



# VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC MULTISYMP TOM ILLNESS

**Department of Veterans Affairs**

**Department of Defense**

## **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](http://www.tricare.mil) or by contacting your regional TRICARE Managed Care Support Contractor

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## Background

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).

Individuals who have been classified with CMI often suffer from multiple symptoms, such as fatigue, headache, muscle and joint pain, concentration and attention problems, and gastrointestinal disorders. Their health problems have not been attributed to any other diagnosable medical conditions and are not satisfactorily explained by standard evaluations or diagnostic testing. The symptoms must be present or frequently recur over more than six months and should be of sufficient severity to interfere with daily function. The clinical spectrum of CMI overlaps with symptoms of other diseases and ill-defined conditions, such as chronic fatigue syndrome (CFS)/myalgic encephalopathy, fibromyalgia, and irritable bowel syndrome (IBS). Other terms that have been used to describe CMI include medically unexplained symptoms, unexplained illnesses, or medically unexplained physical symptoms.

Estimates of the prevalence of a comparable set of symptoms in the general U.S. population provide some context for the relative extent of medically unexplained symptoms in the military and Veteran populations.<sup>1</sup> Based on a prospective cohort study of 500 consecutive patients presenting to a primary care clinic with physical symptoms, a 2005 publication reported that approximately one-third of cases were unresolved and remained unexplained after five years. [1] This is consistent with findings from a study published in 1993 that was based on data for 26 physical symptoms from a broad multi-community survey of more than 13,000 people in the U.S. That large survey reported that approximately one-third of symptoms were not clearly explained by a diagnosed condition.[2]

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.

A 2014 report of an Institute of Medicine (IOM) committee concluded that, despite decades of research, there is no validated cause of, or case definition for either CMI or CMI in Gulf War Veterans. [8] The committee also found that two existing definitions capture the spectrum of multisystem symptoms most

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<sup>1</sup> The reported set of physical symptoms includes: pain (e.g., headache, chest, abdominal, joint), respiratory symptoms (e.g., cough, sore throat, ear or nasal symptoms), and other (e.g., fatigue, dizziness, palpitations), as defined in: Kroenke K, Rosmalen J. Symptoms, syndromes, and the value of psychiatric diagnostics in patients who have functional somatic disorders. *Med Clin N Am.* 2006;90:603–26.

commonly identified in Gulf War Veterans: the Centers for Disease Control and Prevention (CDC) definition [7] and the Kansas definition. [6]

The CDC definition requires one or more symptoms in at least two of the fatigue, pain, and mood and cognition categories to identify a case. The Kansas definition requires symptoms in at least three of the domains of fatigue or sleep, pain, neurologic or cognitive or mood, gastrointestinal, respiratory, and skin to identify a case. The CDC case definition, which has been widely used by researchers, identifies 29-60% of US Gulf War-deployed Veterans as CMI cases depending on the population studied, whereas the Kansas definition identifies CMI in 34% of Gulf War Veterans from Kansas who were the subject of that study. The committee also stated that each definition had particular strengths, including the CDC definition's inclusion of severity indicators and the Kansas definition's exclusionary criteria. The IOM recommended, with reservation, the use of the two existing case definitions from the CDC and Kansas studies, as they are the best reflection of the symptom complexes and provide the VA and DoD with a foundation for clinical treatment and further research.

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. The two case definitions recommended by IOM were intended for the 1990-1991 Gulf War Veteran population and may not be generalizable to other conflicts.

In developing this VA/DoD clinical practice guideline, 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 definitively 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.

## About this Clinical Practice Guideline (CPG)

The Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Working Group (EBPWG) was established and first chartered in 2004, with a mission to advise the “...Health Executive Council on the use of clinical and epidemiological evidence to improve the health of the population across the Veterans Health Administration (VHA) and Military Health System,” by facilitating the development of clinical practice guidelines for the VA and DoD populations. [9] This Clinical Practice Guideline (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.

In 2001, the VA and DoD published a CPG for the Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue (2001 CPG), which was based on evidence reviewed through February 2001. Since the release of that guideline, a growing body of research has expanded the general knowledge and understanding of unexplained symptoms, including new findings regarding the prevalence of the condition among the civilian and military populations and strategies for managing chronic or unexplained symptoms. Recognition of the complex nature of CMI has led to the adoption of new strategies to manage these patients, as well as the development and use of new pharmacotherapies.

Consequently, a recommendation to update the 2001 CPG was initiated in April 2013; this updated CPG will be referred to in this text as the “2014 CMI CPG.” The updated CPG includes objective, evidence-based information on the patient-centered approach to management of CMI, the benefits and harms of pharmacologic and non-pharmacologic therapies, the management of comorbid conditions, best practices for care delivery, and emerging innovations in clinical research and care.

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 disease with a well-

established pathophysiology 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.

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 guideline.

## Scope of this CPG

This Clinical Practice Guideline is designed to assist primary care providers in treating and managing patients with chronic multisymptom illness. It addresses the following elements.

## Population

The patient population of interest for this CPG comprises all adults who may be experiencing CMI. The recommendations within this guideline were developed with a focus on individuals who are eligible for care in the Veterans Health Administration or the Department of Defense healthcare delivery system. It includes deployed and non-deployed Veterans as well as active Service Members. This CPG does not provide recommendations for the treatment of CMI in children or adolescents.

## Intervention

This 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., comorbidities), 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.

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

## Methods

The methodology used in developing the 2014 CMI CPG follows the "Guideline for Guidelines," an internal document of the VA and DoD EBPWG. This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions

(Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, and ultimately, the submission of an updated CMI CPG.

The Champions and Work Group for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Specifically, the Champions for this guideline were responsible for identifying the key questions of greatest clinical relevance, importance, and interest for the management and treatment of patients with CMI. In addition, the Champions assisted in:

1. Conducting the evidence review, including providing direction on inclusion and exclusion criteria;
2. Assessing the level and quality of the evidence;
3. Identifying appropriate disciplines to be included as part of the Work Group;
4. Directing and coordinating the Work Group;
5. Participating throughout the guideline development and review processes.

The VA Office of Quality, Safety and Value, in collaboration with the Medical Command of the DoD, identified four clinical leaders as Champions for the 2014 CMI CPG, Drs. Paul Ciminera, Drew Helmer, and Stephen Hunt from VA and Dr. Aniceto Navarro from DoD.

The Lewin Team (Team), including DutyFirst Consulting and ECRI Institute, was contracted by VA and DoD to support the development of this CPG and conduct the evidence review. The Team held the first conference call in May 2013, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing specific research questions on which to base a systematic review about the management of CMI. The group also identified a list of clinical specialties and areas of expertise that are important and relevant to the treatment and management of CMI, from which the Work Group members were recruited. The specialties and clinical areas of interest included Clinical Dietetics, Family Medicine, Healthcare Systems Management and Policy, Internal Medicine, Gastroenterology, Neurology, Nursing, Pharmacy Benefit Management, Physical Therapy, Psychiatry, Psychology and Surgery.

The guideline development process for the 2014 CMI CPG consisted of the following steps:

- Formulating evidence questions (key questions)
- Conducting the systematic review
- Convening a two and a half day face-to-face meeting with the CPG Champions and Work Group members
- Drafting and submitting a final CPG on the management of CMI to the VA/DoD EBPWG

Appendix A provides a detailed description of each of these tasks.

## Limitations

At present, the treatment of CMI is as much an art as it is a science. While it is difficult to reduce the management of CMI to a simple paradigm or single algorithm, there is increasing agreement that effective, evidence-based treatment strategies have many common elements. Often, perceived differences in treatment approaches may largely reflect differing training traditions, terminology, or theoretical perspectives across clinical disciplines, rather than scientific research.

It is important to note that the Work Group did not formally update all aspects of the 2001 CPG. The Work Group chose to broaden the scope of the updated guideline to encompass chronic multisymptom illness as a whole, rather than focusing on chronic fatigue syndrome and fibromyalgia. The key questions chosen for this CPG are those of the highest priority that would be supported by a comprehensive evidence review. Due to resource limitations, key questions were prioritized based on relative importance and availability of literature to adequately address them.

There is wide appreciation within the 2014 CMI CPG Work Group that the individual symptoms experienced by patients are part of a larger continuum. Often, there may be a lack of evidence regarding the best way in which to address different aspects of the condition. Therefore, the existing evidence for and against various therapies was used to suggest potentially effective approaches for the rest of the continuum. In some cases, 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) were used to formulate treatment recommendations in the absence of more relevant evidence.

Additionally, the systematic review conducted for this CPG examined literature that was published up to February 2014. The Work Group recognizes that several new studies have been published since that time. Consequently, the group reviewed and incorporated new evidence in developing and refining the recommendations, as long as the studies met all *a priori* inclusion criteria for the systematic review.

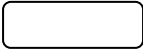



## Algorithm Format

This clinical practice guideline includes an algorithm, which is designed to 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.

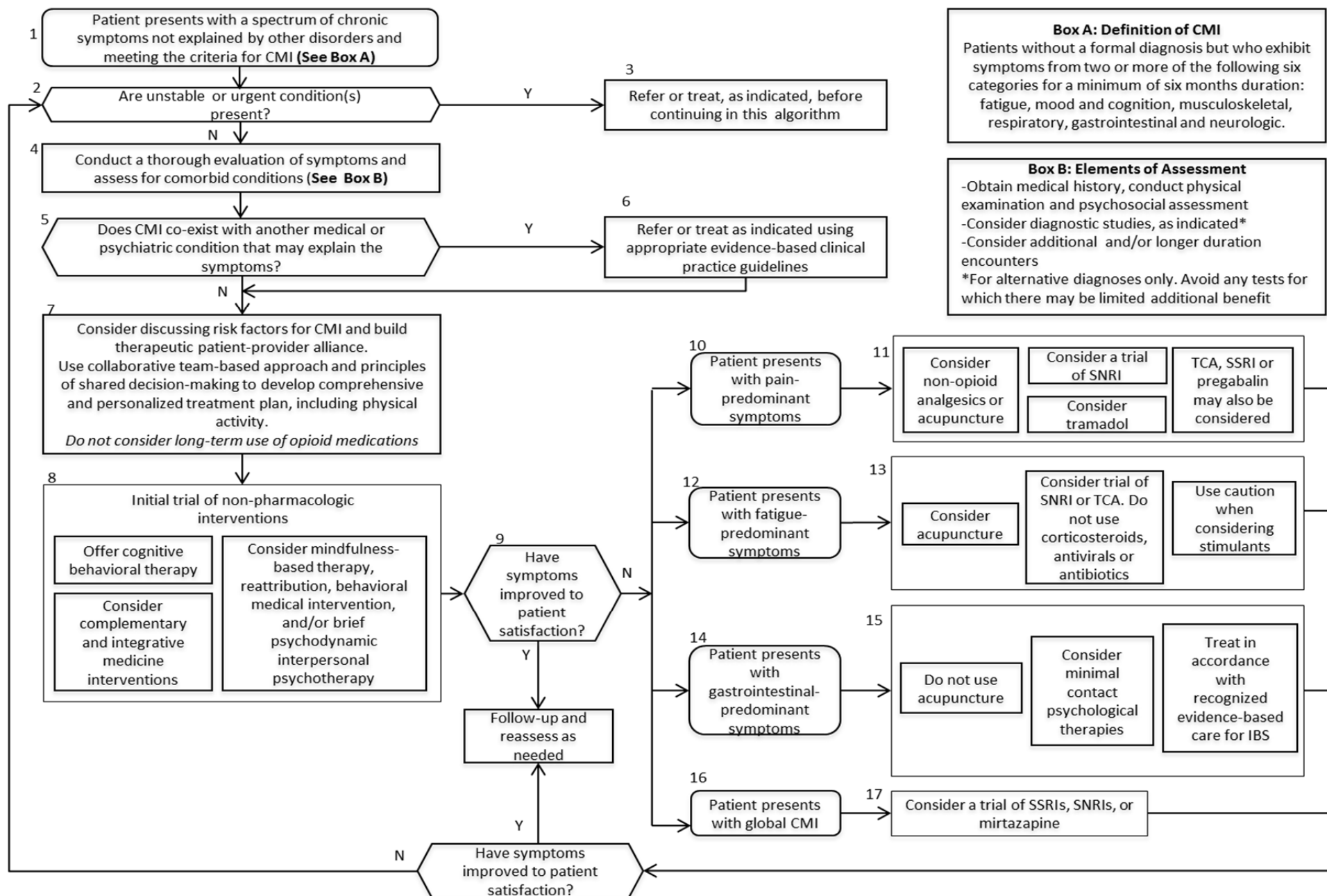
This CPG is not intended to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advances and patterns evolve. This CPG is based on information available at the 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.

## Guideline Working Group

Guideline Working Group*	
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Bolded names are members of the core editing panel. Additional information is available in Appendix C.

## Algorithm



## Recommendations

#	Recommendation	Strength of Recommendation
<b>Diagnosis and Evaluation</b>		
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
<b>Management Strategies</b>		
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: <ul style="list-style-type: none"> <li>a. Communication skills (e.g., active listening, risk communication/perception)</li> <li>b. Empathy skills</li> <li>c. Working with interdisciplinary teams</li> <li>d. The biopsychosocial model</li> <li>e. Risk factors for CMI and analogous conditions</li> <li>f. Military cultural competency</li> <li>g. Deployment related exposures</li> </ul>	Weak For
<b>Therapeutic Interventions for Global CMI</b>		
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	Weak For

#	Recommendation	Strength of Recommendation
	(SNRI), or mirtazapine for the treatment of clinical symptoms of CMI.	
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 the management of patients with CMI	Strong Against
<b>Therapeutic Interventions for Pain-Predominant CMI</b>		
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
<b>Therapeutic Interventions for Fatigue-Predominant CMI</b>		
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
<b>Therapeutic Interventions for Gastrointestinal-Predominant CMI</b>		
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

#	Recommendation	Strength of Recommendation
28	The guideline panel suggests against the use of acupuncture for treatment of patients with gastrointestinal-predominant symptoms of CMI.	Weak Against

## Diagnosis and Assessment of CMI

Chronic multisymptom illness (CMI) is a relatively new label without generally accepted diagnostic criteria given to symptom-based disorders and challenging to diagnose definitively in clinical practice. Due to these factors, literature guiding the identification of CMI is severely limited. The recommendations on diagnosis and assessment in this guideline focus on addressing any urgent or serious threats to the patient including comorbidities, conducting a thorough evaluation of symptoms, identifying any predisposing, precipitating, or perpetuating risk factors, and using appropriate tests to diagnose CMI.

## Recommendation

1. The guideline panel recommends that all patients receive a thorough evaluation of symptoms based on clinical judgment. (Strong For)

## Discussion

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)
- Review of prescribed and over-the-counter medications and supplements
- Routine test results
- Standard health assessments

In obtaining a medical history, the clinician should focus on key symptoms that may suggest a well-defined disease explanation. 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 with which clinicians encounter such complaints in the absence of objective findings. Review all medical records available and track down medical records that might offer important clues, particularly to avoid unnecessary repeat testing. Consider creating a timeline of the most important elements of the patient's history of present illness to clarify temporal associations and longitudinal features of the illness and important contextual factors.

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 has been seen by several clinicians.

In addition to a thorough physical examination, clinicians should perform a careful mental health status examination, 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). [\[11\]](#)

A psychosocial assessment is also critical in evaluating the patient with multisymptom illness 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. [\[12,13\]](#)

**Table 1. Clarification of Symptoms**

<b>Symptom Attributes</b>	<b>Questions</b>
<b>Duration</b>	Has the symptom existed for days, weeks, or months? Has the symptom occurred only intermittently? 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?
<b>Onset</b>	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?
<b>Location</b>	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?
<b>Co-morbidity</b>	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?
<b>Previous Episodes</b>	If the symptoms are episodic, what is the pattern in regard to timing, intensity, triggering events, and response to any prior treatment?
<b>Intensity and impact</b>	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 sleep).
<b>Previous treatment and medications</b>	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 his/her medication bottles on a subsequent visit and document the exact names of the medications. Find out which medications have/have not been helpful.
<b>Past medical, surgical, and psychological history</b>	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 his/her emotional status and past and present issues. Explore stressors such as occupational and family issues.
<b>Patient perception of</b>	Often omitted from the history-taking are questions designed to gain some



Symptom Attributes	Questions
<b>symptoms</b>	understanding of what the patient believes is happening. Ask the patient about his/her hunches and fears.

There is little evidence to predict the impact that diagnostic labels will have on the clinical course of patients with these symptoms. However, clinicians should consider the following:

- Assigning specific diagnostic labels may have implications in the clinical course for an individual with CMI
- 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. Other clinicians may shift their attention/prioritization of the individual's concerns in response to a label.
- The potential risks and benefits of applying a particular diagnostic label to symptom clusters should be weighed by the clinician and discussed with the patient prior to applying such a label
- The clinician should consider symptom-based approaches to managing CMI; such approaches may be useful, without having to rely on specific diagnostic labels.

## Recommendation

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)

## Discussion

Clinicians who are diagnosing patients with CMI often find themselves conducting a battery of diagnostic tests on the patient. However, the studies reviewed on the value of specific tests in patients with CMI were primarily hypothesis generating and designed to detect differences between symptomatic patients and other populations, and not to support development of a diagnostic evaluation for an individual. The evidence shows little benefit for an individual patient, and sometimes indicates risk of harm, in conducting these diagnostic tests. When deciding whether or not to conduct additional testing, consideration should be given for patient preferences, presence of population norms for test values, previously negative test results, and risk and benefit of test procedure. Providers should engage patients in shared decision-making on clinical appropriateness of testing (see management recommendations). Given the lack of available research to support testing, care teams should discuss opportunities for patient participation in approved research studies of diagnostic tests and approaches.

The evidence review revealed 22 studies of assays and assessments that include cholinergic function assessment, cholinergic challenge, genetic testing, immune system testing, neurologic function testing, neuroimaging and muscle testing. Most of the studies reviewed were hypothesis generating and designed to detect a difference between groups (i.e., symptomatic patients and other populations), and not to support development of a diagnostic approach for an individual patient. The findings of these studies may be used to support future research efforts, but there is insufficient evidence to endorse any of these modalities for general clinical use at present. The harms and burdens were considered to

outweigh the benefits for all of these modalities. While some important factors (e.g., complexity, availability of resources) could be qualitatively considered during the evaluation of the use of a diagnostic test for a specific individual with CMI, information regarding other critical factors (e.g., repeatability, accuracy, precision, generalizability to the different deployed populations, Veterans, and Service Members) are not available.

Results were inconsistent or negative in distinguishing CMI patients from healthy Veterans by physiologic measures to include cholinergic function, [14] immune system function, [15-19] and neuropsychological test performance. [16,20-22] Studies of genetic tests were limited in number and scope, so that no definitive test can be recommended. Neuromuscular evaluations to include electrodiagnostic testing [23] and muscle biopsy [24] in UK Gulf War Veterans did not demonstrate a diagnostic predictive value or pathophysiologic explanation for CMI symptoms.

Studies employing neuroimaging modalities such as diffusion tensor imaging, [25] functional MRI, [25] and voxel based morphometry [26] show promising preliminary results, but require further investigation and replication before any of these modalities can be recommended. Arterial spin labeling to measure hippocampal blood flow also shows promising early results, but cannot be recommended at this time due to the poor quality of the evidence. [27] The authors of this guideline recommend continued research of neuroimaging methods for diagnosing CMI.

## Recommendation

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)

## Discussion

The Work Group aimed to identify factors that may predispose individuals to developing CMI (e.g., sex, history of abuse), precipitate the development of CMI (e.g., recent trauma, unexpected military deployment), and factors that may perpetuate CMI (e.g., divorce, unemployment). While there are no randomized trials studying causality, there are a few systematic reviews and cohort studies published since 2000 that either directly studied factors seen in individuals with CMI or indirectly in other medically unexplained illnesses. Studies that were case controlled with at least 500 subjects were included. Eighteen studies were identified that met the workgroup's criteria.

The Work Group believes that understanding and communicating risk factors for CMI with individuals who wish to understand factors that could contribute to their condition potentially enhances provider and patient awareness, engenders trust, and promotes discovery of potentially treatable issues that may reduce the severity of CMI. [28] It should be emphasized, however, that the evidence for the risk factors reviewed is not sufficient for determination of a causal relationship to the predisposition to, precipitation, or perpetuation of CMI. A patient may have CMI and few risk factors, or may not have CMI but have many risk factors. The low predictive value of these risk factors precludes their use for

diagnostic purposes and over reliance may adversely affect the therapeutic alliance with the patient. Multiple studies of symptom based disorders reported a strong association with prior abuse.

Multiple studies of symptom based disorders reported a strong association with prior abuse. Although none of the studies we reviewed directly looked at abuse in CMI, there is a strong association with sexual abuse defined as rape and the lifetime diagnosis of fibromyalgia (OR 3.35), chronic pelvic pain (OR 3.27) and functional gastrointestinal disorders (OR 4.01). [29] Hauser et al. published a meta-analysis of 18 studies that revealed a significant association between fibromyalgia syndrome and self-reported physical and sexual abuse in childhood and adulthood, but not between FMS and emotional abuse. [30]

### **Precipitating Factors**

There were three papers that directly studied potential precipitating factors in individuals with CMI. Powel et al. studied 21,400 individuals deployed to Iraq and Afghanistan from 2004 to 2008 utilizing the Millennium Cohort Study. [31] After adjusting for sex, birth year, education, service branch, pay grade, smoking, alcohol problems, mental health symptoms (including those related to depression, anxiety and PTSD) and baseline CMI, they found no relationship between individuals deployed to areas three miles from a burn pit and CMI, compared with other locations. In 1991 a controlled detonation of the Khamisiyah Ammunition Storage Facility in Iraq was later discovered to have contained chemical weapons (sarin and cyclosarin). The amount of nerve agent in the resultant plume is unclear but it has been postulated that exposure to low-levels of chemical weapons may precipitate CMI. [31] Blanchard et al. using a cross sectional cohort compared 1,061 deployed Gulf War Veterans and 1,128 non-deployed Veterans between 1999 and 2001 with the goal of identifying factors associated with CMI. [5] They found that combat exposure, PTSD, major depression, substance use disorder and anxiety disorders were strongly associated with CMI. On the other hand, the authors did not find a statistically significant association with CMI in 236 individuals who were deployed and likely exposed to Khamisiyah compared to non-exposed deployed Veterans at that time. A systemic review by Gronseth studying Gulf War Syndrome was unable to find sufficient evidence to determine if exposure to toxins encountered during the Persian Gulf War was associated with the development of Gulf War Syndrome. [32] Gronseth points out many limitations in the reviewed studies including a potential bias due to reliance on self-reporting and variations in exposure to a causative factor.

Although CMI occurs in military and non-military populations and is seen in higher rates in deployed compared to non-deployed populations, Blanchard's study is consistent with previous studies in reporting a higher prevalence (28%) of CMI in Gulf War Veterans compared to Veterans from other deployments and that the more combat exposure the stronger the association to CMI. The strong association of the Gulf War and CMI is not just a United States phenomenon. Kelsall et al. reported the strong relationship between CMI and Gulf War deployment, depression and PTSD in Australian military men when compared to individuals actively deployed to non-Gulf War or peacekeeping operations, and when compared to non-deployed military personnel. [33] An explanation of etiology for the increased prevalence of CMI in Gulf War Veterans continues to evade studies.

There are other symptom-based disorders that share features of CMI with strong associations to deployment. Eisen et al. found that compared to non-deployed Veterans, deployed Gulf War Veterans had a higher association with fibromyalgia (OR 2.32) and chronic fatigue syndrome (OR 40.6). Reporting bias was a major limitation to this study. [34] Dhillon and Boyd performed a retrospective cohort study to examine the prevalence of life stressors before, during and after the Persian Gulf War in Veterans who reported chronic fatigue syndrome. [35] They found that individuals who developed CFS after deployment were less educated, wounded in battle, had a traumatic event during war, were demoted two years after war, or unable to work due to an illness or injury. Interestingly a cross sectional survey study by Jamil et al. found that during the Gulf War, military Service Members were more likely than civilians to develop CFS (AOR 6.99) and those living closer to the Kuwait border had higher rates of CFS. [36]

### Perpetuating Factors

We were unable to find any studies directly addressing perpetuating factors of CMI that met our search criteria. One systematic review found that the severity of symptoms in medically unexplained symptoms, somatization disorder and hypochondriasis in the general population may be predictive of symptom persistence. [37]

**Table 2: Risk Factors for CMI**

Risk factor for CMI	Strength of Association/ Correlation	Strength of Directness/ Generalizability	Additional Comments
<b>Predisposing Factors</b>			
Older age (born before 1960)	Moderate positive (AOR 1.4)	Strong	OIF/OEF; Not studied in Operation Desert Storm and Desert Shield (2) Prospectively included deployed individuals
Female	Moderate positive (AOR 1.4)	Strong	Prospectively included deployed individuals
Army vs. Air Force (Army)	Moderate positive (AOR 1.4)	Strong (limited to OIF/OEF)	Likely surrogate marker for combat exposure Prospectively included deployed individuals
Reserve guard members	Weak Reserve Guard negative effect (AOR .84)	Strong (limited to OIF/OEF)	
Officers	Weak Officers negative effect (AOR 0.69)	Strong (limited to OIF/OEF)	Prospectively included deployed individuals
History of sexual abuse (all forms)	Strong positive Non-specific chronic pain (OR 2.20) Functional GI disorders (OR 2.43) Chronic pelvic pain (OR 2.73)	Moderate (Indirect for CMI but consistent across symptom based syndromes)	Half of the studies are females only.

Risk factor for CMI	Strength of Association/ Correlation	Strength of Directness/ Generalizability	Additional Comments
History of sexual abuse (rape)	Strong positive Fibromyalgia (OR 3.35) Function GI disorders (OR 4.01) Chronic pelvic pain (3.27)	Moderate (Indirect for CMI but consistent across symptom based syndromes)	Half of the studies are females only.
History of smoking	Weak positive (AOR 1.2, 1.9)	Strong (both in Desert Storm and Desert Shield and OEF/OIF)	
Alcohol abuse	Moderate positive (AOR 1.2)	Strong (limited to OIF/OEF)	Prospectively included deployed individuals
More education	Weak Bachelor's degree negative association (AOR 0.69)	Strong (limited to OIF/OEF)	Prospectively included deployed individuals
Mental health problem, anxiety, depression, PTSD	Strong positive (AOR 2.3)	Strong (limited to OEF/OIF)	Prospectively included deployed individuals
History of depression and anxiety (pre-war)	Strong positive (AOR 3.2)	Strong (limited to Desert Storm and Desert Shield)	Limitations: Cross sectional study and possible bias
<b>Precipitating Factors</b>			
Higher combat exposure	Moderate positive (clinically significant difference in mean score on Expanded Combat Exposure Scale- one falls in <i>light</i> and one falls in <i>light to moderate</i> )	Strong (limited to Desert Storm and Desert Shield)	Limitations: Questionable clinical significance and relevance of tool
Open air burn pit exposure (deployment within a 3 mile radius of a burn pit)	No statistical association (OR 1.06)	Strong (limited to OIF)	
Gulf War deployment	Strong positive (OR 1.9) Strong positive (OR 2.16)	Strong	Limitations: Cross sectional study and possible bias (4)
Khamsiyah exposure	No statistical association (OR 1.6)	Strong (limited to Desert Storm and Desert Shield)	Possible imprecision of exposure estimate

Note: OR over 1.5 is strong

## Management Strategies for CMI

The literature on the professional management of CMI is extremely limited. The nature of management strategies presents multiple challenges to conducting rigorous double-blind controlled studies. Most of the studies available follow relatively small cohorts of non-military, non-Veteran patients, outside the United States, and are generally rated as moderate quality or below. Drawing on published studies of management approaches from symptom-based and other chronic conditions, the panel extrapolated findings to CMI.

## Recommendation

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)

## Discussion

Caring for the patient with CMI “requires personalized care that is most effective when provided by a team of health professionals”. [38] Patients with CMI often have a complex medical history, ongoing comorbid symptoms and conditions, and psychosocial challenges requiring a variety of skills sets and expertise that extends beyond the competencies of any single individual or profession. CMI patients are at risk for having medication-related problems as well. While there are no clinical trials to provide evidence that patients with CMI should have team-based care, the Institute of Medicine (IOM) in “Gulf War and Health: Treatment for Chronic Multisymptom Illness” recommends that “a team approach and specific expertise” is implemented for patients with CMI. [39]

### **PCMH as a model of team-based care for CMI**

Patient care is enhanced by using a collaborative team-based management approach that emphasizes the relationship between the primary care team and the patient and his or her social support network. [40] Historically, the concept of team-based primary care was first coined in 1967 by the American Academy of Pediatrics (AAP) when they introduced the term “medical home” to describe the care that chronically ill children received in primary care pediatrics. The care delivered to these patients was accessible, continuous, comprehensive, coordinated, family-centered and culturally sensitive. [41] Since that time, the concept of team-based healthcare has evolved into the patient centered medical home (PCMH), which reflects the pediatric medical home model and the chronic care model to promote comprehensive, continuous, accessible, coordinated, planned proactive health care and patient activation. [40] The patient care goal for the PCMH and PACT is to “provide comprehensive, integrated care including follow-up health care, education, and training”. [42]

To be effective, the medical home requires enhanced access, team-based care, population management, care coordination, care management, systems-based approach to quality and safety, and health information technology. [41] Team-based care is a foundational element of the medical home. It refers to the joint effort of various health care professionals from different specialties and training, and with different skills and knowledge. [41] Team-based care fosters an environment of collaborative,

comprehensive health care. A team approach optimizes the patient's outcomes by including members who see the patient from all angles, resulting in a shared appreciation for the patient as a whole.

The multi-disciplinary nature of practice has to be integrated across the continuum of care activities from inquiry and data gathering, to decision making, education, and follow-up for reassessment. This ultimately works towards the common goal of improving patient care and quality of life for patients. A multi-disciplinary approach has been proven through many studies to be beneficial to the patient, including in home health programs. These programs see robust benefits such as reduced hospitalization and emergency room visits for their patients with complex conditions. In preliminary data provided by Reidt et al., records showed that hospitalization and emergency room visits decreased by half after the implementation of their program to include more diverse professionals in a home health program. [43] Studies demonstrating benefit have included patients with complex, chronic problems such as short bowel syndrome, and neonatal care. [44,45]

While it is optimal for patients with CMI to be cared for within a PCMH or PACT, patients with CMI may still benefit from a team-based approach that may not achieve full realization as a PCMH or PACT. [41] Regardless of the terminology used to describe it, the medical home concept has gained recognition as a model of primary care delivery, emphasizing the importance of a team approach to care. Medical home teams are multi-disciplinary in nature, providing a mix of expertise in medical care, mental health care, nursing, and social work.

#### **Team members for CMI team-based care**

Currently, the VHA and DoD have transitioned to team-based care in the form of PACT and PCMH respectively. The PCMH and the PACT serve as the military members' (and their beneficiaries') and Veterans' medical home. The core primary care teams consist of:

- Primary care providers (physician, nurse practitioner, or physician assistant)
- Registered nurses
- Licensed vocational nurses
- Nursing assistants
- Enlisted health care specialists (68W, 4NO, corps man) or their civilian equivalents
- Medical technicians or assistants

Extended members of the PCMH and PACT consist of the following as part of the multi-disciplinary team has been crucial in the management of advanced care for patients. [46]:

- Behavioral medicine clinicians
- Social workers
- Clinical pharmacists
- Dietitians
- Nurse case managers
- Health coaches

- Care coordinators, including dietitians, clinical nurses, social workers, pharmacists and other allied health professionals
- Chaplains

Doctors and other medical providers have been trained to focus on biomedical aspects of health and ensuring involvement of allied health professionals may result in better outcomes for their patients. [47] Successful primary care requires a holistic approach and primary care providers may need to address patient issues for which they might not have enough time or appropriate skills. Other members of the medical home team who are engaged in the care of a patient may be able to catch issues of medication non-adherence (nursing staff), evaluate proper dosing and possible adverse interactions or effects (pharmacists), provide education and suggest community-based support (social worker), detect potential food-drug interaction (dietitian) and, thus, can improve overall outcomes for the patients they serve. [48]

Front line case nurse managers and clinical nurses have great responsibilities which benefit the patient. Those nurses lead by example and support all members of the team to perform to the highest standards. [49] They often focus on developing a rapport with the patient and can inform the team members of changes which could affect the patient's care.

An essential element in the success of the medical home is "optimal communication among team members" which is often operationalized in the form of daily, or twice daily, staff huddles. The climate for taking care of the patient is positive when interdisciplinary care employs a heightened sense of team work and results in benefit for the patient. [49]

### **Care coordination for patients with CMI**

Patients with CMI require ongoing care and need to have timely access to primary care and the appropriate multispecialty team of experts. At the point of separation from active duty military service, care coordination should occur within and between the DoD and VHA. Frequently, the Veteran/military members also receive care in the private sector and care coordination should incorporate care provided by civilian colleagues. The coordination should include:

- Establishment of lead care coordination responsibility among providers
- Notification of all providers involved in a patient's care in accordance with the Health Insurance Portability and Accountability Act (HIPAA)
- Sharing of established VHA/DoD Clinical Practice Guidelines (CPGs) applicable to the specific patient
- Establishment of care-team membership for the patients who require specific expertise (i.e., neurologists who specialize in traumatic brain injury (TBI) or acupuncturists' for pain management)
- Reiteration of access to consultation with or referral to Veteran or military medical centers
- Sharing of the patient-centered treatment plan and updates



- Sharing of all test results and specialist opinions across healthcare systems to avoid redundant testing and consultation and promote a unified approach to management.

### **Behavioral medicine expertise on the team**

As with any chronic condition, living with CMI can be stressful and compound other psychosocial stressors in an individual's life. There is little specific research on the integration of a behavioral health professional in the primary care team for treatment of CMI, but there is evidence to support the use of specific psychotherapies in patients with CMI or specific symptom-based syndromes (see non-pharmacologic recommendations in this CPG). Professional experience tells us that many complex medical conditions benefit from a holistic approach and mental health providers are regularly integrated into the primary care model in both VA and DoD settings. The shared decision-making model takes into consideration patient preferences which, at times, may prohibit the involvement of mental health, often due to lasting stigma in this area. Embedding a mental health provider in the primary care setting streamlines care, expedites the multiple appointments which are often necessary for complex patients, and may reduce the stigma associated with visiting a mental health provider in an identifiable mental health care unit.

The best method for integrating mental health into the primary care management of CMI patients has yet to be identified. A method involving the use of a "consultation letter" to better link mental health and primary care was studied by Hoedeman et al. [50] The study was deemed low grade and identified as having "serious limitations," and did not yield significant improvement in the intervention group. A low grade study by Schaefert et al., also with serious limitations, utilized collaborative group intervention of the primary care team and a psychosomatic medicine specialist. This study yielded a statistically significant decline in use of specialty consultations and visits to emergency rooms at the one-year mark, but the improvement was no longer present at the two-year mark. [51]

The exact skills and training of the mental health provider have not been outlined at this time. The studies discussed above used a range of professionals including psychiatrists, psychosomatic medicine specialists, and staff experienced in biopsychosocial care. Possible disciplines include psychiatric nurse practitioners, clinical social workers, clinical or health psychologists, and psychiatrists. Further study in this area is needed to determine the ideal skill set of mental health providers for this population and best practices for delivery mental health care in a time- and cost-efficient manner.

### **Recommendation**

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)

### **Discussion**

The lack of diagnosis or effective cure can make the management of patients with unexplained symptoms challenging and cause frustration for both the patient and the provider. A high level of trust

between the patient and clinician is required to maintain continuity of care and continue management through regular follow-up appointments. The initial evaluation helps establish a collaborative partnership between the patient and clinician. To strengthen the partnership with the patient, the clinician should: [\[52\]](#)

- 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.
- Explore referral to specialty services as clinically indicated.

Patients have certain common hopes and expectations when they see a clinician. [\[53\]](#) 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 and 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.

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

### **Develop a Treatment Plan**

Ensure that the patient understands the meaning and impact of CMI on his/her 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 treatments 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 CMI and how problems associated with this diagnosis apply to the patient.
- Evaluate the patient's understanding through teach back.
- 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 readiness to begin treatment and identify barriers to treatment.
  - Use motivational interviewing techniques to encourage change talk.
  - Obtain the patient's consent to the treatment plan.
- Empower the patient for self-management
  - Refocus 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.

Given the limited RCTs examining reflective interview/motivational interviewing, we recommend further research is needed in this population before a stronger recommendation can be made in support of this modality for patient care. A reflecting interview technique was studied by Rasmussen et al. with a small sample of mostly female patients with medically unexplained physical symptoms (intervention group n=12 vs. controls n=12). [\[54\]](#) In terms of health care utilization the number of primary care visits did not vary between patients in the reflecting interview condition and the control condition at one year follow up, but total health care costs statistically significantly decreased in the reflecting interview condition. No significant differences were seen in physical health, mental functioning, or health care satisfaction at one year follow up.

## Recommendation

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)

## Discussion

“A good doctor listens to you and then addresses what you’re feeling...I may know a lot about your disease, but I don’t know how you experience your illness.”

--- Thomas Delbanco, MD, Director of General Medicine and Primary Care at Beth Israel Hospital.

The above quote by Dr. Delbanco nicely sums up the quality known variously as a therapeutic relationship, communication skills, rapport, empathy, and emotional intelligence. These qualities have long been prized in psychotherapy, but it is only recently that physicians and medical schools have begun to turn their attention to the role of relationship skills in medicine. Communication skills are oftentimes considered part of the “art” (rather than science) of medicine, and it can be difficult to operationalize emotional intelligence. One of the most powerful components of an effective communication style is the use of validation. The root of validation comes from the Latin *valeo* for “to make strong or worthy.” Validation of patient concerns has been found to improve patient satisfaction and reduce both physical and emotional pain. Physician empathy has been found to increase both patient satisfaction and treatment compliance. [55] Remarkably, in one study by Hojat et al., high levels of physician empathy even resulted in better control of hemoglobin A1c and improved LDL-C control. [55] It has been demonstrated that the physician-patient relationship is an emotional one. A lack of emotional intelligence has even been linked with higher malpractice claims. Communication skills such as active listening, validation, and empathy can be learned and practiced by both students and established professionals.

We do not have any evidence that there is a special need in this population for a higher level mastery of these competencies compared to the general population seeking medical care. It is possible that rapport, warmth, empathy, and active listening skills are basic human needs in any relationship, but they may be particularly important in one where the power imbalance is as pronounced as that of the physician and patient. Individuals with CMI may have an even deeper need for validation because their illnesses are mysterious, misunderstood, and largely idiopathic. Although we need more research to build the evidence base supporting the use of these core competencies with the CMI population, providers may consider skills building educational opportunities to elevate the level of care they provide to these patients.

Use of the biopsychosocial model has found wide acceptance within the field as an important component in the treatment of a wide variety of complex conditions including pain disorders, irritable

bowel syndrome, diabetes, chronic obstructive pulmonary disease, asthma and insomnia. [56] The biopsychosocial model provides healthcare providers with a means to consider the whole person, integrating key pieces of contextual information that may better help the clinical team assess the patient, establish rapport, communicate treatment options, understand needs and discuss risk and benefits.

When using chronic pain as a clinical challenge model analogous to CMI, it is important to observe that the assessment and treatment of pain has gained sophistication over time. The psychogenic pain model presumed that when “a physical cause could not be identified for the pain, the pain was assumed to be psychologically generated” [56]. The psychogenic pain model is no longer widely accepted. [56] The gate-control theory of pain [57] and the biopsychosocial model [58] have provided “important frameworks for better understanding pain to help those experiencing pain find ways to improve their quality of life.” [56] In addition, Guzman et al. led a systematic literature review of randomized controlled trials and found strong evidence that “intensive multidisciplinary biopsychosocial rehabilitation with functional restoration improves function when compared with inpatient or outpatient non-multidisciplinary rehabilitation treatments.” [59] Guzman et al. also went on to determine “moderate evidence that intensive rehabilitation with functional restoration reduces pain when compared with outpatient non-multidisciplinary rehabilitation or usual care.” [59]

Healthcare providers entrusted to care for Service Members require a depth of facility and knowledge of military culture, occupational health and deployment related exposures and stressors. Approximately 30% of recent Veterans of Iraq and Afghanistan reported one or more concern about an occupational or environmental exposure while deployed. These same individuals reported higher burden of symptoms, as well. [60,61]

Training should be provided to healthcare providers in order to ensure an appropriate knowledge base of military culture, military occupational health and potential deployment-related exposures. [62] The VA and DoD healthcare systems currently offer a range of training in military culture and occupational health and safety for healthcare providers.

It must be noted that there is not robust research in the special population of Service Members in this regard, beyond patient satisfaction survey data collection. However, O’Toole et al. led a study, *Building Care systems to improve access for high-risk and vulnerable Veteran populations*, which concluded tailoring the medical model home to the specific needs and challenges facing high risk populations can increase primary care utilization and improve chronic disease monitoring. [63] In the O’Toole et al. study the medical homes were divided into special populations clinic teams designed specifically for the needs of each group, for example, homeless Veterans, women with MST or PTSD, Veterans with mental illness and Veterans with cognitive impairments, and Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Service Members. [63]

Healthcare providers must also be aware of risk factors for chronic multisystem illness and analogous conditions. The panel noted actual knowledge of CMI and differential diagnoses were a core

competency of healthcare providers. See the discussion on assessment for more details about the prevalence of factors associated with CMI and attributed causality.

## Therapeutic Interventions for Global CMI

Global CMI is roughly classified as CMI without a specific predominant set of symptoms (i.e., pain, fatigue, gastrointestinal). Patients categorized as having global CMI may present with a number of symptoms from various categories. The following recommendations are designed to be applicable for all patients with CMI, regardless of their predominant symptoms.

### Recommendation

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)

### Discussion

Peters et al. conducted an RCT to examine the efficacy of aerobic exercise (n = 114) relative to stretching (n = 114) in the management of patients with medically unexplained physical symptoms (MUPS). All training sessions met for one hour twice a week for 10 weeks. Aerobic exercise was designed to meet a target heart rate of 60-65% age-adjusted maximum; stretching training was designed to be non-aerobic (Max heart rate <50% age adjusted maximum). Overall, the age of participants was 44 years and 53% of participants were female. Follow-up was reported at six months after training. The primary outcomes considered by Peters et al. included primary healthcare use, changes on the Hospital Anxiety and Depression Scale (HADS) depression and anxiety scales, SF-36 scales, and somatization scales. Use of healthcare did not differ between aerobic exercise and stretching. The number of physician visits and prescriptions decreased significantly over time for both exercise conditions and was inversely correlated with the number of training sessions attended. The more training sessions attended independent of activity type, the fewer physician visits were scheduled or prescriptions were obtained at six months follow up. Symptom scores on the HADS depression and anxiety scales, SF-36 scales, and somatization scales did not differ as a function of exercise type. Scores improved over time for both conditions, but were not associated with attendance. [\[64\]](#)

Nickel et al. considered the effects of bioenergetic exercises (BE) on the psychotherapeutic treatment results of Turkish immigrants with chronic somatoform disorders. [\[65\]](#) The patients in this study were receiving in-patient treatment in a hospital in Germany that specialized in treating patients with psychosomatic illnesses. Patients were randomly assigned to receive BE (64 patients) or the control condition (64 patients). Patients in the BE group participated in various mind-body exercises that included expression exercises, exercises in setting boundaries, vocal and breathing exercises, and body movement exercises. Patients in the control condition participated in light gymnastic exercises. Each group also received inpatient psychotherapy plus treatment with antidepressants. The exercise therapy in each study group was provided in 60 minute group sessions twice a week over a period of six weeks. The mean age of patients in the BE group was 48.3 years, and 49.4 years in control group. The patients

in each study group were predominantly female (68% female in BE group; 72% female in control group). The primary outcome in the Nickel et al. study was change in symptoms as measured by the symptom checklist (SCL-90-R, Turkish version) and Global Symptom Severity Index (GSI). Secondary outcomes included measures of anger expression. Somatization symptoms significantly improved among patients who received bioenergetics exercise therapy compared to patients in the control group (Mean Difference (MD) between groups: -6.2; 95% CI -8.5 to -3.9,  $p < 0.001$ ). Significant differences were also observed for other symptoms, including feelings of social isolation, depression, anxiety, and hostility. Severity of symptoms improved from baseline to follow up in both groups, but the difference between groups for this outcome did not reach statistical significance. The authors noted that there was no difference in outcomes between men and women. [65]

Two systematic reviews considered the use of exercise as treatment for patients with FMS. Brosseau et al. assessed the effectiveness of strengthening exercises (defined as isometric, isokinetic, or concentric/eccentric resistance exercise with the purpose of increasing muscular strength). The evidence base for this review consisted of five RCTs enrolling a total of 150 adult patients with FMS. The average age and gender of the patients enrolled in the studies was not reported in the review. The duration of treatment ranged from 12 (one study) to 21 weeks (four studies), and the strengthening exercises were performed twice a week in all studies. In four of the studies the control condition was not specified; in one study the control group received flexibility exercises. [66]

The primary outcomes considered in the Brosseau et al. review that focused on the efficacy of strengthening exercises were pain, disability, and quality of life. For the outcome of pain, strengthening exercises showed clinically and statistically significant benefits versus controls for general pain (measured using visual analog scale [VAS]; Relative Difference [RD] 117%). Strengthening exercises also showed clinically and statistically significant benefits in improving disability compared to controls (disability was measured using the Stanford Health Assessment Questionnaire; RD 46%). No clinical or statistical benefit for strengthening exercises versus controls was observed for quality of life (as measured using the Fibromyalgia Impact Questionnaire). In the one study that considered the comparative efficacy of strengthening exercises to flexibility training, the only outcome for which strengthening exercises showed a clinical and statistical benefit was quality of life (RD 23%). [66]

The other review by Nuesch et al. focused on the efficacy of aerobic exercise (AEX). In this review, AEX was one of several treatments considered. The authors performed a comprehensive systematic review of several pharmacological and non-pharmacological treatments for the management of patients with FMS. Other treatments from this review include balneotherapy and multicomponent therapy. The evidence base for AEX consisted of 33 RCTs that enrolled 2,266 patients with an average age range of 34 to 53 years. The majority of the patients in the included studies were female (percent female range 77 to 100). The average duration of treatment across studies was 12 weeks. The controls included the following: non-intervention control (17 studies), minimally-active control (13 studies), and placebo (three studies). In this review controls were classified as follows: waiting list or treatment as usual were classified as non-intervention control, drug placebo or sham intervention as placebo control, and interventions deemed as minimally active (e.g., education, relaxation) as minimally active controls. [67]

The primary outcomes considered in the Nuesch et al. review that focused on the efficacy of aerobic exercise (AEX) were pain and quality of life. Secondary outcomes in this review included fatigue, sleep problems, and drop outs. Data for pain and quality of life were pooled in a network meta-analysis using the standardized mean difference (SMD) to calculate the summary effect size estimates. Network meta-analysis allows for simultaneous analyses of all randomized controlled trials comparing pharmacological and non-pharmacological head-to-head or with a common control intervention, while respecting the full randomization of the included trials. The results Relative Difference is defined by the authors of the review as the absolute benefit divided by the baseline mean (weighted for the intervention and control) indicated a statistical benefit of AEX compared to placebo for improving pain (SMD -0.61; 95% CI -0.88 to -0.337, negative SMD indicates improvement) and quality of life (SMD -0.76; 95% CI -1.15 to -0.38). [\[67\]](#)

### **Alternative Exercise**

Mist et al. conducted a review on the efficacy of land-based alternative exercises for adults ( $\geq 21$  years) with FMS. The evidence base in this review consisted of 16 studies (seven RCTs and nine single arm trials) enrolling a total of 832 patients. The mean age ranges across studies or percent female in studies of mixed gender were not reported. The authors did indicate that five of the included studies enrolled only women. The authors considered the evidence for Qigong (six studies), Tai Chi (five studies), Yoga (three studies), and other exercises (three studies, including Pilates, body movement therapy, and dance). The control conditions included waitlist/no treatment controls or inactive treatment controls (conditions in which a key element of therapy was not received). The duration of treatment across studies ranged from 4 to 28 weeks, and the duration of follow up ranged from 4 to 24 weeks. [\[68\]](#)

Mist et al. analyzed each type of exercise considered in their review (Qigong, Tai Chi, Yoga, and other [Pilates, body movement, and dance]) using the SMD to calculate an estimated summary effect size for the primary outcome of pain. In all but one study, pain was measured using the Fibromyalgia Impact Questionnaire (FIQ). In the other study pain was measured using the McGill Pain Questionnaire. The results of all the analyses indicated a significant benefit of the alternative exercise compared to the control condition in improving pain. The overall summary effect of the six studies assessing the efficacy of Qigong was an SMD of 0.472 (95% CI 0.250 to 0.693,  $p < 0.001$ ). Only one study assessing Qigong reported adverse events. Shoulder pain and plantar fasciitis was reported for two study participants. [\[68\]](#)

## **Recommendation**

8. The guideline panel recommends offering cognitive behavioral therapy, delivered by trained professionals, for patients with CMI. (Strong For)

## **Discussion**

For global CMI, the highest quality evidence reviewed supports the use of CBT. The highest quality studies include outcome measures for multiple symptoms such as pain, fatigue, cognition, distress and



mental health functioning. Donta et al. conducted a large scale multicenter trial comparing effectiveness of cognitive behavioral therapy (CBT) and exercise in Gulf War Veteran's Illnesses (GWVI). [69] They found CBT improved physical symptoms, and both CBT and exercise improved cognitive symptoms and mental health functioning. Kleinstaub et al. conducted a systematic review on the efficacy of short-term psychological therapies for the treatment of medically unexplained physical symptoms. [70] Short-term psychotherapy included CBT, reattribution training, interpersonal psychodynamic therapy, and behavioral medical intervention. For all forms of psychotherapy, intervention statistically significantly improved physical symptoms relative to comparators at the end of treatment. Subgroup analyses indicated that CBT, behavioral medical intervention, and reattribution training all statistically improved physical symptoms at the end of treatment, and at one year follow-up.

Schroder et al. conducted a RCT to compare the effectiveness of CBT or progressive muscle relaxation (PMR) training in the management of MUPS. [71] Overall the age of participants was 48.02 years and 76.9% of participants were female. The interventions consisted of one 90 minute session per week of either group CBT (n = 49) or group PMR (n = 41) training for eight weeks (both treatments given with adherence to follow up was reported at 12 months after baseline. This study showed a reduction in symptom severity and symptom number for somatoform symptoms following CBT relative to waitlist control. [71]

Guarino et al. conducted an RCT to examine the efficacy of CBT and aerobic exercise, alone and in combination, in managing Gulf War Veterans' Illness (GWVI). [72] A total of 1,092 Veterans with GWVI were enrolled in the trial. The study was designed in a 2 x 2 factorial design: CBT plus usual care (n = 286); aerobic exercise plus usual care (n = 269); CBT plus exercise plus usual care (n = 266); and usual care (n = 271). Overall, the average age of participants was 40.7 years, and 40.5% of the participants were female. Exercise sessions were 60 minutes weekly for 12 weeks and were designed to increase activity and allowed participants to choose the types of exercise they liked. CBT sessions took place in groups of three to eight patients with one therapist. Sessions were conducted with the use of a treatment manual, and met for 60-90 minutes weekly for 12 weeks. Follow up was reported at 12 months after baseline.

There is good evidence for the benefit of CBT in pain populations and there is an infrastructure in place within the VA/DoD system for delivery. For pain-predominant CMI the literature on the efficacy of cognitive behavioral therapy for the treatment of fibromyalgia was reviewed. Bernardy et al. conducted systematic review with an evidence base consisting of 23 randomized controlled trials enrolling a total of 1,073 patients. [73] The average age of the patients across studies was 47.5 years, and the majority of patients enrolled in the studies were female (median percent female 96%). Nineteen studies provided traditional CBT (delivered by a trained professional), three studies provided self-managed CBT (provided by a lay person trained to delivery CBT), and two studies provided operant therapy (a modified form of CBT). The comparators included waitlist controls (two studies), attention controls (two studies), active controls (eight studies), and usual care (11 studies). Overall, the median duration of all CBTs was 10 weeks and the median number of sessions was 10. The median follow up across studies was six months. The primary outcomes measured in the review by Bernardy et al. were pain, negative mood, disability, and withdrawal from treatment. [73] The authors of this review pooled data for these outcomes in

separate meta-analyses using the standardized mean difference (SMD) to calculate the summary effect size estimates. The authors performed meta-analyses that combined all studies for each follow-up period (12 weeks and six months), and then conducted separate subgroup analyses for each type of CBT (traditional, self-management, and operant). At 12 weeks, the SMD for pain in the analysis combining all types of CBTs (23 studies) was -0.29 (95% Confidence Interval [CI] -0.47 to -0.11), which indicates a statistically significant benefit of CBTs compared to controls in reducing pain. The SMD in the analysis considering only traditional CBT also showed a statistical benefit of CBT over controls for pain reduction (SMD -0.30; 95% CIs -0.44 to -0.15; 19 studies). However, no statistically significant benefit was observed for self-managed CBT or operant therapy compared to controls. At six months, the SMD for all CBTs and for traditional CBT indicated a statistically significant benefit of CBTs for reducing pain compared to controls (All CBTs: SMD -0.40 [95% CI -0.62 to -0.17]; traditional CBT: -0.28 [-0.43 to -0.214]). The six month meta-analytic results for self-managed CBT and operant therapy were not considered because the analyses consisted of fewer than three studies.

For gastrointestinal (GI) predominant CMI there is moderate quality evidence on the efficacy of cognitive behavioral therapy for the treatment of irritable bowel syndrome. There is also an infrastructure in place for its delivery. CBT is efficacious in and conducive to group format. As with all interventions, CBT can be one component of care in a shared decision-making model and represents a key element of the bio-psychosocial conceptualization of CMI, given the relationships between mental health, physical health, and GI symptoms. Zijdenbos et al. conducted a systematic review on the efficacy of several psychological therapies for the treatment of IBS. [74] The evidence base for the review of standard CBT consisted of 14 RCTs enrolling 1,135 patients. The mean age range was 30.9 to 49.2 years and gender of the patients ranged from 66% to 96% female. The studies compared CBT versus usual care at two months of therapy (five studies), two of which also included a placebo arm, or three months of therapy (eight studies), three of which also included a placebo arm, or CBT vs. placebo at three months of therapy (one study). Long-term follow up at 6, 9, 12, and 15 months was available for some studies and some outcomes (three studies). The primary outcomes measured in the review by Zijdenbos et al. were IBS symptom scores, improvement in abdominal pain, and quality of life. [74] The authors of this review pooled data for these outcomes in separate meta-analyses using the SMD to calculate the summary effect size estimates. When looking at 3 months of treatment, CBT statistically significantly improved symptom scores relative to waitlist or usual care (SMD = 0.58; 95% CI 0.36 to 0.79) but not relative to placebo treatment (SMD = -0.17; 95% CI -0.45 to 0.11). Similarly, when looking at three months of treatment, CBT statistically significantly improved quality of life relative to waitlist or usual care (SMD = 0.92; 95% CI 0.07 to 1.77) but not relative to placebo treatment (SMD = 0.16; 95% CI -0.22 to 0.54), suggesting a treatment expectation bias or placebo response in the patients in the studies with no placebo control. Abdominal pain was not affected by CBT relative to comparator, with the exception of two months treatment in comparison to waitlist or usual care (SMD = 0.45; 95% CI 0.00 to 0.91). At the longest follow up time points, CBT was not superior to waitlist or usual care for any outcomes measured. There were no follow-up data available for the placebo conditions. [74]

Ford et al. conducted an RCT on self-administered CBT with a total of 28 patients (CBT n = 17; controls n = 11). The age and gender of the patients was not reported. This study compared self-administered CBT

to usual management. Treatment duration was five sessions undertaken over 10 weeks. The primary outcome measured in the study was 50% reduction in baseline symptom scores. The authors of this review pooled data for these outcomes in separate meta-analyses using the risk ratio (RR) of symptoms persisting to calculate the summary effect size estimates. The RR for reduction in symptom severity at the end of treatment was  $RR = 1.04$  (95% CI 0.83 to 1.29), indicating that self-administered CBT did not affect symptom severity relative to usual care. [75]

## Recommendation

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)

## Discussion

### Mindfulness-based therapy

There is evidence that participation in a mindfulness-based therapy (MBT) results in pain reduction, improved symptom severity and enhanced quality of life. Preliminary evidence suggests that MBT is more effective if delivered in a structured eight-week group format as compared to eclectic/unspecified MBT approach. A meta-analysis by Lakhan et al. assessed whether an eight-week structured mindfulness intervention, either mindfulness-based stress reduction (MBSR), or mindfulness-based cognitive therapy (MCBT), was more effective than an eclectic/unspecified MBT approach. The study analyzed the effects of structured MBT on pain, symptom severity, quality of life, depression, and anxiety for general somatic symptoms as well as for patients meeting criteria for fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome. Six studies included patients with fibromyalgia, three included patients with IBS, one included patients with CFS, and two with included patients with general or nonspecific somatization disorder. In all studies the participants were predominantly female. The results of the meta-analysis showed small to moderate effect sizes for MBT as compared to waitlist/support group controls for pain reduction ( $SMD = -0.21$ , 95% CI: -0.37, -0.03;  $p < 0.05$ ), symptom severity ( $SMD = -0.40$ , 95% CI: -0.54, -0.26;  $p < 0.001$ ), depression ( $SMD = -0.23$ , 95% CI: -0.40, -0.07,  $p < 0.01$ ), and enhanced quality of life ( $SMD = 0.39$ , 95% CI: 0.19, 0.59;  $p < 0.001$ ). [76]

As with all interventions, MBT can be one component of care in a shared decision-making model and represents a key element of the bio-psychosocial conceptualization of CMI, given the relationships between mental health, physical health, and symptoms.

### Interpersonal psychotherapy

There is good evidence for the benefit of interpersonal psychotherapy in GI populations and there is infrastructure in place for delivery. Further research utilizing group format and male Veteran populations with CMI are still needed. Zijdenbos et al. conducted a systematic review on the efficacy of interpersonal psychotherapy for the treatment of IBS. [74] The evidence base for the review consisted of three RCTs enrolling 460 patients. The mean age range was 30.9 to 49.2 years and gender of the

patients ranged from 59% to 80% female. The efficacy of interpersonal psychotherapy after three months of treatment was compared with usual care or waiting list. Long term follow up at 15 months was available in two studies. The primary outcomes measured in the review by Zijdenbos et al. were IBS symptom scores, improvement in abdominal pain, and quality of life. [74] The authors of this review pooled data for these outcomes in separate meta-analyses using the SMD to calculate the summary effect size estimates. Reductions in symptom severity (SMD = 0.75; 95% CI 0.35 to 1.16) and quality of life (SMD = 0.39; 95% CI 0.03 to 0.75) at the end of three months of treatment were significantly improved relative to control. At the 15 month follow-up, reductions in symptom severity (SMD = 1.20; 95% CI 0.77 to 1.62) and quality of life (SMD = 0.58; 95% CI 0.22 to 0.95) remained significantly improved relative to control. Abdominal pain was not significantly affected by interpersonal psychotherapy relative to control after three months of treatment (SMD = 0.35; 95% CI -0.75 to 0.05) or at the 15 month follow-up time point (SMD = 0.66; 95% CI -0.69 to 2.00). [74]

### **Eye movement desensitization and reprocessing**

Given the limited number of RCTs that examine eye movement desensitization and reprocessing (EMDR), further research is needed in this population before a stronger recommendation can be made in support of this modality for patient care. EMDR is used as a treatment for PTSD, but its utility in other disorders is less well explored. It is thought that, as with PTSD, the reprocessing of stored memories may reduce the severity of somatic symptoms. Additionally, the quality of evidence is somewhat low at this time for EMDR in a CMI population. A systematic review on the efficacy of EMDR was conducted by Van Rood and de Roos, for treatment for the treatment of MUPS, including phantom limb pain (PLP), chronic pain, and war-related MUPS. [77] The evidence base for the review consisted of one RCT, two non-controlled clinical trials, and 13 single cases or case series enrolling a total of 102 patients. The average age of the patients was 43 years (range 22 to 73 years), and the percentage of female patients was 64%. The one RCT employed a pre-post crossover design comparing one session of EMDR with one session of hypnosis; all non-RCTs used an EMDR intervention pretest-posttest design. The number of treatments varied from 1 to 72 sessions with follow-up times ranging from less than one month to over 10 years. The primary outcomes measured in the review by van Rood and de Roos<sup>1</sup> were pain intensity and overall health status. [77] Three studies reporting on chronic pain showed that mean pain intensity scores decreased by 1.2–2 points on a 10-point scale (lower score indicates lower pain intensity) relative to the beginning of treatment. All three studies showed a statistically significant effect, but only one was rated as having a clinically significant effect. Four studies showed that mean pain intensity scores decreased by  $4.7 \pm 0.69$  points on a 10-point scale relative to the beginning of treatment. At long-term follow-up (between 3 weeks and 32 months), mean reduction in pain intensity was  $4.5 \pm 0.8$  points, and 52% of patients ( $n = 11$ ) were pain-free (pain intensity  $<1$ ). All studies showed a statistically significant effect, and three of four were rated as clinically significant. One single case study examined war-related MUPS, and showed improvement in health status on an 11-point scale (a higher score indicates better health status) from a score of 1 pretreatment to a score of 6.5 post treatment and a score of 8 at six months follow up, which was rated as a clinically significant effect.

## **Recommendation**

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)

## Discussion

A range of complementary and integrated medicine (CIM) modalities were assessed for global CMI. CIM modalities for global CMI have been studied for CMI unrelated to deployment, and have not specifically been studied in the setting of CMI subsequent to GW deployment or CMI subsequent to other deployments. The CIM interventions evaluated include the following: biofeedback, alternative exercise, carnosine, and St. John's Wort.

CIM modalities for pain-predominant CMI have been studied for CMI unrelated to deployment, and have not specifically been studied in the setting of CMI subsequent to GW deployment or CMI subsequent to other deployments. For pain predominant CMI, the literature on the efficacy of CIM for the treatment of fibromyalgia was reviewed. The treatments considered included acupuncture, alternative exercise, chiropractic care, hydrotherapy, massage therapy, nutritional supplements, and repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS).

CIM modalities for fatigue-predominant CMI have been studied for CMI unrelated to deployment, and have not specifically been studied in the setting of CMI subsequent to GW deployment or CMI subsequent to other deployments. Our searches identified two systematic reviews that met inclusion criteria and assessed the benefits and harms of CIM treatments for adults with chronic fatigue syndrome. [78] Only those reviews published on, or after 2008 were considered to be part of the evidence base for this key question. In cases where more than one systematic review addressed the same treatment, we selected the more recent and/or comprehensive review. These studies provided meta-analyses of a total of five RCTs and 40 non-RCTs enrolling a total of 5,938 patients. The systematic review by Wang et al. examined acupuncture and/or moxibustion therapy in the management of CFS (40 non-RCTs). [79] The systematic review by Kim et al. considered a range of CIM therapies including dietary interventions (three RCTs), distant healing (one RCT); homeopathy (one RCT), massage (one RCT), and herbal medicine (two RCTs) in the management of CFS. [78] Although the Kim et al. study reported on single trials of single treatments, Jadad ratings were available for each trial. A number of the studies were described as moderate to high quality and included more than 100 participants. Another review was available for the present key question. However, the review by Kim et al. provided more comprehensive data. In general, the studies included in the systematic review for acupuncture and/or moxibustion were rated as low quality by the authors of the review. No RCTs were included in this systematic review. The studies included in the systematic review for other CIM treatments ranged from high quality to low quality, depending upon the intervention. The main methodological limitations in study quality cited by authors was risk of bias due to lack of clarity with respect to blinding, limited sample size, inadequate randomization, lack of reported allocation concealment, or intent-to-treat analysis. [78]

Biofeedback was examined in a single RCT which examined the efficacy of biofeedback for treatment of patients with medically unexplained physical symptoms. [80] Patients were randomly assigned to 10

weekly sessions of biofeedback plus a psychiatric consultation intervention (PCI) or to PCI alone. The PCI intervention involved sending a standardized psychiatric consultation letter to the primary care physicians of all study patients with recommendations for the patient's ongoing medical treatment. The participants in the study were predominantly female (83.3% female in biofeedback group and 75.0% female in PCI group). The primary outcomes in the study on biofeedback plus PCI versus PCI alone were severity of symptoms and physical function. Secondary outcomes included depression and anxiety. Patients randomized to biofeedback plus PCI experienced greater reduction in symptoms (mean difference: -0.77, SE: 0.36,  $p = 0.04$ , effect size estimate: 0.8), and greater improvement in physical function (mean difference: 21.57, SE 6.02,  $p < 0.001$ , effect size estimate not reported), as well as greater reduction in symptoms of depression (mean difference -5.70, SE 2.56,  $p = 0.03$ , effect size estimate 0.81). No significant between group difference was observed on measures of anxiety. [80]

## Recommendation

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)

## Discussion

The Work Group suggested therapeutic trials of selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) or the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine based on inferences from the results of studies conducted in patients with DSM-IV diagnoses of somatoform disorders, the symptoms of which overlap considerably with those of CMI. The mechanism of action of these agents in somatoform disorders is thought to be related to their serotonergic effects. Four short-term clinical trials showed promising improvements in symptom scores and relatively good tolerability in study populations consisting mainly of patients with somatoform disorders with or without depression or anxiety. One advantage of some agents in these classes of antidepressants is that they may treat co-occurring depression and anxiety disorders often seen in patients with CMI. [81-85]

Of the SSRIs and SNRIs, only escitalopram, fluoxetine, sertraline and venlafaxine were studied in our literature search. We are uncertain whether there is a drug class effect, although antidepressants are generally accepted to have little differences in efficacy for major depressive disorder and some differences in tolerability and safety profiles. For CMI, it is reasonable to take the same approach for drug selection that is used for major depressive disorder: base drug selection on symptoms, safety, comorbid conditions, concurrent medication, and response and tolerability to previous antidepressants.

All of the SSRIs have the theoretical potential to worsen cognitive and sleep symptoms of CMI, as they are known to be associated with sedation (which may impair cognition) and/or insomnia. Mirtazapine is associated with a high incidence of somnolence (which may theoretically worsen CMI-related cognitive and fatigue symptoms). It has not been associated with an increased risk of insomnia and has been used to treat insomnia; therefore, it has an advantage over the SSRIs if insomnia is a bothersome symptom in CMI.



Providers should understand the limitations of the suggestion to consider trials of SSRIs, SNRIs and mirtazapine. Few agents have actually been studied. No pharmacologic agents have been evaluated in randomized clinical trials specifically for CMI, although some patients in the clinical trials may have met the definition for CMI used in this guideline. In the studies reviewed for global CMI, none of these antidepressants were evaluated for their effects on fatigue, sleep, and neurocognitive symptoms; their benefits in reducing these symptoms are uncertain. Only venlafaxine was evaluated for (and shown to improve) quality of life. [84]

Escitalopram was the only SSRI compared against placebo in a small (N = 51), moderate-quality, double-blind, randomized clinical trial involving patients with multisomatoform disorder, 29.4% of whom had concurrent depression and 52.9% an anxiety disorder. Escitalopram (10–20 mg/day; N = 25) was statistically and clinically beneficial in reducing somatic symptom scores on the PHQ-15. [85] Escitalopram had a large effect relative to placebo in terms of rate of responders with a number-needed-to-treat of two (95% CI, 2–4). Results for clinician global impression of improvement and severity, psychic, somatic, anxiety, depression, pain and disability also significantly favored escitalopram. The results may overestimate the true effect size of escitalopram therapy because of the small study population. Escitalopram was well tolerated in the study with one withdrawal due to side effects, no serious adverse events, and no increase in adverse effects relative to placebo. The results need to be confirmed in larger well-designed clinical trials that involve patients with CMI and that evaluate the patient's rather than the clinician's subjective global assessment of treatment benefits.

Although not studied in patients with CMI or somatoform disorders, citalopram may be a reasonable substitute for escitalopram at equivalent doses. In the treatment of major depressive disorder, citalopram 20 mg/day and escitalopram 10 mg/day (and their corresponding maximum doses of citalopram 40 mg/day and escitalopram 20 mg/day) produce clinically similar effects. In patients with fibromyalgia, the efficacy of citalopram has been shown to be inconsistent, [86,87] and not recommended in one SRMA. [88]

The effect sizes of fluoxetine and sertraline in reducing somatic symptoms are unknown because neither was compared against placebo; however, the two agents seem to be similar to each other in improving symptoms. Fluoxetine (10–60 mg/day) and sertraline (25–350 mg/day) were compared in a 12-week, fair-quality, open-label randomized trial in 45 patients with a DSM-IV diagnosis of undifferentiated somatoform disorder without depression, anxiety or other Axis I disorders. [83] Both agents reduced somatic symptom scores on the Physical Health Questionnaire (PHQ)-15 from the high severity category (scores greater than 15) to the moderate severity category (scores 10 to 14). There was no statistically significant treatment difference. Large improvements in measures for depression and moderate improvement in measures of general health were seen; however, there were no statistically significant treatment differences. Both treatments were well tolerated, with neither one resulting in withdrawals due to adverse events. The efficacies of these agents in CMI need to be verified in placebo-controlled trials.

Of the SNRIs, venlafaxine showed promising results and was well tolerated in a multicenter, double-blind, placebo-controlled pilot trial. [84] In the pilot trial, 117 primary care outpatients with DSM-IV

diagnoses of multisomatoform disorder (MSD), major depressive disorder and/or generalized anxiety disorder were randomized to either venlafaxine extended-release (ER) capsules or matching placebo. [84] Those who received venlafaxine ER (75–225 mg/day; mean 177 mg/day) showed improvement (from baseline to 12 weeks) in somatic symptom severity as measured on the PHQ-15; however, venlafaxine was statistically better than placebo only at week 8 and was no better than placebo at weeks 4 and 12 / end point. Venlafaxine ER was numerically but not statistically significantly better than placebo in terms of responder rates (percentages of patients with PHQ-15 scores less than 10 / moderate severity; 51% vs. 37%;  $p = 0.08$ ) and produced a faster median time to response than placebo (54 versus 71 days;  $p = 0.01$ ). Secondary outcome measures showed statistically significant improvements in PHQ-15 subscores for pain, Hamilton Rating Scale for Psychic Anxiety, Clinical Global Impression for Improvement, and the McGill Quality of Life Questionnaire total score. There was no difference between treatment groups in terms of withdrawals due to adverse events. Therefore, venlafaxine ER was well tolerated and showed inconsistent and equivocal results; primary efficacy measures failed to show benefit whereas secondary efficacy measures showed some benefits, mainly in terms of pain, anxiety and functional outcomes.

In a separate randomized, open-label clinical trial, venlafaxine was shown to be slightly inferior or similar in effect to mirtazapine. [82] This trial involved 95 outpatients diagnosed with DSM-IV undifferentiated somatoform disorder (USD) without depression, anxiety or other DSM Axis I disorders who were randomized to either mirtazapine (titrated, 15–60 mg/day) or venlafaxine (titrated, 37.5–225 mg/day) therapy of 12 weeks' duration. [82] Venlafaxine was statistically but not clinically inferior to mirtazapine in terms of reduction from baseline to 12 weeks / end point in somatic symptom severity scores on the PHQ-15 survey (difference of –2.3 on a 30-point scale;  $p = 0.046$ ). The reductions in scores were of questionable clinical relevance, as the total PHQ-15 scores remained greater than 15 (“high” severity category) despite the improvements from baseline scores. No statistically significant treatment differences were seen in the secondary outcome measures for depression and general health. Both treatments were well tolerated, with no statistically significant treatment difference in withdrawals due to adverse events. Overall, venlafaxine and mirtazapine were similar in treatment effects. Mirtazapine showed promising effects but has not been evaluated against placebo.

The Work Group also reviewed a clinical trial which showed that levosupiride (a benzamide dopamine  $D_2$ -receptor selective antipsychotic with gastrointestinal prokinetic effects) reduced symptoms in Italian patients with somatoform disorder. [81] The agent is not available in the U.S. Antipsychotics are associated with significant extrapyramidal adverse effects, and the trial results may not be applicable to Americans because of cultural differences in somatization. The Work Group made no recommendation for the use of antipsychotics in CMI.

## Recommendation

12. The guideline panel suggests against the use of doxycycline for the treatment of patients with clinical symptoms of pain-predominant CMI. (Weak Against)

## Discussion



The results of a VA- and DoD-sponsored, moderate-quality, double-blind, placebo-controlled, randomized trial showed that a 12-month course of doxycycline in 491 *Mycoplasma* DNA-positive patients with Gulf War Veterans Illness was ineffective in improving physical function and symptoms. [105] The study did not exclude individuals with fatigue or chronic fatigue syndrome. The reductions in percentages of patients seropositive for *Mycoplasma* were similar in both groups. Doxycycline increased the incidences of nausea and photosensitivity; therefore, the harms outweighed the benefits of therapy. The study authors noted that it was possible that doxycycline-treated patients may have received less medical care because the antibiotic could have treated an undetected infection, and suggested that more studies were needed to determine whether infectious or noninfectious entities are causally related to Gulf War Veterans Illness. The results of this study are applicable to a narrow subpopulation of patients. The use of other antibiotics and combination antibiotics may deserve investigation.

## Recommendation

13. The guideline panel recommends against the long-term use of opioid medications for the management of patients with CMI. (Strong Against)

## Discussion

The use of long-term opioid therapy (lasting three or more months) should be avoided. There is no direct supporting evidence, and any potential benefits are substantially tempered by risks of serious adverse effects and the potential to worsen or confound CMI symptoms. There is also a growing concern about the adverse consequences of opioid misuse, abuse, addiction and diversion on patient, family and public health. The results of a retrospective study in U.S. Veterans with moderate to severe chronic non-cancer pain also showed that, in the setting of a rehabilitative interdisciplinary pain program, patients who were tapered off of opioid therapy experienced similar or larger *improvements* in multidimensional clinical outcomes including pain, physical function and sleep compared with nonopioid-treated patients. [89] The results suggested that opioid therapy was not necessary for improving clinical outcomes and may have reduced physical function in some patients.

There have been no published randomized clinical trials evaluating the short- or long-term efficacy and safety of opioid therapy in patients with CMI. In the related FMS, opioids have also not been studied as isolated drugs in clinical studies. Consensus expert opinion recommends against the use of opioids in FMS [90] as older trials demonstrated inconsistent improvement in pain. [91] In addition to a significant adverse effect profile, the lack of efficacy of opioid analgesics may be due to the inability to target the pathophysiologic processes involved in this central sensitization syndrome. [92]

Since CMI is a heterogeneous condition, some patients may respond to opioid analgesic therapy; however, multimodal, multidisciplinary behavioral and physical therapies with adjunctive non-opioid analgesic therapies remain the therapeutic approach of choice for chronic pain in CMI. Providers considering opioid therapy for patients with CMI should manage opioid-treated patients in concordance with the VA/DoD CPG on Management of Opioid Therapy in Chronic Pain.

As part of the opioid risk-benefit assessments, providers should evaluate patients on an ongoing basis for opioid-related adverse effects that may confound or worsen CMI symptoms. For instance, opioid-

induced hyperalgesia may be confused with CMI-related pain; effects on sleep architecture and sleep-disordered breathing (e.g., central sleep apnea) may contribute to non-restorative sleep; depression may add to CMI symptoms; [93] sedation may worsen fatigue and interfere with physical rehabilitation; androgen deficiency may confound or worsen fatigue, depression, and weakness; and constipation may worsen underlying gastrointestinal symptoms. The safety of opioids in patients with CMI has not been evaluated; this emphasizes the need to re-assess patients for potential harms that may be counterproductive to achieving treatment goals and to individualize opioid therapy decisions.

Short-term, low-dose (less than 100 mg/day morphine milligram equivalents) opioid therapy may be considered in selected patients with *severe* pain that prevents them from participating in behavioral and physical therapies and who experience insufficient pain reduction from adequate trials of other evidence-based, nonopioid pain medications such as acetaminophen, nonsteroidal anti-inflammatory drugs, antiepileptics, tricyclic antidepressants and SNRIs. Tramadol would be a good first opioid to try because of its SNRI effects. The treatment goal of short-term opioid therapy is to reduce pain sufficiently to allow the patient to adhere to his / her personalized treatment plan. Short courses (less than two weeks in duration) of opioids may be considered adequate trials. Patients who respond may be continued on short-term opioid therapy until progress from behavioral and physical therapies is seen and preferably for no more than three months. At that time, opioids may be gradually tapered using a patient-centered care model and regular risk-benefit assessments. Tapering opioids may be facilitated by addressing the other dimensions of the patient's CMI and concomitantly optimizing both non-pharmacologic therapies and non-addictive medications for pain. Tapering off opioids in patients who perceive benefit from such therapy can be difficult; therefore, cautious and selective use of opioid therapy is important. Obtaining an informed patient-provider agreement about the plan to taper off opioids before starting therapy may be helpful.

## **Therapeutic Interventions for Pain-Predominant CMI**

### **Recommendation**

14. The guideline panel recommends considering acupuncture as part of the management of patients with pain-predominant symptoms of CMI. (Weak For)

### **Discussion**

Although the quality of evidence is low for acupuncture, there is some evidence of benefit for pain reduction. As with all interventions, acupuncture can be a component of a personalized proactive, patient-driven model of care, with shared decision making. Unfortunately, there is little evidence currently available on the use of complementary and integrated medicines for CMI. Furthermore, much of the current research on acupuncture discusses short-term rather than long-term effects. There is a lack of high quality evidence on the long-term effects of acupuncture, along with some of the potential cost implications that this treatment can carry for both the patient and the health care system overall. The guideline panel emphasizes the need for more research in this area.

## Studies Comparing Acupuncture to Sham Acupuncture

Langhorst et al. performed a review of the literature and meta-analysis on the benefits and harms of acupuncture for FMS. The evidence base for this review consisted of seven RCTs enrolling a total of 242 adults. Most patients across the studies were female (median percent female 95%). All studies used traditional Chinese acupuncture points, with two studies utilizing standardized points and five studies utilizing an individualized paradigm. Two trials performed electro-acupuncture and five trials performed manual acupuncture. The length of the interventions, excluding follow-up, ranged from 2 to 15 weeks with a median of eight weeks. The median duration of acupuncture treatment was nine sessions (range 6–25). The control condition across all studies was sham or simulated acupuncture. The standardized mean difference was calculated in order to estimate the summary effect size for the following outcomes: pain, fatigue, sleep disturbances, and physical function. The findings demonstrated a small, but significant effect of acupuncture compared to sham for reducing pain (-0.25; 95% CI [-0.49 to -0.02];  $p = 0.04$ ) at post-treatment. The positive effect of acupuncture compared to sham was not observed at later follow-up times. No significant differences were observed between acupuncture and sham for fatigue, sleep disturbances, and physical function at post-treatment or at later follow-up times. Three studies reported on side effects such as discomfort at side of needle sensation, nausea, soreness and worsening of FMS symptoms. The frequency of the side effects reported ranged from 3% to 70% for all types of acupuncture. [94]

## Studies Comparing Acupuncture to Conventional Medicine

Cao et al. performed a review of the literature and meta-analysis on the benefits and harms of Traditional Chinese Medicine (TCM) therapies for FMS. A total of three RCTs enrolling 73 patients compared acupuncture to conventional medicine. Two studies compared acupuncture to amitriptyline, and one study compared acupuncture to ibuprofen. The mean age range of the patients enrolled in the studies was 31 to 50 years. The gender of the patients enrolled in the studies was not reported. Duration of treatment ranged from four to eight weeks. The mean difference was calculated as an estimated summary effect size for pain, which was measured using the Visual Analog Scale. Data for other outcomes considered in the studies comparing acupuncture to conventional medicine (e.g., quality of life, depression, or anxiety) were not reported in a manner that allowed for a meta-analysis to be performed. The results of the analysis indicated that acupuncture was significantly better than conventional medication in reducing pain (MD, -1.78; 95% CI -2.24 to -1.32,  $p < 0.00001$ ). The reported adverse effects of acupuncture were bruising, nausea, fainting, discomfort at the sites of needle insertions or simulated needle insertions, and temporary edema of the hand. Lethargy, nausea, fainting, dry mouth, fatigue, blurred vision, hyperhidrosis, and constipation were reported adverse effects of conventional medications. [95]

## Recommendations

15. The guideline panel recommends 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 peripheral pain symptoms associated with CMI that fail to respond to other non-opioid analgesic medications or non-pharmacologic approaches. (Weak For)

## Discussion

Non-opioid analgesics (i.e., non-steroidal anti-inflammatory drugs) may be useful for treating certain pain symptoms associated with CMI (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. Ibuprofen showed no benefit over placebo for pain, sleep disturbance, duration of stiffness, or fatigue. [96,97] 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. [98]

The evidence reviewed for a recommendation on non-opioid analgesics arose from the 2001 CPG and was limited to non-steroidal anti-inflammatory drugs (NSAID) for chronic fatigue syndrome and fibromyalgia. The guideline panel for the 2014 update did not explicitly assess literature from the year 2000 onwards; however the group chose to carry forward the earlier recommendation regarding non-opioid analgesics into the updated CPG as the historical evidence was acceptable and sufficient.

Since the last set of guidelines in 2001 additional studies have been performed assessing the efficacy of tramadol in the management of FMS. Tramadol is recommended for the treatment of pain due to FMS. [90] A review of the treatment of FMS performed by the European League Against Rheumatism [90] identified two randomized controlled trials. One was a high-quality study of over 300 patients and was of 13 weeks duration. [99] The second was preceded by an open label study and only included responders. [100] Bennett et al. reported positive effects for pain and function, and Russell et al. reported improved pain levels but no change in function. There was no difference between placebo and treated groups for adverse event withdrawals. [90] Most common adverse effects were nausea, dizziness, somnolence, and constipation. [91] Combination tramadol with acetaminophen may be more effective than tramadol monotherapy. [101] Tramadol should be used with some caution due to the possibility of typical opiate withdrawal symptoms with discontinuation and the risk of abuse and dependence. [90] In addition, evidence suggests that tramadol increases the risk of serotonergic syndrome in patients. Providers should use caution and discuss with their patients some of the adverse events associated with the use of tramadol prior to prescribing this medication.

## Recommendations

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)

## Discussion

For pain predominant CMI, the guideline panel relied heavily on studies assessing the efficacy of pharmacologic interventions in the treatment of FMS. The highest quality evidence supported the use of SNRIs, specifically duloxetine and milnacipran, though the treatment effect was small. Hauser et al. conducted a systematic review, which included 10 randomized placebo-controlled trials enrolling a total of 6,038 patients. [102] The majority of patients were female (median 95%) with a mean age of 49 years. Trials had a median duration of 17.5 weeks. SNRIs demonstrated a small incremental effect over placebo in reducing pain and showed insubstantial improvements in quality of life and fatigue scores. [102] For a 50% reduction in pain, the number needed to treat to benefit (NNTB) was 11. Participants were significantly more likely to withdraw from a trial due to side effects when taking a SNRI with a number needed to treat to harm (NNTH) of 11. Reported reasons to stop the medication frequently included nausea, dry mouth, constipation, headache, somnolence/dizziness and insomnia. There was no statistically significant difference in serious adverse events with very rare reports of liver damage and suicidality. [102]

Evidence for the remaining therapeutic regimens was lower quality due to failure to report adequate randomization, lack of reported allocation concealment, no intent to treat analysis, and selective outcome reporting. Other than trials of pregabalin, there were also no trials in other medications with more than 100 patients per group, contributing to increased heterogeneity among trials.

A 2009 meta-analysis of six studies found that tricyclic antidepressants significantly, and substantially, improved pain, fatigue, and sleep in FMS. [103] The clinical benefit of TCAs was less clear in a subsequent network meta-analysis of 15 randomized controlled trials with a total of 1,026 patients that was mostly female with an average age of 42.5 years. [67] In this analysis, TCAs had a statistically significant, but small, improvement in pain and fatigue in patients with FMS. These benefits were no longer statistically significant when the analysis was limited to studies with more than 50 patients per group, and there was also no difference in sleep or quality of life. Overall, 13 studies compared TCA to placebo, 1 compared TCA to SSRI, and 1 compared TCA to aerobic exercise. The median duration of all trials was 12 weeks. Rates of adverse events were not different between TCAs and comparators.

The same network meta-analysis also examined the use of SSRIs in the treatment of FMS, analyzing 10 randomized placebo-controlled trials with a median duration of 12 weeks and enrolling a total of 644 patients. [67] All patients were female and with a mean age of 45 years. Use of SSRIs produced a small to moderate improvement in pain and quality of life but not fatigue. The benefits no longer remained when trials were limited to studies that had 50 patients or more in each arm. Rates of dropout due to adverse events were not different between SSRIs and placebo.

Pregabalin has shown some potential in the treatment of FMS pain. Nuesch et al. conducted a meta-analysis of 4 randomized placebo-controlled trials with a median duration of 12 weeks and enrolling a total of 2,625 patients. [67] The majority of patients were female (median 92.5%) and 49 years of age. Overall, use of pregabalin produced a small improvement in pain but not quality of life or fatigue. [67] When limited to studies with more than 100 patients per group, pregabalin showed a small benefit in pain, quality of life, fatigue and sleep. Rates of dropout due to adverse events were not different between pregabalin and placebo. A single randomized controlled trial of 150 patients has shown

preliminary potential for gabapentin in the treatment of FMS pain. [\[104\]](#) More research is needed to determine the comparative benefit to pregabalin.

## **Therapeutic Interventions for Fatigue-Predominant CMI**

### **Recommendation**

19. The guideline panel recommends considering acupuncture as part of the management of patients with fatigue-predominant symptoms of CMI. (Weak For)

### **Discussion**

Wang et al. conducted a systematic review on the efficacy of acupuncture and/or moxibustion for the treatment of CFS. The evidence base for the review consisted of 40 non-RCTs enrolling a total of 2,266 patients. The age and gender of participants was not reported. Out of 40 trials, 13 reported the use of a control condition. Four studies compared acupuncture and/or moxibustion to Western medical treatment, six studies examined acupuncture and/or moxibustion as an adjunct to other therapies, and three studies compared one form of acupuncture and/or moxibustion to different acupoints or moxibustion materials. Generally, 30-minute treatment sessions were given three times a week for a total of 20-30 sessions. The primary outcome measured was effective improvement in CFS symptoms. “Effectiveness” was defined as a patient reporting more than one third of initial symptoms remitting. No data analyses were presented in this review. All studies included in the systematic review stated that the acupuncture and/or moxibustion treatments were effective, with treatment efficacy ranging from 78.95% to 100% effective in improving CFS symptoms. [\[79\]](#)

### **Recommendation**

20. The guideline panel suggests considering a trial of serotonin–norepinephrine reuptake inhibitor (SNRI) or tricyclic antidepressants (TCA) for patients with clinical symptoms of fatigue-predominant CMI. (Weak For)

### **Discussion**

Meta-analyses of RCTs of patients with FMS lend indirect support for therapeutic trials of TCAs and SNRIs in patients with fatigue-predominant CMI. Given the potential for adverse effects, the small beneficial effect shown in the available trials, and the absence of trials longer than 12 weeks, clinicians should continuously weigh individualized benefits and risks of treatment. Physicians and patients should both have realistic expectations. A small amount of patients may have substantial benefit, while many will have little to no improvement that likely will not outweigh adverse effects. Patients should not be left on therapy after an adequate trial if there is not any noticeable improvement.

#### **SNRI**

SNRIs have been shown to have a slight reduction in fatigue in patients with fibromyalgia, but no benefit in sleep, according to a 2012 Cochrane meta-analysis by Häuser et al. of nine randomized placebo

controlled studies with 5656 participants. [102] More patients in the SNRI group withdrew due to adverse events, though there was no difference in significant adverse events. On subgroup analysis, there was no difference between duloxetine and milnacipran in their effect on fatigue or in withdrawal due to adverse events. There are no RCTs evaluating the use of SNRIs in CFS.

## TCA

Two meta-analyses of TCAs in patients with FMS showed a significant, but not substantial, improvement in both fatigue and sleep relative to comparators. [67,103] The available evidence was of lower quality than that of SNRIs. The randomized controlled trials generally had a small numbers of patients, no reporting of adequate randomization or allocation concealment, no intent to treat analysis, and elective outcome reporting. The duration of the trials was a median of 8 weeks. Dropout rates were not different between TCAs and comparator groups, though caution is prudent in patients with positive suicidal ideations due to the lethality of a TCA overdose. There are no RCTs of TCAs in CFS reported to date.

## Other Antidepressants

Available evidence does not support the use of other anti-depressants for the treatment of fatigue predominant CMI. Meta-analyses have failed to show any significant benefit from SSRIs or monoamine oxidase inhibitor (MAOI) on fatigue or sleep in FMS. [67,103] While one small RCT of a MAOI in CFS showed some mild improvement, [106] the remainder of RCTs of SSRIs and MAOIs in CFS has not found any sustained benefit. [106-109] There was no benefit on fatigue in a randomized controlled crossover trial of mirtazapine in 72 patients with CFS. [110]

Additionally, long-term benefits of all antidepressants are uncertain, and dietary restrictions and the risk of hypertensive crisis limit the clinical utility of MAOIs.

## Other Pharmacologic Therapies

There is no evidence supporting the use of other agents for the treatment of symptoms of fatigue-predominant CMI. Nicotinamide adenine dinucleotide (NADH), an over-the-counter drug that facilitates generation of adenosine triphosphate, did not show any benefit compared to nutritional supplements and psychological therapy at 24 months in a small RCT of 31 CFS patients. [111] In a randomized, placebo-controlled trial (n=20) of CFS patients, no significant improvement was found with growth hormone. [112] In a double-blind RCT of chronic post infectious fatigue patients (n=326), no improvement was found with sulbutiamine, a synthetic thiamine derivative, compared to placebo. [113]

No benefit has been demonstrated with the use of other psychotropic agents for treatment of CFS or treatment of fatigue in FMS. Meta-analyses have failed to show any significant benefit for pregabalin on fatigue or sleep in FMS. [67] A randomized controlled trial of the acetyl cholinesterase inhibitor galantamine in 434 patients with CFS found no benefit in the primary or secondary outcomes. [114] A randomized, placebo-controlled, double-blind trial (n=67) in CFS patients found no improvement with ondansetron, which had been hypothesized to show benefit due to its effects on the serotonin system. [115] An un-blinded study of 40 non-depressed CFS patients compared amisulpride, a non-FDA approved atypical antipsychotic to fluoxetine for twelve weeks, with the amisulpride group showing significant improvement in self report and observer-based measures of fatigue and somatic complaints. [116] There have been no trials of FDA-approved anti-psychotics in CFS patients, and given the varying



degree of action and side-effect profile of the antipsychotics, it is impossible to extrapolate the results to other medications in the class.

Since the last set of guidelines in 2001 there have been no new trials assessing the efficacy of glucocorticoids in the treatment of FMS. Based on consensus expert opinion, glucocorticoids still do not appear beneficial in treating patients with FMS. [\[90\]](#)

## Recommendation

21. The guideline panel suggests against the use of pharmacologic agents for sleep disturbances in CMI. (Weak Against)

## Discussion

There is no evidence for the use of any particular sleep agents in chronic multisymptom illness. Behavioral approaches to sleep disturbance are likely to be more successful than pharmacologic approaches, as the latter do not induce normal sleep. Studies in FMS have found no significant benefit of therapy. Two RCTs of benzodiazepine sedative-hypnotics for the treatment of FM showed no benefit over placebo. [\[97,117\]](#) A RCT of zopiclone, a non-benzodiazepine sedative-hypnotic, also showed no benefit over placebo in the treatment of FM. [\[118\]](#) There were no studies meeting inclusion criteria studying sleep agents in patients with CFS.

## Recommendation

22. The guideline panel suggests against the use of stimulants for the treatment of fatigue-predominant CMI. (Weak Against)

## Discussion

Small studies have found some benefits with the use of 4-6 weeks trial of stimulants in the treatment of CFS. Randomized placebo-controlled studies of 20, 26, and 60 patients showed improvement in fatigue using dexamphetamine (5-15 mg twice daily), lisdexamfetamine (30- 70 mg daily), and methylphenidate (20 mg daily), respectively. [\[119-121\]](#) Reduced food consumption was a prominent side effect with dexamphetamine. Anxiety and insomnia caused two patients to withdraw from lisdexamfetamine treatment. Dry mouth was the only adverse effect noted from methylphenidate in the small, short-term trial.

The benefits and risks associated with long-term stimulant treatment are not known, and the risks of misuse, abuse and withdrawal have to be considered. Without evidence for prolonged use of stimulants, it is currently unclear how short trials of stimulant medication fit into the long-term treatment of individuals with CMI. The guideline panel, therefore, currently suggests against their use, though acknowledging that the low-quality, small trials available do show some benefit over the short term.

## Recommendation



23. The guideline panel recommends against the empiric use of antivirals or antibiotics for fatigue-predominant symptoms of CMI. (Strong Against)

## Discussion

Since CFS can begin abruptly following a viral-like illness, anti-viral therapy has been evaluated for possible benefit in CFS patients. Controlled trials of amantadine and acyclovir showed no benefit with poor tolerability with amantadine, and 12% of acyclovir-treated patient developing reversible renal failure. [122,123] In a randomized clinical trial of 30 patients with CFS and IgG antibody titers against HHV-6 and EBV, valganciclovir did not show statistically significant improvement in the Multi-Dimensional Fatigue inventory at 6 months. [124] Patients taking valganciclovir were more likely to be labeled as a responder by their blinded physician, though. A pharmacy-funded study of valacyclovir in 32 patients with CFS and Epstein-Barr Virus infection claimed benefit from treatment but had nonstandard reporting, and a statistical difference between groups cannot be verified from the manuscript. [125]

## Recommendation

24. The guideline panel recommends against the use of corticosteroids for the treatment of fatigue-predominant CMI. (Strong Against)

## Discussion

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. Mineralocorticoids, in particular, could be beneficial in patients with fatigue since a subset of CFS patients may have neutrally mediated hypotension, with 22 of 23 patients with CFS having a positive tilt-table test in one study. [126]

However, RCTs in patients with CFS have found no significant, sustained benefit in reducing the symptoms of CFS with low dose hydrocortisone (5 to 10mg/day), replacement dose hydrocortisone (25 to 35mg/day), or fludrocortisone (0.1-0.2 mg/day). [127-130] Adrenal suppression was also demonstrated in the 12 week trial of replacement dose hydrocortisone. [129]

Glucocorticoids also still do not appear beneficial in treating patients with FMS based on consensus expert opinion. [90]

Adverse effects are also a concern. Adrenal suppression was demonstrated in the 12 week trial of replacement dose hydrocortisone in patients with CFS. [129] Given the lack of proven benefit, and the risk for adrenal suppression, we currently recommend against the use of corticosteroids for empiric treatment of CMI symptoms.

## Recommendation

25. The guideline panel recommends against the use of immunotherapy for the treatment of the symptoms of fatigue predominant CMI. (Strong Against)

## Discussion

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. It is unknown if any of these immunologic abnormalities may be linked to fatigue-predominant CMI. Immunologic treatments investigated in patients with CFS are still considered experimental. They cannot be recommended for patients with CMI due to the indirect and low quality nature of the available research and a lack of consistent and reproducible evidence that benefits outweigh the harms of treatment.

Some preliminary benefit has been seen with rintatolimod, a Toll Like Receptor (TLR) 3 agonist with immunomodulatory and antiviral properties. In an RCT of 92 CFS patients [131] and a subsequent Phase III multicenter RCT of 234 CFS patients, rintatolimod given intravenously twice weekly for up to 40 weeks showed improvements in capacity to perform activities of daily living and exercise tolerance. However, the FDA did not approve rintatolimod for use in chronic fatigue syndrome in their 2013 review due to concerns over the drug's effectiveness and safety, specifically citing deficiencies in the manufacturer's new drug application in the areas of "clinical, statistical, clinical pharmacology, nonclinical, product quality, and facilities inspection" (FDA press release – see bibliography). Staphylococcus toxoid injections were examined in a preliminary RCT of 28 patients and a follow-up RCT of 100 consecutive female patients who met criteria for both FMS and CFS. [132,133] The follow-up study showed improvements compared to placebo in the primary outcomes of proportion of responders based on global ratings and proportion of patients with a  $\geq 50\%$  symptom reduction. [133] Relapse occurred after the treatment was stopped at six months. Dropouts were equal in the treatment and control groups; local injection site reactions occurred in both groups. The findings need to be confirmed before treatment can be recommended for the general CMI population.

RCTs of Immunoglobulin therapy in patients with CFS have reported mixed results, with two of the four RCTs showing no benefit over placebo. [134-137] Adverse effects included phlebitis (~50%) and constitutional symptoms (~80%), such as headaches, fatigue, and diminished concentration.

Other immunologic therapies have shown no benefit. Dialyzable leukocyte extract (DLE), also known as transfer factor, showed no beneficial effects in a double-blind placebo controlled trial of 90 patients with CFS. [138] Alpha interferon showed no beneficial effects over placebo in a study of 30 CFS patients. [139] Rituximab showed no benefit over placebo in a study of 30 CFS patients in the primary outcome of self-reported fatigue, though the study cited that there were more patients with lasting improvement in the treatment group. [140]

## Therapeutic Interventions for Gastrointestinal-Predominant CMI

### Recommendation

26. The guideline panel suggests treating patients with CMI and predominantly gastrointestinal symptoms, in accordance with recognized evidence-based care for IBS. (Weak For)

## Discussion

Clinical practices for irritable bowel syndrome are well established and are applicable to patients experiencing predominantly gastrointestinal symptoms of CMI. The Work Group suggests that patients with these symptoms be treated according to the evidence-based practices that are currently available through the VA and DoD healthcare systems and other specialty clinical groups.

## Recommendation

27. The guideline panel recommends considering minimal contact psychological therapies for treatment of GI predominant CMI. (Weak For)

## Discussion

There is reasonable evidence to consider minimal in-person contact cognitive behavioral therapy care for an at-need CMI population. Minimal-contact psychological treatments [10–12] place a significant emphasis on self-management of symptoms. Contact with health care professionals varies but is generally limited to a small number of face-to-face sessions (or possibly, none at all), supplemented or replaced by computer-assisted therapy, telephone and/or online support. Pajak et al. conducted a systematic review on the efficacy of minimal contact psychological treatment for the treatment of IBS. [141] This review contained several types of minimal contact psychological treatment, with one or two studies each, but minimal contact CBT was examined in nine trials. Minimal contact was defined as fewer than four face-to-face sessions with a therapist. The evidence base for the review consisted of nine RCTs and one non-RCT enrolling a total of 734 patients (minimal contact CBT n = 367; controls n = 367). The average age of the patients was 40 years, and the percentage of female patients ranged from 71% to 91%. Five studies compared minimal contact intervention to waitlist, three studies compared minimal contact to treatment as usual, and one study compared two different minimal contact interventions. Some studies used a standard CBT treatment arm as an active control, but data from traditional CBT were not used in data analysis and are not presented here. Treatment duration varied from 5 to 10 weeks. Follow-up information was available in a subset of studies for three to six months post-intervention. The primary outcomes measured in the review by Pajak et al. were severity of IBS symptom scores and quality of life. [141] The authors of this review pooled data for these outcomes in separate meta-analyses using the standardized mean difference to calculate the summary effect size estimates. The SMD for reduction in symptom severity at the end of treatment was SMD = 0.83 (95% CI not reported; effect size: Large), indicating that minimal contact cognitive behavioral therapy is superior relative to comparator. Long term follow up at three to six months after the intervention indicated that minimal contact CBT is moderately superior to comparator (SMD = 0.56; 95% CI not reported; effect size: Medium). Quality of life ratings were moderately higher at the end of CBT intervention relative to comparator (SMD = 0.63; 95% CI not reported; effect size: Medium), but this observation became weaker three to six months after the intervention (SMD = 0.20; 95% CI not reported; effect size: Small). [141]

## Recommendation

28. The guideline panel suggest against the use of acupuncture for treatment of patients with gastrointestinal-predominant symptoms of CMI. (Weak Against)

## Discussion

Manheimer et al. conducted a systematic review on the efficacy of acupuncture for the treatment of IBS. [142] The evidence base for the review consisted of 17 randomized controlled trials enrolling a total of 1,806 patients. Age and gender of participants were not reported. Five studies compared acupuncture to sham acupuncture, five studies compared acupuncture to pharmacotherapy, two studies compared acupuncture to probiotics, four studies examined the efficacy of acupuncture as an add-on therapy to traditional Chinese medicine, one study examined the efficacy of acupuncture as an add-on therapy to psychotherapy or in comparison with psychotherapy, and two studies compared the efficacy of acupuncture to usual care/no specific treatment. On average, participants received four treatments per week (range from <1 time per week to seven days per week). Overall, the duration of all trials was 3 to 21 weeks (median four weeks). The primary outcomes considered in the review by Manheimer et al. were symptom severity and quality of life. In the review, four moderate quality studies compared the efficacy of acupuncture relative to sham treatment on symptom severity, three of which assessed quality of life. In these trials, acupuncture did not significantly improve symptom severity (SMD = -0.11; 95% CI -0.35 to 0.13) or quality of life (SMD = -0.03; 95% CI -0.27 to 0.22) relative to sham treatment. In five low-quality studies, the effectiveness of acupuncture was compared with pharmacotherapy for symptom severity. Acupuncture statistically significantly improved symptom severity relative to pharmacotherapy (RR = 1.28; 95% CI 1.12 to 1.45). It should be noted that all five of these trials were conducted in Chinese populations, and generalizability to Western populations may be limited. [142]

## Appendix A: Guideline Development Process

The methodology used in the development of the clinical practice guideline for chronic multisymptom illness (Version 2.0 - 2014) follows the Guideline for Guidelines, an internal working document of the Veterans Health Administration (VHA) and Department of Defense (DoD) Evidence-based Practice Working Group (EBPWG). This document provides information regarding the process of developing guidelines, including the identification and assembly of the Guideline Champions (Champions) and other subject matter experts from within the VA and DoD, known as the Work Group, conduct of a systematic literature review and ultimately, submission of a new CPG.

The Champions and Work Group members for this CPG were charged with developing evidence-based clinical practice recommendations and publishing a guideline document to be used by providers within the VA/DoD healthcare system. Champions were responsible for identifying the key evidence questions of greatest clinical relevance, importance, and interest for rehabilitation of a patient with an upper extremity amputation. In addition, Champions assisted in:

- Conducting the evidence review, including providing direction on inclusion and exclusion criteria
- Assessing the level and quality of the evidence
- Identifying appropriate disciplines to be included as part of the Work Group
- Directing and coordinating the Work Group
- Participating throughout the guideline development and review processes

The VA Office of Quality, Safety and Value, in collaboration with the DoD, identified four clinical leaders as Champions for the 2014 CMI CPG. The Lewin Group (Lewin) and their sub-contractors ECRI Institute and Duty First Consulting, held the first conference call for this Guideline in July 2013, with participation from the contracting officer's representatives (COR), leaders from the VA and DoD evidence-based guideline development program, and the Champions. During this call, the project team discussed the scope of the guideline initiative, the roles and responsibilities of the Champions, the project timeline, and the approach for developing evidence questions for a systematic review on CMI. During this call, the team also established a list of clinical specialties and areas of expertise that are important and relevant to CMI, from which Work Group members were recruited. The specialties areas included dietetics, family practice, internal medicine, nursing, orthopedics, primary care, pharmacy and rheumatology.

## Methodology

The guideline development process for the VA/DoD CMI CPG consisted of the following steps:

- Identifying evidence questions
- Conducting a systematic review of the literature
- Convening a three and a half day face to face meeting with the CPG Champions and Work Group
- Submitting a final CMI CPG on to the VA/DoD Evidence-Based Practice Working Group

The following is a detailed description of each of these steps.

## Formulating Evidence Questions

The Clinical Practice Guideline (CPG) Champions were tasked with identifying key evidence questions to guide the systematic review of the literature on Chronic Multisymptom Illness (CMI). These questions, which were developed in consultation with the Lewin Group's evidence review team, addressed clinical topics of the highest priority for the Veterans Affairs (VA) and Department of Defense (DoD) populations. The key questions follow the population, intervention, comparison, outcome, timing and setting (PICOTS) framework for evidence questions, as established by the Agency for Healthcare Research and Quality (AHRQ). Table A-1 provides a brief overview of the PICOTS typology.

**Table A-1: PICOTS**

<b>P</b>	Patients, Population or Problem	A description of the patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-morbidities, and other patient characteristics or demographics.
<b>I</b>	Intervention or Exposure	Refers to the specific treatments or approaches used with the patient or population. It includes doses, frequency, methods of administering treatments, etc.
<b>C</b>	Comparison	Describes the interventions or care that is being compared with the intervention(s) of interest described above. It includes alternatives such as placebo, drugs, surgery, lifestyle changes, standard of care, etc.
<b>O</b>	Outcome	Describes the specific results of interest. Outcomes can include short, intermediate, and long-term outcomes, or specific results such as quality of life, complications, mortality, morbidity, etc.
<b>(T)</b>	Timing, if applicable	Describes the duration of time that is of interest for the particular patient intervention and outcome, benefit, or harm to occur (or not occur).
<b>(S)</b>	Setting, of applicable	Describes the setting or context of interest. Setting can be a location (such as primary, specialty, or inpatient care).

The Champions and evidence review team carried out several iterations of this process, each time narrowing the scope of the CPG and the literature review by prioritizing the topics of interest. Table A-2 contains the final set of key questions used to guide the systematic review for this CPG.

## Population(s)

The key questions were specific to adults 18 years or older with CMI. Within the review, CMI is defined as patients with a medically unexplained syndrome such as fibromyalgia syndrome, chronic fatigue syndrome, functional gastrointestinal disorder, or with a military specific medically unexplained syndrome, such as Gulf War syndrome or post-deployment syndrome. The definition of CMI also included patients without a formal diagnosis but who exhibit symptoms from two or more of the following six categories for a minimum of 6 months duration: fatigue, mood and cognition, musculoskeletal, respiratory, gastrointestinal and neurologic.

Patients with symptoms lasting less than 6 months, or those who experienced only one of the listed symptoms, or patients with a clearly organic-based disease that explained all/most of their symptoms were not covered in this report.

## ***Interventions***

The diagnostic technologies considered under Key Question 1 of the review fell within the following categories: biomarkers (this included studies of biological markers and neuroimaging studies), neuropsychological test batteries, and sleep studies.

Treatments covered in Key Questions 2 through 4 of the review included the following: pharmacological treatments, such as antibiotics, antidepressants, and pain medications; non-pharmacological treatments, such as psychological therapies, exercise, and hypnosis; and complementary and alternative medicine treatments, such as acupuncture, biofeedback, and nutritional supplements.

Management approaches considered in Key Questions 5 through 9 included: team based approaches, core competencies of the treatment team, patient-provider communication styles, the role of occupational and other rehabilitative services, and patient follow up practices.

Risk factors that may be associated with predisposing, precipitating, and perpetuating ( ) CMI included medical (obesity), psychosocial (abuse history), and occupational/environmental (chemical exposure) with CMI were considered for Key Questions 10 through 12.

## ***Outcomes***

For the treatment and management questions, the outcomes of interest in the systematic review were a reduction in the intensity or frequency of symptoms (e.g., pain, fatigue), improved function, improved quality of life, health care use, and harms. For the diagnostic question, the outcomes of interest were identification of organic disease patterns or a change in treatment/management strategy. For the risk factor studies, the outcome of interest was the degree of association with CMI.

## ***Conducting Systematic Literature Review***

The methods of the systematic review are described below. In part, these methods followed the guidelines for conducting a systematic review set forth by the Agency for Healthcare Research and Quality (AHRQ) in the “Methods Guide for Effectiveness and Comparative Effectiveness Reviews.” Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct>. Additionally, the methods followed the guidance set forth by the VA/DoD in the *Guideline for Guidelines* document.

For all key questions, the following external and internal databases were searched: MEDLINE, EMBASE, (via the OVID SP platform using the one-search and de-duplication features), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. Searches were designed to identify unique reviews, trials, and technology assessments. Searches of the World Wide Web were also performed to capture relevant grey literature that had not been indexed to the databases listed previously. The searches covered the time period of

January 2000 through October 2013. The search strategy was based on a combination of Medical Subject Headings (MeSH) terminology and text key words, and can be found in Table A-3.

The literature searches identified 6,624 citations potentially addressing the key questions of interest. Of those, 4,295 were excluded upon title review for clearly not meeting inclusion criteria (e.g., not pertinent to the topic, not published in English, published prior to study inclusion publication date, or not a full-length article). Overall, 2,329 abstracts were reviewed with 1,426 of those being excluded for the following reasons: not a systematic review or clinical study, did not address a key question of interest to this review, did not enroll population of interest, or published prior to January 2000. A total of 903 full-length articles were reviewed. Of those, 419 were excluded at a first pass review for the following: not addressing a key question of interest, not enrolling the population of interest, not meeting inclusion criteria for clinical study or systematic review, not enrolling sufficient patients for key question 1 or 10-12, or being a duplicate. A total of 484 full-length articles were thought to address one or more key questions and were further reviewed. Of these, 381 were ultimately excluded. Reasons for their exclusion are presented in Figure A-1 below. Overall, 103 studies addressed one or more of the Key Questions and were considered as evidence in the systematic review.

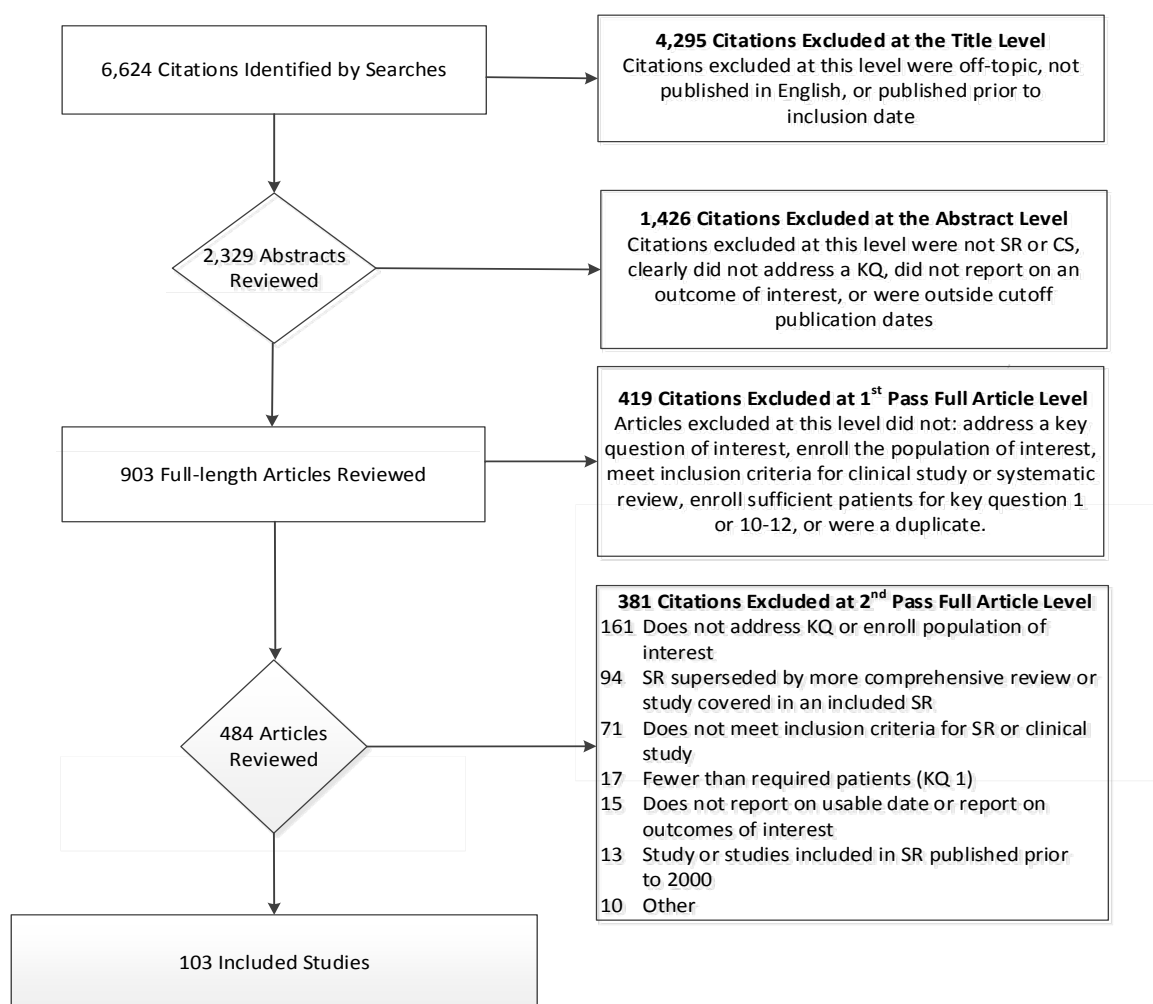
**Table A-2: Key Questions Used in the Systematic Review and Evidence Base Results**

Key question	Evidence Base
<b>Diagnostic Question</b>	
KQ1 For active or inactive military personnel suspected of a medically unexplained war-specific combat disorder such as Gulf War syndrome, are there any tests (e.g., functional MRI) that are confirmatory for a diagnosis of their disorder?	1 RCT and 23 case-control trials
<b>Intervention Questions</b>	
KQ2 For adults with CMI, what are the benefits and harms of pharmacological interventions (e.g., antidepressants, pain relievers)? a. For adults with FM? b. For adults with CFS? c. For adults with functional gastrointestinal disorders?	a. 6 RCTs b. 2 systematic reviews c. 3 systematic reviews d. 5 systematic reviews
KQ3 For adults with CMI, what are the benefits and harms of non-pharmacological interventions (e.g., psychological interventions, hypnosis, exercise therapy, patient and/or family education)? a. For adults with FM? b. For adults with CFS? c. For adults with functional gastrointestinal disorders?	a. 2 systematic reviews and 7 RCTs b. 5 systematic reviews c. 1 systematic review d. 3 systematic reviews
KQ4 For adults with CMI, what are the benefits and harms of complementary and alternative medicine interventions (e.g., acupuncture, biofeedback)? a. For adults with FM? b. For adults with CFS? c. For adults with functional gastrointestinal disorders?	a. 7 RCTs b. 8 systematic reviews c. 2 systematic reviews d. 4 systematic reviews
<b>Management Questions</b>	
KQ5 What management strategies (e.g., team based approach, ongoing case management) lead to improved outcomes for adults with CMI?	1 systematic review and 2 RCTs
KQ6 What core competencies of healthcare professionals lead to improved	1 systematic review and



Key question	Evidence Base
outcomes for adults with CMI?	1 RCT
KQ7 What effect do different communication styles or practices have on the outcomes, including harms, for adults with CMI?	1 RCT
KQ8 Does vocational or other rehabilitation services (e.g., social or peer support programs) lead to improved outcomes for adults with CMI?	No studies identified that address this KQ
KQ9 What follow up practices (e.g., reassessment timeframe, prognostic tools) lead to improved outcomes for adults with CMI?	No studies identified that address this KQ
<b>Risk Factor Questions</b>	
KQ10 What factors (e.g., obesity, history of abuse) predispose an individual to developing CMI?	These questions were combined into one evidence report 9 systematic reviews and 9 individual studies
KQ11 What factors (e.g., recent trauma, unexpected military deployment) precipitate the development of CMI?	
KQ12 What factors (e.g., divorce, unemployment) perpetuate the symptoms of CMI?	

**Figure A-1. Review Flow Diagram**



## Criteria for Study Inclusion/Exclusion

### *General Criteria*

- Clinical studies published on or after January 1, 2000, and systematic reviews of associated symptom based syndromes (i.e., fibromyalgia, chronic fatigue syndrome, and functional gastrointestinal disorders) published on or after January 1, 2008.
- Studies must have been published in English.
- Publication must have been a full clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length, clinical studies were not accepted as evidence.
- Study must have enrolled a patient population in which at least 85% of patients had CMI or associated condition or symptoms.
- Studies enrolled adults 18 years or older. In studies that mixed adults and children, at least 85% of the enrolled patients had to be 18 years or older.
- Studies that enrolled adults with single symptoms or multiple symptoms of less than 6 months duration were excluded.

### *Diagnosis/Evaluation Studies*

- Studies must have evaluated a diagnostic test within an active or inactive military population (e.g., this included studies of Gulf War ill Veterans versus Gulf War well or civilian or non-Gulf War Veterans). Studies considering non-military populations with symptom-based syndromes such as FMS, CFS, or IBS were excluded.
- Study must have been a case control or comparative study that compared diagnostic technology evaluation versus clinical evaluation or different diagnostic technologies.
- Studies must have enrolled  $\geq 50$  patients with at least 10 patients enrolled per study group.
- Studies must have considered diagnostic tests within the following categories: biomarkers (this included studies of biological markers and neuroimaging studies), neuropsychological test batteries, and sleep studies (studies were excluded if they considered only questionnaires or checklists to distinguish populations).

### *Treatment and Management Studies*

- Study must have evaluated a treatment or management strategy for CMI.
- Study must have been a prospective, randomized or nonrandomized comparative trial with an independent control group.
- Crossover trials were considered only if data from the first treatment period were reported separately.
- Study must have enrolled  $\geq 10$  patients per treatment arm.
- The study must have reported data on at least one of the included outcomes.
- Study must have followed patients for at least 4 weeks.
- All subjective outcomes (e.g., pain, aspects of patient function) must have been measured using validated instruments.

- For associated symptom based syndromes, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, only systematic reviews published from 2008 till present that evaluated a treatment strategy were included as evidence in the review.

### *Risk Factor Studies*

- Study must have been a case controlled or a comparative study that compares patients with CMI to another population of patients (e.g., CMI versus Major Depression) or compared patients with CMI who had a risk factor(s) to patients who did not have the factor(s).
- Study must have enrolled  $\geq 500$  patients
- Study must have investigated risk factors for predisposing, precipitating, or perpetuating CMI. Expert opinion papers were not considered as evidence addressing the referral questions.

**Table A-3: Search Strategies**

Concept	Controlled Vocabulary	Keywords
<b>CHRONIC MULTISYMPTOM ILLNESS</b>		
<b>Chronic Multisymptom Illness/Medically Unexplained Illness/Gulf War Syndrome</b>	<p><b><u>MEDLINE (MeSH)</u></b> persian gulf syndrome</p> <p><b><u>EMBASE (EMTREE)</u></b> medically unexplained symptom persian gulf syndrome</p> <p><b><u>PsycINFO</u></b> N/A</p>	<p>chronic multisymptom chronic multi-symptom condition* disease* gulf war gulf war disease gulf war illness gulf war syndrome illness* medically unexplained multi-symptom multisymptom persian gulf symptom* syndrome* undiagnosed unexplained</p>
<b>Individual CMI Variables</b>	<p><b><u>MEDLINE MeSH</u></b> chronic pain cognition disorders fatigue syndrome, chronic fibromyalgia gastrointestinal diseases gastrointestinal motility irritable bowel syndrome memory disorders mood disorders musculoskeletal disease respiration disorders respiratory tract diseases sleep disorders somatoform disorders</p> <p><b><u>EMBASE (EMTREE)</u></b> affective disorders</p>	<p>breathing chronic fatigue chronic pain cognitive cognition fibromyalgia gastrointestinal headache* memory mood* musculoskeletal neurologic* post-concuss* respirat* sleep somatoform</p>

Concept	Controlled Vocabulary	Keywords
	<p>chronic fatigue syndrome  chronic pain  cognitive deficit  concentration  concentration (mental)  fibromyalgia  gastrointestinal disease  headache  memory disorder  mood change  musculoskeletal disease  musculoskeletal disorders  neurologic disease  respiratory tract disease  sleep disorder  somatoform disorder</p> <p><b><u>PsycINFO</u></b>  affective disorders  chronic fatigue syndrome  chronic pain  concentration  fibromyalgia  gastrointestinal disorders  irritable bowel syndrome  memory disorders  sleep disorders  somatoform disorders</p>	
<b>Main CMI Conditions</b>	<p><b><u>MEDLINE (MeSH)</u></b>  fatigue syndrome, chronic  fibromyalgia  irritable bowel syndrome</p> <p><b><u>EMBASE (EMTREE)</u></b>  chronic fatigue syndrome  fibromyalgia</p> <p><b><u>PsycINFO</u></b>  chronic fatigue syndrome  fibromyalgia  irritable bowel syndrome</p>	<p>chronic fatigue  fibromyalgia  irritable bowel</p>
<b>Comorbidity</b>	<p><b><u>MEDLINE MeSH</u></b>  comorbidity</p> <p><b><u>EMBASE (EMTREE)</u></b>  comorbidity</p> <p><b><u>PsycINFO</u></b>  comorbidity</p>	<p>comorbid*  multi-morbid*  multimorbid*</p>
<b>Diagnosis</b>	<p><b><u>MEDLINE (MeSH)</u></b>  autonomic nervous system diseases</p>	<p>autonomic  biomarker*</p>

Concept	Controlled Vocabulary	Keywords
	diagnosis/di di.fs. diagnosis diagnostic imaging “diagnostic tests and procedures” diagnostic tests, routine functional magnetic resonance Imaging functional neuroimaging hematologic tests magnetic resonance imaging neuroimaging tilt-table test  <b><u>EMBASE (EMTREE)</u></b> diagnosis diagnostic agent diagnostic procedure functional magnetic resonance imaging functional neuroimaging laboratory diagnosis neuroimaging  <b><u>PsycINFO</u></b> diagnosis functional magnetic resonance imaging magnetic resonance imaging neuroimaging	blood test* cytokine* diagnos* fMRI functional haematolog* hematolog* magnetic resonance MRI neuroimag* tilt
<b>Therapies (Pharmacological Interventions)</b>	<b><u>MEDLINE (MeSH)</u></b> acetamenophin analgesics, opioid antidepressive agents antidepressive agents, tricyclic anti-inflammatory agents anti-inflammatory agents, non-steroidal drug therapy drug therapy, combination dt.fs. fluoxetine ibuprofen naproxen nonprescription drugs oxycodone paroxetine prednisone serotonin uptake inhibitors sertraline	antidepressant* analgesi* anti-inflam* antiinflam* drug therapy non-steroidal nonsteroidal NSAID* Pharmacotherapy

Concept	Controlled Vocabulary	Keywords
	<p><b><u>EMBASE (EMTREE)</u></b>  analgesic agent  antidepressant, tetracyclic  antidepressant, tricyclic  antidepressive agent  antiinflammatory agent  drug therapy  fluoxetine  ibuprofen  narcotic analgesic agent  naproxen  nonprescription drug  nonsteroid antiinflammatory agent  oxycodone  paracetamol  paroxetine  prednisone  serotonin uptake inhibitor  sertraline</p> <p><b><u>PsycINFO</u></b>  analgesic drugs  antidepressant drugs  antiinflammatory drugs  drug therapy  fluoxetine  nonprescription drugs  paroxetine  serotonin reuptake inhibitors</p>	
<b>Therapies (Non-pharmacological)</b>	<p><b><u>MEDLINE (MeSH)</u></b>  biofeedback, psychology  cognitive therapy  exercise  exercise movement techniques  exercise therapy  motivational interviewing  patient education as a topic  physical therapy modalities  psychotherapy</p> <p><b><u>EMBASE (EMTREE)</u></b>  aerobic exercise  cognitive therapy  exercise  kinesiotherapy  patient education  psychotherapy</p> <p><b><u>PsycINFO</u></b>  aerobic exercise  client education</p>	biofeedback CBT cognitive behavior therapy cognitive therapy exercise patient education physical therapy psychotherapy

Concept	Controlled Vocabulary	Keywords
	cognitive behavior therapy cognitive therapy exercise motivational interviewing physical therapy psychotherapy	
<b>Therapies (Alternative Therapies)</b>	<p><b><u>MEDLINE (MeSH)</u></b>  acupuncture therapy  chiropractic  complementary therapies  herbal medicine  hypnosis  massage  meditation  therapeutic touch  yoga</p> <p><b><u>EMBASE (EMTREE)</u></b>  Acupuncture  alternative medicine  herbal medicine  hypnosis  pilates  reiki  yoga</p> <p><b><u>PsycINFO</u></b>  acupuncture  alternative medicine  hypnosis  “medicinal herbs and plants”  massage  meditation  yoga</p>	acupuncture alternative chiropractic complementary holistic hypnosis massage medicin* meditat* pilates reiki therap* therapeutic touch treatment yoga
<b>Management (Plans of Care)</b>	<p><b><u>MEDLINE (MeSH)</u></b>  case management  goals  institutional management teams  models, organizational  motivation  nursing, team  patient care  patient care team  patient-centered care  quality assurance, health care</p> <p><b><u>EMBASE (EMTREE)</u></b>  case management  patient care  health care delivery  health care quality</p>	care plan goal* team treatment plan patient care

Concept	Controlled Vocabulary	Keywords
	team nursing total quality management treatment planning  <u><b>PsycINFO</b></u> case management "continuum of care" "quality of care" treatment planning work teams	
<b>Management (Provider Attitudes, Provider/Client Communication)</b>	<u><b>MEDLINE (MeSH)</b></u> attitude of health personnel communication communication barriers interpersonal relations nonverbal communication physician-patient relations professional-patient relations  <u><b>EMBASE (EMTREE)</b></u> communication communication skills doctor patient relationship health personnel attitude interpersonal relations nonverbal communication nurse attitude physician attitude  <u><b>PsycINFO</b></u> communication communication skills interpersonal communication psychotherapist attitudes therapist attitudes verbal communication	attitude* communication interpersonal
<b>Management (Professional Competencies)</b>	<u><b>MEDLINE (MeSH)</b></u> clinical competence competency-based education standard of care  <u><b>EMBASE (EMTREE)</b></u> professional competence professional standard  <u><b>PsycINFO</b></u> professional competence	clinical competenc* core professional
<b>Management (Vocational/ Rehabilitation Services)</b>	<u><b>MEDLINE (MeSH)</b></u> counseling peer group psychotherapy, group	counsel* group therapy peer psychotherapy*



Concept	Controlled Vocabulary	Keywords
	rehabilitation self-help groups vocational guidance self-help groups social support vocational guidance <b><u>EMBASE (EMTREE)</u></b> group therapy peer counseling peer group self help support group vocational guidance vocational rehabilitation  <b><u>PsycINFO</u></b> group counseling peers self help techniques social support support groups vocational rehabilitation	self help self-help social support support group* vocational
<b>Management (Outcome Assessment, Follow-up Practices)</b>	<b><u>MEDLINE (MeSH)</u></b> disease-free survival follow-up studies health impact assessment lost to follow-up medical futility needs assessment "outcome and process assessment (health care)" outcome assessment "prognosis (health care)" secondary care symptom assessment treatment failure treatment outcome  <b><u>EMBASE (EMTREE)</u></b> disease free survival evaluation "evaluation and follow up" evaluation research follow up outcome assessment treatment outcome  <b><u>PsycINFO</u></b> evaluation followup studies measurement	assess* evaluat* follow-up follow up monitor* outcome*

Concept	Controlled Vocabulary	Keywords
	psychotherapeutic outcomes treatment effectiveness treatment outcomes	
<b>Risk (Predisposition/Susceptibility)</b>	<p><b><u>MEDLINE (MeSH)</u></b> disease susceptibility hypertension obesity smoking</p> <p><b><u>EMBASE (EMTREE)</u></b> disease predisposition hypertension obesity smoking</p> <p><b><u>PsycINFO</u></b> hypertension obesity tobacco smoking</p>	high blood pressure hypertens* obes* overweight predispos* smoker* smoking susceptibil*
<b>Risk (Contributing Psychosocial/ Developmental Factors)</b>	<p><b><u>MEDLINE (MeSH)</u></b> adult survivors of child abuse alcoholism anxiety anxiety disorders child abuse demography depression mood disorders substance-related disorders unemployment</p> <p><b><u>EMBASE (EMTREE)</u></b> alcoholism anxiety child abuse depression substance abuse unemployment</p> <p><b><u>PsycINFO</u></b> affective disorder alcoholism "depression (emotion)" drug abuse major depression psychosocial factors socioeconomic status unemployment</p>	addict* child abus* depression drug abuse* substance abuse*
<b>Risk (Contributing Occupational/ Environmental Factors)</b>	<p><b><u>MEDLINE (MeSH)</u></b> afghan campaign 2001 biological warfare</p>	afghan* active-duty active duty

Concept	Controlled Vocabulary	Keywords
	chemical warfare agents gulf war iraq war, 2003 - 2011 multiple chemical sensitivity inhalation exposure military medicine military personnel multiple chemical sensitivity smoke inhalation smoke inhalation injury Veterans health  <u><b>EMBASE (EMTREE)</b></u> biological warfare military medicine multiple chemical sensitivity Veterans health  <u><b>PsycINFO</b></u> bioterrorism military personnel	combat deploy* enlist* iraq* military non-deploy* nondeploy* post-deploy* postdeploy* Veteran*
<b>Selected Study Designs/ Publication Types (For Therapy Questions)</b>	<u><b>MEDLINE (MeSH)</b></u> N/A  <u><b>EMBASE (EMTREE)</b></u> meta analysis systematic review  <u><b>PsycINFO</b></u> meta analysis	<b>(as publication type)</b> meta-analysis randomized controlled trial  <b>(keyword in title)</b> systematic* random*  <b>(keyword anywhere)</b> meta analysis meta-analysis metaanalys* random* systematic*
<b>Excluded Concepts (Study Designs/Publication Types)</b>	<u><b>MEDLINE (MeSH)</b></u> animal experiment cadaver case report case study nonhuman  <u><b>EMBASE (EMTREE)</b></u> N/A  <u><b>PsycINFO</b></u> N/A	<b>(keyword in title)</b> proceeding* conference* comment* case* editor* letter* questionnaire* reply  <b>(as publication type)</b> addresses authored book autobiography bibliography biography

Concept	Controlled Vocabulary	Keywords
		book book series case case reports conference abstract conference* conference paper conference proceeding clinical conference collected works comment congresses consensus development conference consensus development conference, nih dictionary directory duplicate publication editorial erratum government publications in vitro interactive tutorial interview lectures letter news periodical index note published erratum reference book retracted publication retraction of publication report short survey video-audio media webcasts

#### **OVID Conventions:**

\* (within or following a term) = truncation character (wildcard)

\* (preceding a term) = denotes major category focus/major MeSH

.ab. = limit to abstract

ADJn = search terms within a specified number (n) of words from each other in any order

exp/ = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)

.de. = limit controlled vocabulary heading

.fs. = floating subheading

.hw. = limit to heading word

.mp. = combined search fields (default if no fields are specified)

.pt. = publication type

.ti. = limit to title

.tw. = limit to title and abstract fields

**Chronic Multisymptom Illness Search Strategy for OVID (Medline, EMBASE, PsycINFO databases)**

	<b>Concepts</b>	<b>Search Statement</b>
1	Chronic Multisymptom Illness/Medically Unexplained Illness/Gulf War Syndrome	medically unexplained symptom/ or persian gulf syndrome/ or (chronic multisymptom or chronic multi-symptom or gulf war disease or gulf war illness or gulf war syndrome or medically unexplained).ti,ab. or ((gulf war or multi-symptom or multisymptom or persian gulf or undiagnosed or unexplained).ti,ab. adj2 (condition* or disease* or illness* or symptom* or syndrome*)).ti,ab.
2	Individual CMI Variables	affective disorders/ or chronic fatigue syndrome/ or chronic pain/ or cognition disorders/ or cognitive deficit/ or concentration/ or "concentration (mental)"/ or fatigue syndrome, chronic/ or fibromyalgia/ or gastrointestinal disease/ or gastrointestinal diseases/ or gastrointestinal disorders/ or gastrointestinal motility/ or headache/ or irritable bowel syndrome/ or memory disorder/ or memory disorders/ or mood change/ or mood disorders/ or musculoskeletal disease/ or musculoskeletal disorders/ or neurologic disease/ or respiration disorders/ or respiratory tract disease/ or respiratory tract disorders/ or sleep disorder/ or sleep disorders/ or somatoform disorder/ or somatoform disorders/ or (breathing or chronic fatigue or chronic pain or cognitive or cognition or fibromyalgia or gastrointestinal or headache* or memory or mood* or musculoskeletal or neurologic* or post-concuss* or respirat* or sleep or somatoform).ti.
3	Main CMI Conditions	chronic fatigue syndrome/ or fatigue syndrome, chronic/ or fibromyalgia/ or irritable bowel syndrome/ or (chronic fatigue or fibromyalgia or irritable bowel).ti.
4	Comorbidity	comorbidity/ or (comorbid* or multi-morbid* or multimorbid*).ti.
5	Diagnosis	autonomic nervous system diseases/di or diagnosis/ or diagnostic agent/ or diagnostic imaging/ or diagnostic procedure/ or "diagnostic tests and procedures"/ or diagnostic tests, routine/ or functional magnetic resonance imaging/ or functional neuroimaging/ or hematologic tests/ or laboratory diagnosis/ or magnetic resonance imaging/ or neuroimaging/ or tilt-table test/ or di.fs. or (autonomic or biomarker* or blood test* or cytokine* or diagnos* or fMRI or functional or haematolog* or hematolog* or magnetic resonance or MRI or neuroimag* or tilt).ti.
6	Therapies (Pharmacological Interventions)	dt.fs. or acetaminophen/ or analgesic agent/ or analgesic drugs/ or analgesics, opioid/ or antidepressant drugs/ or antidepressant, tetracyclic/ or antidepressant, tricyclic/ or antidepressive agent/ or antidepressive agents/ or antidepressive agents, tricyclic/ or antiinflammatory agent/ or anti-inflammatory agents/ or antiinflammatory drugs/ or anti-inflammatory agents, non-steroidal/ or drug therapy/ or drug therapy, combination/ or fluoxetine/ or ibuprofen/ or naproxen/ or narcotic analgesic agent/ or nonprescription drug/ or nonprescription drugs/ or nonsteroid antiinflammatory agent/ or oxycodone/ or paracetamol/ or paroxetine/ or prednisone/ or serotonin reuptake inhibitors/ or serotonin uptake inhibitor/ or serotonin uptake inhibitors/ or sertraline/ or (antidepressant* or analgesi* or anti-inflam* or antiinflam* or drug therapy or non-steroidal or

	Concepts	Search Statement
		nonsteroidal or NSAID* or pharmacotherapy).ti.
7	Therapies (Non-pharmacological Interventions)	aerobic exercise/ or biofeedback, psychology/ or client education/ or cognitive behavior therapy/ or cognitive therapy/ or exercise/ or exercise movement techniques/ or exercise therapy/ or kinesiotherapy/ or motivational interviewing/ or patient education/ or patient education as a topic/ or physical therapy/ or physical therapy modalities/ or psychotherapy/ or (biofeedback or CBT or cognitive behavior therapy or cognitive therapy or exercise or patient education or physical therapy or psychotherapy).ti.
8	Therapies (Alternative/Complementary Interventions)	acupuncture/ or acupuncture therapy/ or alternative medicine/ or chiropractic/ or complementary therapies/ or herbal medicine/ or hypnosis/ or massage/ or "medicinal herbs and plants"/ or meditation/ or pilates/ or reiki/ or therapeutic touch/ or yoga/ or (acupuncture or chiropractic or hypnosis or massage or meditat* or pilates or reiki or therapeutic touch or yoga).ti. or ((alternative or complementary or holistic) adj2 (medicin* or therap* or treatment*)).ti.
9	Management (Plans of Care)	case management/ or "continuum of care"/ or goals/or health care delivery/ or health care quality/ or models, organizational/ or institutional management teams/ or motivation/ or nursing, team/ or patient care/ or patient care team/ or patient-centered care/ or quality assurance, health care/ or "quality of care"/ or team nursing/ or total quality management/ or treatment planning/ or work teams/ or (care plan or goal* or team or treatment plan or patient care).ti.
10	Management (Provider Attitudes, Provider/Client Communication)	attitude of health personnel/ or communication/ or communication barriers/ or communication skills/ or doctor patient relationship/ or health personnel attitude/ or interpersonal communication/ or interpersonal relations/ or nonverbal communication/ or nurse attitude/ or physician attitude/ or physician-patient relations/ or professional-patient relations/ or psychotherapist attitudes/ or therapist attitudes/ or verbal communication/ or (attitude* or communication or interpersonal).ti.
11	Management (Professional Competencies)	clinical competence/ or competency-based education/ or professional competence/ or professional standard/ or standard of care/ or ((clinical or professional or core) adj2 competenc*).ti.
12	Management (Vocational/Rehabilitation Services)	counseling/ or group counseling/ or group therapy/ or peer counseling/ or peer group/ or peers/ or psychotherapy, group/ or rehabilitation/ or self help/ or self-help groups/ or self help techniques/ or social support/ or support group/ or support groups/ or vocational guidance/ or vocational rehabilitation/ or (counsel* or group therapy or peer or psychotherapy* or self help or self-help or social support or support group* or vocational).ti.
13	Management (Outcomes Assessment, Follow-up Practices)	disease-free survival/ or disease free survival/ or evaluation/ or "evaluation and follow up"/ or evaluation research/ or follow up/ or follow-up studies/ or health impact assessment/ or lost to follow-up/ or measurement/ or medical futility/ or needs assessment/ or "outcome and process assessment (health care)"/ or outcome assessment/ or "prognosis (health care)"/ or psychotherapeutic outcomes/ or secondary care/ or symptom

	Concepts	Search Statement
		assessment/ or treatment effectiveness/ or treatment failure/ or treatment outcome/ or treatment outcomes/ or (assess* or evaluat* or monitor* or outcome* or follow-up or follow up).ti.
14	Risk (Predisposition/Susceptibility)	disease predisposition/ or disease susceptibility/ or hypertension/ or obesity/ or smoking/ or tobacco smoking/ or (high blood pressure or hypertens* or obes* or overweight or predispos* or smoker* or smoking or susceptibil*).ti.
15	Risk (Contributing Psychosocial/Developmental Factors)	adult survivors of child abuse/ or alcoholism/ or affective disorder/ or anxiety/ or anxiety disorders/ or child abuse/ or demography/ or depression/ or "depression (emotion)"/ or drug abuse/ or major depression/ or mood disorders/ or psychosocial factors/ or socioeconomic status/ or substance abuse/ or substance-related disorders/ or unemployment/ or (addict* or child abus* or depression or drug abuse* or substance abuse*).ti.
16	Risk (Contributing Occupational/ Environmental Factors)	afghan campaign 2001/ or biological warfare/ or bioterrorism/ or chemical warfare agents/ or gulf war/ or iraq war, 2003-2011/ or inhalation exposure/ or military medicine/ or military personnel/ or multiple chemical sensitivity/ or smoke inhalation/ or smoke inhalation injury/ or Veterans health/ or (afghan* or active-duty or active duty or combat or deploy* or enlist* or iraq* or military or non-deploy* or nondeploy* or post-deploy* or postdeploy* or Veteran*).ti.
17	Selected Study Designs/ Publication Types (For Therapy Questions)	(systematic* or random*).ti. or (meta analysis or meta-analysis or metaanalys* or random* or systematic*).mp. or (meta-analysis or randomized controlled trial).pt.
18	Combined Search Strings [CMI Concepts AND (key questions OR study designs/publication types)]	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
19		6 or 7 or 8
20		1 and 2 and 4
21		1 and 2 and 4 and 18
22		1 and (2 or 4)
23		(1 or (2 and 4)) and 18
24		2 and 4
25		(1 or (2 and 4)) and 17 and 19
26		(1 or 3 or (2 and 4)) and systematic review*.mp.
27		20 or 21 or 22 or 23 or 24 or 25 or 26
28	Limits to Search results (2000-present; human only; English)	limit 27 to english language
29		limit 28 to human
30		limit 29 to yr="2000 -Current"
31		limit 30 to humans [Limit not valid in PsycINFO; records were retained]
32	Excluded Concepts (Study Designs/Publication Types)	31 not ((proceeding* or conference* or comment* or case* or editor* or letter* or questionnaire* or reply).ti. or (animal experiment/ or cadaver/ or case report/ or case study/ or nonhuman/) or (addresses or authored book or autobiography or bibliography or biography or book or book series or case or case reports or conference abstract or conference* or conference paper or conference proceeding or clinical conference or collected works or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or erratum or government publications or in vitro or interactive

	Concepts	Search Statement
		tutorial or interview or lectures or letter or news periodical index or note or published erratum or reference book or retracted publication or retraction of publication or report or short survey or video-audio media or webcasts).pt.)
33	Search Results Sorted by Date Removal of Duplicates between Databases	limit 32 to yr="2000 - 2005"
34		limit 32 to yr="2006 - 2009"
35		limit 32 to yr="2010 -Current"
36		remove duplicates from 33
37		remove duplicates from 34
38		remove duplicates from 35
39	Final Search Results (Excluded Sets and Duplicates Removed)	36 or 37 or 38

### Convening the Face-to-Face Meeting

In consultation with the Contracting Officer Representative, the Champions, and the Work Group, the Lewin Team convened a three and a half day face-to-face meeting of the CPG Champions and Work Group members on January 14-17, 2014. These experts were gathered to develop and draft the clinical recommendations for an update to the 2001 CPG. Lewin presented findings from the evidence review of the key questions in order to facilitate and inform the process.

Under the direction of the Champions, the Work Group members were charged with interpreting the results of the evidence review, and asked to retain, revise, or reject each recommendation from the 2001 CPG. In addition, members developed new clinical practice recommendations, not presented in the 2001 CPG, based on the 2013 evidence review. At this meeting, Work Group members were assigned to one of four smaller subgroups depending on their area of clinical expertise.

### Grading Recommendations

This CPG uses the GRADE methodology to assess the quality of the evidence base and assign a grade for the strength for each recommendation. The GRADE system uses the following four domains to assess the strength of each recommendation: [\[143\]](#)

- Balance of desirable and undesirable outcomes
- Confidence in the quality of the evidence
- Values and preferences
- Other implications, as appropriate, e.g.,:
  - Resource Use
  - Equity
  - Acceptability
  - Feasibility
  - Subgroup considerations

The following sections further describe each domain.

**Balance of desirable and undesirable outcomes** refers to the size of anticipated benefits (e.g., increased longevity, reduction in morbid event, resolution of symptoms, improved quality of life (QoL), decreased



resource use) and harms (e.g., decreased longevity, immediate serious complications, adverse event, impaired quality of life, increased resource use, inconvenience/hassle) relative to each other. This domain is based on the understanding that the majority of clinicians will offer patients therapeutic or preventive measures as long as the advantages of the intervention exceed the risks and adverse effects. The certainty or uncertainty of the clinician about the risk-benefit balance will greatly influence the strength of the recommendation.

Some of the discussion questions that fall under this domain include:

- Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?
- Are the desirable anticipated effects large?
- Are the undesirable anticipated effects small?
- Are the desirable effects large relative to undesirable effects?

**Confidence in the quality of the evidence** reflects the quality of the evidence base and the certainty in that evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength. The evidence review used for the development of recommendations for CMI, conducted by ECRI, assessed the confidence in the quality of the evidence base and assigned a rate of “High”, “Moderate”, “Low” or “Very Low”.

The elements that go into the confidence in the quality of the evidence include:

- Is there high or moderate quality evidence that answers this question?
- What is the overall certainty of this evidence?

**Values and preferences** is an overarching term that includes patients’ perspectives, beliefs, expectations, and goals for health and life. More precisely, it refers to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the therapeutic or preventive measures in relation to one another. For some, the term “values” has the closest connotation to these processes. For others, the connotation of “preferences” best captures the notion of choice. In general, values and preferences increase the strength of the recommendation when there is high concordance and decrease it when there is great variability. In a situation in which the balance of benefits and risks are uncertain, eliciting the values and preferences of patients and empowering them and their surrogates to make decisions consistent with their goals of care becomes even more important. A recommendation can be described as having “similar values”, “some variation”, or “large variation” in typical values and preferences between patients and the larger populations of interest.

Some of the discussion questions that fall under the purview of values and preferences include:

- Are you confident about the typical values and preferences and are they similar across the target population?
- What are the patient’s values and preferences?

- Are the assumed or identified relative values similar across the target population?

**Other implications** consider the practicality of the recommendation, including resources use, equity, acceptability, feasibility and subgroup considerations. Resource use is related to the uncertainty around the cost-effectiveness of a therapeutic or preventive measure. For example statin use in the frail elderly and others with multiple comorbidities may not be effective and depending on the societal benchmark for willingness to pay, may not be a good use of resources. Equity, acceptability, feasibility and subgroup considerations require similar judgments around the practicality of the recommendation.

The framework below was used by the Work Group to guide discussions on each domain.

**Table A-4: Evidence to Recommendation Framework**

Decision Domain	Judgment
Balance of desirable and undesirable outcomes	
Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa? Are the desirable anticipated effects large? Are the undesirable anticipated effects small? Are the desirable effects large relative to undesirable effects?	Benefits outweigh harms/burden Benefits slightly outweigh harms/burden Benefits and harms/burden are balanced Harms/burden slightly outweigh benefits Harms/burden outweigh benefits
Confidence in the quality of the evidence	
Is there high or moderate quality evidence that answers this question? What is the overall certainty of this evidence?	High Moderate Low Very low
Values and preferences	
Are you confident about the typical values and preferences and are they similar across the target population? What are the patient's values and preferences? Are the assumed or identified relative values similar across the target population?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations):	
Are the resources worth the expected net benefit from the recommendation? What are the costs per resource unit? Is this intervention generally available? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions Is there lots of variability in resource requirements across settings?	Various considerations

The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which combines the four domains. [\[143\]](#)

The GRADE of a recommendation is based on the following elements:

- Four decision domains used to determine the strength and direction (described above)
- Relative strength (Strong or Weak)
- Direction (For or Against)

The relative strength of the recommendation is based on a binary scale, “Strong” or “Weak.” A strong recommendation indicates that the Work Group is highly confident that desirable outcomes outweigh undesirable outcomes. If the Work Group is less confident of the balance between desirable and undesirable outcomes, they present a weak recommendation.

Similarly, a recommendation for a therapy or preventive measure indicates that the desirable consequences outweigh the undesirable consequences. A recommendation against a therapy or preventive measure indicates that the undesirable consequences outweigh the desirable consequences.

Using these elements, the grade of each recommendation is presented as part of a continuum:

- Strong For (or “We recommend offering this option ...”)
- Weak For (or “We suggest offering this option ...”)
- Weak Against (or “We suggest not offering this option ...”)
- Strong Against (or “We recommend against offering this option ...”)

Note that weak (For or Against) recommendations may also be termed “Conditional,” “Discretionary,” or “Qualified”. Recommendations may be conditional based upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented. Recommendations may be at the discretion of the patient and clinician or they may be qualified with an explanation about the issues that would lead decisions to vary.

### **Drafting and Submitting the Final CPG**

Following the face-to-face meeting, the Champions and Work Group members were given writing assignments for the update of specific sections of the 2001 CPG that would form the narrative text for the 2014 CPG. During this time, the Champions also revised the 2001 algorithms and identified the content for the guideline summary and pocket card, as part of the provider toolkits that will be developed by the Evidence-Based Practice Working Group (EBPWG) following the publication of the 2014 CPG. The CMI CPG Champions and Work Group developed several drafts of the Guideline, submitting the final document to the VA/DoD Evidence-Based Practice Working Group in October 2014.

## Appendix B: Pharmacotherapy

### PHARMACOLOGIC AGENTS FOR CHRONIC MULTISYMPTOM ILLNESS

Refer to current Product Information for additional prescribing information.

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Escitalopram <a href="#">[1]</a>	10–20 mg/d; titrate up from 10 mg/d to 20 mg/d after 1 month.  Adequate Trial: 12 weeks	Global	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Nausea</li> <li>• Nasopharyngitis</li> <li>• Insomnia</li> <li>• Sexual dysfunction</li> <li>• Suicidal ideation</li> <li>• QTc prolongation</li> <li>• Serotonin syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Improved somatic symptom severity, depression, pain, anxiety.</li> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• Citalopram (20–40 mg/d) may be a reasonable substitute for escitalopram.</li> </ul>
Fluoxetine <a href="#">[2-6]</a>	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	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Headache</li> <li>• Insomnia</li> <li>• Nervousness</li> <li>• Anxiety</li> <li>• Somnolence</li> <li>• Asthenia</li> <li>• Diarrhea</li> <li>• Anorexia</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> <li>• QTc prolongation</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• MAOIs contraindicated within 5 weeks of discontinuing fluoxetine</li> <li>• Contraindicated with pimozide or thioridazine; avoid with other QTc prolonging drugs</li> <li>• Consider long elimination half-life during dosage titration and drug discontinuation</li> </ul>
Sertraline <a href="#">[2]</a>	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*	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Somnolence</li> <li>• Dry mouth</li> <li>• Constipation</li> <li>• Dizziness</li> <li>• Sexual dysfunction</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• Conditional risk of QTc prolongation<sup>†</sup></li> </ul>
Venlafaxine <a href="#">[7]</a>	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	Global*	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Headache</li> <li>• Fatigue</li> <li>• Dizziness</li> <li>• Constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Improved pain, anxiety, quality of life but not somatic symptom severity</li> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> </ul>

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Venlafaxine Extended- release [8]	weeks		<ul style="list-style-type: none"> <li>• Tremor</li> <li>• Dry mouth</li> <li>• Increased blood pressure</li> <li>• Sexual dysfunction</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> <li>• QTc prolongation</li> <li>• Discontinuation syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Taper dose slowly when discontinuing therapy to avoid withdrawal symptoms</li> </ul>
	75–225 mg/d; titrate up by 75 mg/d at intervals of at least 1 week  Adequate Trial: 12 weeks			
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*	<ul style="list-style-type: none"> <li>• Somnolence</li> <li>• Dizziness</li> <li>• Dry mouth</li> <li>• Increased appetite</li> <li>• Weight gain</li> <li>• Constipation</li> <li>• Increased cholesterol</li> <li>• Neutropenia</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• High incidence of somnolence (&gt;50%)</li> <li>• Low doses may be useful for insomnia</li> <li>• Conditional risk of QTc prolongation<sup>†</sup></li> <li>• Infrequent sexual dysfunction</li> </ul>
Duloxetine [9]	60–120 mg/d; titrate up from 20–30 mg by 20–30 mg/d over 2 weeks  Adequate trial: 12 weeks  <ul style="list-style-type: none"> <li>• Do not ordinarily use in patients with hepatic insufficiency.</li> <li>• Not recommended in patients with severe renal impairment (CrCl &lt;30 ml/min)</li> </ul>	Pain Fatigue	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Headache</li> <li>• Dry mouth</li> <li>• Fatigue</li> <li>• Somnolence</li> <li>• Constipation</li> <li>• Insomnia</li> <li>• Urinary retention</li> <li>• Serotonin syndrome</li> <li>• Suicidal ideation</li> <li>• Hepatotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• MAOIs contraindicated within 5 days of discontinuing duloxetine</li> <li>• Doses above 60 mg/d have no evidence of additional benefit and increase the risk of adverse events</li> </ul>
Milnacipran [9]	100 mg/d (100–200mg/d) in 2 divided doses; titrate up from 12.5 mg by 12.5–50	Pain Fatigue	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Headache</li> <li>• Constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> </ul>

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
	mg/d per week over 3–4 weeks  Adequate trial: 12 weeks  <ul style="list-style-type: none"> <li>Do not ordinarily use in patients with substantial alcohol use or chronic liver disease.</li> <li>Not recommended in patients with end-stage renal disease.</li> <li>Dose in patients with severe renal impairment (5–29 ml/min): 50–100 mg/d in 2 divided doses</li> </ul>		<ul style="list-style-type: none"> <li>Insomnia</li> <li>Dizziness</li> <li>Hot flush</li> <li>Serotonin syndrome</li> <li>Suicidal ideation</li> <li>Increased blood pressure and heart rate</li> <li>Urinary retention</li> <li>Hepatotoxicity</li> <li>Withdrawal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>MAOIs contraindicated within 5 days of discontinuing milnacipran</li> <li>Contraindicated in patients with uncontrolled narrow-angle glaucoma.</li> </ul>
Amitriptyline <a href="#">[6,10]</a>	10-50 mg daily  Adequate trial: 6-8 weeks  Use lower doses in the elderly	Pain Fatigue	<ul style="list-style-type: none"> <li>Dry mouth</li> <li>Fatigue</li> <li>Sedation</li> <li>Vasovagal reaction</li> <li>Orthostatic hypotension</li> <li>Constipation</li> <li>Urinary retention</li> <li>QTc prolongation; conduction abnormalities</li> <li>Suicidal ideation</li> </ul>	<ul style="list-style-type: none"> <li>Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>Contraindicated with cisapride</li> <li>Avoid use with QTc prolonging drugs, anticholinergics</li> <li>Use with caution in patients with cardio- or cerebrovascular disease</li> </ul>
Pregabalin <a href="#">[6,10]</a>	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	<ul style="list-style-type: none"> <li>Dizziness</li> <li>Somnolence</li> <li>Headache</li> <li>Weight gain</li> <li>Angioedema</li> <li>Suicidal ideation</li> <li>Peripheral edema</li> <li>Withdrawal symptoms</li> <li>Blurred vision; visual field</li> </ul>	<ul style="list-style-type: none"> <li>Dose of 600 mg/d was studied but showed no additional benefit and increased the risk of adverse events</li> </ul>

Agent (Reference)	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
			changes	
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.  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	Pain	<ul style="list-style-type: none"> <li>• Drowsiness</li> <li>• Nausea</li> <li>• Insomnia</li> <li>• Headache</li> <li>• Ejaculatory disorder</li> <li>• Dizziness</li> <li>• Decreased libido</li> <li>• Diaphoresis</li> <li>• Weakness</li> <li>• Constipation</li> <li>• Diarrhea</li> <li>• Dry mouth</li> <li>• Akathisia</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Also available in immediate-release tablets (20–60 mg/d)</li> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• Most sedating SSRI</li> <li>• Potent anticholinergic effects</li> </ul>
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	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Dry mouth</li> <li>• Somnolence</li> <li>• Insomnia</li> <li>• Hyperhidrosis</li> <li>• Suicidal ideation</li> <li>• Serotonin syndrome</li> <li>• QTc prolongation</li> </ul>	<ul style="list-style-type: none"> <li>• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs</li> <li>• Avoid using citalopram with other QTc prolonging drugs</li> </ul>

<sup>†</sup> 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.

## Appendix C: Participant List

<b>CDR Roderick Bacho, PhD</b> Clinical Psychology Walter Reed National Military Medical Center Bethesda, MD	<b>Lt Col Matthew B. Carroll, MD</b> Rheumatology Keesler Air Force Base Biloxi, MS
<b>MAJ Joseph G. Cheatham, MD</b> Gastroenterology Walter Reed National Military Medical Center Bethesda, MD	<b>Paul Ciminera, MD, MPH</b> Director, Post 9/11 Era Environmental Health Program Post-Deployment Health VHA Office of Public Health Washington, DC
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<b>Ernest Degenhardt, COL USA (Ret.) MSN, RN, ANP, FNP</b> Chief, Office of Evidence Based Practice Clinical Performance Directorate US Army Medical Command Ft. Sam Houston, TX	<b>Corinne K.B. Devlin MSN, RN, FNP-BC</b> Family Nurse Practitioner Chronic Disease Clinical Practice Guideline Coordinator US Army Medical Command Quality Management Division, Office of Evidence Based Practice
<b>Matthew Friedman, MD</b> Mental Health White River Jct, VT	<b>Col. Michael R. Gauron, MD, MS</b> Family Practice Nellis AFB Las Vegas, NV
<b>Francine Goodman, PharmD, BCPS</b> Clinical Pharmacy Specialist Pharmacy Benefits Management Strategic Healthcare Group Hines VA Medical Center	<b>LT Nelson Guadalupe, D.H.ED, MS, RD, LD, CHES</b> Clinical Dietician Walter Reed National Military Medical Center Bethesda, MD
<b>Drew Helmer, MD</b> Internal Medicine Director War Related Illness and Injury Study Center, New Jersey	<b>Stephen Hunt, MD</b> Internal Medicine VA Puget Sound Health Care System Seattle, WA
<b>Penny Kaye Jensen, DNP</b> Nursing West Valley CBOC, UT	<b>David Kearney, MD</b> Gastroenterology VA Puget Sound Health Care System, WA
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<b>MAJ Joshua Mitchell, MD</b> Internal Medicine Walter Reed National Military Medical Center Bethesda, MD	<b>Lt. Col. Aniceto Navarro, MD</b> Psychiatry / Internal Med Walter Reed National Military Medical Center Bethesda, MD



<b>Matthew Reinhard, PhD</b> Neurocognitive Psychology War Related Illness and Injury Study Center Washington DC	<b>M. Eric Rodgers, PhD, FNP, BC</b> Acting Director VA/DoD Evidence-Based CPG Program Office of Quality, Safety and Value Department of Veterans Affairs Washington, DC
<b>Robert Selvester, MD</b> Family Practice Naval Air Station Corpus Christi Corpus Christi, TX	<b>MAJ Georgette A Trezvant, MSW</b> Social Work Malcolm Grow Medical Clinics and Surgery Center Joint Base Andrews, MD
<b>LCDR Jacqueline Vanmoerkerque, DPT</b> Physical Therapy CAPMED/Fort Belvoir Community Hospital, VA	<b>Fernando Zambrana, MD</b> Primary Care Daytona, FL VAMC

## References

1. Jackson JL, Passamonti M. The outcomes among patients presenting in primary care with a physical symptom at 5 years. *J Gen Intern Med*. Nov 2005;20(11):1032-1037.
2. Kroenke K, Price RK. Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Arch Intern Med*. Nov 8 1993;153(21):2474-2480.
3. Committee on Gulf War and Health: Treatment for Chronic Multisymptom Illness, Board on the Health of Select Populations, Institute of Medicine. Gulf War and health: Treatment for chronic Multisymptom Illness. Washington, DC: National Academies Press (US); 2013.
4. Hyams KC, Wignall FS, Roswell R. War syndromes and their evaluation: From the U.S. Civil War to the Persian Gulf war. *Ann Intern Med*. Sep 1 1996;125(5):398-405.
5. Blanchard MS, Eisen SA, Alpern R, et al. Chronic multisymptom illness complex in Gulf War I veterans 10 years later. *Am J Epidemiol*. Jan 1 2006;163(1):66-75.
6. Steele L. Prevalence and patterns of Gulf War illness in Kansas veterans: Association of symptoms with characteristics of person, place, and time of military service. *Am J Epidemiol*. Nov 15 2000;152(10):992-1002.
7. Fukuda K, Nisenbaum R, Stewart G, et al. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *Jama*. Sep 16 1998;280(11):981-988.
8. Institute of Medicine. *Chronic Multisymptom Illness in Gulf War Veterans: Case definitions reexamined*. Washington, DC 2014.
9. U.S. Department of Veterans Affairs. VA/DoD evidence-based practice guideline work group. [http://www.healthquality.va.gov/Evidence\\_Based\\_Clinical\\_Guidelines.asp](http://www.healthquality.va.gov/Evidence_Based_Clinical_Guidelines.asp).
10. Proposal for clinical algorithm standards. Society for medical decision making committee on standardization of clinical algorithms. *Med Decis Making*. Apr-Jun 1992;12(2):149-154.
11. Koenig HG. An abbreviated Mini-Mental State Exam for medically ill older adults. *J Am Geriatr Soc*. Feb 1996;44(2):215-216.
12. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. *Jama*. Nov 10 1999;282(18):1737-1744.
13. Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *Jama*. Dec 14 1994;272(22):1749-1756.
14. Haley RW, Charuvastra E, Shell WE, et al. Cholinergic autonomic dysfunction in veterans with Gulf War illness: Confirmation in a population-based sample. *JAMA Neurol*. Feb 2013;70(2):191-200.
15. Brimacombe M, Zhang Q, Lange G, Natelson B. Immunological variables mediate cognitive dysfunction in gulf war veterans but not civilians with chronic fatigue syndrome. *Neuroimmunomodulation*. 2002;10(2):93-100.
16. Ishoy T, Knop J, Suadican P, Guldager B, Appleyard M, Gyntelberg F. Increased psychological distress among danish Gulf War veterans--without evidence for a neurotoxic background. The danish Gulf War study. *Dan Med Bull*. Feb 2004;51(1):108-113.
17. O'Bryan TA, Romano PJ, Zangwill BC. Human leukocyte antigens in Gulf War veterans with chronic unexplained multiple symptoms. *Mil Med*. Dec 2003;168(12):1015-1018.
18. Skowera A, Stewart E, Davis ET, et al. Antinuclear autoantibodies (ana) in Gulf War-related illness and chronic fatigue syndrome (CFS) patients. *Clin Exp Immunol*. Aug 2002;129(2):354-358.
19. Vojdani A, Thrasher JD. Cellular and humoral immune abnormalities in Gulf War veterans. *Environ Health Perspect*. Jun 2004;112(8):840-846.
20. Lange G, Tiersky LA, Scharer JB, et al. Cognitive functioning in Gulf War illness. *J Clin Exp Neuropsychol*. Apr 2001;23(2):240-249.

21. Storzbach D, Campbell KA, Binder LM, et al. Psychological differences between veterans with and without Gulf War unexplained symptoms. Portland environmental hazards research center. *Psychosom Med*. Sep-Oct 2000;62(5):726-735.
22. Storzbach D, Rohlman DS, Anger WK, Binder LM, Campbell KA. Neurobehavioral deficits in Persian Gulf veterans: Additional evidence from a population-based study. *Environ Res*. Jan 2001;85(1):1-13.
23. Joseph TK, Foster L, Pasquina PF. Decreased prevalence of peripheral nerve pathology by electrodiagnostic testing in Gulf War veterans. *Mil Med*. Nov 2004;169(11):868-871.
24. Rose MR, Sharief MK, Priddin J, et al. Evaluation of neuromuscular symptoms in UK Gulf War veterans: A controlled study. *Neurology*. Nov 9 2004;63(9):1681-1687.
25. Rayhan RU, Stevens BW, Timbol CR, et al. Increased brain white matter axial diffusivity associated with fatigue, pain and hyperalgesia in Gulf War illness. *PLoS One*. 2013;8(3):e58493.
26. Chao LL, Abadjian L, Hlavin J, Meyerhoff DJ, Weiner MW. Effects of low-level sarin and cyclosarin exposure and Gulf War illness on brain structure and function: A study at 4t. *Neurotoxicology*. Dec 2011;32(6):814-822.
27. Li X, Spence JS, Buhner DM, et al. Hippocampal dysfunction in Gulf War veterans: Investigation with ASL perfusion MR imaging and physostigmine challenge. *Radiology*. Oct 2011;261(1):218-225.
28. Santos SL, Helmer D, Teichman R. Risk communication in deployment-related exposure concerns. *J Occup Environ Med*. Jun 2012;54(6):752-759.
29. Paras ML, Murad MH, Chen LP, et al. Sexual abuse and lifetime diagnosis of somatic disorders: A systematic review and meta-analysis. *Jama*. Aug 5 2009;302(5):550-561.
30. Hauser W, Kosseva M, Uceyler N, Klose P, Sommer C. Emotional, physical, and sexual abuse in fibromyalgia syndrome: A systematic review with meta-analysis. *Arthritis Care Res (Hoboken)*. Jun 2011;63(6):808-820.
31. Powell TM, Smith TC, Jacobson IG, et al. Prospective assessment of chronic multisymptom illness reporting possibly associated with open-air burn pit smoke exposure in Iraq. *J Occup Environ Med*. Jun 2012;54(6):682-688.
32. Gronseth GS. Gulf war syndrome: A toxic exposure? A systematic review. *Neurol Clin*. May 2005;23(2):523-540.
33. Kelsall HL, McKenzie DP, Sim MR, Leder K, Forbes AB, Dwyer T. Physical, psychological, and functional comorbidities of multisymptom illness in Australian male veterans of the 1991 Gulf War. *Am J Epidemiol*. Oct 15 2009;170(8):1048-1056.
34. Eisen SA, Kang HK, Murphy FM, et al. Gulf War veterans' health: Medical evaluation of a U.S. Cohort. *Ann Intern Med*. Jun 7 2005;142(11):881-890.
35. Dhillon K, Boyd KC. The effect of war stressors and life events on Gulf War veterans with chronic fatigue syndrome symptoms. *Military Psychology*. 2010;22 (2):87-97.
36. Jamil H, Hamdan TA, Grzybowski M, Arnetz BB. Health effects associated with geographical area of residence during the 1991 Gulf War: A comparative health study of Iraqi soldiers and civilians. *US Army Med Dep J*. Jul-Sep 2011:87-96.
37. olde Hartman TC, Borghuis MS, Lucassen PL, van de Laar FA, Speckens AE, van Weel C. Medically unexplained symptoms, somatisation disorder and hypochondriasis: Course and prognosis. A systematic review. *J Psychosom Res*. May 2009;66(5):363-377.
38. Voelker R. Veterans' complex chronic illness requires personalized care, says IOM. *Jama*. Feb 20 2013;309(7):646.
39. Institute of Medicine, Board on the Health of Select Populations. *Gulf War and health: Treatment for chronic Multisymptom Illness*. 2013.

40. Wagner EH, Coleman K, Reid RJ, Phillips K, Abrams MK, Sugarman JR. The changes involved in patient-centered medical home transformation. *Prim Care*. Jun 2012;39(2):241-259.
41. Arend J, Tsang-Quinn J, Levine C, Thomas D. The patient-centered medical home: History, components, and review of the evidence. *Mt Sinai J Med*. Jul-Aug 2012;79(4):433-450.
42. Reisinger HS, Hunt SC, Burgo-Black AL, Agarwal MA. A population approach to mitigating the long-term health effects of combat deployments. *Prev Chronic Dis*. 2012;9:E54.
43. Reidt S, Morgan J, Larson T, Blade MA. The role of a pharmacist on the home care team: A collaborative model between a college of pharmacy and a visiting nurse agency. *Home Healthc Nurse*. Feb 2013;31(2):80-87; quiz 88-89.
44. Modi BP, Langer M, Ching YA, et al. Improved survival in a multidisciplinary short bowel syndrome program. *J Pediatr Surg*. Jan 2008;43(1):20-24.
45. Sneve J, Kattelman K, Ren C, Stevens DC. Implementation of a multidisciplinary team that includes a registered dietitian in a neonatal intensive care unit improved nutrition outcomes. *Nutr Clin Pract*. Dec-2009 Jan 2008;23(6):630-634.
46. Selan M. A multidisciplinary approach to gastrostomy management in home enteral nutrition patients. *Eur J Clin Nutr*. Dec 2012;66(12):1374.
47. Thoresen L, Rothenberg E, Beck AM, Irtun O. Doctors and nurses on wards with greater access to clinical dietitians have better focus on clinical nutrition. *J Hum Nutr Diet*. Jun 2008;21(3):239-247.
48. Reta A, Dashtaei A, Lim S, Nguyen T, Bholat MA. Opportunities to improve clinical outcomes and challenges to implementing clinical pharmacists into health care teams. *Prim Care*. Dec 2012;39(4):615-626.
49. Cook M, Hyrkas K. Interprofessional and team working. *J Nurs Manag*. Apr 2010;18(3):245-247.
50. Hoedeman R, Blankenstein AH, van der Feltz-Cornelis CM, Krol B, Stewart R, Groothoff JW. Consultation letters for medically unexplained physical symptoms in primary care. *Cochrane Database Syst Rev*. 2010(12):Cd006524.
51. Schaefer R, Kaufmann C, Wild B, et al. Specific collaborative group intervention for patients with medically unexplained symptoms in general practice: A cluster randomized controlled trial. *Psychother Psychosom*. 2013;82(2):106-119.
52. Stuart MR, Lieberman JA. *The fifteen minute hour: Applied psychotherapy for the primary care physician, 2nd ed*. Vol 2. Westport, Connecticut: Praeger Publications; 1993.
53. Marple RL, Kroenke K, Lucey CR, Wilder J, Lucas CA. Concerns and expectations in patients presenting with physical complaints: Frequency, patient perceptions and actions, and 2-week outcome. *Arch Intern Med*. 1997;157:1482-1488.
54. Rasmussen NH, Furst JW, Swenson-Dravis DM, et al. Innovative reflecting interview: Effect on high-utilizing patients with medically unexplained symptoms. *Dis Manag*. Dec 2006;9(6):349-359.
55. Hojat M, Louis DZ, Markham FW, Wender R, Rabinowitz C, Gonnella JS. Physicians' empathy and clinical outcomes for diabetic patients. *Acad Med*. Mar 2011;86(3):359-364.
56. Hunter CL, Goodie JL, Oordt MS, Dobmeyer AC. *Integrated behavior health in primary care: Step-by-step guidance for assessment and intervention*. Washington, DC: American Psychological Association; 2009.
57. Melzack R, Wall P. Pain mechanisms: A new theory. *Science*. 1965;150(3699):971-979.
58. Engel GL. The need for a new medical model: A challenge for biomedicine. *Science*. 1977;196(4286):129-136.
59. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary rehabilitation for chronic low back pain: Systematic review. *Bmj*. Jun 23 2001;322(7301):1511-1516.

60. Helmer DA, Rossignol M, Blatt M, Agarwal R, Teichman R, Lange G. Health and exposure concerns of veterans deployed to Iraq and Afghanistan. *J Occup Environ Med.* May 2007;49(5):475-480.
61. McAndrew LM, Teichman RF, Osinubi OY, Jasien JV, Quigley KS. Environmental exposure and health of Operation Enduring Freedom/Operation Iraqi Freedom veterans. *J Occup Environ Med.* Jun 2012;54(6):665-669.
62. Spelman JF, Hunt SC, Seal KH, Burgo-Black AL. Post deployment care for returning combat veterans. *J Gen Intern Med.* Sep 2012;27(9):1200-1209.
63. O'Toole TP, Pirraglia PA, Dosa D, et al. Building care systems to improve access for high-risk and vulnerable veteran populations. *J Gen Intern Med.* Nov 2011;26 Suppl 2:683-688.
64. Peters S, Stanley I, Rose M, Kaney S, Salmon P. A randomized controlled trial of group aerobic exercise in primary care patients with persistent, unexplained physical symptoms. *Fam Pract.* Dec 2002;19(6):665-674.
65. Nickel M, Cangoez B, Bachler E, et al. Bioenergetic exercises in inpatient treatment of Turkish immigrants with chronic somatoform disorders: A randomized, controlled study. *J Psychosom Res.* Oct 2006;61(4):507-513.
66. Brosseau L, Wells GA, Tugwell P, et al. Ottawa panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: Part 1. *Phys Ther.* Jul 2008;88(7):857-871.
67. Nuesch E, Hauser W, Bernardy K, Barth J, Juni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: Network meta-analysis. *Ann Rheum Dis.* Jun 2013;72(6):955-962.
68. Mist SD, Firestone KA, Jones KD. Complementary and alternative exercise for fibromyalgia: A meta-analysis. *J Pain Res.* 2013;6:247-260.
69. Donta ST, Clauw DJ, Engel CC, Jr., et al. Cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: A randomized controlled trial. *Jama.* Mar 19 2003;289(11):1396-1404.
70. Kleinstaub M, Witthoft M, Hiller W. Efficacy of short-term psychotherapy for multiple medically unexplained physical symptoms: A meta-analysis. *Clin Psychol Rev.* Feb 2011;31(1):146-160.
71. Schroder A, Heider J, Zaby A, Gollner R. Cognitive behavioral therapy versus progressive muscle relaxation training for multiple somatoform symptoms: Results of a randomized controlled trial. *Cogn Ther Res.* 2013;37(2):296-306.
72. Guarino P, Peduzzi P, Donta ST, et al. A multicenter two by two factorial trial of cognitive behavioral therapy and aerobic exercise for Gulf War veterans' illnesses: Design of a veterans affairs cooperative study (CSP #470). *Control Clin Trials.* Jun 2001;22(3):310-332.
73. Bernardy K, Klose P, Busch AJ, Choy EH, Hauser W. Cognitive behavioural therapies for fibromyalgia. *Cochrane Database Syst Rev.* 2013;9:Cd009796.
74. Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quatero AO. Psychological treatments for the management of irritable bowel syndrome. *Cochrane Database Syst Rev.* 2009(1):Cd006442.
75. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. *Gut.* Mar 2009;58(3):367-378.
76. Lakhan SE, Schofield KL. Mindfulness-based therapies in the treatment of somatization disorders: A systematic review and meta-analysis. *PLoS One.* 2013;8(8):e71834.
77. van Rood Y, de Roos C. EMDR in the treatment of medically unexplained symptoms: A systematic review. *J EMDR Pract Res.* 2009;3(4):248-263.

78. Kim K-W, Chung W-S, Song M-Y, Chung S-H. Complementary and alternative medicine treatments in the management of chronic fatigue syndrome: A systematic review of randomized controlled trials. *Orient Pharm Exp Med*. 2013;13(2):85-93.
79. Wang T, Zhang Q, Xue X, Yeung A. A systematic review of acupuncture and moxibustion treatment for chronic fatigue syndrome in China. *Am J Chin Med*. 2008;36(1):1-24.
80. Katsamanis M, Lehrer PM, Escobar JI, Gara MA, Kotay A, Liu R. Psychophysiologic treatment for patients with medically unexplained symptoms: A randomized controlled trial. *Psychosomatics*. May-Jun 2011;52(3):218-229.
81. Altamura AC, Di Rosa A, Ermentini A, et al. Levosulpiride in somatoform disorders: A double-blind, placebo-controlled cross-over study. *Int J Psychiatry Clin Pract*. 2003;7(3):155-159.
82. Han C, Pae CU, Lee BH, et al. Venlafaxine versus mirtazapine in the treatment of undifferentiated somatoform disorder: A 12-week prospective, open-label, randomized, parallel-group trial. *Clin Drug Investig*. 2008;28(4):251-261.
83. Han C, Pae CU, Lee BH, et al. Fluoxetine versus sertraline in the treatment of patients with undifferentiated somatoform disorder: A randomized, open-label, 12-week, parallel-group trial. *Prog Neuropsychopharmacol Biol Psychiatry*. Feb 15 2008;32(2):437-444.
84. Kroenke K, Messina N, 3rd, Benattia I, Graepel J, Musgnung J. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. *J Clin Psychiatry*. Jan 2006;67(1):72-80.
85. Muller JE, Wentzel I, Koen L, Niehaus DJ, Seedat S, Stein DJ. Escitalopram in the treatment of multisomatoform disorder: A double-blind, placebo-controlled trial. *Int Clin Psychopharmacol*. Jan 2008;23(1):43-48.
86. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia--a randomized, double-blind, placebo-controlled study. *Eur J Pain*. 2000;4(1):27-35.
87. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: A meta-analysis. *J Gen Intern Med*. Sep 2000;15(9):659-666.
88. Hauser W, Arnold B, Eich W, et al. Management of fibromyalgia syndrome--an interdisciplinary evidence-based guideline. *Ger Med Sci*. 2008;6:Doc14.
89. Murphy JL, Clark ME, Banou E. Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. *Clin J Pain*. Feb 2013;29(2):109-117.
90. Carville SF, Arendt-Nielsen S, Bliddal H, et al. Eular evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis*. Apr 2008;67(4):536-541.
91. Paci E, Buiatti E, Seniori Costantini AS, et al. Aplastic anemia, leukemia and other cancer mortality in a cohort of shoe workers exposed to benzene. *Scand J Work Environ Health*. Oct 1989;15(5):313-318.
92. Ngian GS, Guymer EK, Littlejohn GO. The use of opioids in fibromyalgia. *Int J Rheum Dis*. Feb 2011;14(1):6-11.
93. Scherrer JF, Svrakic DM, Freedland KE, et al. Prescription opioid analgesics increase the risk of depression. *J Gen Intern Med*. Mar 2014;29(3):491-499.
94. Langhorst J, Klose P, Musial F, Irnich D, Hauser W. Efficacy of acupuncture in fibromyalgia syndrome--a systematic review with a meta-analysis of controlled clinical trials. *Rheumatology (Oxford)*. Apr 2010;49(4):778-788.
95. Cao H, Liu J, Lewith GT. Traditional Chinese medicine for treatment of fibromyalgia: A systematic review of randomized controlled trials. *J Altern Complement Med*. Apr 2010;16(4):397-409.
96. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: A double blind, placebo controlled trial. *J Rheumatol*. Apr 1989;16(4):527-532.

97. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A double-blind, placebo-controlled study. *Arthritis Rheum.* May 1991;34(5):552-560.
98. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum.* Nov 1986;29(11):1371-1377.
99. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: A double-blind, randomized, placebo-controlled study. *Am J Med.* May 2003;114(7):537-545.
100. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* Oct 2000;6(5):250-257.
101. Clauw DJ. Pharmacotherapy for patients with fibromyalgia. *J Clin Psychiatry.* 2008;69 Suppl 2:25-29.
102. Hauser W, Urrutia G, Tort S, Uceyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. *Cochrane Database Syst Rev.* 2013;1:Cd010292.
103. Hauser W, Bernardy K, Uceyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: A meta-analysis. *Jama.* Jan 14 2009;301(2):198-209.
104. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* Apr 2007;56(4):1336-1344.
105. Donta ST, Engel CC, Jr., Collins JF, et al. Benefits and harms of doxycycline treatment for Gulf War veterans' illnesses: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* Jul 20 2004;141(2):85-94.
106. Natelson BH, Cheu J, Pareja J, Ellis SP, Policastro T, Findley TW. Randomized, double blind, controlled placebo-phase in trial of low dose phenelzine in the chronic fatigue syndrome. *Psychopharmacology (Berl).* Apr 1996;124(3):226-230.
107. Hickie IB, Wilson AJ, Wright JM, Bennett BK, Wakefield D, Lloyd AR. A randomized, double-blind placebo-controlled trial of moclobemide in patients with chronic fatigue syndrome. *J Clin Psychiatry.* Sep 2000;61(9):643-648.
108. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet.* Mar 30 1996;347(9005):858-861.
109. Wearden AJ, Morriss RK, Mullis R, et al. Randomised, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry.* Jun 1998;172:485-490.
110. Stubhaug B, Lie SA, Ursin H, Eriksen HR. Cognitive-behavioural therapy v. Mirtazapine for chronic fatigue and neurasthenia: Randomised placebo-controlled trial. *Br J Psychiatry.* Mar 2008;192(3):217-223.
111. Santaella ML, Font I, Disdier OM. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J.* Jun 2004;23(2):89-93.
112. Moorkens G, Wynants H, Abs R. Effect of growth hormone treatment in patients with chronic fatigue syndrome: A preliminary study. *Growth Horm IGF Res.* Apr 1998;8 Suppl B:131-133.
113. Tiev KP, Cabane J, Imbert JC. [treatment of chronic postinfectious fatigue: Randomized double-blind study of two doses of sulbutiamine (400-600 mg/day) versus placebo]. *Rev Med Interne.* Oct 1999;20(10):912-918.
114. Blacker CV, Greenwood DT, Wesnes KA, et al. Effect of galantamine hydrobromide in chronic fatigue syndrome: A randomized controlled trial. *Jama.* Sep 8 2004;292(10):1195-1204.

115. The GK, Bleijenberg G, Buitelaar JK, van der Meer JW. The effect of ondansetron, a 5-HT<sub>3</sub> receptor antagonist, in chronic fatigue syndrome: A randomized controlled trial. *J Clin Psychiatry*. May 2010;71(5):528-533.
116. Pardini M, Guida S, Primavera A, Krueger F, Cocito L, Gialloreti LE. Amisulpride vs. Fluoxetine treatment of chronic fatigue syndrome: A pilot study. *Eur Neuropsychopharmacol*. Mar 2011;21(3):282-286.
117. Quijada-Carrera J, Valenzuela-Castano A, Povedano-Gomez J, et al. Comparison of tenoxicam and bromazepam in the treatment of fibromyalgia: A randomized, double-blind, placebo-controlled trial. *Pain*. May-Jun 1996;65(2-3):221-225.
118. Gronblad M, Nykanen J, Konttinen Y, Jarvinen E, Helve T. Effect of zopiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial. *Clin Rheumatol*. Jun 1993;12(2):186-191.
119. Blockmans D, Persoons P, Van Houdenhove B, Bobbaers H. Does methylphenidate reduce the symptoms of chronic fatigue syndrome? *Am J Med*. Feb 2006;119(2):167.e123-130.
120. Olson LG, Ambrogetti A, Sutherland DC. A pilot randomized controlled trial of dexamphetamine in patients with chronic fatigue syndrome. *Psychosomatics*. Jan-Feb 2003;44(1):38-43.
121. Young JL. Use of lisdexamfetamine dimesylate in treatment of executive functioning deficits and chronic fatigue syndrome: A double blind, placebo-controlled study. *Psychiatry Res*. May 15 2013;207(1-2):127-133.
122. Plioplys AV, Plioplys S. Amantadine and l-carnitine treatment of chronic fatigue syndrome. *Neuropsychobiology*. 1997;35(1):16-23.
123. Straus SE, Dale JK, Tobi M, et al. Acyclovir treatment of the chronic fatigue syndrome. Lack of efficacy in a placebo-controlled trial. *N Engl J Med*. Dec 29 1988;319(26):1692-1698.
124. Montoya JG, Kogelnik AM, Bhangoo M, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. *J Med Virol*. Dec 2013;85(12):2101-2109.
125. Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: Thirty-six months follow-up. *In Vivo*. Sep-Oct 2007;21(5):707-713.
126. Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *Jama*. Sep 27 1995;274(12):961-967.
127. Cleare AJ, Heap E, Malhi GS, Wessely S, O'Keane V, Miell J. Low-dose hydrocortisone in chronic fatigue syndrome: A randomised crossover trial. *Lancet*. Feb 6 1999;353(9151):455-458.
128. Koper R. [uterine rupture complicated by amniotic liquor embolia and blood clotting syndrome]. *Ginekol Pol*. Jul 1975;46(7):795-798.
129. McKenzie R, O'Fallon A, Dale J, et al. Low-dose hydrocortisone for treatment of chronic fatigue syndrome: A randomized controlled trial. *Jama*. Sep 23-30 1998;280(12):1061-1066.
130. Peterson PK, Pheley A, Schroepel J, et al. A preliminary placebo-controlled crossover trial of fludrocortisone for chronic fatigue syndrome. *Arch Intern Med*. Apr 27 1998;158(8):908-914.
131. Strayer DR, Carter WA, Brodsky I, et al. A controlled clinical trial with a specifically configured rna drug, poly(I).Poly(C12U), in chronic fatigue syndrome. *Clin Infect Dis*. Jan 1994;18 Suppl 1:S88-95.
132. Andersson M, Bagby JR, Dyrehag L, Gottfries C. Effects of staphylococcus toxoid vaccine on pain and fatigue in patients with fibromyalgia/chronic fatigue syndrome. *Eur J Pain*. 1998;2(2):133-142.
133. Zachrisson O, Regland B, Jahreskog M, Jonsson M, Kron M, Gottfries CG. Treatment with staphylococcus toxoid in fibromyalgia/chronic fatigue syndrome--a randomised controlled trial. *Eur J Pain*. 2002;6(6):455-466.



134. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. *J Psychiatr Res.* Jan-Feb 1997;31(1):133-147.
135. Lloyd A, Hickie I, Wakefield D, Boughton C, Dwyer J. A double-blind, placebo-controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med.* Nov 1990;89(5):561-568.
136. Peterson PK, Shepard J, Macres M, et al. A controlled trial of intravenous immunoglobulin g in chronic fatigue syndrome. *Am J Med.* Nov 1990;89(5):554-560.
137. Vollmer-Conna U, Hickie I, Hadzi-Pavlovic D, et al. Intravenous immunoglobulin is ineffective in the treatment of patients with chronic fatigue syndrome. *Am J Med.* Jul 1997;103(1):38-43.
138. Lloyd AR, Hickie I, Brockman A, et al. Immunologic and psychologic therapy for patients with chronic fatigue syndrome: A double-blind, placebo-controlled trial. *Am J Med.* Feb 1993;94(2):197-203.
139. See DM, Tilles JG. Alpha-interferon treatment of patients with chronic fatigue syndrome. *Immunol Invest.* Jan-Mar 1996;25(1-2):153-164.
140. Fluge O, Bruland O, Risa K, et al. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PLoS One.* 2011;6(10):e26358.
141. Pajak R, Lackner J, Kamboj SK. A systematic review of minimal-contact psychological treatments for symptom management in irritable bowel syndrome. *J Psychosom Res.* Aug 2013;75(2):103-112.
142. Manheimer E, Cheng K, Wieland L, et al. Acupuncture for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev.* 2012;5.
143. Andrews J, Guyatt G, Oxman AD, et al. Grade guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol.* Jul 2013;66(7):719-725.