

# Management of Chronic Multisymptom Illness: Synopsis of the 2021 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline



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## Abstract

In 2019, senior leaders within the US Department of Veterans Affairs and the US Department of Defense commissioned the update of a clinical practice guideline for managing chronic multisymptom illness. Clinical experts were assembled across both agencies to systematically review evidence and to develop treatment recommendations based on that evidence. This effort resulted in the development of 29 evidence-based recommendations for providing care for individuals with chronic multisymptom illness.

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Chronic multisymptom illness (CMI) is a condition characterized by multiple poorly understood symptoms not better accounted for by other behavioral or physical health conditions. For military personnel deployed during the Gulf War (1990-1991), CMI, termed Gulf War illness in this cohort, was highly prevalent and is considered the signature medical condition of this conflict.<sup>1</sup> However, CMI is not unique to Gulf War veterans. The prevalence of CMI in veterans of modern wars is estimated to be between 25% and 49.5%,<sup>2,3</sup> whereas population studies suggest that 26% to 35% of primary care patients present with a somatoform disorder and 40% to 49% have at least 1 medically unexplained physical symptom.<sup>4</sup> Along with a decrease in quality of life, CMI imposes a significant burden of illness and disability for many service members and veterans as well as for nonmilitary patients.

There is neither a unique *International Classification of Diseases, Tenth Revision*

code for CMI nor a universally accepted clinical case definition and standardized terminology for CMI. The Institute of Medicine<sup>5,6</sup> (now the National Academy of Medicine) recognizes 2 case definitions for research purposes, the Centers for Disease Control and Prevention<sup>5</sup> and Kansas<sup>6</sup> definitions. Both case definitions require that patients have chronic symptoms from multiple body systems or domains, such as fatigue, mood/cognition, sleep, gastrointestinal, and pain.<sup>5,6</sup> The case definitions for CMI overlap with other symptom-based conditions, including fibromyalgia syndrome (FMS), irritable bowel syndrome (IBS), and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). There are relatively few clinical trials of treatments for CMI and fewer systematic reviews of evidence-based treatments, thus making it difficult for providers to effectively manage and treat patients with CMI.

The 2021 Department of Veterans Affairs/Department of Defense (VA/DoD)



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*Affiliations continued at the end of this article.*

Clinical Practice Guideline (CPG) for the Management of CMI<sup>7</sup> provides practitioners an evidence-based approach to assess, to care for, and to manage patients with CMI. Recommended categories of interventions include behavioral health, complementary and integrative health, and pharmacologic treatments.<sup>2</sup> These interventions are summarized in [Table 1](#). The CPG also provides guidance for delivering these treatments by a patient-centered approach including shared decision-making to set treatment goals as well as ensuring effective risk communication. The [Figure](#), supported by additional information in [Table 2](#), is an algorithm that was developed to assist clinicians in providing evidence-based, patient-centered care.

#### **GUIDELINE DEVELOPMENT PROCESS**

The CPG Work Group developed key recommendations based on methods established by the VA/DoD Evidence-Based Practice Guideline Work Group<sup>8</sup> and aligned with standards for trustworthy guidelines by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the quality of the evidence base and to assign a grade for the strength of each recommendation.<sup>9,10</sup> The CPG Work Group included a multidisciplinary team of practicing clinician stakeholders with areas of expertise in the fields of internal medicine, psychiatry, occupational and environmental medicine, nutrition, gastroenterology, pharmacology, rheumatology, neurology, behavioral health, social work, psychology, nursing, and physical therapy.

The guideline panel developed 12 key questions to guide the evidence review. These key questions followed the population, intervention, comparison, outcome, timing, and setting framework, as established by the Agency for Healthcare Research and Quality.<sup>11</sup> Primary outcomes included improved functional status as well as improved quality of life, with secondary outcomes of reduction in intensity, frequency, and duration of pain, in fatigue, and in bowel-related symptoms. The systematic

search of peer-reviewed literature, conducted by ECRI Institute, included published clinical evidence and related information available through April 7, 2020. The search methods and results are detailed in the full guideline ([www.healthquality.va.gov](http://www.healthquality.va.gov)).<sup>7</sup>

Given the limited number of studies on CMI alone, the Work Group considered evidence-based treatments of CMI and CMI-like conditions (ie, FMS, IBS, and ME/CFS). Effective treatments of CMI-like conditions may help some patients with CMI; however, the extent to which treatments of CMI-like conditions are generalizable to CMI remains unclear. In addition, this CPG may have some relevance to other conditions that are manifested with multiple chronic symptoms and functional limitations that are commonly present in service members and veterans. Thus, these recommendations may be helpful adjuncts to the current guidelines for the management of mild traumatic brain injury or posttraumatic stress disorder, especially when patients report multiple chronic symptoms that are not readily explained by these or other health conditions.<sup>8</sup> Finally, whereas this CPG focuses on patients who report suffering with more than 1 symptom, some patients may report suffering from a single, prominent unexplained symptom rather than the multiple symptoms referred to in the term CMI. The recommendations contained in this CPG may be helpful in these situations as well.

#### **BEHAVIORAL TREATMENTS**

The Work Group considered behavioral treatments such as cognitive-behavioral therapy, mindfulness-based treatments, exercise, and other behavioral interventions. Together, the evidence supported recommending cognitive-behavioral therapy and mindfulness-based treatments for patients with CMI and related syndromes, considering exercise for patients with symptoms consistent with FMS and emotion-focused treatments for patients with symptoms consistent with FMS or IBS. There was preliminary evidence that psychodynamic therapies may be effective for patients with symptoms consistent with IBS. However,

TABLE 1. Recommendations

1. We recommend against the long-term use of opioid medications for the management of chronic pain in patients with CMI.
2. We recommend against offering mifepristone for patients with CMI.
3. We suggest offering cognitive-behavioral therapy for CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.
4. We suggest offering mindfulness-based therapies for patients with CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.
5. There is insufficient evidence to recommend for or against the use of biofeedback modalities in patients with CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.
6. There is insufficient evidence to recommend for or against the use of manual musculoskeletal therapies for patients with CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.
7. We suggest considering an emotion-focused therapy for patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.
8. There is insufficient evidence to recommend for or against offering relaxation therapy for patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.
9. There is insufficient evidence to recommend for or against the use of guided imagery and hypnosis modalities in patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.
10. There is insufficient evidence to recommend for or against offering a trial of mirtazapine, selective serotonin reuptake inhibitors, or amitriptyline for the treatment of pain and improved functional status in patients with CMI and symptoms consistent with fibromyalgia.
11. We suggest offering a trial of serotonin-norepinephrine reuptake inhibitors for the treatment of pain and improved functional status in patients with CMI and symptoms consistent with fibromyalgia.
12. We suggest offering pregabalin for the treatment of pain in patients with CMI and symptoms consistent with fibromyalgia.
13. We suggest against offering nonsteroidal anti-inflammatory drugs for the treatment of chronic pain related to CMI and symptoms consistent with fibromyalgia.
14. We suggest offering yoga or tai chi for patients with CMI and symptoms consistent with fibromyalgia.
15. We suggest offering manual acupuncture as part of the management of patients with CMI and symptoms consistent with fibromyalgia.
16. There is insufficient evidence to recommend for or against the use of deep tissue massage modalities in patients with CMI and symptoms consistent with fibromyalgia.
17. We suggest offering physical exercise for patients with CMI and symptoms consistent with fibromyalgia.
18. There is insufficient evidence to recommend for or against offering tricyclic antidepressants for the management of gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome.
19. There is insufficient evidence to recommend for or against the use of antispasmodics for gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome.
20. We suggest offering linaclotide and plecanatide for patients with CMI and symptoms consistent with irritable bowel syndrome with constipation who do not respond to a trial of osmotic laxatives.
21. There is insufficient evidence to recommend for or against offering lubiprostone for patients with CMI and symptoms consistent with irritable bowel syndrome with constipation who do not respond to a trial of osmotic laxatives.
22. There is insufficient evidence to recommend for or against offering eluxadoline for patients with CMI and symptoms consistent with irritable bowel syndrome with diarrhea.
23. We suggest offering a 14-day course of rifaximin for gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome without constipation.
24. There is insufficient evidence to recommend for or against offering soluble fiber supplements for gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome.
25. There is insufficient evidence to recommend for or against offering alosetron for gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome.
26. There is insufficient evidence to recommend for or against offering selective serotonin reuptake inhibitors for the management of gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome.

*Continued on next page*

TABLE 1. Continued

27. There is insufficient evidence to recommend for or against considering psychodynamic therapies for patients with CMI and symptoms consistent with irritable bowel syndrome.
28. There is insufficient evidence to recommend for or against offering duloxetine for patients with CMI and symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome.
29. We recommend against offering stimulants for treatment of fatigue in patients with CMI and symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome.

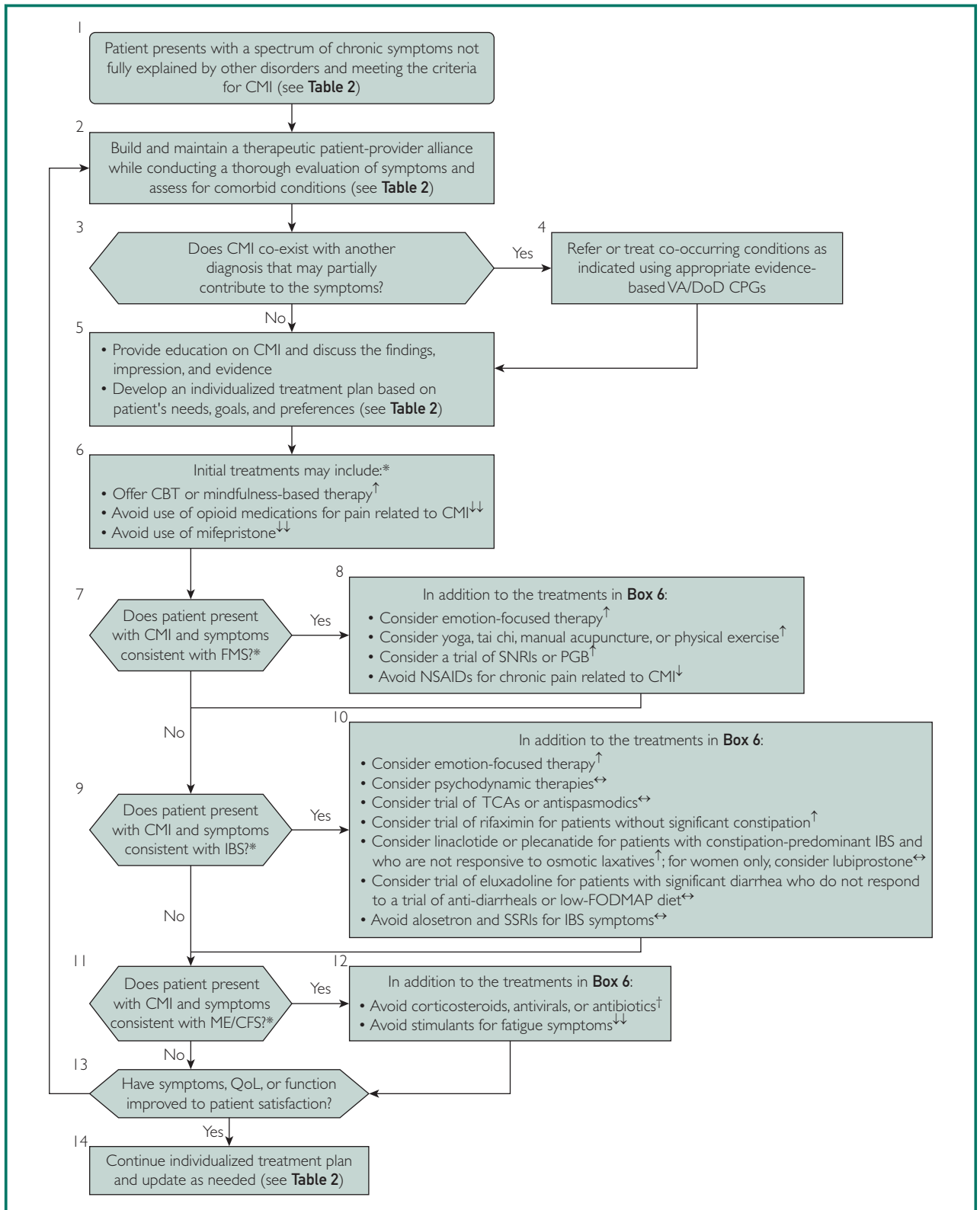
CMI, chronic multisymptom illness.

there were too few studies for the Work Group to recommend this treatment. Behavioral treatments were delivered in various settings and by different approaches, with little evidence to suggest that any modality is superior to another. Adherence to treatments also varied, highlighting the importance of considering patient preferences and resource availability. Here we review cognitive-behavioral therapy, mindfulness-based treatments, and exercise, which had the most evidence.

Cognitive-behavioral therapy had the greatest evidence, with multiple studies in patients with Gulf War illness,<sup>12</sup> FMS,<sup>13</sup> IBS,<sup>14</sup> and ME/CFS<sup>15,16</sup> consistently finding significant improvement in health function, health-related quality of life, or physical function. These studies include the largest clinical trial among veterans with Gulf War illness that randomized 1092 veterans with Gulf War illness to cognitive-behavioral therapy, aerobic exercise, cognitive-behavioral therapy plus aerobic exercise, or treatment as usual.<sup>12</sup> Veterans who received cognitive-behavioral therapy had higher odds of experiencing at least a 7-point increase in health function (cognitive-behavioral therapy alone or cognitive-behavioral therapy plus exercise) than those who did not receive cognitive-behavioral therapy.<sup>12</sup> A meta-analysis of 29 studies found strong support for cognitive-behavioral therapy for patients with FMS, with 44.3% of participants in the cognitive-behavioral therapy arms improving 20% or more on health-related quality of life compared with 31.5% of participants in the control arms.<sup>13</sup> A meta-analysis of 9 clinical trials for patients

with IBS found that cognitive-behavioral therapy led to greater improvements in daily functioning than control.<sup>14</sup> Finally, a systematic review found that after exclusion of an outlier, there was evidence that cognitive-behavioral therapy improved physical functioning in ME/CFS compared with control.<sup>15</sup> This finding was supported by 2 subsequent clinical trials for ME/CFS that found evidence for cognitive-behavioral therapy's improving physical functioning.<sup>17,18</sup>

There was also strong evidence supporting mindfulness-based therapies for patients with CMI and symptoms consistent with FMS, IBS, or ME/CFS. A clinical trial for patients with FMS found that mindfulness-based stress reduction reduced functional impairment more than treatment as usual at the end of treatment and at 12-month follow-up.<sup>19</sup> A randomized controlled trial (RCT) for patients with FMS found that meditation awareness training led to significant reductions in functional impairment compared with a control, which provided education on cognitive-behavioral theory immediately after the intervention and at 6 months of follow-up.<sup>20</sup> Another RCT found that mindfulness-based cognitive therapy for patients with IBS improved quality of life by 32% in the mindfulness-based cognitive therapy arm compared with 3% in the waitlist control arm after treatment and by 39% compared with 1% at the 6-week follow-up.<sup>21</sup> The results of the reviewed studies are consistent with a meta-analysis that reviewed quality of life outcomes for 2 clinical trials for FMS and 3 clinical trials for IBS.<sup>22</sup> The meta-analysis found small to



moderate effect sizes for mindfulness-based therapy compared with waitlist or support group controls for enhanced quality of life.<sup>22</sup> Additional research is needed to confirm the effectiveness of mindfulness-based therapies and to refine delivery parameters including training of providers, delivery modalities (eg, digital media), and target patient groups (eg, all genders) with CMI, including those with symptoms of FMS, IBS, or ME/CFS.

In patients with symptoms consistent with FMS, physical exercise was found to be effective. This recommendation was based, in part, on an RCT by Donta et al<sup>12</sup> in 2003, which reported that exercise alone and in combination with cognitive-behavioral therapy improved fatigue, distress, cognitive symptoms, and mental health functioning in patients with FMS. A systematic review by Brosseau et al<sup>23</sup> in 2008 found that strengthening exercises had a clinically and statistically significant benefit in reducing disability, although there was no change in FMS impairment or quality of life. Finally, a meta-analysis by Nüesch et al<sup>24</sup> evaluated the efficacy of aerobic exercise in patients with FMS and found a statistical benefit of aerobic exercise in improving quality of life and pain.

### COMPLEMENTARY AND INTEGRATED HEALTH INTERVENTIONS

Research on traditional medical and pharmacologic interventions has illustrated the limitations these interventions have in reducing CMI disability and improving quality of life. With the complex range of symptoms and limited success with conventional Western medicine, complementary and integrative health presents a more holistic approach to

address the constellation of symptoms afflicting patients with CMI. Two complementary and integrative health interventions had adequate strength of evidence to support consideration for use in clinical practice. These were yoga or tai chi for patients with CMI and symptoms consistent with FMS and manual acupuncture as part of management for patients with CMI and symptoms consistent with FMS.

A Cochrane review by Theadom et al<sup>25</sup> compared various mind-body interventions (eg, biofeedback, mindfulness, and movement therapies) and attention placebo control with standard care (medications) for patients with FMS after the intervention's conclusion and at 3 and 6 months. Among the movement therapies, 3 RCTs examined yoga and 1 examined qi-gong. The 3 yoga studies and 1 qi-gong study used physical functioning outcomes, which found improvement at both 3-month ( $P<.01$ ) and 6-month ( $P<.01$ ) follow-up. Theadom et al<sup>25</sup> also reviewed 3 tai chi and 1 Pilates intervention. The Pilates intervention and 2 of the 3 tai chi interventions demonstrated significant improvements in self-reported physical functioning after intervention and after a 3-month follow-up period compared with attention controls.<sup>25</sup>

An RCT by Maddali Bongsi et al<sup>26</sup> compared the efficacy of tai chi with educational courses performed twice weekly during 4 months. Outcome measures assessed changes in disability, quality of life, pain, fatigue, sleep quality, and mood. All scores significantly improved in the intervention but not in the control group. A comparative effectiveness RCT by Wang et al<sup>27</sup> recruited 226 adults with FMS to compare tai chi (n=151) with aerobic exercise (n=75) on

**FIGURE.** Algorithm for management of chronic multisymptom illness (CMI). CBT, cognitive-behavioral therapy; CPG, clinical practice guideline; VA/DoD, Department of Veterans Affairs/Department of Defense; FMS, fibromyalgia syndrome; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS, irritable bowel syndrome; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; NSAID, nonsteroidal anti-inflammatory drug; PGB, pregabalin; QoL, quality of life; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant. \*Recommended interventions are not rank ordered; consider interventions based on individual patient needs, goals, and preferences. †There has been no new evidence since the 2014 CMI CPG to suggest any benefit for steroids, antivirals, or antibiotics. As such, the Work Group recommends against using these agents to treat CMI and symptoms consistent with ME/CFS. † indicates a “Weak for” recommendation strength; ‡ indicates a “Weak against” recommendation strength; †† indicates a “Strong against” recommendation strength; ↔ indicates a “Neither for nor against” recommendation strength.

TABLE 2. Sidebars for the CMI Algorithm

Case Definition of Chronic Multisymptom Illness
Chronic multisymptom illness is characterized by multiple, persistent symptoms (eg, fatigue, headache, arthralgias, myalgias, concentration and attention problems, and gastrointestinal disorders) across more than 1 body system. The symptoms must be present or frequently recur for more than 6 months and should be severe enough to interfere with daily functioning.
Elements of Assessment
<ul style="list-style-type: none"> <li>● Obtain medical history and military/deployment history.</li> <li>● Conduct psychosocial assessment including psychological trauma history.</li> <li>● Conduct physical examination.</li> <li>● Consider diagnostic studies, as indicated, for rule-out of alternative diagnoses only; avoid any tests for which there may be limited additional benefit.</li> <li>● Consider additional or longer duration encounters.</li> </ul>
Individualized Treatment Plan
<ul style="list-style-type: none"> <li>● Using a whole/holistic health approach, identify individual treatment goals (eg, return to work, improved quality of life, resumption of recreational activities).</li> <li>● Describe treatment options and engage in shared decision-making discussion and shared goal setting in support of the individual's aspiration and purpose for health and well-being.</li> <li>● Maximize use of nonpharmacologic therapies (eg, CBT, CIH interventions [see <a href="https://www.va.gov/wholehealth/">https://www.va.gov/wholehealth/</a>], aerobic exercise).</li> <li>● Develop personal health plan and timeline for follow-up and monitor progress toward personal goals.</li> <li>● Maintain continuity and caring relationship through in-person or virtual modalities.</li> <li>● Provide education (both for improved health literacy and whole/holistic health self-care) and engage families/caregiver/support person, if available.</li> <li>● Based on patient needs, consider referral to case manager and establish interprofessional care team.</li> </ul>
CBT, cognitive-behavioral therapy; CIH, complementary and integrative health.

the primary outcome of the revised FMS impact questionnaire scores and to test whether tai chi's effectiveness is dose or duration dependent. Both interventions were supervised, and participant adherence was encouraged. Results favored tai chi to aerobic exercise, and greater improvement was demonstrated with a longer duration of treatment.<sup>27</sup>

A systematic review for IBS that included 6 RCTs of yoga<sup>28</sup> (Hatha, conventional, and Iyengar) with 264 participants found support for yoga. Both yoga and yoga plus conventional treatments resulted in significant improvements in IBS Severity Scoring System and IBS—Quality of Life scores after a 3-month intervention period compared with waitlist controls. Yoga interventions improved diarrhea-predominant IBS better than loperamide did. There were no differences between yoga and a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (ie, FODMAP diet).

Although the confidence in the quality of the evidence related to yoga and tai chi was low, no studies reported significant differences in adverse effects between the active and control groups. Limitations also included low enrollment of male participants, limiting direct applicability to the military and veteran populations, and low to moderate levels of adherence during the trials, perhaps reflecting variation in patient values and preferences for yoga. Another limitation of yoga is the need for supervision in performing the activity for therapeutic reasons.<sup>28</sup>

A systematic review of 12 RCTs by Zhang et al<sup>29</sup> suggested that manual acupuncture improves quality of life both immediately after treatment and up to 3 months after treatment in patients with FMS compared with sham acupuncture. The quality of life benefit was observed only in the manual acupuncture trials reviewed, hence the specification for manual acupuncture in the recommendation.<sup>29</sup> A

separate systematic review by Zheng et al<sup>30</sup> found that acupuncture improved quality of life in patients with IBS at both the end of treatment and 2 months afterward compared with Western medicine but not compared with sham acupuncture. Zheng et al<sup>30</sup> suggested that acupuncture may benefit patients with IBS. However, the evidence was not considered strong enough to merit a distinct recommendation for acupuncture for these patients. The evidence available for the role of acupuncture in ME/CFS was too low quality to consider making a recommendation. Across all studies, however, adverse events were mild and infrequent.

Acupuncture can be costly, given specialty training requirements; therefore, access to acupuncture may be limited by lack of coverage by insurance or unavailability of trained practitioners. Self-administered acupuncture (eg, “battlefield” or “auricular” acupuncture) is becoming more widespread for treatment of pain, for example, but was not explicitly included in the CPG review.<sup>31</sup> Not all patients may be comfortable with acupuncture because of concern about needles or a perception that acupuncture is not part of a Western medicine paradigm. Others may find the nonpharmacologic and “Eastern” nature of acupuncture attractive. Regardless, more research on the efficacy and mechanism of action of acupuncture in patients with CMI is required. Studies should focus on optimal treatment durations, global primary outcomes such as quality of life and functioning, and high-quality study design and implementation with double-blind, sham-controlled interventions in diverse and representative samples.

### PHARMACOTHERAPY

Our limited understanding of the pathophysiologic mechanism of CMI and the challenges of establishing a case definition balancing the unique nature of CMI in relationship to other potentially overlapping and similarly complex conditions have constrained research oriented toward the more targeted treatments, such as pharmacologic agents.<sup>32</sup> There are no Food and Drug

Administration (FDA) approved drugs for the treatment of CMI, and agent selection is based mainly on targeting the predominant symptom complex (ie, CMI with symptoms consistent with FMS, IBS, or ME/CFS). On the other hand, several medications are FDA approved for FMS and IBS; the Work Group reviewed the evidence supporting the use of these and other pharmacotherapies for patients with CMI.

A systematic review found that serotonin-norepinephrine reuptake inhibitors provide beneficial outcomes for pain relief in patients with FMS vs controls and improvements in Patient Global Impression of Change scores and patient’s quality of life scores.<sup>33</sup> Within the serotonin-norepinephrine reuptake inhibitor class of drugs, duloxetine is FDA approved for the management of FMS. The CPG also suggests offering pregabalin to treat pain in patients with CMI and symptoms consistent with FMS.<sup>7</sup> The evidence suggests that pregabalin, which is also FDA approved for FMS, provides substantial pain relief (30% to 50%), as assessed by the Brief Pain Inventory, and improvements in Patient Global Impression of Change scores.<sup>34,35</sup>

For the treatment of CMI and symptoms consistent with IBS, drug selection is based mainly on the IBS symptoms of constipation, diarrhea, or mixed. For CMI and symptoms consistent with IBS-constipation, the CPG suggests offering linaclotide and plecanatide for patients who do not respond to a trial of osmotic laxatives. In one systematic review and meta-analysis involving 6 RCTs that assessed a total of 6472 patients, linaclotide (290 mg/d) and plecanatide (3 mg/d) were more effective than placebo in meeting the FDA response end point for IBS with constipation at a 12-week follow-up.<sup>36,37</sup>

For patients with CMI and symptoms consistent with IBS without constipation, the CPG suggests offering a 14-day course of rifaximin for gastrointestinal symptoms. A systematic review and meta-analysis of RCTs compared the efficacy of rifaximin (550 mg, 3 times a day for 14 days) vs placebo in 2 RCTs involving 1260 participants (625 assigned to rifaximin, 635 assigned to



placebo) meeting Rome II criteria for IBS-diarrhea or IBS-mixed.<sup>17</sup> This study found that those randomly assigned to rifaximin were significantly less likely to fail to achieve FDA-defined treatment response and to experience improvements in stool consistency at 12-week follow-up.<sup>38</sup>

The CMI CPG makes no recommendation in favor of any pharmacologic agent for the management of CMI and symptoms consistent with ME/CFS but does recommend against the use of stimulants. A double-blind RCT of 135 patients with ME/CFS provides indirect evidence against therapeutic trials of KPAX002 (methylphenidate hydrochloride plus supplement) in patients with CMI and symptoms consistent with ME/CFS.<sup>39</sup> In this study, KPAX002 did not significantly improve fatigue-related symptoms compared with placebo. The CPG Work Group believes the harms/burden of stimulant use (ie, the potential for abuse, increased aggression or hostility, exacerbation of bipolar illness, exacerbation of hypertension, exacerbation of Raynaud phenomenon, headache, nausea with methylphenidate hydrochloride) outweighed any potential benefits.<sup>40</sup>

Primarily because potential risks may outweigh any benefits, the CMI CPG recommends against the use of mifepristone, a potent antagonist of progesterone and cortisol, and recommends against the long-term use of opioid medications for the management of patients with CMI.

Providers should always consult the medication prescribing information for warnings, precautions, contraindications, and dosing considerations when pharmacologic agents are considered to manage CMI or CMI-related symptoms.

## DISCUSSION

The most important message from the 2021 update to the CMI CPG is the existence of several evidence-supported treatment options for CMI, particularly for patients with symptoms consistent with FMS, IBS, or ME/CFS. Clinicians can use the recommendations and supporting documentation of the CMI CPG to suggest constructive options for

management of this debilitating condition. Given the documented clinician perceptions of the difficulty of managing CMI and a frequently expressed patient perspective of clinicians' not knowing about CMI or its management,<sup>41</sup> this CPG should be broadly disseminated and shared to improve the quality of care for patients with CMI.

This CMI CPG is the second update for the original VA/DoD CPG, "Management of Medically Unexplained Symptoms: Chronic Pain and Fatigue," which was updated in 2014 as the VA/DoD CPG for "Management of Chronic Multisymptom Illness." Progress has been made in the past 20 years to investigate efficacious treatment of CMI; however, these efforts are hampered by many challenges. The change in the CPG title reflects the changes in the conceptualization and nomenclature related to the condition and other symptom-based syndromes. These conditions are unique because there are persistent uncertainties in their case definitions and a lack of a clear understanding of the pathophysiologic process.<sup>32</sup> Consequently, there are no reliable biomarkers on which to base a diagnosis. The heterogeneity of CMI makes it challenging to select and to test outcomes. The VA/DoD Common Data Elements Work Group is addressing this by harmonizing outcome measurement for CMI.<sup>42</sup> There is no question that these features of CMI have restricted the research necessary to establish solid evidence for potential treatments, which is the foundation of a robust CPG.

A nearly concurrent evidence-based synthesis of Gulf War illness treatments concluded that the best evidence supports the treatment of Gulf War illness with a combination of cognitive-behavioral therapy with or without exercise and 2 distinct mindfulness-based interventions. Studies of these interventions demonstrated improvement in several key symptoms and functional outcomes in individuals with Gulf War illness, such as cognitive functioning and fatigue.<sup>12,43-45</sup> This finding is consistent with the recommendations of this CMI CPG, although the CPG also recommends other promising evidence-supported interventions.<sup>7</sup> The evidence synthesis concluded

that ongoing, single-arm, pilot nonpharmacologic, pharmacologic, and medical device interventions currently under investigation to treat symptoms of Gulf War illness might help identify potentially promising interventions but would not bolster the evidence base guiding clinicians about which treatments are most likely to be effective in clinical practice.<sup>43</sup> The topic of CMI needs larger, more rigorously designed and executed trials to demonstrate and to confirm efficacious treatments.

This revised CPG for CMI parallels changes in health care. We see the emergence of more holistic approaches to health care, such as the Whole Health model in Veterans Affairs, which may be particularly important for individuals with conditions such as CMI. These care models prioritize the optimization of health overall as the key to effective care. An important consideration addressed in the CPG is the need to identify and to treat all comorbid conditions, such as posttraumatic stress disorder, depression, and diabetes, among many others. Proper and definitive treatment of these conditions can improve symptoms, reduce the risk of complications from these conditions, and clarify the residual symptoms that may be attributed to CMI.

In conditions like CMI with prominent chronic symptoms that can interfere with function, effective care involves personalized, integrated, team-based care that orients forward goals that are more functional and lean heavily on self-care for maintaining or improving quality of life. Specific examples of self-management activities include attending to mental health and well-being, developing resilience to stress, maintaining healthy sleep and rest, achieving optimal nutrition for metabolic health, and optimizing physical stamina and strength to support activities of daily living and activities that bring joy and meaning to life.<sup>43</sup> Because there is variability in the severity of illness in CMI, the CPG encourages a stepped approach to care. Clinicians are encouraged to begin with recommendations for more accessible, lower risk, and less resource intense interventions and to add or to switch

to less accessible, higher risk, and more expensive approaches if necessary. Similarly, the CPG encourages clinicians to match the intensity of the recommended intervention to the severity or negative impact of the symptom and to monitor for response at appropriate intervals.

The CPGs have emerged as an essential tool used across the health care spectrum to improve and standardize care for almost every health condition, with the ultimate goal of improving health outcomes through disease management. In addition to being a decision support tool for clinicians, they also provide a foundation for additional educational resources and can support quality improvement activities, guide researchers, and inform public policy.<sup>44</sup> In addition to potential benefits, there are certain limitations and even potential harms associated with the development and implementation of CPGs.<sup>45</sup> Limitations in a particular CPG may result from the methodology of the guideline development or deficiencies in the quantity and quality of the research on which the guideline recommendations are based. Standardization of the mechanics of care does not equate with standardizing the quality of care and may work contrary to the provision of personalized care.

Given the complex and incompletely defined nature of CMI, the limitations and potential harms associated with this CPG may be even more relevant. The research related to CMI is limited and the quality is often poor, which can result in a CPG with a simplistic, fragmented algorithm based on a weak evidence base. To protect against these challenges, the recommendations in this CPG were developed according to GRADE methodology.<sup>46,47</sup> The updated CPG includes findings from recent research, is better organized, is more comprehensive in terms of overall approaches to care, and is more user friendly than the earlier (2014) version of the CPG. Most important, we remind clinicians to take a holistic approach in evaluating and managing patients with CMI, to elicit patient goals, to engage caregivers, and to use a team-based approach to care planning as indicated.

## CONCLUSION

This article highlights the 2021 CMI CPG recommendations, summarizing evidence-based treatment, and suggests management options for patients with CMI. Chronic multisymptom illness is a chronic and debilitating condition that can be challenging to diagnose and to treat, frustrating patients, caregivers, and clinicians alike. The aim of this paper is to provide a concise review for clinicians and to serve as a tool for developing a treatment plan with the goal of improving quality of life and function for patients. Recommendations should be considered in the context of a holistic and patient-centered approach to care for individuals with CMI.

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**Abbreviations and Acronyms:** CMI, chronic multisymptom illness; CPG, clinical practice guideline; FDA, Food and Drug Administration; FMS, fibromyalgia syndrome; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; RCT, randomized controlled trial; VA/DoD, Department of Veterans Affairs/Department of Defense

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