue	• Nausea • Headache • Dry mouth • Fatigue • Somnolence • Constipation • Insomnia • Urinary retention • Serotonin syndrome • Suicidal ideation • Hepatotoxicity	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated within 5 days of discontinuing duloxetine • Doses above 60 mg/d have no evidence of additional benefit and increase the risk of adverse events
Milnacipran [9]	100 mg/d (100-200mg/d) in 2 divided doses; titrate up from 12.5 mg by 12.5–50 mg/d per week over 3–	Pain Fatigue	• Nausea • Headache • Constipation • Insomnia • Dizziness	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
	4 weeks Adequate trial: 12 weeks Do not ordinarily use in patients with substantial alcohol use or chronic liver disease. Not recommended in patients with end-stage renal disease. Dose in patients with severe renal impairment (5–29 ml/min): 50–100 mg/d in 2 divided doses		• Hot flush • Serotonin syndrome • Suicidal ideation • Increased blood pressure and heart rate • Urinary retention • Hepatotoxicity • Withdrawal symptoms	within 5 days of discontinuing milnacipran • Contraindicated in patients with uncontrolled narrow-angle glaucoma.
Amitriptyline [6,10]	10-50 mg daily Adequate trial: 6-8 weeks Use lower doses in the elderly	Pain Fatigue	• Dry mouth • Fatigue • Sedation • Vasovagal reaction • Orthostatic hypotension • Constipation • Urinary retention • QTc prolongation; conduction abnormalities • Suicidal ideation	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Contraindicated with cisapride • Avoid use with QTc prolonging drugs, anticholinergics • Use with caution in patients with cardio- or cerebrovascular disease
Pregabalin [6,10]	300-450 mg/d divided BID-TID, starting at 150 mg/d and increasing by 150 mg/d every week Adequate trial: 8 weeks Adjust dose based on renal function	Pain	• Dizziness • Somnolence • Headache • Weight gain • Angioedema • Suicidal ideation • Peripheral edema • Withdrawal symptoms • Blurred vision; visual field changes	• Dose of 600 mg/d was studied but showed no additional benefit and increased the risk of adverse events
Paroxetine controlled release [6,11]	62.5 mg/d (12.5–75 mg/d), starting at 25 mg/d and increasing by 12.5 mg/d at intervals of at least 1 week.	Pain	• Drowsiness • Nausea • Insomnia • Headache • Ejaculatory disorder • Dizziness	• Also available in immediate-release tablets (20–60 mg/d) • Contraindicated with MAOIs and within 14 days of starting or stopping

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
	Adequate trial: 12 weeks Severe renal impairment (CrCl <30 ml/min) or severe hepatic impairment: Use lower starting dose. Elderly: 12.5–50 mg/d		• Decreased libido • Diaphoresis • Weakness • Constipation • Diarrhea • Dry mouth • Akathisia • Suicidal ideation • Serotonin syndrome	MAOIs • Most sedating SSRI • Potent anticholinergic effects
Citalopram [6,12,13]	20-40 mg/d; titrate up at intervals of at least 1 week Adequate trial: 8-16 weeks Elderly (>60 y) and Hepatic Impairment: Max 20 mg/d	Pain	• Nausea • Dry mouth • Somnolence • Insomnia • Hyperhidrosis • Suicidal ideation • Serotonin syndrome • QTc prolongation	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Avoid using citalopram with other QTc prolonging drugs

† Associated with risk of torsade de pointes in the presence of other risk factors for QTc prolongation (e.g. high dose, hypokalemia, hypomagnesemia, drug interaction or congenital long QT).

* Equivocal efficacy; not compared with placebo.

Additional Resources

For more information, refer to the VA/DoD Evidence-based Clinical Practice Guideline for the Management of Chronic Multisymptom Illness, found at: http://www.healthquality.va.gov/

In addition, the following other resources may be helpful:

1. **War Related Illness and Injury Study Center**– a National VA Post-Deployment Health Resource which provides post-deployment health expertise to Veterans and their healthcare providers through clinical programs, research, education, and risk communication. Find out more here: http://www.warrelatedillness.va.gov/

2. **Department of Veterans Affairs Office of Public Health** – an office within the Veterans Health Administration which serves as the leader and authority in public health. Learn more about it here: http://www.publichealth.va.gov/

3. **Deployment Health Clinical Center** – a site designed to provide a gateway to information on deployment health and healthcare for healthcare providers, service members, veterans, and their families. Check it out here: http://www.pdhealth.mil/