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

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 Department of Veterans Affairs or 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 by contacting your regional TRICARE Managed Care Support Contractor.

Version 3.0 – 2021

Prepared by:

The Management of Chronic Multisymptom Illness Work Group

With support from:

The Office of Quality and Patient Safety, VA, Washington, DC

&

Office of Evidence Based Practice, Defense Health Agency

Version 3.0 – 2021

Based on evidence reviewed through April 7, 2020

Table of Contents

I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee (HEC) "… 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 (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.(1) The development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In October 2014, the VA and DoD published a CPG for the Management of Chronic Multisymptom Illness (2014 CMI CPG), which was based on evidence reviewed through October 2013. Since the release of that CPG, a growing body of research has expanded the evidence base and understanding of chronic multisymptom illness (CMI). Consequently, a recommendation to update the 2014 CMI CPG was initiated in 2019.

This CPG provides an evidence-based framework for evaluating and managing care for adults 18 years or older who are eligible for care in the VA and/or DoD healthcare systems, and who have a diagnosis of CMI.

Successful implementation of this CPG will:

- Enhance the assessment of the patient's condition
- Enhance collaboration with the patient, family, and caregivers to determine optimal management
- Minimize preventable complications and morbidity of CMI
- Optimize individual health outcomes and quality of life for patients with CMI

II. Background

Chronic multisymptom illness is a critical healthcare issue for the VA and DoD, given its high prevalence in Gulf War Veterans (GWV; largely considered Veterans from Operations Desert Shield and Desert Storm, 1990 – 1991), as well as other deployed and non-deployed Veteran cohorts. It is characterized by multiple, persistent symptoms (e.g., fatigue, headache, arthralgias, myalgias, concentration and attention problems, and gastrointestinal disorders) across more than one body system. The symptoms must be present or frequently recur for more than six months and severe enough to interfere with daily functioning.

While symptoms of CMI should not be better accounted for by another behavioral health or physical health condition, patients with CMI often have multiple comorbidities. The presence of other behavioral or physical health conditions that contribute to relevant symptoms does not preclude a diagnosis of CMI. Furthermore, CMI can overlap with other symptom-based conditions, such as fibromyalgia (FMS), irritable bowel syndrome (IBS), and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); therefore, a whole person approach is very important to management decisions for CMI patients.

After every military combat deployment in modern history, significant numbers of Service Members have reported illnesses characterized by chronic, medically unexplained symptoms;(2) however, the labels given to these illnesses and symptoms have varied by cohort and era.(3) Some of these labels tended to

reinforce the problematic notion that the symptoms were simply "in the individual's head" or of psychological origin rather than being "physiologic" or having a physical origin. Other terms previously used to describe CMI include "medically unexplained symptoms," "unexplained illnesses," or "persistent physical symptoms" (for a discussion on terminology, see Shine et al. [2014]).(4-6) Uncertainty in diagnostic labeling can contribute to individuals feeling they have a lack of control over their health and well-being.

Regardless of terminology, clinicians will recognize patients with CMI from the preceding descriptions. Many clinicians struggle to help patients with CMI (7) and will likely find the recommendations and supporting documentation in the CPG helpful to guide their approach to management decision making. Enhanced understanding of CMI and related conditions by the clinician after reviewing the CPG will facilitate more positive and productive interactions between the clinician and the patient with CMI and likely result in better care management decisions, clearer treatment goals, and better outcomes.

Two existing definitions – the U.S. Centers for Disease Control and Prevention (CDC) definition (8) and the Kansas definition (9) – most accurately characterize the hallmark constellation of multisystem symptoms that comprise CMI. The CDC definition requires a person to have one or more symptoms in at least two of the three categories of fatigue, musculoskeletal (MSK), and mood/cognition for at least six months. The Kansas definition requires a person to have symptoms for at least six months in at least three of the following domains: fatigue or sleep, pain, neurologic, cognitive, mood, gastrointestinal, respiratory, or skin. The CDC definition, which has been widely used by researchers, identified CMI in 29 – 60% of GWV (depending on the population studied), whereas the Kansas definition identified CMI in 34% of GWV from Kansas who were participants in the original study.(8, 9) A National Academy of Medicine (NAM, formerly known as the Institute of Medicine [IOM]) committee has noted each definition has particular strengths, including the CDC's inclusion of severity indicators and the Kansas definition's exclusionary criteria, as well as limitations.(10)

In a 2017 report on VA claims and Gulf War Illness (GWI), a historical, collective term for certain medical conditions among Veterans who have served in Southwest Asia since 1990, the U.S. Government Accountability Office (GAO) recommended the VA develop a plan to create a singular case definition of GWI/CMI.(11) The GAO also noted that a 2014 IOM report recommended that the Kansas and CDC definitions be used in the interim.(10) The VA planned and initiated two projects using advanced chart review and annotation tools and machine learning that are expected to be completed by 2021. The VA is also working with an oversight expert steering committee, including DoD, academia, and other experts, to prepare a new case definition that is expected to be ready for peer review by 2022.

The prevalence of CMI in Veterans of modern wars is estimated to be between 25% and 49.5%.(12, 13) Chronic multisymptom illness was particularly prevalent among Veterans deployed during the Gulf War (1990 – 1991) and was considered the signature medical condition of this conflict. Population-based studies have consistently demonstrated a higher prevalence and severity of symptom reporting related to CMI in GWV than in non-deployed Veterans who served at the same time or other control groups.(13) A 2020 study reported a 10% greater prevalence of CMI in deployed versus non-deployed GWV.(13) New-onset CMI was also highly prevalent one year after deployment among Service Members deployed in support of Operations Enduring, Iraqi Freedom, and New Dawn (OEF/OIF/OND).(12) There is a higher

prevalence of CMI in female GWV and OEF/OIF/OND Veterans compared to male Veterans of these conflicts, with the overall prevalence of CMI increasing in both sexes over time.(13, 14)

While symptom-based illnesses may be particularly prevalent among deployed Veterans, CMI is not unique to those who have served in the military, those who served during any specific combat era, or those who were deployed to either combat or non-combat environments. Studies suggest that approximately 30% of primary care patients have a symptom-based illness and 40 – 49% have at least one medically unexplained symptom.(15)

Chronic multisymptom illness imposes a significant burden of illness and disability, with a subsequent decrease in quality of life (QoL) for many Service Members, Veterans, their family members, and caregivers. Therefore, it is important to provide a timely diagnosis as well as proactive, accessible, effective care and management of CMI. Management must address CMI, and not solely comorbid conditions. This is particularly relevant for behavioral health treatments, like cognitive behavioral therapy (CBT). There are differences in many behavioral health and complementary and integrative health (CIH) treatments for CMI compared to comorbid conditions (e.g., CBT for CMI versus CBT for depression). Recommendations for behavioral therapies can sometimes be misinterpreted as a recommendation for behavioral therapy for mental health conditions, which will not address CMI.

In developing this CPG, the Work Group reviewed randomized controlled trials (RCTs), meta-analyses, and systematic reviews (SRs). Given the limited number of studies on CMI alone, the Work Group considered evidence-based treatments for CMI and CMI-like conditions (i.e., fibromyalgia [FMS], irritable bowel syndrome [IBS], and myalgic encephalomyelitis/chronic fatigue syndrome [ME/CFS]). Effective treatments for CMI-like conditions may help some patients with CMI, however, the extent to which treatments for CMI-like conditions are generalizable to CMI remains unclear.

While other chronic conditions were not specifically included in this CPG's systematic evidence review, this CPG may have some relevance to conditions that manifest with multiple chronic symptoms and functional limitations, sometimes attributed to specific events or conditions, such as mild traumatic brain injury (mTBI) or posttraumatic stress disorder (PTSD). These conditions also commonly present in Service Members and Veterans with CMI. Thus, this CPG's recommendations may apply to patients with such conditions and are likely to be a helpful adjunct to the current guidelines for the management of mTBI, PTSD, and major depressive disorder (MDD), especially when patients report multiple chronic symptoms that are not readily explained by these or other health conditions.

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through April 7, 2020. It is intended to provide general guidance on best evidence-based practices (see Appendix A for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care (SOC).

A. Guideline Audience

This CPG is designed primarily to assist healthcare providers and teams in managing patients with CMI and related conditions. This guideline seeks to inform providers with practical evidence-based recommendations for the most common scenarios involving patients with CMI.

B. Guideline Population

The patient population of interest for this CPG is adults 18 years or older who are eligible for care in the VA and/or DoD healthcare systems, and who have a diagnosis of CMI.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The current document is an update to the 2014 CMI CPG. There are several substantial changes since 2014. First, and most fundamentally, the 2021 CPG took a different approach to CMI and the related conditions of IBS, FMS, and ME/CFS. The 2014 CMI CPG's algorithm approached CMI with predominant symptoms reflecting each related condition as an entity ("fatigue-predominant CMI"), while the 2021 version focused more explicitly on the CMI population. This means that we incorporated the evidence as a second step in our evidence synthesis. We also organized the presentation of the recommendations reflecting the primacy of CMI, in general, followed by recommendations based on findings in the other populations.

In addition, while both iterations of the CPG have the same number of recommendations, the interventions to consider and avoid for CMI have changed. The 2014 CMI CPG developed several recommendations on diagnosis, evaluation, and management strategies, which the 2021 CMI CPG has considered to be part of SOC. In addition to being organized by secondary conditions, recommendations have also been grouped by the type of intervention (e.g., pharmacologic, behavioral).

The 2021 CMI CPG includes a comprehensive summary of information gaps and research needs. The summary reflects common issues identified across recommendations and includes intervention and recommendation-specific gaps.

Finally, this CPG has included an additional appendix on relevant behavioral therapies. Users of the CPG who are not familiar with the nuances and distinctions of specific behavioral therapies will likely find this resource helpful. It may also facilitate the identification of providers who utilize some of these interventions.

The 2021 VA/DoD CMI CPG used stricter methodology than previous iterations. For additional information on GRADE or CPG methodology, see Appendix A.

B. Components of the Guideline

The 2021 VA/DoD CMI CPG is the second update to this CPG. It provides clinical practice recommendations for the care of patients with CMI (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, a section that identifies areas needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card. These can be found at https://www.healthquality.va.gov/index.asp.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Office of Evidence Based Practice, Defense Health Agency, identified the following four clinicians to serve as Champions (i.e., leaders) of this CPG's Work Group: Drew A. Helmer, MD, MS and Stephen C. Hunt, MD, MPH from the VA and Lt Col Wendy Chao, DO and COL Aniceto Navarro, MD, FAPA from the DoD.

The Work Group comprised individuals with the following areas of expertise: internal medicine, psychiatry, nutrition, gastroenterology, pharmacology, rheumatology, neurology, behavioral health, social work, psychology, nursing, and physical therapy. See Table 1 for a list of Work Group members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review
- Identifying discussion topics for the patient focus group and considering the patient perspective
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, Duty First Consulting, and Anjali Jain Research & Consulting was contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**Drew A. Helmer, MD, MS (Champion)**
	Stephen C. Hunt, MD, MPH (Champion)
	Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
	Molly Cloherty, LDN
	David Kearney, MD
	Lisa McAndrew, PhD
	Mitchell Nazario, PharmD
	Tiffany Smoot, MSN, RN
	Rachel Zhang, LCSW
Department of Defense	**Lt Col Wendy Chao, DO (Champion)**
	COL Aniceto Navarro, MD, FAPA (Champion)
	Lt Col Pamela Blueford, LCSW
	MAJ Nicole H. Brown, PT, DPT, OCS, SCS, TPS
	COL William Brown, PhD, FNP-BC, FAANP
	Jennifer Felsing, MSN
	Maj Sarah Kelly, PharmD
	MAJ Joetta Khan, PhD, MPH, RD, LD
	Col Patrick Monahan, MD, MPH
	MAJ Rachel Robbins, MD, FACP
VA Evidence Based Practice, Office of Quality and Patient Safety ***Veterans Health Administration***	M. Eric Rodgers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	Rene Sutton, BS, HCA
Office of Evidence Based Practice ***Defense Health Agency***	Corinne K. B. Devlin, MSN, RN, FNP-BC
	Elaine Stuffel, MHA, BSN, RN
The Lewin Group	Clifford Goodman, PhD
	Erika Beam, MS
	Ben Agatston, JD, MPH
	Daniel Emont, MPH
	Matthew Heron, BS
ECRI	Kris D'Anci, PhD
	Kelley Tipton, MPH
	Joann Fontanarosa, PhD
	Amber Moran, MA
	Alison Gross, MLS
Sigma Health Consulting	Frances Murphy, MD, MPH
	James Smirniotopoulos, MD
Anjali Jain Research & Consulting	Anjali Jain, MD
Duty First Consulting	Rachel Piccolino, BA
	Mary Kate Curley, BA

*Additional contributor contact information is available in Appendix E.

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(16) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the NAM's principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(17) Appendix A provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to craft each recommendation and determine its strength. Per GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see Grading Recommendations): (18)

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

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). 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 incorporates the four domains.(19) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

Based on the GRADE approach, if the Work Group believes all or almost all informed people would recommend for or against an intervention, they develop a *Strong* recommendation.(19) If, after assessing these domains, the Work Group believes that most informed people would recommend the intervention, but a substantial number would not, it generally assigns a *Weak* designation to the recommendation.(19) Nevertheless, a *Weak* recommendation is clinically important and evidence-based.

In some instances, there is insufficient evidence on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence

review may have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this is expressed in the CPG may vary. In such instances, the Work Group may include among its set of recommendations an insufficient evidence statement for an intervention that may be in common practice even though it is not supported by clinical evidence, and particularly if there may be other risks of continuing to use it (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group may decide to not include this type of statement about an intervention. For example, the Work Group may remain silent where there is an absence of evidence for a rarely used intervention. In other cases, an intervention may have a favorable balance of benefits and harms but may be a SOC for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see Table 2).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend …
Weak for	We suggest …
Neither for nor against	There is insufficient evidence to recommend for or against …
Weak against	We suggest against …
Strong against	We recommend against …

It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care). The strength of each recommendation is shown in the Recommendations section.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. For instance, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach that is independent of the clinical topic of interest. Therefore, recommendations on topics for which it may be inherently more difficult to design and conduct rigorous studies (e.g., RCTs) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(20, 21) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see Appendix A.

B. Categorization of 2014 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, this typically requires revision of a CPG's previous versions based on new evidence or as scheduled subject to time-based expirations.(22) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.(23)

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).(24, 25) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in Recommendation Categorization. The 2021 CPG recommendation categories can be found in Recommendations. Appendix D outlines the 2014 CMI CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions[a]

Evidence Reviewed	Recommendation Category	Definition
Reviewed[b]	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed[c]	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

[a] Adapted from the NICE guideline manual (2012) (24) and Garcia et al. (2014) (25)

[b] The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

[c] The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*. Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),(23) as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team). The disclosure form inquiries regarding any relevant financial and intellectual interests or other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquiries regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

The CPG Work Group and CPG development team (see Table 1) submitted written disclosure statements twice during the CPG development process to reveal any potential COI in the past 24 months and verbal

disclosure statements at each meeting in the format consistent with guidance from the VA National Center for Ethics in Health Care.(16, 23) Potential instances of conflicts of interest among the project team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team. If an instance of potential or actual COI had been reported, it would have been referred to the VA and DoD program offices and reviewed with the CPG Work Group Champions. The VA and DoD program offices and the CPG Work Group Champions would have determined whether, and if so, what, further action was appropriate (e.g., excusing Work Group members from selected relevant deliberations or removal from the Work Group). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available upon request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.(20, 26) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a virtual patient focus group on March 12, 2020. The focus group aimed to gain insights into patients with CMI of potential relevance and incorporate these into the CPG as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and the impacts of their care on their lives.

The patient focus group comprised a convenience sample of one person. The Work Group acknowledges this convenience sample is not representative of all patients with CMI within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. Given the single patient, the Work Group supplemented the focus group with resources from the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC GWVI). For more information on the patient focus group methods and findings, see Appendix B. The patient focus group participant was provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see Drafting and Finalizing the Guideline. Once the Work Group completed a near-final draft, they identified experts from the VA and DoD healthcare systems and outside organizations to review that draft. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG where justified, in accordance with the evidence.

F. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with CMI. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified within VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through

publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. Patient-centered Care

Guideline recommendations are intended to consider patient needs and preferences and represent a whole/holistic health approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole health/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.(27, 28) A whole/holistic health approach (https://www.va.gov/wholehealth/) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making. Shared decision making was emphasized in *Crossing the Quality Chasm,* an IOM (now NAM) report, in 2001.(29) Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or settings of care, especially where there may be patient heterogeneity in risks and benefits. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences. A whole/holistic health approach to care that includes shared decision making and shared goal setting is equally important in making sustainable behavioral and lifestyle changes. Also, providers need to align treatment recommendations with the individual's values and purpose for health and well-being.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of CMI. Many Veterans, Service Members, and their family members have one or more co-occurring conditions. Because CMI is sometimes accompanied by co-occurring conditions, it is often best to manage CMI collaboratively with an interprofessional team. Some co-occurring conditions may require early specialist consultation to determine any necessary changes in treatment or to establish a common understanding of

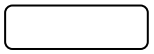
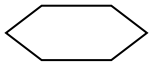
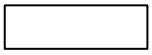
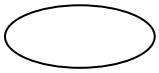
how care will be coordinated. This may entail reference to other VA/DoD CPGs (e.g., osteoarthritis [OA],[a] MDD,[b] PTSD,[c] and substance use disorders [SUD][d]).

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in managing patients with CMI. This algorithm format represents a simplified flow of the management of patients with CMI and helps foster efficient decision making by providers. It includes:

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

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.(30) Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, 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 algorithm

Appendix G contains alternative text description of the algorithm.

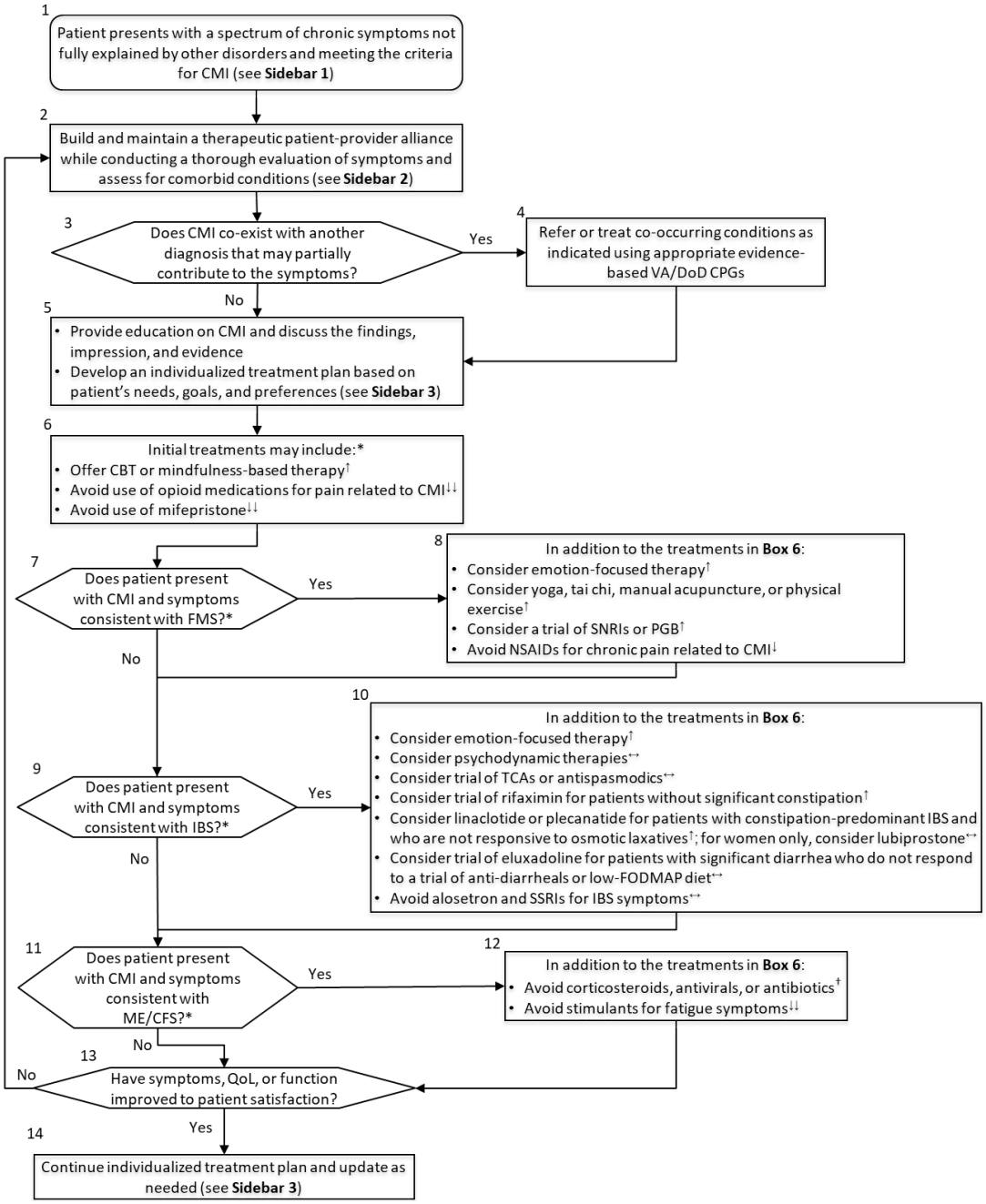
[a] See the VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip & Knee Osteoarthritis. Available at: https://www.healthquality.va.gov/guidelines/cd/oa/

[b] See the VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: https://www.healthquality.va.gov/guidelines/mh/mdd/

[c] See the VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Reaction. Available at: https://www.healthquality.va.gov/guidelines/mh/ptsd/

[d] See the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: https://www.healthquality.va.gov/guidelines/mh/sud/

Algorithm: Management of CMI



* 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

Abbreviations: CBT: cognitive behavioral therapy; CMI: chronic multisymptom illness; CPG: clinical practice guideline; DoD: Department of Defense; FMS: fibromyalgia syndrome; FODMAP: fermentable oligo-, di-, mono-saccharides, and polyols; IBS: irritable bowel syndrome; ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome; NSAID: nonsteroidal anti-inflammatory drug; PGB: pregabalin; QoL: quality of life; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; VA: Department of Veterans Affairs

Sidebar 1: Case Definition of CMI

Chronic multisymptom illness is characterized by multiple, persistent symptoms (e.g., fatigue, headache, arthralgias, myalgias, concentration and attention problems, and gastrointestinal disorders) across more than one body system. The symptoms must be present or frequently recur for more than six months and should be severe enough to interfere with daily functioning.

Sidebar 2: Elements of Assessment

- Obtain medical history and military/deployment history
- Conduct psychosocial assessment including psychological trauma history
- Conduct physical examination
- Consider diagnostic studies, as indicated, for rule-out of alternative diagnoses only; avoid any tests for which there may be limited additional benefit
- Consider additional and/or longer duration encounters

Sidebar 3: Individualized Treatment Plan

- Using a whole/holistic health approach, identify individual treatment goals (e.g., return to work, improved QoL, resumption of recreational activities)
- 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
- Maximize use of non-pharmacologic therapies (e.g., CBT, CIH interventions,* aerobic exercise)
- Develop personal health plan and timeline for follow-up and monitor progress toward personal goals
- Maintain continuity and caring relationship via in-person and/or virtual modalities
- Provide education (both for improved health literacy and whole/holistic health self-care) and engage families/caregiver/support person, if available
- Based on patient needs, consider referral to case manager and establish interprofessional care team

Abbreviations: CBT: cognitive behavioral therapy; CIH: complementary and integrative health; QoL: quality of life

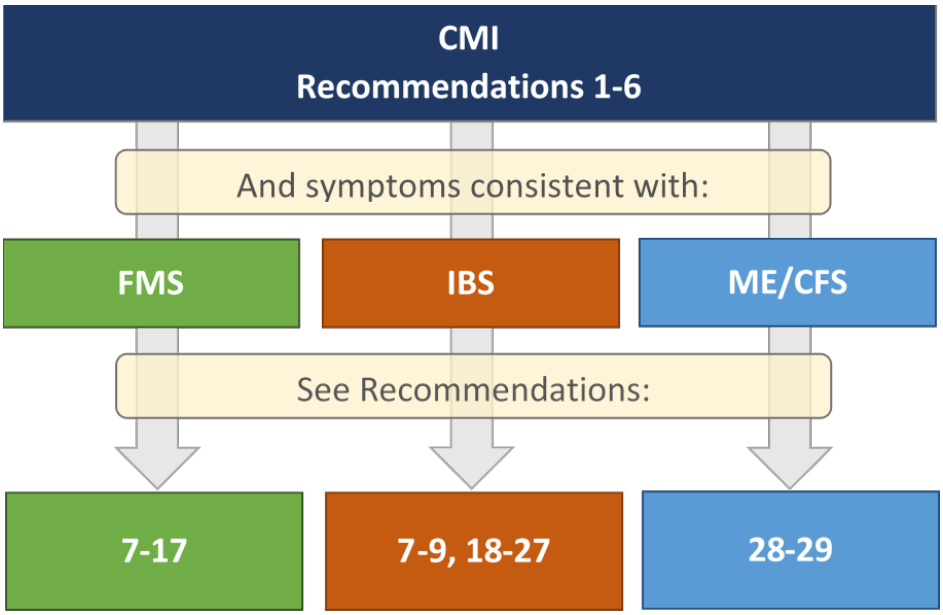
*See https://www.va.gov/wholehealth/

IX. Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains as per the GRADE approach (see Summary of Guideline Development Methodology). These domains include confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Recommendations are presented as treatment for CMI in general, which includes FMS, IBS, and ME/CFS. Then, recommendations focus on CMI and symptoms consistent with FMS, IBS, and/or ME/CFS. The recommendation order is depicted by Figure 1. Interventions are then organized by type (i.e., pharmacotherapy, behavioral health, CIH, physical exercise).

Figure 1. Recommendation Organization Flowchart



Recommendations are presented in Table 4.

Table 4. Recommendations

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment of CMI	*a. Pharmacotherapy*	1.	We recommend against the long-term use of opioid medications for the management of chronic pain in patients with CMI.	Strong against	Reviewed, Amended
		2.	We recommend against offering mifepristone for patients with CMI.	Strong against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment of CMI (cont.)	*b. Behavioral Health*	3.	We suggest offering cognitive behavioral therapy for CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.	Weak for	Reviewed, New-replaced
		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.	Weak for	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-added
	c. Complementary and Integrative Health	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.	Neither for nor against	Reviewed, New-added
Treatment of CMI and Symptoms Consistent with FMS or IBS	*a. Behavioral Health*	7.	We suggest considering an emotion-focused therapy for patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.	Weak for	Reviewed, New-replaced
	b. Complementary and Integrative Health	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.	Neither for nor against	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-added

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment of CMI and Symptoms Consistent with FMS	*a. Pharmacotherapy*	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.	Neither for nor against	Reviewed, New-replaced
		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.	Weak for	Reviewed, New-replaced
		12.	We suggest offering pregabalin for the treatment of pain in patients with CMI and symptoms consistent with fibromyalgia.	Weak for	Reviewed, Amended
		13.	We suggest against offering nonsteroidal anti-inflammatory drugs for the treatment of chronic pain related to CMI and symptoms consistent with fibromyalgia.	Weak against	Reviewed, New-replaced
	b. Complementary and Integrative Health	14.	We suggest offering yoga or tai chi for patients with CMI and symptoms consistent with fibromyalgia.	Weak for	Reviewed, New-replaced
		15.	We suggest offering manual acupuncture as part of the management of patients with CMI and symptoms consistent with fibromyalgia.	Weak for	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-added
	c. Physical Exercise	17.	We suggest offering physical exercise for patients with CMI and symptoms consistent with fibromyalgia.	Weak for	Reviewed, New-replaced
Treatment of CMI and Symptoms Consistent with IBS	*a. Pharmacotherapy*	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.	Neither for nor against	Reviewed, New-added
		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.	Neither for nor against	Reviewed, New-replaced
		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.	Weak for	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Treatment of CMI and Symptoms Consistent with IBS (cont.)	*a. Pharmacotherapy (cont.)*	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.	Weak for	Reviewed, New-added
		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.	Neither for nor against	Reviewed, New-replaced
		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.	Neither for nor against	Reviewed, New-added
		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.	Neither for nor against	Reviewed, New-added
	b. Behavioral Health	27.	There is insufficient evidence to recommend for or against offering psychodynamic therapies for patients with CMI and symptoms consistent with irritable bowel syndrome.	Neither for nor against	Reviewed, New-replaced
Treatment of CMI and Symptoms Consistent with ME/CFS	*a. Pharmacotherapy*	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.	Neither for nor against	Reviewed, New-replaced
		29.	We recommend against offering stimulants for treatment of fatigue in patients with CMI and symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome.	Strong against	Reviewed, New-replaced

[a] For additional information, see Grading Recommendations.

[b] For additional information, see Recommendation Categorization and Appendix D.

A. Treatment of CMI

a. Pharmacotherapy

Recommendation

1. We recommend against the long-term use of opioid medications for the management of chronic pain in patients with CMI.
   (Strong against | Reviewed, Amended)

Discussion

The 2014 CMI CPG recommended against the long-term use of opioid medications for the management of patients with CMI and did not identify any studies addressing the short- or long-term efficacy and safety of opioid therapy in patients with CMI. This CPG's systematic evidence review found no RCTs evaluating the short- or long-term efficacy and safety of opioid therapy in patients with CMI. The 2017 VA/DoD CPG for Opioid Therapy for Chronic Pain (OT CPG) recommends against initiating long-term opioid therapy (LOT) for chronic pain. The harms/burden of LOT, including the potential development of an opioid use disorder (OUD) and the risk of overdose-related death, far outweigh the benefits of LOT.

As outlined in the 2017 OT CPG, there is a rapidly growing understanding of LOT's significant harms, even at daily doses lower than a 50 milligram (mg) oral morphine equivalent. Increased opioid prescribing from 1999 to 2008 was paralleled by an increase in admissions for the treatment of SUD, and increased mortality, morbidity, and opioid-related overdose death rates.(31) At the same time, there is a lack of high quality evidence that LOT improves pain, function, and/or QoL. The 2017 OT CPG's systematic evidence review identified no studies evaluating the effectiveness of LOT for outcomes lasting longer than 16 weeks. Given the lack of evidence showing sustained functional benefit of LOT and moderate evidence outlining harms, the 2017 OT CPG made a *Strong against* recommendation for the initiation of opioid therapy for chronic pain; non-opioid and non-pharmacologic treatments are preferred.

Opioids are readily available in a wide range of chemical classes (e.g., natural, synthetic, and semi-synthetic) and dosage forms (e.g., immediate and long-acting oral formulations, transdermal patches, injections, and suppositories) and are relatively inexpensive. While some patients with CMI may express interest in a trial of opioid therapy, there is neither an indication nor clinical evidence to support the use of opioid therapy in the treatment of chronic pain related to CMI.

The Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2014 CMI CPG and the 2017 OT CPG. Therefore, this is a *Reviewed, Amended* recommendation. The Work Group noted the lack of evidence in support of LOT for CMI and that the harms significantly outweighed potential benefits. For those who are on chronic opioid therapy, a prescription of naloxone is recommended for risk mitigation. Thus, the Work Group decided upon a *Strong against* recommendation.

Further research is needed on the benefits and harms of less addictive pharmacologic interventions in patients with chronic pain related to CMI.

Recommendation

2. We recommend against offering mifepristone for patients with CMI.
   (Strong against | Reviewed, New-added)

Discussion

Mifepristone is a potent antagonist of progesterone and cortisol indicated for the termination of intrauterine pregnancy through a U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) program. It is also indicated for the management of hyperglycemia in patients with Cushing's syndrome. It has FDA boxed warnings related to the termination of intrauterine pregnancy, requiring that pregnancy be excluded in females before initiation of therapy, and pregnancy must be avoided during treatment and for one month after stopping treatment with mifepristone. It also has boxed warnings for bacterial infection and bleeding when used as an abortifacient.

An RCT by Golier et al. (2016) compared the effect of mifepristone (200 mg/day) to placebo in GWV with CMI.(32) The study's primary and secondary outcomes demonstrated no difference in physical functioning, general mental health status, cognitive functioning, or fatigue-related symptoms between mifepristone and placebo at 12 weeks of treatment. The strength of evidence for these outcomes was low and the study included no information on adverse events (AEs).

Although Golier et al. (2016) did not report on AEs, AEs occurring in greater than 10% of patients in the product literature include cardiovascular, central nervous system, metabolic (hypokalemia in 34 – 44% of patients), gastrointestinal, genitourinary, neuromuscular, and respiratory events.(32) Golier et al. (2016) demonstrated no therapeutic benefit with mifepristone for CMI, and mifepristone has an indication for termination of pregnancy, boxed warnings, and extensive side effects, especially in women. It also has many interactions with drugs metabolized by CYP3A with simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic indices as being contraindicated for combined use. As a result, few providers and patients may be willing to try this medication. The drug is not available in the VA National Formulary. While it is on the DoD formulary for Military Treatment Facilities (MTF), it may not be available at all MTFs.

The Work Group systematically reviewed evidence related to this recommendation (32) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was low and the harms/burden outweighed the benefits. Given the lack of therapeutic benefit across all the outcomes, AEs and boxed warnings, and the potentially restricted availability, the Work Group decided upon a *Strong against* recommendation.

Further research is needed to better understand the benefits and harms of pharmacologic interventions in patients with CMI. Our systematic evidence review did not identify any SRs addressing the benefits and harms of pharmacologic interventions in patients with CMI. The pharmacologic interventions of interest in the review included stimulants, neuropathic medications, monoclonal antibodies, N-methyl-D-aspartic acid (NMDA) receptor agonists, analgesics, antibiotics, antidepressants, and other medications (e.g., low-dose naltrexone, oral corticosteroids [e.g., prednisone], intranasal insulin, and intranasal xylitol). The reasons for this dearth of research include the complex nature of CMI as a distinct disease entity, the lack of a clear understanding of the pathophysiology of CMI, and the ongoing debate over the optimal case definition of

CMI. Such research will depend upon improving our understanding of the pathophysiology of CMI and refining the current case definitions, which will better serve the clinical care needs of patients with CMI.

b. Behavioral Health

Recommendation

3. We suggest offering cognitive behavioral therapy for CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome. **(Weak for | Reviewed, New-replaced)**

Discussion

An RCT by Donta et al. (2003) randomized 1,092 Veterans with GWI to either CBT (n=286), aerobic exercise (AEX) (n=269), CBT plus AEX (n=266), or treatment as usual (TAU) (n=271).(33) Cognitive behavioral therapy was delivered in groups of three to eight Veterans with one therapist using a treatment manual. Improvement was defined as a seven-point or greater increase in health function at 12 months. The authors found that 11.5% of Veterans randomized to TAU improved, 11.7% of Veterans randomized to exercise alone improved, 18.4% of Veterans randomized to CBT plus exercise improved, and 18.5% of Veterans randomized to CBT alone improved. Analyses found a statistically significant higher odds of participants receiving CBT experiencing at least a seven point increase in health function (CBT alone or CBT plus exercise) compared to those who did not receive CBT (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.21 to 2.41; p=0.005).(33)

An SR and meta-analysis by Bernardy et al. (2018) is the strongest evidence supporting CBT for FMS.(34) This SR reviewed 29 studies, 15 of which included health-related quality of life (HRQoL) as an outcome, with a 20% or greater improvement in QoL as the primary outcome. The SR found a statistically significant difference between CBT and control (active or non-active) with 44.3% of participants in the CBT arms improving 20% or more on HRQoL (95% CI: 0 to 0.26) as compared to 31.5% of participants in the control arms. There was no difference between the arms at the six month follow-up (95% CI: -0.03 to 0.40).

Within the SR, 10 studies compared traditional CBT to control and three studies compared acceptance-based CBT to control.(34) Traditional CBT seeks to change the cognitions and behaviors thought to maintain pain, while acceptance-based CBT seeks to facilitate acceptance of internal experiences and symptoms and encourages actions consistent with one's values. These sub-analyses found traditional CBT improved HRQoL by 20% or more compared to control at the end of treatment (95% CI: 0.04 to 0.21) and at six months follow-up (95% CI: 0.02 to 0.22). In addition, acceptance-based CBT improved HRQoL by 20% or more compared to control at the end of treatment (95% CI: 0.08 to 0.75) and at least six months follow-up (95% CI: 0.53 to 0.81). Two studies compared CBT to pharmacologic therapy and did not find a difference between the arms at the end of treatment (95% CI: -0.04 to 0.80) or at least six months follow-up (95% CI: -0.07 to 0.81) in improving HRQoL by 20% or more.(34)

An SR and meta-analysis of nine RCTs by Laird et al. (2017) were the strongest evidence for CBT in treating IBS.(35) The SR compared CBT to control and found that CBT led to greater improvements in daily functioning compared to control (95% CI: 0.38 to 0.71; p<0.001).(35) Another SR and meta-analysis of seven trials by Li et al. (2014) also found CBT to be more effective in improving HRQoL compared to control at the end of treatment (95% CI: 0.24 to 0.74).(36)

An SR of four studies by Smith et al. (2015) compared CBT to control for ME/CFS.(37) The SR did not find a difference between CBT and control (95% CI: -7.47 to 27.77). However, a sensitivity analysis, which excluded an outlier, found evidence that CBT improved physical functioning compared to control (95% CI: 1.05 to 10.99). The review also included one study that found CBT improved QoL as compared to control (n=58; mean 2.81 versus 3.26; p=0.02).(37)

Two clinical trials conducted after the SR also supported CBT for improving physical functioning among patients with ME/CFS. Wiborg et al. (2015) compared large-group CBT, small-group CBT, and waitlist control, and found both CBT groups had improvements in health function compared to control (n=204; 95% CI: 0.22 to 0.81; p<0.001).(38) Janse et al. (2018) compared internet-delivered CBT with protocol-driven feedback and internet-delivered CBT with feedback on demand to waitlist control (n=24).(39) The study found that internet-delivered CBT with feedback on demand improved physical functioning (95% CI: -0.6 to 11; p=0.0297) and reduced overall impairment (95% CI: -530 to -182; p<0.0001) at six months compared to control. Internet-delivered CBT with protocol-driven feedback reduced overall impairment at six months (95% CI: -514.7 to -161.9; p=0.0002), but there was no difference in physical functioning compared to control.(39)

In these studies, CBT was delivered in a variety of settings (i.e., individual, group, telehealth, and internet). While there were few head-to-head comparisons between modalities, there was also little evidence suggesting any modality is more effective than another. This suggests that the mode of delivery for CBT should be based on patient preferences and available resources. Moreover, there are different CBT approaches for CMI, including traditional CBT and acceptance-based CBT, and little data on whether one of these approaches is more efficacious (see Appendix J).

There was variation in adherence to CBT, particularly in the Donta et al. (2003) trial of Veterans with GWI, where only 36 to 38% of Veterans attended two-thirds or more of the 12 treatment sessions.(33) This suggests CBT may not be acceptable to all patients. Therefore, patient preferences and their availabilities should be considered when recommending CBT over another behavioral health intervention.

The Work Group systematically reviewed evidence related to this recommendation (34-39) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(33) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence for use of CBT for CMI and symptoms consistent with FMS, IBS, and ME/CFS was low. The body of evidence had limitations, primarily indirectness in examining patients with FMS, IBS, and ME/CFS as opposed to CMI. Despite these limitations, there were a great number of clinical trials and consistency across conditions (i.e., CMI, FMS, IBS, and ME/CFS). The benefits outweighed the harms given the positive effect of CBT on health function and QoL and the very low risk of harms. There is some variation in patient values and preferences. Thus, the Work Group decided upon a *Weak for* recommendation.

To better understand the efficacy of CBT, more research is needed to determine how and for whom CBT is efficacious and how to best implement CBT for CMI in the VA and DoD healthcare systems.

Recommendation

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.
   (Weak for | Reviewed, New-replaced)

Discussion

Mindfulness-based Stress Reduction for Patients with FMS

Pérez-Aranda et al. (2019) found that mindfulness-based stress reduction (MBSR) reduced functional impairment greater than TAU at end of treatment (95% CI: -19.59 to -8.97) and at 12 month follow-up (95% CI: -16.64 to -4.26).(40) Mindfulness-based stress reduction reduced functional impairment greater than an active multicomponent treatment (FibroQoL, which included psychoeducation and hypnosis) at the end of treatment (95% CI: -16.13 to -5.67) with no differences at follow-up (95% CI: -10.69 to 1.57). The study included 225 participants (75 randomized to MBSR, 75 randomized to FibroQoL, and 75 randomized to TAU). There were relatively few AEs reported in the study and similar rates of AEs reported for MBSR (n=3 had notable increases in physical symptoms) as compared to FibroQoL (n=1 had notable increases in physical symptoms).

Meditation Awareness Training for Patients with FMS

An RCT by Van Gordon et al. (2017) found meditation awareness training (MAT) to be more effective than a control arm which educated participants on cognitive behavioral theory.(41) Meditation awareness training (n=74) included weekly group sessions for eight weeks and a compact disc (CD) of guided meditations to facilitate daily self-practice. The control (n=74) included weekly group education sessions without meditation for eight weeks. In this RCT, 83.1% of patients were female, and the authors did not report AEs. Meditation awareness training led to significant reductions in functional impairment as compared to control immediately following the intervention (95% CI: -8.24 to -4.25), as well as at six months follow-up (95% CI: -13.76 to -7.76). Meditation awareness training also led to significant reductions in pain immediately after the intervention and at six months follow-up, compared to the control group.(41)

Mindfulness-based Cognitive Therapy for Patients with IBS

An RCT by Henrich et al. (2020) evaluated the effects of mindfulness-based cognitive therapy (MBCT) for patients with IBS and investigated its therapeutic mechanisms.(42) The study randomized 67 female participants with IBS symptoms for more than six months to MBCT for IBS versus a waitlist control. Sessions were two hours long, with one hour of home practice, for six weeks. Results indicated a significantly greater improvement in quality of life in MBCT as compared to waitlist control at the end of treatment and follow-up. Quality of life was improved by 32% in the MBCT arm compared to 3% in the waitlist control arm at post-treatment and was improved by 39% compared to 1% at the six week follow-up. Results also indicated a significantly greater improvement in IBS symptoms in MBCT as compared to waitlist control at follow-up.(42)

Mindfulness-based Therapies

The results of the reviewed studies are consistent with a meta-analysis of 12 randomized clinical trials of mindfulness-based therapy (MBT) for symptom-based conditions including FMS and IBS.(43) The meta-analysis was conducted in 2013 and thus not included in this CPG's systematic review.

For QoL outcomes, the meta-analysis included two clinical trials for FMS and three clinical trials for IBS, with a total of 411 participants across studies.(43) The meta-analysis showed small to moderate effect sizes for MBT compared to waitlist or support group controls for enhanced QoL (95% CI: 0.19 to 0.59). There was also evidence that MBT reduced pain (95% CI: -0.37 to -0.03), symptom severity (95% CI: -0.54 to -0.26), and depression (95% CI: -0.40 to -0.07) as compared to control.

The Work Group systematically reviewed evidence related to this recommendation (40-42) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed*, *New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including indirectness and few studies. However, this was balanced by there being consistent benefits across trials. Some of the trials were large and well-designed, and the benefits outweighed the potential harms. Thus, the Work Group decided upon a *Weak for* recommendation.

Additional research is needed to support offering mindfulness-based therapies, delivered by trained professionals, using different delivery modalities (e.g., digital media) and for patients of all sexes with CMI, including those with symptoms of FMS, IBS, or ME/CFS.

Recommendation

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.
   (Neither for nor against | Reviewed, New-added)

Discussion

While this CPG's systematic evidence review found no direct studies on biofeedback modalities in patients with CMI, evidence of biofeedback on CMI is gained indirectly via studies on FMS, IBS, or CFS. An RCT by Windthorst et al. (2017) compared Heart Rate Variability Biofeedback Therapy (HRV-BF) to Graded Exercise Training (GET) in patients with CFS.(44) The RCT, which included 28 female patients with CFS, found significant improvements in mental functioning after HRV-BF over time, but not after GET. All participants had eight, 50-minute weekly individual training sessions. Thirteen had training in HRV-BF and 15 in GET. The patients kept diaries and recorded their intensity of fatigue, daily activities, and training at home. The RCT found a significant improvement in mental functioning at the five month follow-up with HRV-BF, but not GET. Adverse events were reported and included one patient with a migraine (HRV-BF), one with depression (GET), and one with weight gain (GET).(44)

A literature review by Reneau et al. (2020) examined the effect of Heart Rate Variability Biofeedback on FMS-related chronic pain using the Theory of Symptoms Self-Management.(45) The SR found only one study that enrolled patients with FMS only and that used FMS pain in the outcome measures, HRV-BF as an intervention, was peer-reviewed in English, and included adult participants (aged >17 years). The study

included 12 female patients with FMS, consisted of 10 weekly clinic sessions and 20-minute home exercises twice daily, and utilized visual feedback on a computer and verbal coaching to improve respiratory rates. After the 10 sessions, the study showed no significant improvement in functional status or QoL, and no data were provided for the three month follow-up. Participants reported that the HRV-BF device was easy to use, they benefited from the treatment, and they would recommend it to others.(45)

A Cochrane review by Goldenberg et al. (2019) compared biofeedback to a variety of control conditions in patients with IBS including no treatment, attention control, relaxation, counseling, hypnotherapy, SOC, and sham biofeedback.(46) The review included eight RCTs totaling 300 patients with IBS and reported no AEs in either group. In one RCT, both the biofeedback and cognitive therapy groups (n=29) demonstrated improved QoL after treatment, but the other seven RCTs did not report QoL outcome data.(46)

Some variation in patient preferences is likely given the heterogeneity in the types of biofeedback provided. Biofeedback can be an inexpensive treatment option, with the main cost being provider training and equipment. Moreover, it does not require frequent patient visits because it can be done at home once the patient is trained.

The Work Group systematically reviewed evidence related to this recommendation (44-46) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations including poor quality of individual studies, small sample sizes, samples that were majority female, and heterogeneity in the types of biofeedback used. The possible mental health and other benefits outweighed the potential harms. There is likely some variation in patient preferences, and the Work Group considered the resource use and feasibility of this recommendation. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Further research is needed on the use of biofeedback modalities for CMI given the large research gap in this area. Research should use physical function, QoL, and AEs as patient-centered critical outcomes.

c. Complementary and Integrative Health

Recommendation

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.
   (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group assessed musculoskeletal (MSK) manual therapy (also called spinal manipulative therapy, spinal mobilization, and osteopathic manipulation) as part of a range of CIH modalities for the treatment of CMI. Musculoskeletal manual therapy is a common treatment offered to patients for many conditions. Since the evidence for MSK manual therapy in the treatment of CMI is limited, this recommendation was supported by indirect evidence. While there are studies on CIH modalities for patients with symptoms consistent with FMS, IBS, and ME/CFS, they have not focused on the military population.

This CPG's systematic evidence review found one SR by Clar et al. (2014) where MSK manual therapy was assessed in patients with FMS, IBS, or ME/CFS as a stand-alone treatment.(47) This SR consisted of seven SRs and 12 RCTs that examined patients with MSK and non-musculoskeletal conditions treated with manual therapy. Clar et al. (2014) assessed MSK manual therapy compared to other treatment modalities such as resistance training, waitlist control, sham treatment, ultrasound, or SOC. When MSK manual therapy was compared to control or other conservative interventions, it appeared that osteopathic manipulation was favored for IBS and ME/CFS when measuring improvements in QoL. For patients with FMS, there was no difference in QoL between patients receiving spinal manipulation compared to a variety of control conditions.(47)

The confidence in the quality of the evidence for this SR was very low.(47) The original SR evidence quality was rated as fair; however, the RCTs reviewed in the SR that focused on FMS, IBS, or ME/CFS were of lower quality and the evidence proved inconclusive for these conditions. The main methodological limitations were risk of bias due to a large variation in the type of manual therapy studied, limited sample sizes, lack of reported allocation concealment, and lack of intention-to-treat analysis. The FMS, IBS, and ME/CFS-related studies were downgraded further for limitations/indirectness and imprecision.(47)

The Work Group systematically reviewed evidence related to this recommendation (47) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. Musculoskeletal manual therapy requires a one-to-one provider to patient ratio. Also, this treatment is not always available in the VA or DoD and is often received outside of these healthcare systems, with patients incurring out of pocket costs. In addition, this treatment may be time prohibitive for patients. Patients may not be familiar with MSK manual therapy, and MSK manual therapy may not be acceptable to patients as some may consider it a nonstandard treatment modality. On the other hand, MSK manual therapy is a relatively low-risk intervention for patients with CMI, with no AEs reported for patients with FMS, IBS, or ME/CFS.(47) Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed to evaluate the effectiveness of MSK manual therapy in CMI and active duty and Veteran populations. Higher quality studies focusing on military populations that are randomized, large, and report clearly on key outcomes are required.

B. Treatment of CMI and Symptoms Consistent with Fibromyalgia or Irritable Bowel Syndrome

a. Behavioral Health

Recommendation

7. We suggest considering an emotion-focused therapy for patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.
   (Weak for | Reviewed, New-replaced)

Discussion

Evidence suggests emotion-focused therapy improves QoL and functional status for patients with CMI and symptoms consistent with FMS or IBS.(48-50) Lumley et al. (2018) found treatment with emotional awareness and expression therapy (EAET) was associated with improvements in QoL and functional status

in patients with FMS (n=230). More than twice as many participants reported improving "much/very much" with EAET compared to an FMS education intervention (34.8% versus 15.4%).(48) In addition, Thakur et al. (2017) demonstrated EAET can lead to improvements in QoL in patients with IBS (n=106).(49)

Consistent with previous studies, an RCT by Montero-Marín et al. (2017) found that treatment with attachment-based compassion therapy (ABCT) was associated with improvements in QoL and functional status in patients with FMS (n=42). The absolute risk reduction in ABCT compared to relaxation increased by 40.0%, with an NNT=3 based on criteria of ≥50% FIQ reduction after treatment.(50) Consistently across the included studies, there was evidence of benefit in the critical outcomes related to QoL and function.

The QoL and functional benefits detected in these studies of emotion-focused therapy outweigh the risks of the reported harms. For example, only one mild AE was reported among EAET participants with FMS and the EAET group reported the lowest frequency of "very much worse/worse" response to the patient global perception of change measure after the intervention and follow-up.(48) In the report of EAET among patients with IBS, the investigators recorded changes in negative emotions anticipating a possible increase among those receiving EAET; a difference between groups was not detected and no other AEs were reported.(49) Therefore, given the possibility of benefit indicated in these studies and the very low risk of harm, the balance supports the use of emotion-focused therapy.

There is likely some variation in patient preferences for emotion-focused therapies and some patients may not be good candidates for this type of treatment given physical and mental limitations. Patients must be able to cognitively participate in this specific treatment and process the material being taught. Moreover, this treatment can be burdensome because it requires frequent visits with a provider, and access may be limited since there are few providers with adequate training. However, these limitations are inherent in many psychotherapies and some patients may prefer individual and focused attention.

The Work Group systematically reviewed evidence related to this recommendation (48-50) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including indirectness and few studies. However, some of the trials were large and well-designed, and the consistent benefits across trials clearly outweighed the potential harms. Thus, the Work Group decided upon a *Weak for* recommendation.

b. Complementary and Integrative Health

Recommendation

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.
   (Neither for nor against | Reviewed, New-replaced)

Discussion

Two RCTs evaluated relaxation therapy for the treatment of FMS, which encompassed several treatment styles. Amirova et al. (2017) compared manual muscular relaxation therapy (MMRT) to attention controls and waitlisted patients. After one month, there was no significant improvement in function or QoL outcomes.(51) In a longer RCT by Tomas-Carus et al. (2018), patients with FMS performed breathing exercises for three months, and there was no improvement in functional outcomes compared to control

patients.(52) In Tomas-Carus et al. (2018), there was a focus on specific aspects of functioning (i.e., daily living, pain, and fatigue), but the results were not statistically significant.

Although not included in this CPG's systematic evidence review, an SR by Lahmann et al. (2010) contained two small RCTs and evaluated relaxation therapy for the treatment of IBS.(53) In one small RCT, functional relaxation (FR) therapy performed in a group setting improved functional impairment scores compared to enhanced medical care (EMC).(53) The improvement in function was evident immediately after treatment and at three months follow-up, but there was no significant change in social improvement. The autogenic therapy (AT) relaxation approach in Shinozaki et al. (2010) focused on relaxing the entire body, in contrast to FR, through breathing and relaxation exercises.(54) Although this eight week study did not demonstrate improvements in overall QoL or functional scores, some subsets of functional scores (pain and social functioning) did improve compared to the control group.(54)

There were no physical harms associated with any form of relaxation therapy evaluated and the Work Group determined that the harms and benefits were balanced given the benefits to function and sole focus on IBS. There is likely some variation in patient values and preferences regarding breathing exercises. Relaxation is an acceptable modality and is part of other CIH practices (e.g., yoga, meditation). Relaxation therapy alone may be acceptable to Veterans or Service Members or as part of a broader whole/holistic health treatment plan.

The specific relaxation therapies studied may not be available or feasible in all settings since they require experienced practitioners; however, many of the therapies are conducive to being delivered via telehealth, which has been growing exponentially in VA. Therapists may be more familiar with MMRT in the U.S. compared to other relaxation therapies. On the other hand, therapists in the U.S. may not be well versed in FR and AT techniques since they were developed and are more commonly practiced outside the U.S.

The Work Group systematically reviewed evidence related to this recommendation (51, 52) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. All the studies were limited by small treatment group sizes, variation in patient recruitment with the potential for bias, and lack of statistical significance for the critical outcomes of QoL, functional status, and AEs. Additionally, relaxation therapy was only studied in FMS and IBS. The lack of evidence related to CMI in general, and ME/CFS, limited the generalizability of this recommendation. The harms and benefits were balanced. Since there were some benefits for certain patient groups, no significant safety concerns, and the modality was acceptable overall, the Work Group decided upon a *Neither for nor against* recommendation.

The studies reviewed suggest relaxation therapy may help treat the pain and functional impairment associated with FMS and IBS. Whether this is true for patients with CMI or ME/CFS is a potential area for future research. It may also be beneficial to study whether relaxation therapy in combination with other CIH modalities or behavioral health interventions, or as part of a comprehensive whole/holistic health treatment plan, can improve QoL and functional outcomes.

Recommendation

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.
   (Neither for nor against | Reviewed, New-added)

Discussion

This CPG's systematic evidence review did not find direct studies on guided imagery or clinical hypnosis for CMI; therefore, the Work Group evaluated indirect studies for FMS and IBS. An RCT by Onieva-Zafra et al. (2019) examined the effects of a home-based guided imagery relaxation program for patients with FMS.(55) The study showed significant improvements in physical function and reductions in pain. The 60 participants (all female) were randomly assigned to two groups. Thirty participants received three 1.5-hour group sessions on how to use the guided imagery compact disk (CD) and completed four to five guided imagery exercise sessions per week at home. The control group received 1.5-hour group lessons that included group discussions.(55)

An SR by Zech et al. (2017) compared a variety of guided imagery and hypnosis modalities in patients with FMS, including traditional hypnosis with or without CBT, physiotherapy, SOC, autogenic training, and attention control, all compared to a waitlist control group.(56) The SR, which included nine RCTs totaling 457 patients with 95 to 100% female participants, demonstrated no significant improvements or benefits. No AEs were reported in any of the studies. An RCT by Boltin et al. (2015) compared Guided Affective Imagery (GAI) with lifestyle modifications to lifestyle modifications alone in patients with IBS.(57) The study included 15 patients in the GAI group and 19 in the control group and found improvements in QoL and a decrease in symptom severity in the GAI group. The GAI sessions were three hours in length and there were individual sessions once per week, with eight sessions in total. They reported no AEs.

Shahbazi et al. (2016) examined hypnotherapy versus standard care in patients with IBS.(58) This study included 30 individuals in the hypnotherapy group and 30 in the standard care group and found a significant improvement in IBS-related QoL in the hypnotherapy group. Thirteen patients from each group were excluded due to a lack of cooperation, migration, severe psychological problems, or death, but the author did not remove the AEs from this group when analyzing results.

An RCT by Phillips-Moore et al. (2015) compared the use of "gut-related" imagery, hypnosis, and relaxation therapy in patients with IBS, with 17 patients per treatment group.(59) The study found a significant improvement in vitality, social functioning, and mental health in those receiving the therapies. While there was no difference in demonstrated improvement between the hypnosis and relaxation therapy groups, all three groups demonstrated improvement in the severity of their IBS symptoms, and no AEs were reported.

An SR by Schaefert et al. (2014) included eight RCTs and compared hypnosis to a variety of interventions including education, supportive therapy, SOC, and control in patients with IBS.(60) The studies included 464 patients and there was some evidence that hypnosis led to symptom relief and a decrease in global gastrointestinal scores and bloating/distension. The studies had high dropout rates; only 290 patients (62%) remained at the end of therapy and only 171 patients (36%) remained at the end of the long-term follow-up.

There is likely some variation in patient preferences regarding guided imagery and hypnosis modalities, as indicated by the low retention rates in the RCTs. Treatment with the use of guided imagery and hypnosis can be inexpensive, with the main cost being provider training and equipment, such as relaxation CDs. VA now has internal provider skills training available for both guided imagery and clinical hypnosis. Guided imagery and hypnosis do not require frequent patient visits because they can be done at home once the patient is trained in self-care skills. Guided imagery and hypnosis are feasible treatment options when trained providers are available.

The Work Group systematically reviewed evidence related to this recommendation (55-60) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations including poor quality of individual studies, small sample sizes, high dropout rates, mostly female participants, and heterogeneity in the types of guided imagery and hypnosis used. The possible benefits outweighed the potential harms given that there is no evidence of AEs. There is likely some variation in patient preferences regarding guided imagery and hypnosis modalities, and the Work Group considered the resource use and feasibility of this recommendation. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Further research is needed on the use of guided imagery and hypnosis modalities in CMI given the large research gap in this area. Research should use more male participants and physical function, QoL, and AEs as patient-centered critical outcomes.

C. Treatment of CMI and Symptoms Consistent with Fibromyalgia

a. Pharmacotherapy

Recommendation

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.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

A large SR by Welsch et al. (2018 b) showed mirtazapine improved average pain intensity and sleep problems compared to control, but this was based on low quality evidence.(61) Of note, the proportion of participants achieving 20% or greater improvement in QoL over 7 to 13 weeks (n=586) was not different for mirtazapine compared to placebo. The SR also found that 50% of people experienced a 30% or greater reduction in pain compared with 30% with placebo, although the evidence was low quality.(61)

Similar findings were reported for tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). A Cochrane review by Moore et al. (2015) showed that amitriptyline, a TCA, provided substantial (50%) pain relief versus placebo in 591 patients over 6 to 24 weeks.(62) Although not included in this CPG's systematic evidence review, a large Cochrane review found that SSRIs for patients with FMS including fluoxetine, paroxetine, and citalopram showed benefit versus placebo when evaluating if at least 30% pain reduction was achieved (95% CI: 0.01 to 0.2).(63) The SR also evaluated two small studies

comparing fluoxetine versus placebo using the QoL Fibromyalgia Impact Questionnaire (FIQ) total score. Results showed that fluoxetine provided benefit over placebo.

Additionally, in a small network meta-analysis in patients with FMS, Nüesch et al. (2013) found SSRIs improved QoL and pain but not fatigue.(64) This study analyzed 10 randomized placebo-controlled trials with a median duration of 12 weeks and enrolled a total of 644 patients. Dropout rates were not significantly different between the SSRI arms and placebo.(64) It is important to treat patients with an adequate trial of antidepressants before determining effectiveness, which can be as long as 6 to 12 weeks depending on the drug.

There was no difference in AEs between mirtazapine and control or placebo in 606 participants over 7 to 13 weeks.(61) Similarly, in an SR, the SSRI paroxetine showed no difference in serious AEs when compared to placebo in two studies (n=84).(63) On the other hand, a Cochrane intervention review by Moore et al. (2015) (n=318) demonstrated that while amitriptyline provided more pain relief than placebo (number needed to treat [NNT] was 4.1), it was associated with more AEs than placebo (number needed to harm [NNH] was 3.3; 78% with amitriptyline versus 48% with placebo).(62) The AEs were generally not serious but could be troublesome enough to deter patients from taking amitriptyline.

There is likely a large variation in patient preferences. Since all of these medications are also used to treat mental health disorders, there may be a stigma associated with taking them. Another factor to consider is that patients with security clearances or who work in high profile positions may fear that these medications could impact their career progression or cause additional reporting burden. Also, since these patients are commonly taking multiple medications to manage chronic diseases, the Work Group urges providers to review drug-drug interactions when adjusting pharmacotherapies. Although these medications are readily available and fairly inexpensive, many patients may not want to take them.

The Work Group systematically reviewed evidence related to this recommendation (61, 62, 65) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(64) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes. In one analysis, although TCAs had a statistically significant, but small, improvement in pain in patients with FMS, these benefits were no longer statistically significant when the analysis was limited to studies with ≥50 patients per treatment group.(64) Additionally, the population studied was predominantly female and there was indirectness given that the patient population had FMS and not CMI. The benefits to pain relief and improvements in QoL outweighed AEs, except in the case of amitriptyline, which had more AEs than placebo, but most were mild. Patient values and preferences may vary widely. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

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.
    (Weak for | Reviewed, New-replaced)

Discussion

A large SR by Welsch et al. (2018 a) found that serotonin-norepinephrine reuptake inhibitors (SNRIs) provide additional beneficial outcomes for pain relief in patients with FMS versus controls in studies ranging from 12 to 27 weeks in length.(65) In addition, SNRIs led to improvements in Patient Global Impression of Change (PGIC) scores in 2,918 patients over 12 to 27 weeks versus controls and were shown to improve the QoL of patients versus controls.

Other studies have had different findings, but these studies were smaller and of lower quality. One such study showed no difference between desvenlafaxine and placebo on self-reported mean pain intensity scores (n=82). There was no difference in serious AEs between SNRIs and control or placebo in 13,464 patients over 8 to 27 weeks.(65)

There is likely a large variation in patient preferences and the demonstrated benefits should be weighed against patient concerns. Since SNRIs are also used to treat mental health disorders, there may be a stigma associated with taking them. Similarly, patients with security clearances or who work in high profile positions may fear that taking SNRIs could impact their career progression or cause additional reporting burden. Also, since patients commonly take multiple medications to manage chronic diseases, the Work Group urges providers to review drug-drug interactions when adjusting pharmacotherapies. While SNRIs are readily available and fairly inexpensive, many patients may not want to take them.

The Work Group systematically reviewed evidence related to this recommendation (65) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(64) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes in the constituent studies of the SR and indirectness since the population studied was predominantly female and the patient population had FMS, not CMI. While the benefits to pain relief and improvements in QoL and PGIC scores outweighed AEs, patient values and preferences may impact their willingness to use SNRIs. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

12. We suggest offering pregabalin for the treatment of pain in patients with CMI and symptoms consistent with fibromyalgia.
    (Weak for | Reviewed, Amended)

Discussion

A large SR suggests pregabalin (PGB) provides substantial pain relief (30 to 50%), as assessed by the Brief Pain Inventory (BPI) (n=1,874), and based on improvements in PGIC scores in patients with FMS (n=1,869).(66, 67) Cooper et al. (2017) found that treatment with gabapentin was associated with a 30% or greater reduction in pain using the BPI in 49% of patients versus 31% taking placebo (n=150).(66)

Derry et al. (2016) found PGB had a substantial benefit and decreased pain by 50% in 24% of patients taking 300 to 600 mg of PGB daily versus 14% of patients taking placebo.(67) A total of 1,874 patients were evaluated over 8 to 26 weeks in five separate studies. Pregabalin was found to decrease pain by 30% or greater in 39% of patients taking 300 to 600 mg of PGB daily versus 28% of patients taking placebo. Patient Global Impression of Change scores were "much or very much improved" with NNTs for these outcomes ranging from 7 to 14.(67)

Although gabapentin is widely used at the VA, the Work Group found no new evidence in support of this medication for the treatment of CMI and symptoms consistent with FMS. Gabapentin is an older medication, so most new research since the publication of the 2014 CMI CPG has evaluated PGB. Both medications impart their effects using the same pathway. The main difference is that PGB is a schedule V controlled substance while gabapentin is not due to pregabalin's potential for abuse. In addition, the pharmacokinetic and pharmacodynamic characteristics of gabapentin require longer dose titration periods and higher doses resulting in a higher pill burden than with PGB.

There were no significant group differences in the rates of serious AEs between gabapentin and placebo in 150 patients studied over 12 weeks.(66) In addition, there was no difference in serious AEs between patients taking PGB versus placebo (n=1,238) over 8 to 26 weeks.(67) However, another study demonstrated that the presence of any AE favored placebo over PGB (n=687 patients).(67)

There is likely some variation in patient preferences regarding this treatment. Some patients may not want to take additional medications if they already take medications to treat other chronic conditions. The cost of PGB is slightly higher than gabapentin, although it is now available as a generic so the cost differential may decrease. Of note, PGB is approved by the FDA to treat FMS whereas gabapentin is not. At the time of this publication, prior authorization is no longer required in the DoD, but it is still required at VA. Most providers treat patients with gabapentin first because of its lower cost and easier access since it is a non-controlled substance in most states. Non-controlled medications have a longer expiration date (365 days versus 180 days), which reduces a provider's administrative burden of re-writing notes and prescriptions. In addition, some pharmacies have stricter quantity limits for controlled substances, so using gabapentin allows for longer supplies regardless of location, which also eases compliance. Also, gabapentin is currently controlled in five states, and this number may increase over time, decreasing any perceived benefit over PGB.

The Work Group systematically reviewed evidence related to this recommendation (66, 67) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. There were limitations associated with the body of evidence, including indirectness and imprecision. Given the benefits to pain relief and improved PGIC and BPI scores and the low frequency of AEs, the benefits slightly outweighed the harms/burden. Patient interest in using these medications likely varies because patients may not want to take an additional medication and PGB is a controlled substance. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

13. We suggest against offering nonsteroidal anti-inflammatory drugs for the treatment of chronic pain related to CMI and symptoms consistent with fibromyalgia.
    (Weak against | Reviewed, New-replaced)

Discussion

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely for the treatment of chronic pain in patients with FMS.(68) A Cochrane review by Derry et al. (2017) assessed pain relief in patients with FMS.(68) Six randomized, double-blind studies evaluating a total of 292 patients using pain relief as the main outcome consistently demonstrated no significant difference between NSAIDs and placebo. The duration of the double-blind period of the studies varied between three and eight weeks. No serious AEs were reported in either group but there were more patients with AEs in the NSAIDs group.(68)

Despite the general use of NSAIDs among Veterans and DoD beneficiaries, there is some variation in the acceptability of these medications. Those with gastrointestinal risks such as a history of a gastrointestinal bleed or stomach ulcers and those with or at high risk for kidney disease, vascular disease (including heart attacks and strokes) or diabetes should avoid or limit their intake of NSAIDs.

The Work Group discussed the use of NSAIDs in patients with CMI and symptoms consistent with FMS at length and determined they are acceptable to use for short durations (i.e., 10 days or less) to treat acute pain or injury not related to FMS.(69) The use of NSAIDs beyond 10 days should be provided under the care and supervision of a healthcare provider. Long-term use of NSAIDs should be avoided when possible.

The Work Group systematically reviewed evidence related to this recommendation (68) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had limitations including indirectness and imprecision. There was a lack of evidence showing benefits over placebo in treating moderate to severe pain, and there was a slightly higher but non-significant risk of harms in the NSAID groups. Thus, the harms/burden slightly outweighed the benefits. Patient values and preferences were somewhat varied given the risks of taking NSAIDs in certain populations. Thus, the Work Group decided upon a *Weak against* recommendation.

b. Complementary and Integrative Health

Recommendation

14. We suggest offering yoga or tai chi for patients with CMI and symptoms consistent with fibromyalgia.
    (Weak for | Reviewed, New-replaced)

Discussion

A Cochrane review by Theadom et al. (2015) evaluated the benefits and harms of various movement therapies compared to standard care for patients with FMS.(70) The review included three RCTs specifically for yoga. These three RCTs, plus one randomized controlled pilot study on qi gong, were combined to assess post-intervention QoL as measured by the FIQ-R. Overall, 79% of the patients enrolled in these four studies were assigned to do yoga. In the three month and six month follow-up periods, these

movement therapies led to greater improvements compared to TAU. However, these improvements were not significant after a shorter follow-up period of 8 – 14 weeks.(70)

An SR by Zhou et al. (2019) looked at the effects of exercise in patients with IBS.(71) Six RCTs on yoga (254 patients) were included. The SR favored Iyengar yoga over waitlist control with respect to physical functioning after six weeks for adolescents and young adults (18 to 26 years old) and at two months follow-up (young adults only). Video yoga (both Hatha and Iyengar) also led to significant improvements (reduction) in functional disability. Remedial yoga (60 minutes, three times per week) and yoga combined with medications, both showed significant improvements in IBS Severity Scoring System and IBS-Quality of Life scores after a three month intervention period compared to waitlist controls. There was, however, no significant difference in QoL demonstrated in a three month intervention of yoga versus a low-fermentable oligo-, di-, mono-saccharides, and polyols (FODMAP) diet at 12- and 24-weeks follow-up.(71)

Theadom et al. (2015) also reviewed three RCTs that looked specifically at tai chi.(70) One of these RCTs, in addition to one randomized prospective controlled trial on Pilates, provided QoL outcome assessments for patients with FMS. Most of the enrolled patients (57%) in the analysis of the two studies were assigned to perform tai chi. Overall, these movement therapies demonstrated significant improvements post-intervention and after a three month follow-up period compared to attention controls. The review also assessed two tai chi-focused RCTs along with the RCT on Pilates for self-reported physical functioning, comparing the movement therapies to attention controls. Most of the enrolled patients (57%) in the analysis of the two studies were assigned to perform tai chi. Overall, these movement therapies demonstrated significant improvements post-intervention and after a three month follow-up period compared to attention controls. The review also assessed two tai chi-focused RCTs along with the RCT on Pilates for self-reported physical functioning, comparing the movement therapies to attention controls. Most of the enrolled patients (75%) were assigned tai chi as their intervention. There were significant improvements that favored the movement therapy post-intervention and at three months follow-up.(70)

The Wang et al. (2018) RCT determined the effectiveness of tai chi interventions compared with core standard treatment with aerobic exercise and tested whether the effectiveness of tai chi depends on its dosage or duration.(72) Patients (n=151) were assigned to one of four intervention groups (tai chi for once or twice per week for either 12 or 24 weeks) and 75 patients were assigned to the control group (aerobic exercise twice per week for 24 weeks). Researchers assessed both QoL with the FIQ-R as well as function with the SF-36 tools and regardless of treatment group, assessments were made at 12, 24, and 52 weeks. FIQ-R scores improved in all intervention and control groups; however, the combined tai chi groups improved more than the aerobic exercise group at 24 weeks (p=0.03). Additionally, those who received tai chi for 24 weeks showed greater improvement in FIQ-R scores than those who received it for 12 weeks (p=0.007). At 52 weeks, those who had the most intensive regimen of tai chi had significantly better FIQ-R scores compared to aerobic exercise (p=0.01). Of note, there was no statistically significant between-group differences on the SF-36 at any time point.(72)

In an RCT by Bongi et al. (2016), 44 patients with FMS performed tai chi (two lessons per week) and were compared to a group that received education on FMS twice weekly.(73) Scores on the FIQ-R tool showed significant improvements in QoL for those assigned to the tai chi group at four months. The study also demonstrated significant improvements in physical functioning in the tai chi group at four months, but no improvements in social functioning during the same period.

The 2014 CMI CPG Work Group found enough evidence to strongly recommend "incorporating appropriate elements of physical activity as part of a comprehensive and integrated treatment plan for patients with CMI." The 2014 CMI CPG cited one SR (Mist et al. [2013]) related to yoga and tai chi for patients with FMS.(74) The analyses indicated there was a significant benefit to exercise compared to control in improving pain.(74) While the 2021 CPG Work Group decided not to include pain reduction as a critical outcome in the systematic evidence review, Theadom et al. (2015) and Bongi et al. (2016), in addition to an RCT by Wong et al. (2018), demonstrated a significant decrease in pain in FMS patients who exercised.(70, 73, 75) This is consistent with the prior recommendation.

The Work Group systematically reviewed evidence related to this recommendation (70-75) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(74) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low, downgraded for indirectness and imprecision. However, the evidence shows yoga and tai chi may improve physical functioning and quality of life in patients with FMS. Offering yoga and tai chi as treatment, therefore, should be considered for patients with CMI and symptoms consistent with FMS, integrating shared decision making, patient-centered goal setting, and discussion of risks versus benefits. Indeed, no reviewed studies showed significant differences in AEs between exercise and control groups, and one large study comparing tai chi to AEX found no difference in AEs after one year.(72) Thus, the benefits outweighed the harms/burdens. Since these studies enrolled mainly female patients, the results may not be generalizable to the VA/DoD CMI population. There also is some variation in patient values and preferences. The resource requirements for yoga and tai chi can be relatively low as patients can access these types of exercises via free websites, low-cost videos, and handouts from clinicians. Yoga and tai chi are also becoming increasingly feasible as forms of exercise in VA/DoD populations. Yoga and tai chi are covered benefits in VA, which improves accessibility for Veterans. Also, DoD bases often offer yoga or tai chi through recreational programs, on-site gyms, or through CIH. Since yoga and tai chi are relatively low risk exercises and non-pharmacologic and noninvasive options for treatment of CMI, the Work Group decided upon a *Weak for* recommendation.

Recommendation

15. We suggest offering manual acupuncture as part of the management of patients with CMI and symptoms consistent with fibromyalgia.
    (Weak for | Reviewed, New-replaced)

Discussion

An SR of 12 RCTs by Zhang et al. (2019) suggests manual acupuncture improves QoL both immediately after treatment and up to three months after treatment in patients with FMS compared to sham acupuncture.(76) The SR considered studies of both manual and electro-acupuncture compared to sham acupuncture or amitriptyline. When manual and electro-acupuncture were disaggregated, the QoL benefit was observed only in the manual acupuncture trials. In the constituent trials, mild AEs were reported more commonly in the active than the sham acupuncture or amitriptyline groups when reported. However, this is a subjective impression of the results as there was no statistical test of differences in AEs between groups in the SR.(76)

An RCT by Garrido-Ardila et al. (2020) failed to show a QoL benefit of acupuncture over physiotherapy in patients with FMS.(77) This was a very low quality study because no intention-to-treat analysis was performed. Also, there were no observed differences in AEs between the acupuncture and physiotherapy groups.(77)

In other SRs of ME/CFS (78) and IBS,(79) AEs associated with acupuncture were uncommon and mild, suggesting that acupuncture is generally safe.

The Work Group determined that the SR of acupuncture in patients with ME/CFS did not effectively support the use of acupuncture since it equated acupuncture and moxibustion (i.e., the burning of herbs for therapeutic benefit) in its intervention group.(78) A separate SR by Zheng et al. (2019) found acupuncture improved QoL in patients with IBS at both the end of treatment and two months afterward compared to Western medicine, but not compared to sham acupuncture.(79) One trial in the same SR compared acupuncture and Chinese medicine to Chinese medicine alone, and the combination treatment demonstrated greater improvements in QoL. Zheng et al. (2019) suggested acupuncture may benefit patients with IBS, but the evidence was not considered strong enough to merit a distinct recommendation for the use of acupuncture for these patients.(79)

There was considerable variability in the length of acupuncture treatment, comparison groups, and outcome assessments in these studies of acupuncture, while the evidence consistently suggested a low risk to treatment. Although there was no evidence that acupuncture affects function, acupuncture was generally favored over comparative treatments in improving certain efficacy outcomes (e.g., pain, fatigue, gastrointestinal symptoms).

There is likely some variability in patient preferences for acupuncture given some individuals' discomfort with needles. Moreover, there may be a sex bias in acceptability since almost all study participants were women in Zhang et al. (2019) (76) and Garrido-Ardila et al. (2020).(77) sex was not reported in the other SRs. Manual acupuncture is administered by trained professionals, representing a fairly high resource need and time commitment for patients. Training can also be lengthy and costly, and while VA has increased hiring of trained acupuncturists, they are not available at all sites of care for Service Members and Veterans, as indicated in the Veteran Engagement Session reports to the RAC GWVI. Acupuncture is a covered VA benefit and can be offered through the community care contract when not available at medical facilities.

The Work Group systematically reviewed evidence related to this recommendation (76-79) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. Limitations included largely female patient samples and variability in the types of acupuncture assessed. The benefits on QoL outweighed potential AEs, which tend to be minor and uncommon. Patient preferences should be considered, especially given some individuals' discomfort with needles, and the availability of trained acupuncturists is likely to limit the widespread use of this intervention. Thus, the Work Group decided upon a *Weak for* recommendation.

More definitive studies focusing on patients with CMI are warranted since evidence suggests acupuncture is beneficial to patients with FMS. Careful attention should be paid to study design, choice of intervention,

use of appropriate comparison groups, choice of outcomes (prioritizing more global, patient-centered measures [e.g., function, QoL]), and the use of rigorous statistical analyses. Studies that elucidate the mechanism of action of acupuncture in patients with CMI would also be beneficial.

Recommendation

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.
(Neither for nor against | Reviewed, New-added)

Discussion

Yuan et al. (2015) performed an SR examining the effectiveness of massage to improve HRQoL, pain, pressure pain threshold, fatigue, stiffness, anxiety, depression, and sleep.(80) This SR evaluated 10 RCTs with a total of 478 participants. Participants' ages ranged from 43.5 to 53.7 years, and, notably, 97.4% were female. The six types of massage evaluated were Swedish, connective tissue, manual lymphatic drainage, myofascial release, shiatsu, and a combination of multiple styles. None of the included studies were completed after 2013. Most studies focused on HRQoL as a primary outcome.

Treatment outcomes were assessed upon study completion or over a short (1 to 3 months), medium (3 to 12 months), or long (>12 months) period.(80) No meta-analysis of the studies was performed because the individual studies used various measures, and there was a high risk of study bias. Despite these limitations, several modalities showed positive outcomes such as improvements in fatigue, stiffness, and QoL (myofascial release), improvements in depression and QoL (manual lymphatic drainage), and improvements in pain, fatigue, sleep, and QoL (shiatsu). In a direct comparison between manual lymphatic drainage and connective tissue massage on stiffness, depression, and QoL, the latter proved superior. Finally, Swedish massage did not improve outcomes.(80)

A large body of evidence supports the benefits of massage therapy for various conditions.(81) However, when reviewing the benefits of massage therapy for CMI, the Work Group's confidence in the quality of the evidence was very low. There is likely some variation in patient preferences as some individuals may be uncomfortable with the touching associated with massage therapies. Additionally, although massage therapy is a benefit covered in the VA for treating pain,(82) it is not a covered benefit by TRICARE.(83) Massage therapy can be costly if paid for out of pocket by patients.

The Work Group systematically reviewed evidence related to this recommendation (80) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. This determination was made because only two (84, 85) of 10 studies in the SR by Yuan et al. (2015) had a low risk of bias.(80) Moreover, the heterogeneity of the massage techniques and outcomes used in the reviewed studies prevented a meta-analysis from being conducted, limiting comparisons of study results and conclusions. The benefits slightly outweighed the harms/burden, and there was no evidence that massage therapy was harmful. Massage therapies were consistently beneficial, although effects were often short-lasting. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Evidence suggests that most massage therapies improve HRQoL in patients with FMS. However, the overall study quality was low. Therefore, more high-quality studies that limit bias are essential to ensure that

providers have the best evidence available to counsel CMI patients on those massage therapies that are most beneficial.

c. Physical Exercise

Recommendation

17. We suggest offering physical exercise for patients with CMI and symptoms consistent with fibromyalgia.
    (Weak for | Reviewed, New-replaced)

Discussion

This CPG's systematic evidence review did not identify any SRs or meta-analyses related to this recommendation. A small RCT by Kerr et al. (2019) compared a detoxification program to waitlist controls undergoing TAU for the treatment of Veterans with GWI.(86) The detoxification program consisted of daily AEX, Finnish sauna, and proprietary nutritional supplements. The study assessed the program's effects on HRQoL and physical function. These data are indirect since multiple other interventions were implemented simultaneously. Thus, it is difficult to identify the specific effects of physical activity on HRQoL and physical function. Given the limitations of Kerr et al. (2019), the Work Group ultimately decided to exclude it and used evidence from the 2014 CMI CPG's systematic evidence review.(86)

Donta et al. (2003) conducted an RCT to compare the effectiveness of CBT, AEX, CBT plus AEX, and TAU in improving physical functioning and reducing the symptoms of GWI.(33) Exercise sessions were 60 minutes weekly for 12 weeks, conducted with the use of a treatment manual, and designed to increase activity and allow participants to choose the types of exercises they liked most. The study did not find a difference between groups for the primary outcome of improvement in physical function, but the secondary outcomes did show positive results. The authors reported that both exercise alone, and in combination with CBT, significantly improved fatigue, distress, cognitive symptoms, and mental health functioning, but did not have a significant impact on pain. There were few serious AEs associated with exercise reported, with only a single event of a back injury that required surgery.(33)

Peters et al. (2002) conducted an RCT to examine the efficacy of AEX (n=114) relative to stretching (n=114) in the management of patients with medically unexplained physical symptoms (MUPS).(87) All study participants were receiving care at the National Health Service (NHS) in England. All training sessions met for one hour, twice a week, for 10 weeks. During AEX, the goal was for patients to attain a target heart rate of 60 to 65% of their age-adjusted maximum; stretching was designed to be non-aerobic (max heart rate of <50% of age-adjusted maximum). No difference in healthcare utilization was found between the AEX and stretching groups. Symptom scores on the Hospital Anxiety and Depression Scale (HADS), SF-36 scale, and somatization scales did not differ between groups. Scores improved over time for both groups but were not associated with improvements in attendance. The study did not report AEs.(87)

An SR by Brosseau et al. (2008) evaluated the use of exercise in patients with FMS.(88) This SR assessed the effectiveness of strengthening exercises (defined as isometric, isokinetic, or concentric/eccentric resistance exercise) and included five RCTs enrolling a total of 150 adult patients with FMS. The treatment duration ranged from 12 to 21 weeks and strengthening exercises were performed twice a week. The primary outcomes were improvements in pain, disability, and QoL. Strengthening exercises showed

clinically and statistically significant benefits versus controls for general pain using the Visual Analog Scale (VAS). Strengthening exercises also showed clinically and statistically significant benefits in improving disability scores compared to controls, as measured using the Stanford Health Assessment Questionnaire. No clinical or statistically significant benefit of strengthening exercises versus controls was observed for QoL, measured using the FIQ. 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 statistically significant benefit was QoL. The study did not report AEs.(88)

A meta-analysis by Nüesch et al. (2013) evaluated the efficacy of AEX in patients with FMS.(64) Although this study did not specifically examine a CMI population, the Work Group considered it indirect evidence. In the analysis, AEX was one of several treatments reviewed and the authors developed a comprehensive SR of several pharmacologic and non-pharmacologic treatments for the management of patients with FMS. The review included 33 RCTs that enrolled 2,266 patients in total and the average duration of treatment across studies was 12 weeks. Data on the primary outcomes, pain and QoL, were pooled in a network meta-analysis. The results indicated a statistical benefit for AEX compared to placebo in improving pain and QoL. The study did not report AEs.(64)

The Work Group systematically reviewed evidence related to this recommendation (86) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(33, 64, 87, 88) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low, downgraded for indirectness and imprecision. The body of evidence had significant limitations, including small sample sizes, lack of blinding, reporting bias, and baseline differences in the study populations. However, the above evidence did show HRQoL benefits of exercise (fatigue, distress, cognitive symptoms, and mental health functioning), one of the critical outcomes of interest.(32,64) The benefits outweighed the potential harms/burden. There is some variation in patient values and preferences for exercise given differences in age and fitness. Given the overall known health benefits of exercise in the general population, coupled with the evidence supporting HRQoL benefits in CMI patients, offering exercise as a treatment should be considered for CMI patients with symptoms consistent with FMS. Thus, the Work Group decided upon a *Weak for* recommendation.

There is currently a lack of literature examining the effects of exercise on CMI. There is a need for high quality RCTs that evaluate the safety and effectiveness of exercise as a possible treatment for patients with CMI.

D. Treatment of CMI and Symptoms Consistent with Irritable Bowel Syndrome

a. Pharmacotherapy

Recommendation

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.
(Neither for nor against | Reviewed, New-added)

Discussion

An SR and network meta-analysis of RCTs by Black et al. (2020) compared the efficacy of TCAs (desipramine, doxepin, amitriptyline, imipramine, trimipramine) to placebo in seven RCTs involving 559 participants meeting criteria for irritable bowel syndrome-diarrhea (IBS-D) or irritable bowel syndrome-mixed (IBS-M).(89) This SR and network meta-analysis included only RCTs with a dichotomous assessment of overall response to treatment, either for global IBS symptoms or for improvement in abdominal pain. A binary assessment of global improvement has excellent psychometric properties and detects minimally clinically important differences in symptoms; as such it is considered standard in IBS clinical trials.

The network meta-analysis of RCTs by Black et al. (2020) assessed the efficacy of the following categories of treatment: soluble fiber, antispasmodic drugs, peppermint oil, and gut-brain neuromodulators (including TCAs).(89) For improvement in global IBS symptoms, TCAs ranked second in efficacy (defined as failure to achieve improvement in global symptoms at four to 12 week follow-up [relative risk (RR): 0.66; 95% CI: 0.53 to 0.83]) based on data from nine RCTs that randomly assigned 355 patients to active treatment (of note, peppermint oil capsules, not included in this CPG because it is categorized as a nutritional supplement, ranked first; the results were very similar to outcomes for TCAs). The results also indicated that TCAs ranked first in efficacy for improvement in abdominal pain (defined as failure to achieve improvement in abdominal pain at four to 12 week follow-up [RR: 0.53; 95% CI: 0.34 to 0.83]), though for abdominal pain the results were based only on data from four RCTs involving 92 patients.(89) The longer term efficacy of TCAs for IBS remains unknown.

An assessment of AEs indicated a greater rate of total AEs in the treatment groups compared to placebo (RR: 1.59; 95% CI: 1.26 to 2.06), though none of the treatments studied in Black et al. were more likely than placebo to discontinue participation in the trial due to AEs. The most common AEs from TCAs are dry mouth, constipation, and drowsiness. Of note, these side effects are typically dose-dependent, and the dosages typically used for treatment of IBS (e.g., 10 to 25 mg q hs) are considerably lower than those used to treat depression. However, caution is warranted given the relatively small number of patients analyzed in the SR and also since detailed information on individual AEs was not provided in Black et al.

Another SR, Xie et al. (2015), which included five RCTs that assessed 428 patients, found that those randomly assigned to TCAs were significantly more likely to achieve improvement in global IBS symptoms at follow-up of at least seven days in (RR: 1.36; 95% CI: 1.07 to 1.71).(90) The studies assessed were of generally high quality and there was no evidence of publication bias. Most studies did included not distinguish between clinical subtypes of IBS. Xie et al. also assessed differences in QoL for those taking

TCAs versus placebo (one study; n=34) using the SF-36 and found no difference in outcomes between groups. In addition, they assessed dropout due to treatment side effects (evaluated in three studies of TCAs) and the pooled RR of dropout in the TCA group was not significantly higher (RR: 1.92; 95% CI: 0.89 to 4.17; p=0.10).(90)

There is likely a large variation in patient preferences given the stigma associated with taking antidepressants. In addition, some patients might prefer to address their symptoms by other means, such as through a trial of a low-FODMAP diet or other antidiarrheal agents (e.g., loperamide). This intervention is inexpensive and, although side effects are more common from TCAs than placebo, they are usually mild (e.g., sedation, anticholinergic effects such as dry mouth or palpitations). The Work Group also noted that this class of medications should be avoided in populations at a high risk of suicide or the elderly.

The Work Group systematically reviewed evidence related to this recommendation (89, 90) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low due to risk of bias and indirectness of outcomes. The benefits (i.e., improved IBS outcomes) slightly outweighed the harms/burden (i.e., mild side effect profile). There is likely a large variation in patient values and preferences. Providers should consider TCAs for patients with CMI and abdominal pain and diarrheal symptoms and avoid TCAs for populations at high risk of suicide or the elderly. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Further research is needed to examine the effectiveness of TCAs, including large RCTs in patients meeting the criteria for CMI.

Recommendation

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.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

An SR and meta-analysis of RCTs by Black et al. (2020) compared the efficacy of antispasmodics to placebo in patients meeting the criteria for IBS.(89) This SR and meta-analysis found that those randomly assigned to an antispasmodic (i.e., trimebutine, otilonium, pinaverium, mebeverine, pirenzepine, cimetropium, hyoscine, drotaverine, pargeverine) were less likely to fail to achieve improvements in global IBS symptoms (RR: 0.75). There were no differences in AEs in the population taking antispasmodics compared to placebo, no evidence that one antispasmodic was superior to the others, and rates of AEs did not differ between agents.

There is likely some variation in patient preferences since some patients may prefer to address their symptoms by other means (e.g., fiber supplements, TCAs, dietary changes). However, although antispasmodics may be a feasible and efficacious intervention, none of the specific antispasmodics evaluated in Black et al. (2020) (listed above) are available in the U.S.(89) Although dicyclomine is a widely used antispasmodic within the VA and DoD, the Work Group found no evidence to guide the use of this agent. Thus, the Work Group could not recommend for or against the use of dicyclomine in patients with

CMI and symptoms consistent with IBS. Of note, dicyclomine should be avoided in the elderly due to the potential for anticholinergic side effects.

The Work Group systematically reviewed evidence related to this recommendation (89) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low given the risk of bias and indirectness. For the antispasmodics analyzed in Black et al. (2020), the benefits (i.e., improvements in IBS-D symptoms) and harms/burden are balanced, but as noted above, none of the antispasmodics reviewed are available in the U.S. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed on the safety and effectiveness of dicyclomine, a widely used and available antispasmodic in the U.S., for the treatment of patients with CMI and symptoms consistent with IBS.

Recommendation

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. **(Weak for | Reviewed, New-replaced)**

Discussion

Guanylate cyclase-C agonists such as linaclotide and plecanatide may improve symptoms and QoL in patients with IBS with constipation who have not responded to a trial of osmotic laxatives.(91, 92) In one SR and meta-analysis involving six RCTs, which assessed a total of 6,472 patients, linaclotide (290 mg/day) (OR: 2.43; 95% CI: 1.48 to 3.98; NNT=6) and plecanatide (3 mg/day, OR: 1.87; 95% CI: 1.47 to 2.38, NNT=9; 6 mg/day, OR: 1.92; 95% CI: 1.48 to 2.48; NNT=9) were more effective than placebo in meeting the FDA responder endpoint for IBS with constipation at a 12 week follow-up. The quality of most studies was good.

Evidence for AEs was derived from five RCTs and found that linaclotide (290 mg/day) and plecanatide (3 or 6 mg/day) were more likely than placebo to experience diarrhea and study withdrawal due to diarrhea at 12 week follow-up.(91) Rates of diarrhea as an AE occurred in approximately 3 to 6% of patients.(91) Evidence from 5 RCTs indicates no difference between linaclotide (290 mg/day) and plecanatide (3 mg/day) in efficacy based on the FDA responder endpoint at 12 to 26 weeks follow-up, and no difference in the incidence of diarrhea or study withdrawal rates between these agents.(91)

In another SR involving four RCTs, which assessed a total of 1,773 patients, linaclotide (266 mg, 290 mg, or 300 mg) was compared to placebo and the number failing to achieve adequate improvement at 12 weeks was assessed.(91, 92) The quality of most studies was fair. Outcomes for clinically meaningful improvement in IBS-related quality of life favored linaclotide (RR: 0.78; 95% CI: 0.72 to 0.86). The long-term efficacy and safety of plecanatide was demonstrated in an analysis of 2,272 patients with follow-up of up to 53 weeks, which found a safety profile similar to the 12 week results. The long-term safety and efficacy of linaclotide remains poorly studied.

There is some variation in patient preferences as some patients may be resistant to taking these medications due to side effects. These medications are rarely used at the VA and offered only after other

treatments (e.g., osmotic laxatives) have failed per VA Criteria For Use. For TRICARE to approve their use, two previous treatments must have already failed, and prior authorization is required. These medications must be prescribed under the care of a specialist, which also limits their availability.

The Work Group systematically reviewed evidence related to this recommendation (91, 92) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The benefits slightly outweighed the harms/burden. Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

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.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

Three RCTs in an SR by Li et al. (2016) for patients with IBS with constipation demonstrated improvements in bowel-related outcomes for those treated with lubiprostone compared to placebo at one month, but the difference was no longer significant after three months of treatment (for frequency of spontaneous bowel movements, constipation severity, stool consistency, or degree of straining).(93) The only outcome significantly improved in the three RCTs assessed was degree of abdominal bloating, which was significantly improved among those assigned to lubiprostone at all time points. The strength of evidence was low. Additionally, AEs such as nausea, vomiting, and diarrhea were common (incidence rate [IR]: 2.4 – 75%); however, the incidence of serious AEs was low (<5%) and most were unrelated to lubiprostone treatment.(93)

There is some variation in patient preferences, as some patients may oppose starting a new medication. Providers should consider an osmotic laxative or another agent to loosen stools before prescribing lubiprostone because patients often respond well to other treatments. As the long-term safety profile of lubiprostone is unknown and given the paucity of evidence suggesting significant clinical benefit, we recommend limiting prescription to those who have persistent constipation despite treatment with osmotic agents, and utilizing a limited treatment course (e.g., 12 weeks). The VA Criteria For Use and FDA-approved indication currently apply only to women. Lubiprostone is generally acceptable to patients and feasible as a treatment. This drug requires prior authorization for TRICARE coverage and currently is not used in the VA.

The Work Group systematically reviewed evidence related to this recommendation (93) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The benefits slightly outweighed the harms/burden. Adverse events were common, while the incidence of serious AEs was low (<5%) and mostly unrelated to lubiprostone treatment.(93) Patient values and preferences somewhat varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

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.
(Neither for nor against | Reviewed, New-replaced)

Discussion

In a network meta-analysis that included data from four RCTs involving 1,967 patients who received eluxadoline and 1,155 patients who received placebo, Black et al. (2020) found eluxadoline to be superior to placebo in the treatment of bowel-related outcomes in patients with IBS-D and IBS-M at 12 weeks.(94) The benefit over placebo appears modest. In this SR and meta-analysis, patients assigned to receive eluxadoline (100 mg BID) and eluxadoline (75 mg BID) were less likely to fail to achieve the FDA-recommended endpoint at 12 weeks (for 100 mg BID, RR: 0.87; 95% CI: 0.83 to 0.91; for 75 mg BID, RR: 0.89; 95% CI: 0.84 to 0.94).(94) The FDA-recommended endpoint involves a composite of improvement in abdominal pain and stool consistency. When assessed according to failure to achieve a global IBS symptom response, patients assigned to receive eluxadoline (100 mg BID) and eluxadoline (75 mg BID) were less likely to fail to achieve a global IBS symptom response (for 100 mg BID, RR: 0.78; 95% CI: 0.68 to 0.90; for 75 mg BID, RR: 0.81; 95% CI: 0.68 to 0.98).(94) Although these short-term outcomes indicate a benefit for eluxadoline, longer term follow-up data are lacking.

In terms of safety, although there was no difference in overall AEs compared to placebo in four RCTs at 12 weeks, there was a higher risk of trial dropout for those assigned to eluxadoline due to AEs, such as nausea, constipation and abdominal pain.(94) The risk of trial dropout was similar for the 75 mg BID and 100 mg BID dosages. Following FDA approval, reports of pancreatitis were reported following use of this agent. Eluxadoline is contraindicated in patients without a gallbladder, which appears to be a risk factor for serious pancreatitis following use of eluxadoline. In addition, the FDA lists the following contraindications to use of eluxadoline: history of pancreatitis, sphincter of Oddi dysfunction, severe liver disease, chronic or severe constipation, alcohol abuse, or suspected intestinal obstruction. The U.S. Drug Enforcement Administration (DEA) has classified eluxadoline as a schedule IV controlled substance, as a drug with a low potential for abuse and low risk of dependence.

There is some variation in patient preferences. Some patients may prefer trying dietary modifications (e.g., a low-FODMAP diet) instead of medication. Others may choose to try loperamide (Imodium®) first, as it is more commonly used clinically and relatively inexpensive. Additionally, there are VA requirements for trials of alternative anti-diarrheals and TRICARE requirements for prior authorization, which may complicate or delay obtaining eluxadoline.

The Work Group systematically reviewed evidence related to this recommendation (94) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The harms/burden slightly outweighed the benefits and require screening patients carefully for contraindications. Patient values and preferences somewhat varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

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.
    (Weak for | Reviewed, New-added)

Discussion

An SR and meta-analysis of RCTs by Black et al. (2020) compared the efficacy of rifaximin (550 mg, three times a day for 14 days) versus placebo in two RCTs involving 1,260 participants (625 assigned to rifaximin, 635 assigned to placebo) meeting Rome II criteria for IBS-D or IBS-M.(94) This study found that those randomly assigned to rifaximin were significantly less likely to fail to achieve FDA-defined treatment response (RR: 0.92; 95% CI: 0.86 to 0.98) and experience improvements in stool consistency at 12 week follow-up (RR: 0.69 for failure to achieve FDA-defined treatment response). Rifaximin is prescribed as a 14-day treatment course. The long-term outcomes of rifaximin remain poorly studied. An assessment of AEs in these studies indicated no difference in overall AEs between treatment groups at 12 week follow-up.

There is likely some variation in patient preferences. For instance, some patients may prefer to address their symptoms by other means (e.g., trying a low-FODMAP diet or addressing stress-related triggers of symptoms). The Work Group also noted that rifaximin is expensive.

The Work Group systematically reviewed evidence related to this recommendation (94) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low due to imprecision and indirectness. There was also a lack of reported AEs in the treatment group compared to placebo. The benefits slightly outweighed the harms/burden. Patient values and preferences varied somewhat. Thus, the Work Group decided upon a *Weak for* recommendation.

More research is needed to better understand the effectiveness of rifaximin in patients meeting the criteria for CMI and symptoms consistent with IBS.

Recommendation

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.
    (Neither for nor against | Reviewed, New-replaced)

Discussion

Fiber supplements, also known as soluble fiber, have had mixed results in improving IBS symptoms.(89) One SR found no difference between soluble fiber (ispaghula husk only) and placebo at four to 12 weeks of treatment (RR for failure to achieve global IBS symptom improvement: 0.78; 95% CI: 0.59 to 1.02).(89) Nagarajan et al. (2015) demonstrated modest improvements in patients who received fiber compared to placebo at four to 16 weeks of treatment, although there was significant variation in responses to the treatment.(95) However, after sensitivity analysis was performed, the improvement in global symptoms was no longer evident, which is consistent with Black et al. (2020).(89) The two studies demonstrated no

difference in total AEs between soluble fiber (ispaghula husk) and placebo between four to 12 weeks of follow-up.(89, 95)

There is some variation in patient preferences since some patients may choose to increase fiber through dietary changes, while others may prefer to take soluble fiber supplements. Fiber supplementation is feasible, acceptable, affordable, and widely available in the VA and DoD. There are patient subgroup considerations because patients diagnosed with IBS-M or experiencing symptoms of diarrhea may benefit more from soluble fiber than other populations.

The Work Group systematically reviewed evidence related to this recommendation (89, 95) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The benefits slightly outweighed the harms/burden. There is some variation in patient values and preferences. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

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. **(Neither for nor against | Reviewed, New-added)**

Discussion

An SR and meta-analysis of RCTs by Black et al. (2020) compared the efficacy of alosetron versus placebo.(94) Three of the RCTs included patients who met the criteria for IBS-D or IBS-M. This SR found that those randomly assigned to alosetron (1 mg, BID) were more likely to demonstrate improvements in global IBS symptoms (two studies; n=1,154). One study (n=353) found superior stool consistency in patients taking alosetron. There were greater overall AEs in the groups taking alosetron compared to placebo (five studies; n=2,813). In some cases, the AEs led to withdrawal from the study.

The most common AE while taking alosetron is constipation. However, alosetron was withdrawn from the U.S. market due to cases of ischemic colitis. Alosetron was subsequently reintroduced, under a risk evaluation and mitigation strategy, and is FDA-approved for the treatment of women with severe IBS-D who do not respond to other treatments.

There is likely a large variation in patient preferences related to the use of alosetron for IBS, given the potential for ischemic colitis, an uncommon but potentially severe complication. In addition, some patients may prefer to address their symptoms using other, safer agents for IBS (e.g., fiber, other antidiarrheals, dietary changes). The Work Group concluded that alosetron is likely to be unacceptable to many patients given that it requires additional monitoring, has the potential to cause ischemic colitis, and should only be considered in women with severe IBS-D refractory to other treatments.

The Work Group systematically reviewed evidence related to this recommendation (94) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low given the risk of bias and indirectness. The harms/burden (i.e., risk of death from ischemic colitis) slightly outweighed

the benefits (i.e., improvement in IBS-D symptoms). There is likely a large variation in patient values and preferences. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed to better understand the effectiveness and safety of alosetron in patients meeting the criteria for CMI and symptoms consistent with IBS.

Recommendation

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.
    (Neither for nor against | Reviewed, New-added)

Discussion

An SR and meta-analysis of RCTs by Black et al. (2020) compared the efficacy of SSRIs to placebo in four RCTs involving 256 participants meeting criteria for IBS-D or IBS-M.(89) This SR and meta-analysis found that those randomly assigned to SSRIs did not achieve greater improvements in global IBS symptoms at follow-ups of four to 12 weeks. There was no difference in total AEs compared to placebo. Another SR by Xie et al. (2015) assessed improvements in QoL for those taking SSRIs versus placebo (two studies; n=205) using the SF-36 and found no difference in outcomes between groups; there was also no difference in global improvement in IBS symptoms (RR: 1.38; 95% CI: 0.83 to 2.28). Furthermore, there was no difference in risk of dropout due to AEs for those assigned to SSRIs.(90)

There is likely some variation in patient preferences given the stigma associated with taking antidepressants. In addition, some patients may prefer to address their symptoms by other means, such as through a trial of other agents for IBS (e.g., fiber supplements, osmotic laxatives, dietary changes). The Work Group also noted that SSRIs are inexpensive and have a similar side effect profile to placebo, but there is no evidence that they improve IBS symptoms.

The Work Group systematically reviewed evidence related to this recommendation (89, 90) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low due to risk of bias, imprecision, and indirectness. Given the lack of evidence that SSRIs improve IBS outcomes and lead to more AEs than placebo, the benefits and harms are balanced. Additionally, there is likely some variation in patient values and preferences. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

More research is needed to examine the effectiveness of SSRIs in populations meeting the criteria for CMI and symptoms consistent with IBS.

b. Behavioral Health

Recommendation

27. There is insufficient evidence to recommend for or against offering psychodynamic therapies for patients with CMI and symptoms consistent with irritable bowel syndrome.
(Neither for nor against | Reviewed, New-replaced)

Discussion

Evidence suggests psychodynamic therapy may improve mental health and daily functioning in patients with IBS.(35, 96-100) An SR by Laird et al. (2017) assessed the effect of psychotherapy on mental health and daily functioning in adults with IBS in three RCTs.(96, 97, 100) All three RCTs contained sample sizes >100 participants, ranged from 69 to 79% female, and offered between seven to 10 individualized treatment sessions. Two of the RCTs found that psychodynamic therapy improved HRQoL for individuals with IBS.(96, 97)

An SR conducted by Zijdenbos et al. (2009) had slightly different findings.(98) This SR examined the efficacy of interpersonal psychotherapy for the treatment of IBS and concluded that psychological interventions may be slightly superior to TAU or waitlist controls in improving abdominal pain and quality of life. The SR consisted of three RCTs that included 460 patients with a mean age between 30.9 and 49.2 years, and the percentage of female participants ranged between 59 to 80% of the total.(96, 97, 99)

There is some variation in patient preferences. Psychodynamic therapy can be burdensome because it requires frequent visits. Additionally, some individuals may not be good candidates for psychodynamic therapy given physical (e.g., limb loss) and cognitive limitations (e.g., brain injury or dementia). There may be limited access to this treatment due to a lack of providers with adequate training.

The Work Group systematically reviewed evidence related to this recommendation (35) and considered the assessment of the evidence put forth in the 2014 CMI CPG.(98) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including a small number of studies, a majority female population, differing lengths of treatment and follow-up, and the use of inconsistent instruments to measure outcomes of interest.(35, 96-98) The benefits to mental health and daily functioning in individuals with IBS outweighed the potential harms/burden, including having to attend multiple therapy sessions. There is some variation in patient values and preferences. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

There are a limited number of studies that have assessed psychodynamic therapy for the treatment of CMI. Additional studies should include a more diverse patient sample (e.g., sex, race, and age), and standardize treatments across various parameters (e.g., sessions, lengths, follow-up, control/standard care). Researchers should explore additional delivery modalities (e.g., online versus in-person, group versus individual) and standardize outcomes measured (e.g., QoL, symptom reduction, daily functioning).

E. Treatment of CMI and Symptoms Consistent with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

a. Pharmacotherapy

Recommendation

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. **(Neither for nor against | Reviewed, New-replaced)**

Discussion

A double-blind RCT of 60 patients with ME/CFS by Arnold et al. (2015) lends indirect support for therapeutic trials of duloxetine in patients with CMI and symptoms consistent with ME/CFS.(101) In this study, duloxetine did not significantly improve fatigue-related symptoms or function, while it was slightly favored over placebo for mental fatigue and demonstrated improvements in the Clinical Global Impression – Severity scale (CGI-S). Other assessments, most notably Patient Global Impression of Improvement (PGI-I) scores and function, were inconclusive. Importantly, ≥5% of patients developed AEs, most commonly somnolence, dizziness, headache, and dry mouth.(101) Given the potential for AEs, the small benefit demonstrated in the available trial, and the absence of more robust evidence, clinicians should continue to weigh individual benefits against the risks of treatment. Only a slight benefit was seen with duloxetine in the specific domains of the Clinical Global Impression – Improvement scale (CGI-I) and mental fatigue.

There is a large variation in patient values and preferences since duloxetine is a psychoactive drug and some patients may prefer non-pharmacologic therapies. Duloxetine is readily available in the VA/DoD with no prior authorization required.

The Work Group systematically reviewed evidence related to this recommendation (101) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes and unclear randomization and allocation methods. The benefits of duloxetine (i.e., slight improvement in mental fatigue and CGI-S) were balanced by its potential harms (e.g., nausea, somnolence, dizziness, headache, dry mouth). Thus, the Work Group decided upon a *Neither for nor against* recommendation.

There is a general paucity of research on medications that can be used to effectively treat ME/CFS and more specifically CMI. Since this recommendation is based on data extrapolated from studies on ME/CFS, more research is needed on the safety and effectiveness of duloxetine, and more broadly SNRIs, for patients with fatigue related to CMI.

Recommendation

29. We recommend against offering stimulants for treatment of fatigue in patients with CMI and symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome.
(Strong against | Reviewed, New-replaced)

Discussion

A double-blind RCT of 135 patients with ME/CFS by Montoya et al. (2018) provides indirect evidence against therapeutic trials of KPAX002 (methylphenidate hydrochloride + supplement) in patients with CMI and symptoms consistent with ME/CFS.(102) In this study, KPAX002 did not significantly improve fatigue-related symptoms, measured using the Checklist Individual Strength (CIS), which is a 20-item fatigue questionnaire, or VAS measuring fatigue compared to placebo. There was no significant difference between placebo and KPAX002 with regard to AEs;(102) however, methylphenidate hydrochloride has a risk for abuse and stimulants have been increasingly associated with overdose deaths.(103) In 2015-2016, the U.S. had an increase of 33.3% in psychostimulant involved deaths.(103) Beyond its abuse potential, the FDA has also issued warnings on this drug due to risk of priapism and cardiovascular events to include stroke, myocardial infarction, and sudden cardiac death.(104) Given the lack of benefit, absence of more robust evidence, and FDA black box warnings for methylphenidate hydrochloride's abuse potential, it is recommended clinicians avoid prescribing this medication.

There is likely some variation in patient values and preferences as some patients may wish to avoid stimulants or medications in general, while other patients might be eager for a pharmacologic intervention to ameliorate their fatigue. It is important to note that KPAX002 was not approved by the FDA and, as such, the data from this recommendation was extrapolated to methylphenidate hydrochloride alone, which is available in the VA/DoD.

The Work Group systematically reviewed evidence related to this recommendation (102) and considered the assessment of the evidence put forth in the 2014 CMI CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including small sample sizes and potential bias, as the study was led by the person who developed KPAX002.(102) The harms/burden (i.e., the potential for abuse, increased aggression or hostility, exacerbation of bipolar illness, exacerbation of hypertension, exacerbation of Raynaud's phenomenon, headache, nausea with methylphenidate hydrochloride) outweighed any benefits.(104) There was some variation in patient values and preferences. Thus, the Work Group decided upon a *Strong against* recommendation.

In general, there is a paucity of rigorous, adequately-powered RCTs on stimulants as treatments for ME/CFS and CMI.

X. Research Priorities

During the development of the 2021 CMI CPG, the Work Group identified topics needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs.

The Work Group identified several critical gaps in the evidence base for treatments of CMI, which fell into seven broad categories that cut across the types of interventions evaluated in this CPG. The purpose of highlighting the shortcomings of the extant CMI literature is to spur researchers and policymakers to design and fund studies. The gaps span the spectrum of the National Institutes of Health research roadmap, which describes a rational progression of research activities from basic discovery (bench and animal research), to clinical research (safety and efficacy), to effectiveness and implementation research. Although our summary is primarily based on a review of the research literature, with a focus on RCTs and meta-analyses, it is important to note that providers play a key role in generating hypotheses, which can aid in the prioritization of research and discovery activities. Providers are closest to patients and can communicate to research teams the suffering and impact of CMI observed in their patients and can also share promising interventions and practices that might form the basis for more systematic investigation. Of course, patients themselves can also share their experiences and inform research priorities.

Although each of the areas highlighted below is considered important to advance our understanding of CMI, the Work Group recommends prioritizing some gaps to move the field forward. These "fundamental gaps" and other areas where additional research is needed are summarized below in priority order.

A. Fundamental Research Gaps

a. Lack of a single, generally accepted, research case definition of CMI

The IOM recommended the use of two empirically validated case definitions for CMI research – the Kansas definition and the CDC definition.(105) However, many studies published before and after 2014 used alternative or "homegrown" definitions. In addition, the rigor in applying these case definitions has varied by study. Moreover, the documentation of adherence to one or both of these definitions is often inadequate, which limits the generalizability of the findings and application to individual patient care. Finally, many studies adapt the Kansas or CDC case definitions to target symptoms of interest (e.g., chronic widespread pain, cognitive difficulties), requiring high levels of symptomatology for the specific clinical manifestation. This effectively identifies a subgroup of patients with CMI, which increases the specificity of the indication for use but also limits the generalizability to CMI and inclusion in this CPG. The possibility of subgroups of CMI based on pathophysiology and clinical relevance should be further explored and better understood.

b. Lack of RCTs focused on patients with CMI/GWI, using a validated case definition

This limitation was recognized at the outset of the update of the 2014 CMI CPG and the Work Group agreed to include studies of patients with FMS, IBS, and ME/CFS in addition to those with CMI. These conditions are presumed to be similar to CMI, although empiric data supporting this assumption is not strong. Thus, studies of FMS, IBS, and ME/CFS were interpreted as indirect and of lower quality evidence with regard to CMI. However, without the inclusion of studies on similar conditions, the Work Group would have had few relevant studies to include in the updated CPG. The Work Group had extensive discussions about the limitations of this approach and the serious nature of this gap in existing research. To advance our understanding of the treatment of CMI, research studies must recruit and study patients with CMI and characterize those samples in detail; this will help to better inform clinical decision making.

c. Lack of a clear understanding of the pathophysiology of CMI

An increased understanding of the pathophysiology of CMI is needed if treatments are to be identified that specifically and effectively target the etiologies or drivers of the condition. This gap is one of the greatest barriers in CMI research and ultimately CMI patient treatment. This lack of clarity has led to intervention studies that use analogous, similar-appearing syndromes (i.e., FMS, IBS, ME/CFS) that may overlap, but not fully capture, the pathophysiological mechanisms of CMI. It is also possible that there are clinically relevant subcategories of CMI with different pathophysiological processes involved.

Additional research to clarify the specific etiologic and pathophysiological processes involved in CMI and any relevant CMI subgroups will allow researchers and clinicians to identify, study, and implement treatments that more specifically engage the whole person and more effectively treat CMI. This research should focus on determining whether (and to what extent) CMI, as a discrete condition, overlaps with other symptom-based syndromes (i.e., FMS, IBS, and ME/CFS). Such research must explicitly justify the selection of specific interventions and putative mechanisms of action of the intervention, based on our current understanding of the pathophysiology.

B. Additional Research Gaps

a. Lack of understanding of the predisposing factors and the primary and secondary prevention of CMI

Much of the available research on CMI has focused on civilians and Veterans. Because deployment during military service appears to be a strong risk factor for the development of CMI, the VA and DoD could make substantial contributions to the understanding of the pre-morbid risk factors, precipitating factors, prevention, early detection, and early treatment of CMI. Large, prospective cohort studies and qualitative studies of deployed personnel could help to identify factors that place individuals at increased risk of developing CMI, which in turn could guide efforts aimed at prevention, early recognition, and treatment.

Risk assessment studies should consider environmental and chemical exposures, physiological parameters, and psychological measures. The VA and DoD, and other healthcare organizations, utilize electronic health records (EHRs), which could be leveraged to create large data sets to calculate and validate risk scores. Better tools to define the risk of CMI could play a key role in primary and secondary prevention of CMI, which may substantially alter its course, lifetime morbidity, and associated costs. Studies of military personnel, military Veterans or retirees, and non-military civilians are needed to better define risk factors for deployment-related and non-deployment-related CMI. There have not yet been studies designed to assess preventive strategies for CMI. Studies of pharmacologic interventions and behavioral interventions among populations considered at high risk of developing CMI would be useful to guide future preventive health efforts.

b. Comprehensive, standardized, validated outcome measures

Studies of CMI have overwhelmingly focused on isolated aspects and not the whole-person impact. Many studies have focused on a single outcome or symptom, which limits the understanding of the overall impact of an intervention. Few studies evaluated for the update of this CPG reported on QoL, functional outcomes, or AEs, further limiting the understanding of the overall impact of tested treatments. There has been an overall lack of standardized or validated outcomes measures utilized in studies of CMI and few, if

any, studies have explicitly acknowledged the draft common data elements for GWI (also known as CMI in the cohort of deployed GWV [1990 – 1991]).

More extensive use of standardized, common measures to characterize study samples and outcomes would enhance the consistency of research as well as facilitate comparisons and the cross-study integration of findings. Several projects to establish Common Data Elements (CDE) of relevance to CMI are ongoing, including the National Institute of Neurological Disorders and Stroke (NINDS) CDE's and DoD Congressionally Directed Medical Research Programs (CDMRP) Gulf War Illness Research Program (GWIRP) CDE's.(106, 107) Future study designs should aim to capture a more comprehensive picture of outcomes (QoL, AEs, and functional outcomes).

c. Evidence-based, high quality study designs

The Work Group found that the quality of studies reviewed for the updated CPG was mostly poor. Study designs often had multiple methodological shortcomings and many were small, underpowered, and lacked a control group. In addition, the study participants were often inadequately characterized, skewed by sex, and drawn from a non-military/Veteran population, limiting relevance to Service Members and Veterans. Studies that did include a comparison group often used an inadequate comparison group. In some studies, the treatment was not standardized and lacked a comprehensive description (e.g., number of sessions or other details of behavioral interventions, fidelity assessment). Data analysis techniques were often inappropriate or flawed, limiting the validity of conclusions. Future efforts should aim to improve study design, support the use of RCTs and prospective longitudinal studies that include a relevant sample, reach adequate power, provide adequate and specific descriptions of interventions, and use appropriate data analysis techniques.

For promising interventions, more focused studies on key parameters (e.g., duration of treatment, mode of delivery) that promote feasibility, acceptability, and optimized efficacy are required. Few studies have examined the specific factors that could optimize treatments. This was particularly true for non-pharmacologic treatments, as few were theoretically-based and many did not identify the mechanisms of treatment. This makes it difficult to determine whether small effect sizes were from treatments targeting the wrong mechanisms, or ineffectively targeting correct mechanisms. Grounding treatments in theory and identifying mechanistic targets *a priori* are necessary to improve non-pharmacologic and CIH interventions.

Clinical trials comparing the efficacy of evidence-based treatments are needed to provide guidance when choosing the best treatments for CMI. In addition, there have been few studies on the contextual factors that promote feasibility, acceptability, and optimized efficacy. Specifically, more studies examining the best mode of treatment delivery, duration of treatment, best model of care, moderators of treatment efficacy, and appropriate treatment providers are needed. No studies have examined the incremental impact of combining evidence-based treatments or sequencing treatments (e.g., starting with non-pharmacologic approaches), which are important considerations when determining the best methods to deliver treatments with proven efficacy. Critically, there have been few comparative effectiveness studies.

d. Studies on the implementation of the few evidence-based interventions

Veterans and Service Members with CMI often report poor satisfaction with the care they receive. Providers similarly report dissatisfaction with treating patients with CMI. Research on other conditions has shown that developing evidence-based treatments is not adequate to change the quality of care. There is a need for research aimed at translating evidence-based treatments into care that accelerates uptake and sustains delivery. The Veteran Focus Group and briefing from the RAC GWVI Listening Sessions attest to patient and caregiver impatience regarding progress in this area.

Multiple factors likely influence the uptake of treatment including providers' knowledge and recognition of CMI, providers' perceptions of competence in CMI, facility and system-level support for improving care for patients with CMI, the complexity and lack of clarity on the best evidence-based treatments, the accessibility of evidence-based treatments in the healthcare system, among others. These factors also influence Veterans' and Service Members' relationships with providers and the healthcare system, which is sometimes characterized by distrust and a sense of betrayal. Additional research is needed on the impact of whole/holistic health approaches to care that shift focus from disease-based management to patient-centered care, establishing trusted relationships, and empowering and equipping Veterans to meet their health and well-being goals. In addition, research on new models for identifying and treating patients with CMI, and the efficacy of provider education and training related to CMI, is needed.

C. Recommendation-Specific Research Gaps

- Further research is needed on the benefits and harms of less addictive pharmacologic interventions in patients with chronic pain related to CMI.
- Further research is needed to better understand the benefits and harms of pharmacologic interventions in patients with CMI. Our systematic evidence review did not identify any SRs addressing the benefits and harms of pharmacologic interventions in patients with CMI. The pharmacologic interventions of interest in the review included stimulants, neuropathic medications, monoclonal antibodies, NMDA receptor agonists, analgesics, antibiotics, antidepressants, and other medications (e.g., low-dose naltrexone, oral corticosteroids [e.g., prednisone], intranasal insulin, and intranasal xylitol). The reasons for this dearth of research include the complex nature of CMI as a distinct disease entity, the lack of a clear understanding of the pathophysiology of CMI, and the ongoing debate over the optimal case definition of CMI. Such research will depend upon improving our understanding of the pathophysiology of CMI and refining the current case definitions, which will better serve the clinical care needs of patients with CMI.
- To better understand the efficacy of CBT, more research is needed to determine how and for whom CBT is efficacious and how to best implement CBT for CMI in the VA and DoD healthcare systems.
- Additional research is needed to support offering mindfulness-based therapies, delivered by trained professionals, using different delivery modalities (e.g., digital media) and for patients of all sexes with CMI, including those with symptoms of FMS, IBS, or ME/CFS.

- Further research is needed on the use of biofeedback modalities for CMI given the large research gap in this area. Research should use physical function, QoL, and AEs as patient-centered critical outcomes.
- More research is needed to evaluate the effectiveness of MSK manual therapy in CMI and active duty and Veteran populations. Higher quality studies focusing on military populations that are randomized, large, and report clearly on key outcomes are required.
- The studies reviewed suggest relaxation therapy may help treat the pain and functional impairment associated with FMS and IBS. Whether this is true for patients with CMI or ME/CFS is a potential area for future research. It may also be beneficial to study whether relaxation therapy in combination with other CIH modalities or behavioral health interventions, or as part of a comprehensive whole/holistic health treatment plan, can improve QoL and functional outcomes.
- Further research is needed on the use of guided imagery and hypnosis modalities in CMI given the large research gap in this area. Research should use more male participants and physical function, QoL, and AEs as patient-centered critical outcomes.
- More definitive studies focusing on patients with CMI are warranted since evidence suggests acupuncture is beneficial to patients with FMS. Careful attention should be paid to study design, choice of intervention, use of appropriate comparison groups, choice of outcomes (prioritizing more global, patient-centered measures [e.g., function, QoL]), and the use of rigorous statistical analyses. Studies that elucidate the mechanism of action of acupuncture in patients with CMI would also be beneficial.
- Evidence suggests that most massage therapies improve HRQoL in patients with FMS. However, the overall study quality was low. Therefore, more high-quality studies that limit bias are essential to ensure that providers have the best evidence available to counsel CMI patients on those massage therapies that are most beneficial.
- There is currently a lack of literature examining the effects of exercise on CMI. There is a need for high quality RCTs that evaluate the safety and effectiveness of exercise as a possible treatment for patients with CMI.
- Further research is needed to examine the effectiveness of TCAs, including large RCTs in patients meeting the criteria for CMI.
- More research is needed on the safety and effectiveness of dicyclomine, a widely used and available antispasmodic in the U.S., for the treatment of patients with CMI and symptoms consistent with IBS.
- More research is needed to better understand the effectiveness of rifaximin in patients meeting the criteria for CMI and symptoms consistent with IBS.
- More research is needed to better understand the effectiveness and safety of alosetron in patients meeting the criteria for CMI and symptoms consistent with IBS.
- More research is needed to examine the effectiveness of SSRIs in populations meeting the criteria for CMI and symptoms consistent with IBS.

- There are a limited number of studies that have assessed psychodynamic therapy for the treatment of CMI. Additional studies should include a more diverse patient sample (e.g., sex, race, and age), and standardize treatments across various parameters (e.g., sessions, lengths, follow-up, control/standard care). Researchers should explore additional delivery modalities (e.g., online versus in-person, group versus individual) and standardize outcomes measured (e.g., QoL, symptom reduction, daily functioning).
- There is a general paucity of research on medications that can be used to effectively treat ME/CFS and more specifically CMI. More research is needed on the safety and effectiveness of duloxetine, and more broadly SNRIs, for patients with fatigue related to CMI.
- In general, there is a paucity of rigorous, adequately-powered RCTs on stimulants as treatments for ME/CFS and CMI.

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see Table A-1).

Table A-1. PICOTS (108)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, quality of life, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting

Due to resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion in the systematic evidence review (see Table A-2).

Using the GRADE approach, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see Outcomes); however, only critical outcomes were used to determine the overall quality of evidence (see Grading Recommendations).

a. Population(s)

- Key Questions 1, 5, 7, 9 – 12
    - Including: Active duty Service Members or Veterans ≥18 years old who meet the case definition of CMI

b. Interventions

- Key Question 1 – Pharmacotherapy:
    - Stimulants: Methylphenidate
    - Neuropathic medications: PGB, gabapentin

- Monoclonal antibodies: Rituximab
- Other: Low-dose naltrexone (≤5.0 mg), oral corticosteroids (prednisone, prednisolone, pregnenolone), mifepristone (RU 486), intranasal insulin, xylitol nasal
- Analgesics: Tramadol, acetaminophen, ibuprofen, naproxen, diclofenac, etodolac, indomethacin, ketorolac, meloxicam, nabumetone, piroxicam, celecoxib
- Antibiotics: D-cycloserine, doxycycline
- Antidepressants
  - TCAs: Amitriptyline, desipramine, nortriptyline, imipramine
  - SNRIs: Duloxetine, milnacipran, venlafaxine, desvenlafaxine, levomilnacipran
  - SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine

- Key Question 2 – Pharmacotherapy:
  - Analgesics: Tramadol, acetaminophen, ibuprofen, naproxen, diclofenac, etodolac, indomethacin, ketorolac, meloxicam, nabumetone, piroxicam, celecoxib
  - Neuropathic medications: PGB, gabapentin
  - Skeletal muscle relaxants: Cyclobenzaprine
  - Antidepressants
    - TCAs: Amitriptyline, desipramine, nortriptyline, imipramine
    - SNRIs: Duloxetine, milnacipran, venlafaxine, desvenlafaxine, levomilnacipran
    - SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine
  - Novel therapy: Low-dose naltrexone (≤5.0 mg)
- Key Question 3 – Pharmacotherapy:
  - Antispasmodics: Peppermint oil, trimebutine, dicyclomine, hyoscyamine
  - Anti-diarrheals: Diphenoxylate hydrochloride 2.5 mg with atropine sulfate 0.025 mg, loperamide, eluxadoline, alosetron
  - Bile acid binders: Cholestyramine, colestipol, colesevelam
  - Antidepressants
    - TCAs: Amitriptyline, desipramine, nortriptyline, imipramine
    - SNRIs: Duloxetine, milnacipran, venlafaxine, desvenlafaxine, levomilnacipran
    - SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine
  - Antibiotics: Rifaximin
  - Neuropathic medications: PGB, gabapentin

- Guanylate cyclase-C agonists: Linaclotide
- Osmotic laxatives: Polyethylene glycol (PEG), milk of magnesia
- Bulk-forming laxatives (fiber supplements): Methylcellulose, psyllium
- Constipation: Linaclotide, lubiprostone, plecanatide, tegaserod
- Other: Tenapanor (sodium/hydrogen exchanger 3 inhibitor), clonidine (alpha-2-agonist)

- Key Question 4 – Pharmacotherapy:
  - Anxiolytics/Antidepressants/Atypical antipsychotics
    - TCAs: Amitriptyline, desipramine, nortriptyline, imipramine
    - SNRIs: Duloxetine, milnacipran, venlafaxine, desvenlafaxine, levomilnacipran
    - SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vortioxetine
    - Buspirone
    - Trazodone
    - Benzodiazepines: Alprazolam, chlordiazepoxide, clonazepam, diazepam, lorazepam, oxazepam, temazepam, triazolam
    - Quetiapine
    - Analgesics: Tramadol, acetaminophen, ibuprofen, naproxen, diclofenac, etodolac, indomethacin, ketorolac, meloxicam, nabumetone, piroxicam, celecoxib
    - Neuropathic medications: PGB
    - Stimulants: Modafinil, methylphenidate
    - Other
      - Oral corticosteroids: Prednisone, prednisolone, pregnenolone
      - Immunoglobulin
- Key Questions 5, 6 – CIH interventions: Acupuncture, biofeedback, clinical hypnosis, guided imagery, massage therapy, meditation, tai chi/qi gong, yoga, chiropractic care
- Key Questions 7, 8 – Behavioral health interventions: CBT (minimum of 12 sessions), mind-body bridging, peer support groups, relaxation therapy, mindfulness-based therapy, behavioral medical intervention, psychotherapy
- Key Question 9 – Physical exercise interventions:
  - Physical activity and exercise: Aerobic, resistance training
- Key Question 10: Physical therapy, occupational therapy, osteopathic treatments
- Key Question 11 – Patient education: Educational tools for patients, methods to improve treatment adherence, family education methods and effectiveness

- Key Question 12 – Provider training and education:
    - Education tools for providers (continuing medical education, print, mobile apps, web-based)
    - Education on: Communication, shared decision making, patient-centered care/whole health, core competencies

c. Comparators

- Key Questions 1 – 4: Placebo, another listed medication
- Key Questions 5, 6: Active control/sham treatment, Usual care (which should be an active intervention), Gulf War health education (KQ 5), or education (KQs 5 and 6)
- Key Questions 7, 8: Usual care, waitlist, active comparator, attention/time control
- Key Questions 9, 10: Usual care, active comparator, attention/time control
- Key Question 11: Usual care, another tool
- Key Question 12: Non-CMI related education/training, none/no training

d. Outcomes

- Key Question 1:
    - Critical outcomes: Functional status, pain-related symptoms, bowel-related symptoms, fatigue-related symptoms, adverse events (harms)
    - Important outcomes: Depression symptoms, QoL
- Key Question 2:
    - Critical outcomes: Functional status, adverse events (harms)
    - Important outcomes: Pain-related symptoms, QoL
- Key Question 3:
    - Critical outcomes: Bowel-related outcomes (for IBS-D, IBS-C, IBS-mixed), adverse events (harms)
    - Important outcomes: Functional status, QoL
- Key Question 4:
    - Critical outcomes: Fatigue-related symptoms, functional status, adverse events (harms)
    - Important outcomes: QoL
- Key Questions 5 – 7, 9, 10:
    - Critical outcomes: QoL, functional status, adverse events (harms)
- Key Question 8:
    - Critical outcomes: QoL, functional status
- Key Question 11

- Critical outcomes: Improve function, improved QoL
- Important outcomes: Reduction in intensity/frequency/duration and interference of symptoms (e.g., pain, fatigue), healthcare utilization, adherence

- Key Question 12
  - Critical outcomes: Improved function, reduction in intensity/frequency/duration and interference of symptoms (e.g., pain, fatigue), improved QoL
  - Important outcomes: Healthcare utilization, adherence

e. Timing

- Key Questions 1 – 12: Minimum follow-up four weeks

f. Settings

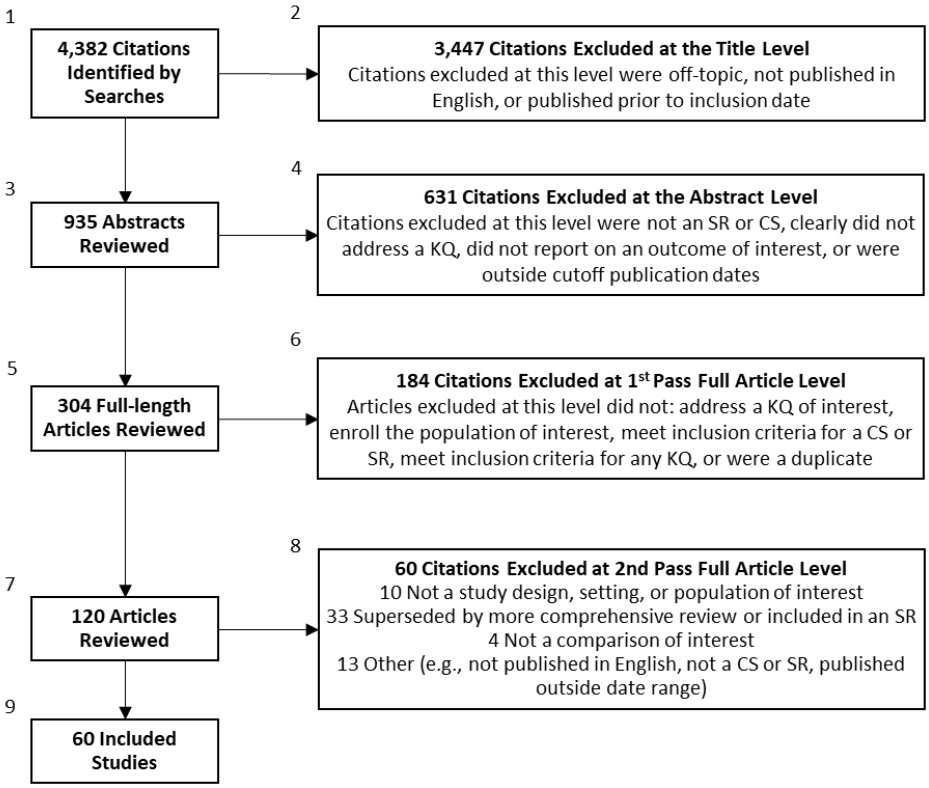
- Key Questions 1 – 10: Outpatient
- Key Questions 11, 12: Any

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

Figure A-1 below outlines the systematic evidence review's screening process (see also the General Criteria for Inclusion in Systematic Review and Key Question Specific Criteria). In addition, Table A-2 indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 4,382 citations identified by searches
    a. Right to Box 2: 3,447 citations excluded at the title level
        i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
    b. Down to Box 3
2. Box 3: 935 abstracts reviewed
    a. Right to Box 4: 631 citations excluded at the abstract level
        i. Citations excluded at this level were not an SR or clinical study, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
    b. Down to Box 5

3. Box 5: 304 full-length articles reviewed
    a. Right to Box 6: 184 citations excluded at 1st pass full article level
        i. Articles excluded at this level did not: address a KQ of interest, enroll the population of interest, meet inclusion criteria for a clinical study or SR, meet inclusion criteria for any KQ, or were a duplicate
    b. Down to Box 7
4. Box 7: 120 articles reviewed
    a. Right to Box 8: 60 citations excluded at 2nd pass full article level
        i. 10 not a study design, setting, or population of interest
        ii. 33 superseded by more comprehensive review or included in an SR
        iii. 4 not a comparison of interest
        iv. 13 other (for example, not published in English, not a clinical study or SR, published outside date range)
    b. Down to Box 9
5. Box 9: 60 included studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For adults with CMI, what are the benefits and harms of pharmacologic interventions?	1 RCT
2	For adults with fibromyalgia, what are the benefits and harms of pharmacologic interventions for pain-related symptoms, function and quality of life?	5 SRs
3	For adults with IBS, what are the benefits and harms of pharmacologic interventions for gastrointestinal symptoms, function and quality of life?	7 SRs, 2 RCTs
4	For adults with CFS, what are the benefits and harms of pharmacologic interventions for fatigue symptoms, function and quality of life?	2 RCTs
5	For adults with CMI, what are the benefits and harms of complementary and integrative health interventions for CMI-related outcomes, function and quality of life?	1 RCT
6	For adults with fibromyalgia, IBS, or CFS, what are the benefits of complementary and integrative health interventions for function and quality of life?	11 SRs, 15 RCTs
7	For adults with CMI, what are the benefits and harms of behavioral health interventions for CMI-related outcomes, function and quality of life?	1 RCT
8	For adults with fibromyalgia, IBS, or CFS what are the benefits of behavioral health interventions for function and quality of life?	5 SRs, 9 RCTs
9	For adults with CMI, what are the benefits and harms of physical exercise interventions for CMI-related outcomes, function and quality of life?	1 RCT
10	For adults with CMI, what are the benefits of osteopathic therapy, physical therapy, and occupational therapy interventions for function and quality of life?	No evidence
11	Does patient education improve physical function and quality of life outcomes for adults with CMI?	No evidence
12	For adults with CMI, does provider training and education improve outcomes?	No evidence
	Total Evidence Base	**60 studies**

Abbreviations: CMI: chronic multisymptom illness; FDA: U.S. Food and Drug Administration; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- RCTs or SRs published on or after October 1, 2013, to April 7, 2020. If multiple SRs address a KQ, we selected the most recent and/or comprehensive review. SRs were supplemented with RCTs published after the SR.
- Studies must be published in English.
- Publication must be a full clinical study or SR; abstracts alone were not included. Similarly, letters, editorials, and other publications that are not full-length clinical studies were not accepted as evidence.
- SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence grading used by the Evidence-based Practice Centers of the AHRQ). If an existing review did not assess the overall quality of the evidence, evidence from the SR must be reported in a manner that allows us to judge the overall risk of bias, consistency, directness, and precision of evidence. We did not use an existing review as evidence if we were not able to assess the overall quality of the evidence in the review.
- Intervention studies must be a prospective RCT with an independent control group. Crossover trials were not included unless they reported data for the first phase of the study separately.
- Study must have enrolled >20 patients (10 per study group); small sample size is associated with increased risk of bias and we downgrade small sample-sized studies in the GRADE domain of precision: One downgrade for imprecision of a single study with <200 patients/arm and two downgrades for imprecision for <50 total patients. Note: Cochrane SRs will downgrade two levels for <50 patients/arm; where this downgrade has been incorporated into their assessment of risk of bias, we did not perform an additional downgrade for imprecision.
- Study must have enrolled at least 85% of patients who meet the study population criteria: adults aged 18 years or older with CMI. For studies examining indirect patient populations, studies must have enrolled at least 85% of patients with the relevant condition.
- Study must have reported on at least one outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- KQs specific to CMI included individual studies. RCTs were the first line of evidence. For KQs 11 and 12, non-RCTs were considered.
- KQs specific to indirect populations (FMS, IBS, and ME/CFS) included SRs. Following a best-evidence approach, RCTs were considered if there was no available SR for a treatment or outcome of interest.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in Table A-3. See Appendix F for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
MEDLINE and EMBASE	October 1, 2013, to April 7, 2020	EMBASE.com
In Process Medline and PubMed-unique content	October 1, 2013, to April 7, 2020	PubMed.gov
PsycINFO	October 1, 2013, to April 7, 2020	PsycINFO
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	October 1, 2013, to April 7, 2020	Cumulative Index to Nursing and Allied Health Literature (CINAHL)

C. Developing Evidence-based Recommendations

In consultation with the VA Evidence Based Practice, Office of Quality and Patient Safety and the Office of Evidence Based Practice, Defense Health Agency, the Lewin Team convened a four-day virtual recommendation development meeting on July 14 – 17, 2020, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the first day of the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. Where appropriate, the Work Group carried forward and modified recommendations from the 2014 CMI CPG as necessary (see Categorization of 2014 Clinical Practice Guideline Recommendations). The Work Group also developed new recommendations not included in the 2014 CMI CPG based on the 2020 evidence review.

As the Work Group drafted recommendations, they also rated each recommendation based on a modified GRADE and USPSTF methodology. Recommendations were rated by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Grading Recommendations

Per GRADE, each recommendation's strength and direction is determined by the following four domains:(18)

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base supporting a recommendation. The options for this domain include: *High*, *Moderate*, *Low*, or *Very low*. This is a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see Outcomes). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.(20, 21)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).(18)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved quality of life, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired quality of life). The options for this domain include: *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they may apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include: *similar values*, *some variation*, or *large variation*. For instance, there may be *some variation* in patient values and preferences for a recommendation on the use of acupuncture, as some patients may dislike needles. When patient values seem homogeneous, this domain may increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain may decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see Appendix B).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain include, e.g.: resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population may be geographically remote from an intervention (e.g., complex radiological equipment); a drug may be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	Among the designated critical outcomes, what is the lowest quality of relevant evidence? How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	What is the magnitude of the anticipated desirable outcomes? What is the magnitude of the anticipated undesirable outcomes? Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	Benefits outweigh harms/burdens Benefits slightly outweigh harm/burden Benefits and harms/burdens are balanced Harms/burdens slightly outweigh benefits Harms/burdens outweigh benefits

Decision Domain	Questions to Consider	Judgment
Patient values and preferences	What are the patients' values and preferences? Are values and preferences similar across the target population? Are you confident about typical values and preferences?	Similar values Some variation Large variation
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	What are the costs per resource unit? Is this intervention generally available? What is the variability in resource requirements across the target population and settings? Are the resources worth the expected net benefit from the recommendation? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in Table 3.

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review. *Reviewed*, *New-added* recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, *New-replaced* recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed*, *Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, *Deleted* refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on CMI; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus

also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed*, *Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed*, *Amended* recommendations were modified from the previous CPG with a nominal change. *Not reviewed*, *Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the Recommendations. The recommendation categories from the 2014 CMI CPG are noted in Appendix D.

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see External Peer Review). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the EBPWG for approval. The Work Group considered the EBPWG's feedback and revised the CPG as appropriate to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The final 2021 CPG and toolkit products were submitted to the EBPWG in May 2021.

Appendix B: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited participants for the focus group, with support from the Champions, other Work Group members, and individuals at the patient focus group location as needed. While participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed and the Work Group approved a patient focus group guide covering these topics.

Due to the start of the COVID-19 pandemic, participants did not feel comfortable traveling to the focus group location. As a result, the meeting was held via conference call and only one participant was able to join the call. The focus group facilitator led the discussion and used the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

In addition, the Work Group was briefed on three Veteran listening sessions held by the RAC GWVI. The workgroup included a number of clinicians who have regularly and for decades provided care for Gulf War veterans and other Service Members and veterans with CMI, as well as being involved in numerous research and quality improvement projects focusing on individuals with CMI.

B. Patient Focus Group Findings

a. Some Veterans consider that they have been improperly diagnosed and are unaware of Gulf War Syndrome and/or CMI. After being properly diagnosed, patient education on CMI can be highly valuable.

- It can take years for patients to receive an accurate diagnosis of Gulf War Syndrome and/or CMI.
- Patients often receive other diagnoses (e.g., FMS, IBS) before being diagnosed with CMI.
- A major barrier to diagnosis is the difficulty in communicating symptoms.
- Education and understanding of their illness is particularly important to patients because it helps with coping and symptom management.

b. Patients with CMI experience a constellation of symptoms that can affect many aspects of life, including work and interpersonal relationships.

- The complex and diverse nature of CMI means that patients can experience a wide range of symptoms.
- Symptoms can have a significant impact on a patient's daily activities, including job performance, as well as interpersonal relationships with friends, family, and caregivers.

c. Patient-centered care and shared decision making are highly important in finding an optimal set of treatments, especially since medications and other therapies can have significant side effects.

- Patient-centered care and shared decision making have been instrumental in improving the participant's care.
- Medications used to treat many of the common CMI symptoms are associated with significant side effects.
- Alternative treatments outside of standard medications may benefit some patients who are struggling to manage their CMI symptoms.

d. Support groups can be very helpful because many patients with CMI are frustrated, lonely, and disengaged, and therefore in need of companionship, understanding, and support.

- Support groups can be beneficial for those diagnosed with CMI or who have undiagnosed conditions.
- Sharing experiences around common symptoms is particularly helpful.

e. It can be difficult for patients to establish eligibility for healthcare services through the VA, resulting in frustration with VA providers. Patients may need help getting the benefits for which they are qualified.

- The participant noted multiple issues with VA providers that can negatively affect illness and treatment.
- Many Veterans have difficulties receiving VA benefits and, therefore, treatments.

Appendix C: Evidence Table

Table C-1. Evidence Table[a,b,c,d]

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
1. We recommend against the long-term use of opioid medications for the management of chronic pain in patients with CMI.	Strong against	**Additional references**: (31)	Strong against	Reviewed, Amended
2. We recommend against offering mifepristone for patients with CMI.	Not applicable	(32)	Strong against	Reviewed, New-added
3. We suggest offering cognitive behavioral therapy for CMI and symptoms consistent with fibromyalgia, irritable bowel syndrome, or myalgic encephalomyelitis/chronic fatigue syndrome.	Strong for	(33-39)	Weak for	Reviewed, New-replaced
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.	Weak for	(40-42) **Additional references**: (43)	Weak for	Reviewed, New-replaced
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.	Not applicable	(44-46)	Neither for nor against	Reviewed, New-added

[a] 2014 Strength of Recommendation column: The 2014 VA/DoD CMI CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2014 strength of recommendation indicates that more than one 2014 VA/DoD CMI CPG recommendation is covered by the 2021 recommendation. "Not applicable" indicates that the 2021 VA/DoD CMI CPG recommendation was a new recommendation, and therefore does not have an associated 2014 strength of recommendation.

[b] Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called "Additional References") includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

[c] 2021 Strength of Recommendation column: The 2021 VA/DoD CMI CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

[d] Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
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.	Not applicable	(47)	Neither for nor against	Reviewed, New-added
7. We suggest considering an emotion-focused therapy for patients with CMI and symptoms consistent with fibromyalgia or irritable bowel syndrome.	Weak for	(48-50)	Weak for	Reviewed, New-replaced
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.	Weak for	(51, 52) **Additional references**: (53, 54)	Neither for nor against	Reviewed, New-replaced
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.	Not applicable	(55-60)	Neither for nor against	Reviewed, New-added
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.	Weak for	(61, 62, 64, 65) **Additional references:** (63)	Neither for nor against	Reviewed, New-replaced
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.	Weak for	(64, 65)	Weak for	Reviewed, New-replaced
12. We suggest offering pregabalin for the treatment of pain in patients with CMI and symptoms consistent with fibromyalgia.	Weak for	(66, 67)	Weak for	Reviewed, Amended
13. We suggest against offering nonsteroidal anti-inflammatory drugs for the treatment of chronic pain related to CMI and symptoms consistent with fibromyalgia.	Weak for	(68) **Additional references**: (69)	Weak against	Reviewed, New-replaced
14. We suggest offering yoga or tai chi for patients with CMI and symptoms consistent with fibromyalgia.	Weak for	(70-75)	Weak for	Reviewed, New-replaced
15. We suggest offering manual acupuncture as part of the management of patients with CMI and symptoms consistent with fibromyalgia.	Weak for	(76-79)	Weak for	Reviewed, New-replaced

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
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.	Not applicable	(80) **Additional references**: (81-85)	Neither for nor against	Reviewed, New-added
17. We suggest offering physical exercise for patients with CMI and symptoms consistent with fibromyalgia.	Strong for	(33, 64, 86-88)	Weak for	Reviewed, New-replaced
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.	Not applicable	(89, 90)	Neither for nor against	Reviewed, New-added
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.	Weak for	(89)	Neither for nor against	Reviewed, New-replaced
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.	Weak for	(91, 92)	Weak for	Reviewed, New-replaced
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.	Weak for	(93)	Neither for nor against	Reviewed, New-replaced
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.	Weak for	(94)	Neither for nor against	Reviewed, New-replaced
23. We suggest suggest offering a 14-day course of rifaximin for gastrointestinal symptoms for patients with CMI and symptoms consistent with irritable bowel syndrome without constipation.	Not applicable	(94)	Weak for	Reviewed, New-added
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.	Weak for	(89, 95)	Neither for nor against	Reviewed, New-replaced
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.	Not applicable	(94)	Neither for nor against	Reviewed, New-added

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
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.	Not applicable	(89, 90)	Neither for nor against	Reviewed, New-added
27. There is insufficient evidence to recommend for or against offering psychodynamic therapies for patients with CMI and symptoms consistent with irritable bowel syndrome.	Weak for	(35, 98) **Additional references**: (96, 97, 99, 100)	Neither for nor against	Reviewed, New-replaced
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.	Weak for	(101)	Neither for nor against	Reviewed, New-replaced
29. We recommend against offering stimulants for treatment of fatigue in patients with CMI and symptoms consistent with myalgic encephalomyelitis/chronic fatigue syndrome.	Weak against	(102) **Additional references**: (103, 104)	Strong against	Reviewed, New-replaced

Appendix D: 2014 Recommendation Categorization Table

Table D-1. 2014 CMI CPG Recommendation Categorization Table[a,b,c,d,e,f]

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2014 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
1	The guideline panel recommends that all patients receive a thorough evaluation of symptoms based on clinical judgment.	Strong for	Not reviewed, Deleted	–	–
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	Not reviewed, Deleted	–	–
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	Reviewed, Deleted	–	–
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	Not reviewed, Deleted	–	–

[a] 2014 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2014 VA/DoD CMI CPG.
[b] 2014 CPG Recommendation Text column: This contains the wording of each recommendation from the 2014 VA/DoD CMI CPG.
[c] 2014 CPG Strength of Recommendation column: The 2014 VA/DoD CMI CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2014 VA/DoD CMI CPG were: Strong for, Weak for, N/A, Weak against, or Strong against.
[d] 2014 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2014 VA/DoD CMI CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[e] 2021 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2021 VA/DoD CMI CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.
[f] 2021 CPG Recommendation # column: For recommendations that were carried forward to the 2021 VA/DoD CMI CPG, this column indicates the new recommendation(s) to which they correspond.

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2014 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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	Not reviewed, Deleted	–	–
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	Reviewed, Deleted	–	–
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	Reviewed, New-replaced	Reviewed, New-replaced	17
8	The guideline panel recommends offering cognitive behavioral therapy, delivered by trained professionals, for patients with CMI.	Strong for	Reviewed, New-replaced	Reviewed, New-replaced	3
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	Reviewed, New-replaced	Reviewed, New-replaced	4
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	Reviewed, New-replaced	Reviewed, New-replaced	8, 14, 15

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2014 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG 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	Reviewed, Amended	Reviewed, New-replaced	10, 11
12	The guideline panel suggests against the use of doxycycline for the treatment of patients with clinical symptoms of CMI.	Weak against	Reviewed, Deleted	–	–
13	The guideline panel recommends against the long-term use of opioid medications for the management of patients with CMI.	Strong against	Reviewed, Not changed	Reviewed, Amended	1
14	The guideline panel suggests considering acupuncture as part of the management of patients with pain-predominant symptoms of CMI.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	15
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	Reviewed, New-replaced	Reviewed, New-replaced	13
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	Reviewed, Deleted	–	–
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	Reviewed, Amended	Reviewed, Amended	11
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	Reviewed, Amended	Reviewed, New-replaced; Reviewed, Amended	10, 12
19	The guideline panel recommends considering acupuncture as part of the management of patients with fatigue-predominant symptoms of CMI.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	15

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2014 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
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	Reviewed, New-replaced	Reviewed, New-replaced	28
21	The guideline panel suggests against the use of pharmacologic agents for sleep disturbances in CMI.	Weak against	Reviewed, New-replaced	–	–
22	The guideline panel suggests against the use of stimulants for the treatment of fatigue-predominant CMI.	Weak against	Reviewed, Amended	Reviewed, New-replaced	29
23	The guideline panel recommends against the empiric use of antivirals or antibiotics for the treatment of fatigue-predominant CMI.	Strong against	Reviewed, Deleted	–	–
24	The guideline panel recommends against the use of corticosteroids for the treatment of fatigue-predominant CMI.	Strong against	Reviewed, Deleted	–	–
25	The guideline panel recommends against the use of immunotherapy for the treatment of the symptoms of fatigue predominant CMI.	Strong against	Reviewed, New-replaced	–	–
26	The guideline panel suggests treating patients with CMI and predominantly gastrointestinal symptoms, in accordance with recognized evidence-based care for IBS.	Weak for	Not reviewed, Deleted	Reviewed, New-replaced	20 – 22, 24
27	The guideline panel recommends considering minimal contact psychological therapies for treatment of gastrointestinal-predominant CMI.	Weak for	Reviewed, New-replaced	Reviewed, New-replaced	7, 8, 27
28	The guideline panel suggests against the use of acupuncture for treatment of patients with gastrointestinal-predominant symptoms of CMI.	Weak against	Reviewed, New-replaced	Reviewed, New-replaced	15

Appendix E: Participant List

Jennifer Ballard-Hernandez, DNP, RN, FNP-BC
Cardiovascular Clinical Nurse Advisor
Office of Nursing Services/VACO
Cardiology Nurse Practitioner
Tibor Rubin VA Medical Center
Long Beach, CA

Lt Col Pamela Blueford, LCSW
Chief, Mental Health Branch
Air Force District of Washington
Joint Base Andrews, MD

MAJ Nicole H. Brown, PT, DPT, OCS, SCS, TPS
Chief, Outpatient Physical Therapy
Brooke Army Medical Center
Fort Sam Houston, TX

COL William Brown, PhD, FNP-BC, FAANP
Chief, Center for Nursing Science & Clinical Inquiry
Landstuhl Regional Medical Center, Germany

Lt Col Wendy Chao, DO
Chief, Neurology Services
Department of Medicine
San Antonio Military Medical Center
Fort Sam Houston, TX

Molly Cloherty, LDN
Dietitian and Nutritionist
Veterans Health Administration
Pittsburgh, PA

Jennifer Felsing, MSN
Virtual Health Director and Clinical Nurse Officer in Charge
Brooke Army Medical Center
Fort Sam Houston, TX

Drew A. Helmer, MD, MS
Deputy Director, Center for Innovations in Quality, Effectiveness and Safety
Michael E. DeBakey VA Medical Center
Houston, TX

Stephen C. Hunt, MD, MPH
VA National Director, Post-Deployment Integrated Care Initiative
VA Puget Sound Health Care System
Seattle, WA

David Kearney, MD
Staff Physician, Gastroenterology Section
VA Puget Sound Health Care System
Seattle, WA

Maj Sarah Kelly, PharmD
Chief, Pharmacy Operations
Keesler Air Force Base
Biloxi, MS

LTC Joetta Khan, PhD, MPH, RD, LD
Director, Education and Research
Nutrition Care Department
Walter Reed National Military Medical Center
Bethesda, MD

Lisa McAndrew, PhD
Acting Director of Research
War Related Illness and Injury Study Center
VA New Jersey Health Care System
East Orange, NJ

Col Patrick Monahan, MD, MPH
Director, Integrated Clinical Skills
Uniformed Services University of the Health Sciences
Bethesda, MD

COL Aniceto Navarro, MD, FAPA
Consultation Liaison Psychiatry/Geriatric Psychiatry
Fort Belvoir Community Hospital
Fort Belvoir, VA

Mitchell Nazario, PharmD
National PBM Clinical Program Manager for Pain and Substance Abuse
Veterans Health Administration
Hines, IL

MAJ Rachel Robbins, MD, FACP
Associate Program Director, Rheumatology Fellowship
Walter Reed National Military Medical Center
Bethesda, MD

Tiffany Smoot, MSN, RN
Nurse Navigator – Community Care
VA Eastern Kansas Health Care System
Topeka, KS

Rachel Zhang, LCSW
Case Manager
Special Infectious Disease Clinic (HIV Clinic)
VA San Diego Healthcare System
San Diego, CA

Appendix F: Literature Review Search Terms and Strategy

A. EMBASE and Medline in EMBASE.com syntax (all questions)

Set #	Concept	Strategy
#1	Condition: Persian Gulf/Gulf War Syndrome	'persian gulf syndrome'/de OR 'persian gulf syndrome' OR (('persian gulf' OR Persian) NEXT/2 (syndrome OR illness*))
#2		'gulf war illness'/de OR 'gulf war illness' OR (('gulf war' OR gulf) NEXT/2 (syndrome OR illness*))
#3	Condition: Chronic Multisymptom Illness	'chronic multisymptom':ti OR 'chronic multi-symptom':ti OR 'chronic multisymptom illness'/de
#4		(Chronic* OR deployment* OR postdeployment* OR 'post deployment*) 'NEXT/2 (multisymptom* OR multi-symptom*)
#5		('cmi' OR 'gwi' OR 'medically unexplained' OR 'unexplained illness*' OR 'unexplained symptom*' OR 'medically unexplained symptom'/de) AND (veteran* OR deploy* OR postdeployment* OR 'post deployment*' OR soldier* OR military OR 'air force' OR 'armed forces' OR army OR marine* OR navy OR 'service member*' OR servicemen OR servicewomen OR 'active duty' OR persia* OR gulf*)
#6	Combine Condition	#1 OR #2 OR #3 OR #4 OR #5
#7	Condition: Fibromyalgia	'fibromyalgia'/de OR 'fibromyalgia syndrome'/de OR fibromyalg*:ti,ab OR 'myofascial pain'/de 'myofascial pain syndrome'/de OR 'muscular rheumatism'
#8	Condition: Irritable Bowel Syndrome	'irritable colon'/exp/dm_dm,dm_th,dm_dt OR 'irritable bowel OR (Irritable NEXT/2 (bowel OR colon OR intestin*)):ti,ab OR ((mucus OR mucous) NEXT/2 colitis):ti,ab OR (IBS AND bowel*)
#9	Condition: Chronic Fatigue Syndrome	'chronic fatigue syndrome'/exp/dm_co,dm_dm, dm_rh,dm_th
#10		'chronic fatigue'/mj OR 'chronic fatigue syndrome'/exp/mj
#11		(chronic OR fatigue) NEXT/2 (fatigue OR syndrome OR disorder)
#12		"myalgic encephalomyelitis" OR "Royal Free Disease" OR "Systemic Exertion Intolerance Disease"
#13	Combine Chronic Fatigue Syndrome	#9 OR #10 OR #11 OR #12
#14	Pharmacotherapy	dt.fs OR ('drug therapy' OR 'drug therapies' OR 'combination drug therap*' OR pharma*):ti OR 'drug therapy'/de OR 'combination drug therapy'/mj
#15	Analgesics	'anti-inflammatory'/exp OR 'antiinflammatory agent'/exp OR 'nonsteroid antiinflammatory agent'/exp OR 'naproxen'/mj OR 'ibuprofen'/mj OR 'paracetamol'/mj OR 'analgesic agent'/mj OR 'lidocaine'/mj OR 'mexiletine'/de OR 'tramadol'/de OR 'celecoxib'/de
#16		('pain reliever*' OR anti-inflam* OR antiinflam* OR non-steroid* OR nonsteroid* OR NSAID*):ti OR (naproxen OR ibuprofen OR advil OR medipren OR motrin OR nuprin OR rufen OR paracetamol OR acetaminophen OR Tylenol OR mexiletine OR ryzolt OR rybix OR lidocaine OR tramadol OR ultram OR etodolac OR indomethacin OR ketorolac OR meloxicam OR nabumetone OR piroxicam OR celecoxib):ti,ab,tn
#17	Combine Analgesics	#15 OR #16

Set #	Concept	Strategy
#18	Antianxiety Agents	'anxiolytic agent'/exp OR 'benzodiazepine derivative'/exp/mj OR 'alprazolam'/de OR 'clonazepam'/de OR 'zolpidem'/de OR 'trazodone'/de OR 'buspirone'/de OR 'temazepam'/de OR 'sodium oxybate'/de OR (alprazolam OR chlordiazepoxide OR clonazepam OR diazepam OR lorazepam OR oxazepam OR temazepam OR triazolam OR trazodone OR 'quetiapine buspirone' OR Xanax OR niravam OR klonopin OR ambien OR sonata OR oleptro OR restoril OR xyrem):ti,ab,tn
#19	Antibiotics	'doxycycline'/de OR 'rifaximin'/de OR 'cycloserine'/de OR (doxycycline OR rifaximin OR d-cycloserine):ti,ab
#20	Antidepressants (e.g., SSRI, SNRI, mirtazapine, tricyclics)	'antidepressant agent'/exp OR 'tetracyclic antidepressant agent'/exp OR 'tricyclic antidepressant agent'/exp OR 'mirtazapine'/exp OR mirtazapine OR tricyclic* OR tetracyclic* OR SSRI* OR SNRI* OR 'serotonin update inhibitor'/mj OR 'serotonin noradrenalin reuptake inhibitor'/mj OR antidepress*:ti OR 'fluoxetine'/mj OR (fluoxetine OR serotonin OR amitriptyline OR desipramine OR nortriptyline OR imipramine OR duloxetine OR Cymbalta OR milnacipran OR savella OR venlafaxine OR Effexor OR 'Effexor XR' OR desvenlafaxine OR Pristiq OR Levomilnacipran OR Fetzima OR citalopram OR escitalopram OR fluvoxamine OR paroxetine OR sertraline OR vortioxetine):ti,ab,tn
#21	Anti-diarrheals	'antidiarrheal agent'/mj OR 'anti-diarrhea*':ti OR 'anti diarrhea*':ti OR 'loperamide'/de OR (alosetron OR loperamide OR 'diphenoxylate hydrochloride' OR lomotil OR Imodium OR eluxadoline OR cholestyramine OR colestipol OR colesevelam):ti,ab,tn
#22	Antispasmodics	'cholinergic receptor blocking agent'/mj OR 'spasmolytic agent'/exp OR 'trimebutin'/de OR 'dicycloverine'/mj OR anticholinergic*:ti OR dicyclomine:ti OR antispasmodic*:ti OR anti-spasmodic*:ti OR 'peppermint oil*':ti,ab OR trimebutine:ti,ab OR 'hyoscyamine'/de OR hyoscyamine:ti,ab
#23	Bulk-forming Laxatives (fiber supplements)	'fiber'/exp/mj OR (fiber OR methylcellulose OR psyllium OR reguloid OR konsyl):ti,ab OR (Citrucel OR Metamucil OR fiberall):ti,ab,tn
#24	Constipation	'guanylate cyclase-C agonists'/de OR 'linaclotide'/de OR 'chloride channel activator'/de OR 'serotonin 5-HT4 receptor antagonist' OR (linzess OR linaclotide OR plecanatide OR lubiprostone OR tegaserod):ti,ab,tn
#25	Corticosteroids	'corticosteroid'/exp/mj OR (betamethasone OR corticoid* OR cortisone OR corticosteroid* OR dexamethasone OR glucocorticoid* OR hydrocortisone OR methylprednisolone OR prednisolone OR predisone OR pregnenolone OR steroid* OR triamcinolone):ti,ab
#26	Monoclonal Antibodies (immunotherapy)	Immunotherap*:ti OR 'immunotherapy'/exp/mj OR (monoclonal OR rituximab OR immunoglobulin)
#27	Muscle Relaxers	Cyclobenzaprine:ti,ab OR flexeril:ti,ab,tn OR flexmid:ti,ab,tn
#28	Neuropathic Medications	Pregabalin/de OR pregabalin*:ti,ab OR gabapentin/de OR gabapentin*:ti,ab OR lyrica:ti,ab,tn OR neurotonin:ti,ab
#29	Novel (or other) Therapies	'tenapanor'/de OR 'clonidine'/de OR 'naltrexone'/de OR (naltrexone OR 'intranasal insulin' OR 'xylitol nasal'):ti,ab
#30	Osmotic Laxatives	'macrogol'/exp/mj OR (macrogol OR 'polyethylene glycol' OR laxative OR linaclotide OR 'milk of magnesia'):ti,ab
#31	Stimulants	'methylphenidate'/de OR 'modafinil'/de OR (methylphenidate OR modafinil OR provigil):ti,ab,tn
#32	Complementary Integrative Medicine	'alternative medicine'/exp OR "CIM" OR "CAM" OR "integrative medicine" OR "integrative therap*" OR "complementary therap*" OR "complementary medicine" OR "alternative therap*" OR "alternative medicine" OR ((complementary OR alternative) NEXT/2 (therap* OR medicine))

Set #	Concept	Strategy
#33	CMI Interventions	'acupuncture'/exp OR acupuncture OR 'biofeedback'/exp OR (biofeedback OR bio-feedback):ti,ab OR 'chiropractic manipulation'/exp OR 'chiropractic'/exp OR chiropract*:ti,ab OR 'hypnosis'/exp/mj OR (hypnosis OR hypnotic):ti,ab OR 'guided imagery'/de OR (guide* NEXT/2 imagery) OR 'massage'/exp/mj OR massage*:ti,ab OR 'meditation'/exp OR meditate OR meditation OR 'tai chi'/de OR "tai chi" OR taichi OR 'qigong'/de OR qigong OR 'qi gong' OR 'yoga'/exp OR yoga
#34	Combine Complementary Integrative Medicine	#32 OR #33
#35	Behavioral Health Interventions	'behavioral health'/de OR 'behavioral health care'/de OR 'behavior therapy'/exp OR (('behavi* NEXT/3 health*'):ti) OR (((behavior* OR behaviour* OR cognitive OR emotion* OR 'mental health' OR mindful* OR psych*) NEAR/2 (coach* OR counsel* OR intervention* OR manag* OR support* OR therap* OR treat* OR train*)):ti,ab)
#36		'behavioral medicine'/de OR ('behavioral medicine' OR 'behavioral medical intervention' OR 'behavioral intervention'):ti,ab OR 'behavior change'/de
#37	Cognitive Behavior Therapy	'cognitive behavioral therapy'/exp/mj OR 'cognitive therapy'/exp OR 'cognitive behavior* therap*' OR 'cbt' OR 'cognitive behavior*' OR 'rational emotive behavior therapy' OR 'motivational enhancement therapy'/de OR 'motivational enhanc*':ti,ab
#38	Mind Body Bridging	'mind body medicine'/de OR 'mind body bridging' OR 'mind body' OR (mind NEXT/2 body)
#39	Mindfulness	'mindfulness based stress reduction'/de OR 'mindfulness based cognitive therapy'/de OR 'mindfulness meditation'/de OR 'mindfulness training'/de OR 'mindfulness based intervention'/de OR 'mindfulness based therapy'/de OR 'mindfulness'/exp OR (mindfulness OR 'mindfulness based'):ti,ab
#40	Peer Support	'peer group'/exp OR "peer group" OR (peer* NEXT/2 (support* OR therap* OR counsel* OR consult* OR advise* OR instruct* OR facilitat* OR group* OR rehab*)) OR ((social OR support) NEAR/2 (group* OR peer*)) OR 'self help'/de OR 'self help':ti,ab
#41	Psychotherapy	'psychotherapy'/exp/mj OR 'psychosocial care'/de OR 'counseling'/exp OR 'patient counseling'/exp/mj OR (psychosocial OR psychotherap*):ti,ab
#42	Relaxation Therapy	'relaxation training'/de OR "relaxation therapy":ti OR (relax* NEXT/2 (therap* OR rehab* OR technique* OR train*)):ti,ab
#43	Combine Behavior Health Interventions	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
#44	Physical Activity Interventions	'exercise'/exp OR 'muscle exercise'/exp OR 'physical activity'/exp OR 'aerobic exercise'/exp OR 'physical activity, capacity and performance'/exp OR 'exercise intensity'/de OR 'fitness'/de OR 'resistance training'/de OR 'cardiorespiratory fitness'/de OR 'moderate intensity exercise'/de OR 'pilates'/de OR 'treadmill'/de OR 'walking'/exp OR 'weight training'/de
#45		Exercise* OR fitness OR workout OR 'work out' OR 'physical activity' OR isometric* OR 'weight training' OR (train* NEAR/3 (weight* OR resistance)) 'weight lift*' OR 'weight bearing' OR walk* OR run OR running OR jog OR jogging OR swim* OR 'cross train*' OR pilates OR 'dynamic exercise*' OR aerobics OR ((aerobic OR circuit* OR interval* OR aquatic* OR muscle* OR class OR classes OR cardio) NEAR/3 (exercis* OR fitness OR training)) OR 'high intensity interval*' OR hiit OR ((exercise OR (physical NEAR/2 activity)) AND (change* OR improve* OR modif* OR increase*)) OR sedentary:ti,ab OR 'sedentary lifestyle'/exp OR 'physical inactivity'/exp OR 'laziness'/exp
#46		Cycle OR cycling OR sport OR biking OR bike OR stretch OR stretching OR hike OR hiking OR 'body movement' OR mobility OR 'daily life activit*' OR active OR activity OR activities

Set #	Concept	Strategy
#47	Combine Physical Activity	#44 OR #45 OR #46
#48	Physical/ Occupational Therapy, Osteopathic Treatments	'physiotherapy'/exp OR 'occupational therapy'/de OR 'physical medicine'/exp OR 'manipulative medicine'/exp OR 'cryotherapy'/exp OR 'kinesiotherapy'/exp OR 'magnetotherapy'/de OR 'radiofrequency therapy'/exp OR 'thermotherapy'/exp OR 'ultrasound therapy'/exp OR 'osteopathic medicine'/exp OR 'osteopathic manipulation'/de OR 'acupressure'/exp OR 'bodywork'/exp OR 'vibration therapy'/exp
#49		((therapy OR therapist OR medicine OR treatment) NEAR/3 (occupation* OR physical OR manipulat* OR cryo* OR kinesio* OR osteo*)) OR physiotherapy OR physiotherapist OR kinesiotherapy OR kinesiotherapist OR ((physical OR muscular OR muscle* OR joint* OR skeletal OR musculoskeletal) NEAR/3 (manipulation OR stretch OR stretching OR pressure OR resistance)) OR acupressure OR reflexology OR 'trigger point therapy' OR cryotherapy OR 'osteopathic manipulative treatment' OR hands-on
#50	Patient Education	'patient participation'/exp OR 'patient education'/exp OR 'consumer health information'/exp OR 'health literacy'/exp OR educate OR education OR information OR literacy
#51	Patient Education Tools	'moblie application' OR (mobile AND (application* OR app*)) OR 'mobile phone' OR 'cell phone' OR 'cellular phone' OR 'technology' OR 'electronic device' OR 'social media' OR website* OR web-based OR webbased OR 'iphone' OR smartphone OR 'tablet computer' OR 'ipad' OR 'I phone' OR android OR blackberry OR computer OR laptop OR internet
#52	Provider Training and Education	(('continuing education'/exp OR 'continuing medical education' OR CME OR education OR training OR instruction OR curriculum) AND ('medical personnel'/exp OR 'medical personnel' OR physician* OR provider* OR clinician* OR nurse* OR therapist* OR doctor* OR counselor* OR 'medical staff')) OR 'medical education training'/exp OR 'medical education'/exp
#53		'mobile phone' OR 'cell phone' OR 'cellular phone' OR 'technology' OR 'electronic device' OR 'social media' OR website* OR web-based OR webbased OR 'iphone' OR smartphone OR 'tablet computer' OR 'ipad' OR 'I phone' OR android OR blackberry OR computer OR laptop OR internet OR webinar* OR 'moblie application' OR (mobile AND (application* OR app*))
#54		'patient provider communication'/de OR ((patient* OR provider*) NEXT/2 communicat*) OR ((interpersonal OR intrapersonal) NEXT/2 (communication* OR skill*)) OR 'interpersonal communication'/exp OR 'verbal communication'/exp OR 'verbal communicat*' OR 'doctor patient relationship'/de
#55	Combine Provider Training and Education	#52 OR #53 OR #54
#56	KQ1	#6 AND (#14 OR #17 OR #19 OR #20 OR #26 OR #28 OR #29 OR #31) For adults with CMI, what are the benefits and harms of pharmacologic interventions?
#57	KQ2	#7 AND (#17 OR #20 OR #27 OR #28 OR #29) For adults with fibromyalgia, what are the benefits and harms of pharmacologic interventions for pain-related symptoms, function and quality of life?
#58	KQ3	#8 AND (#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #28 OR #29 OR #30) For adults with IBS, what are the benefits and harms of pharmacologic interventions for gastrointestinal symptoms, function and quality of life?
#59	KQ4	#13 AND (#17 OR #18 OR #24 OR #26 OR #31) For adults with CFS, what are the benefits and harms of pharmacologic interventions for fatigue symptoms, function and quality of life?

Set #	Concept	Strategy
#60	KQ5	#6 AND #34 For adults with CMI, what are the benefits and harms of complementary and integrative health interventions for CMI-related outcomes, function and quality of life?
#61	KQ6	(#7 OR #8 OR #13) AND #34 For adults with fibromyalgia, IBS, or CFS, what are the benefits of complementary and integrative health interventions for function and quality of life?
#62	KQ7	#6 AND #43 For adults with CMI, what are the benefits and harms of behavioral health interventions for CMI-related outcomes, function and quality of life?
#63	KQ8	(#7 OR #8 OR #13) AND #43 For adults with fibromyalgia, IBS, or CFS what are the benefits of behavioral health interventions for function and quality of life?
#64	KQ9	#6 AND #47 For adults with CMI, what are the benefits and harms of physical exercise interventions for CMI-related outcomes, function and quality of life?
#65	KQ10	#6 AND #48 For adults with CMI what are the benefits of osteopathic therapy, physical therapy, and occupational therapy interventions for function and quality of life?
#66	KQ11	#6 AND (#50 OR #51) Does patient education improve physical function and QoL outcomes for adults with CMI?
#67	KQ12	#6 AND #55 For adults with CMI, does provider training and education improve outcomes?
#68	Combine All CMI Sets	#56 OR #60 OR #62 OR #64 OR #65 OR #66 OR #67
#69	Combine All Fibro, IBS, CFS Sets	#57 OR #58 OR #59 OR #61 OR #63
#70	Remove Unwanted Publication Types From CMI Set	#68 NOT ('conference abstract'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR book OR 'case report'/exp OR editorial OR letter OR note/it)
#71	Apply Study Types to Fibro, IBS, CFS Sets	#69 NOT ('conference abstract'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR book OR 'case report'/exp OR editorial OR letter OR note/it)
#72		#71 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR cochrane*:ti,ab OR meta*:ti,ab OR systematic*:ti,ab OR random*:ti,ab OR trial*:ti,ab OR databases:ti,ab OR pooled:ti,ab OR searched:ti,ab OR 'controlled trial' OR 'control group' OR 'matched controls')
#73		#70 OR #72
#74	Apply Limits, Remove Pediatric and Animal Populations	#73 AND ([English]/lim AND [1-7-2013]/sd NOT [27-3-2020]/sd)
#75		#74 NOT ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim OR animal* OR mouse OR mice OR rat OR rats OR sheep OR canine* OR dog OR dogs OR equine)

B. PsycINFO in OVID Syntax (for KQ5, KQ6, KQ7, KQ8, KQ9, KQ10, KQ11, and KQ12)

Set #	Concept	Strategy
#1	Condition: Persian Gulf/Gulf War Syndrome/Chronic Multisymptom Illness	'persian gulf syndrome'.ti. or ('persian gulf' adj2 (syndrome or illness*)).mp. or 'persian war syndrome'.ti. or ('persian war' adj2 (syndrome or illness*)).mp. or 'gulf war illness'.ti. or ('gulf war' adj2 (syndrome or illness*)).mp.
#2		((Chronic* or deployment* or postdeployment* or 'post deployment*') adj2 (multisymptom* or multi-symptom*)).mp.
#3		(veteran* or deploy* or postdeployment* or 'post deployment*' or soldier* or military or 'air force' or 'armed forces' or army or marine* or navy or 'service member*' or servicemen or servicewomen or 'coast guard' or 'active duty' or persia* or gulf*).mp. or exp Military Families/ or exp Military Personnel/ or exp Military Veterans/ or exp Military Deployment/ or exp Combat Experience/ or exp Army Personnel/
#4		exp chronic illness/ or ('cmi' or 'gwi').mp. or 'chronic multisymptom'.ti,ab. or 'chronic multi-symptom'.ti,ab.
#5		((unexplained adj1 (symptom or symptoms or illness or illnesses)) or (medically adj2 unexplained)).mp.
#6	Combine CMI	**(#1 OR #2 OR #3) AND (#4 OR #5)**
#7	Condition: Fibromyalgia	exp fibromyalgia/ or fibromyalg*.ti,ab. or myofascial pain.mp. or exp Myofascial Pain/ or muscular rheumatism.ti,ab.
#8	Condition: Irritable Bowel Syndrome	irritable bowel syndrome.mp. or exp Irritable Bowel Syndrome/ OR (((Irritable adj2 (bowel or colon or intestin*)) or ((mucus or mucous) adj2 colitis)).ti,ab. or (IBS and bowel).mp.)
#9	Condition: Chronic Fatigue Syndrome	chronic fatigue syndrome.mp. or exp Chronic Fatigue Syndrome/ OR ((chronic adj2 fatigue).mp, or (fatigue adj2 syndrome*).mp. or (fatigue adj2 disorder*).mp. OR ('myalgic encephalomyelitis' or 'royal free disease' or 'systemic exertion intolerance disease').mp.
#10	Complementary and Integrative Health Interventions	exp alternative medicine/ or ('complementary integrat* medicine' or 'complementary alternative medicine' or cim or cam).ti,ab. or ((integrat* or alternat* or complement*) adj3 (therap* or medicine or treatment* or program*)).ti,ab.
#11		acupuncture/ or acupuncture.ti,ab. or massage/ or massage*.ti,ab. OR chiropract*:ti,ab.
#12		Biofeedback/ or biofeedback.mp. or neurofeedback.mp. or exp hypnotherapy/ or (hypnotherapy or hypnosis).ti,ab. or meditation/ or meditate.ti,ab. or meditation.ti,ab. or exp guided imagery/ or guided imagery.ti,ab. or (guide* adj2 imagery).mp. or (tai chi or taichi).ti,ab. or (qigong or qi gong).ti,ab. or yoga/ or yoga.ti,ab.
#13		exp aromatherapy/ or (aromatherapy* or Spiritual* or naturopath* or homeopath* or 'health coach*').ti,ab.
#14	Combine CIM	**#10 OR #11 OR #12 OR #13**
#15	Behavioral Health Interventions	('behavior* health' or (behavi* adj3 health*)).mp. or exp health care psychology/
#16		exp behavioral medicine/ or exp behavior therapy/ or exp behavior modification/ or (behav* adj2 (medicine or intervention* or change* or modification*)).ti,ab. or exp behavior change/ or exp psychotherapy/ or psychotherap*.ti,ab.

Set #	Concept	Strategy
#17		exp mindfulness/ or exp mindfulness-based interventions/ or exp meditation/ or exp awareness/ or exp self-compassion/ or 'mindfulness-based'.ti,ab. or mindfulness.ti,ab. or meditat*.ti. or (self* adj2 (aware* or compassion)).ti,ab.
#18		exp psychotherapy/ or psychotherap*.ti,ab. or exp psychotherapeutic techniques/ or exp relaxation therapy/ or psychosocial*.ti,ab. or ((pscyho* or relax*) adj2 (therap* or rehab* or technique* or train*)).ti.
#19		exp cognitive behavior therapy/ or exp cognitive therapy/ or (cognitive adj1 (behavior* or therap*)).ti. or 'cbt'.mp. or 'multidisciplinary rehabilitation treatment'.mp.
#20		exp mind body therapy/ or *dualism/ or 'mind body'.mp. or (mind adj2 body).mp.
#21		exp peer counseling/ or (peer* adj2 (support* or therap* or counsel* or consult* or advise* or instruct* or facilitat* or group* or rehab*)).ti,ab. or ((social or support) adj2 (group* or peer*)).ti,ab. or (exp support groups/ and (peer* or social).ti,ab.) or exp self-help techniques/ or exp self-management/ or 'self help'.ti,ab.
#22	Combine Behavioral Health Interventions	**#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21**
#23	Physical Activity Interventions	Exp exercise/ OR exp physical activity/ OR exp aerobic exercise/ OR 'exercise.mp. OR physical activity.mp.
#24		Exp running/ OR exp walking/ OR Exercise* OR 'physical activit*' OR isometric* OR 'weight training' OR (train* adj3 (weight* OR resistance)) OR 'weight lift*' OR 'weight bearing' OR walk* OR run* OR jog* OR swim* OR 'cross train*' OR 'dynamic exercise*' OR aerobics OR ((aerobic OR circuit* OR interval* OR aquatic* OR muscle* OR class OR classes) adj3 (exercis* OR fitness OR training))
#25		Cycle OR cycling OR biking OR bike OR stretching OR hike OR hiking OR 'body movement' OR mobility OR 'daily life activit*' OR active OR activity OR activities
#26		(exercise OR (physical adj2 activity)) AND (change* OR improve* OR modif* OR increase*)
#27		Sedentary.ti,ab. OR sedentary.ti,ab. OR 'laziness'/exp OR lazy.ti,ab OR laziness.ti,ab OR inactive.ti,ab OR inactivity.ti,ab
#28	Combine Physical Activity	**#23 OR #24 OR #25 OR #26 OR #27**
#29	Physical/ Occupational Therapy, Osteopathic Treatments	Exp physical therapy/ OR occupational therapy/ OR exp physical treatment methods/ OR exp osteopathic medicine/ OR ((occupation* OR physical OR manipulat* OR osteopath* OR cryo* OR kinesio* OR magnet* OR radiofrequency OR ultrasound OR vibration) adj3 (treatment* OR therapy OR therapist OR medicine OR program OR programs)) OR acupressure OR osteopathy
#30		physiotherapy OR physiotherapist OR kinesiotherapy OR kinesiotherapist OR ((physical OR muscular OR muscle* OR joint* OR skeletal OR musculoskeletal) adj3 (manipulation OR stretch OR stretching OR pressure OR resistance)) OR reflexology OR 'trigger point therapy' OR cryotherapy OR 'osteopathic manipulative treatment' OR hands-on
#31	Combine Physical Therapy	**#29 OR #30**
#32	Patient Education	exp client education/ OR client participation/ or exp health information/ OR exp health promotion/ OR exp health education/ or exp health knowledge/ or exp health literacy/ or exp treatment compliance/ OR ((exp family members/ OR exp caregivers/ OR exp patients/ OR exp consumer/) AND exp education/)

Set #	Concept	Strategy
#33		Exp mobile phones/ OR exp mobile applications/ OR exp technology/ OR exp computer applications/ OR exp internet/ OR exp computer assisted instruction/ OR ((mobile OR cell* OR android*) adj1 (phone* OR app OR apps OR application*)) OR technology OR device OR social media OR website* OR web-based OR webbased OR iphone OR smartphone OR tablet OR ipad OR laptop OR android* OR blackberry OR computer OR internet OR text OR texts OR instant messag* OR skype
#34		Exp educational programs/ OR exp teaching methods/ OR ((education* OR learn* OR literacy OR literate) adj3 (program* OR materials OR tool OR tools OR method OR methods))
#35		**Patient* OR caregiver* OR family OR family member* OR consumer* OR client*) adj3 (educat* OR information OR literacy OR knowledge OR compliance OR participat*)**
#36	Combine Education	**#32 OR #33 OR #34 OR #35**
#37	Provider Training and Education	(Exp continuing education/ OR exp professional development/) AND (exp medical education/ OR exp medical personnel/ OR exp physicians/ OR exp clinicians/)
#38		(CME OR continuing medical education OR continuing education OR educat* OR training OR train OR instruct* OR curriculum OR teach OR teaching) AND (doctor* OR provider* OR physician* OR clinician* OR nurse* OR specialist* OR therapist* OR counselor* 'medical personnel' OR 'medical staff')
#39		(exp medical personnel/ OR exp physicians/ OR exp clinicians/ OR doctor* OR provider* OR physician* OR clinician* OR nurse* OR specialist* OR therapist* OR counselor* 'medical personnel' OR 'medical staff') AND (Exp mobile phones/ OR exp mobile applications/ OR exp technology/ OR exp computer applications/ OR exp internet/ OR exp computer assisted instruction/ OR ((mobile OR cell* OR android*) adj1 (phone* OR app OR apps OR application*)) OR technology OR device OR social media OR website* OR web-based OR webbased OR iphone OR smartphone OR tablet OR ipad OR laptop OR android* OR blackberry OR computer OR internet OR text OR texts OR instant messag* OR skype)
#40		exp Communication/ or exp Interpersonal Communication/ or patient provider communication.mp. OR ((patient* OR provider*) adj2 (communicat* OR relationship)) OR interpersonal communicat*.mp. OR interpersonal skill*.mp. OR verbal communication.mp. OR communicat*.mp. OR doctor patient relationship.mp.
#41	Combine Provider Training and Education	**#37 OR #38 OR #39 OR #40**
#42	KQ5	#6 AND #14 For adults with CMI, what are the benefits and harms of complementary and integrative health interventions for CMI-related outcomes, function and quality of life?
#43	KQ6	(#7 OR #8 OR #9) AND #14 For adults with fibromyalgia, IBS, or CFS, what are the benefits of complementary and integrative health interventions for function and quality of life?
#44	KQ7	#6 AND #22 For adults with CMI, what are the benefits and harms of behavioral health interventions for CMI-related outcomes, function and quality of life?
#45	KQ8	(#7 OR #8 OR #9) AND #22 For adults with fibromyalgia, IBS, or CFS what are the benefits of behavioral health interventions for function and quality of life?

Set #	Concept	Strategy
#46	KQ9	#6 AND #28 For adults with CMI, what are the benefits and harms of physical exercise interventions for CMI-related outcomes, function and quality of life?
#47	KQ10	#6 AND #31 For adults with CMI what are the benefits of osteopathic therapy, physical therapy, and occupational therapy interventions for function and quality of life?
#48	KQ11	#6 AND #36 Does patient education improve physical function and QoL outcomes for adults with CMI?
#49	KQ12	#6 AND #41 For adults with CMI, does provider training and education improve outcomes?
#50	Combine CMI Sets	**#42 OR #44 OR #46 OR #47 OR #48 OR #49**
#51	Combine Fibro, IBS, CFS Sets	**#43 OR #45**
#52	Apply Study Design/ Pub Types	**#50 NOT (chapter OR "column/opinion" OR "comment/reply" OR dissertation OR editorial OR encyclopedia entry OR interview OR letter OR authored book OR book OR edited book OR encyclopedia OR dissertation abstract OR electronic collection).pt. OR** (abstract collection OR bibliography OR chapter OR clarification OR "column/opinion" OR "comment/reply" OR dissertation OR editorial OR encyclopedia entry OR "erratum/correction" OR letter OR obituary OR poetry OR publication information OR reprint OR retraction OR review-book OR review-media OR review-software & other).dt.
#53		**#51 AND (meta analysis/ or systematic review/ or systematic review.ti. or meta-analysis or meta* or systematic* or random* or rct or trial or search* or databases or pooled or searched or studies or evidence base* or controlled trial* or control group or matched controls).mp.**
#54		**#52 OR #53**
#55		**Limit #54 to (human and english language and yr="2013 - 2020")**

C. Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Set #	Concept	Strategy
#1	Chronic Multisymptom	"persian gulf syndrome" OR "Persian gulf illness" OR "Persian gulf" OR MH "Persian gulf syndrome" OR "gulf war illness" OR "gulf war syndrome" OR "gulf war"
#2		(TI chronic AND TI (symptom* OR syndrome* OR illness*)) AND ("gulf war" OR "Persian war") OR "chronic multisymptom"
#3		('cmi' OR 'gwi' OR 'medically unexplained' OR unexplained) AND (veteran* OR deploy* OR soldier* OR military OR 'active duty' OR persia* OR gulf*)
#4		#1 OR #2 OR #3
#5	Fibroymalgia	MH "fibromyalgia" OR TI fibromyalg* OR AB fibromyalg* OR MM "myofascial pain syndromes" "myofascial pain syndrome" OR "muscular rheumatism"
#6	Irritable Bowel Syndrome	"MH irritable bowel syndrome" OR TI "irritable bowel" OR TI IBS OR (TI Irritable AND TI (bowel OR colon))
#7	Chronic Fatigue Syndrome	MM "chronic fatigue syndrome" OR "chronic fatigue syndrome" OR (TI fatigue AND TI (syndrome OR disorder OR chronic)) OR "myalgic encephalomyelitis"
#8		**#4 OR #5 OR #6 OR #7**
#9		**#8** AND English AND 20130101-20201231 AND Academic journals AND exclude MEDLINE records
#10		**#9 Limiters:** Publication type: journal article, meta analysis, meta synthesis, randomized controlled trial, systematic review

Appendix G: Alternative Text Descriptions of Algorithm

A. Algorithm: Management of Chronic Multisymptom Illness

1. The algorithm begins with Box 1, in the shape of a rounded rectangle: "Patient presents with a spectrum of chronic symptoms not fully explained by other disorders and meeting the criteria for CMI (see Sidebar 1)"
2. Box 1 connects to Box 2, in the shape of a rectangle: "Build and maintain a therapeutic patient-provider alliance while conducting a thorough evaluation of symptoms and assess for comorbid conditions (see Sidebar 2)"
3. Box 2 connects to Box 3, in the shape of a hexagon, asks the question: "Does CMI co-exist with another diagnosis that may partially contribute to the symptoms?
    a. If the answer is "Yes" to Box 3, then Box 4, in the shape of a rectangle: "Refer or treat co-occurring conditions as indicated using appropriate evidence-based VA/DOD CPGs"
        i. Box 4 connects to Box 5
    b. If the answer is "No" to Box 3, then Box 5
4. Box 5, in the shape of a rectangle, a bulleted list: "Provide education on CMI and discuss the findings, impression, and evidence; Develop an individualized treatment plan based on patient's needs, goals, and preferences (see Sidebar 3)"
5. Box 5 connects to Box 6, in the shape of a rectangle: "Initial treatments may include*" and the bulleted list, "Offer CBT or mindfulness-based therapy$^{\uparrow}$; Avoid use of opioid medications for pain related to CMI$^{\downarrow\downarrow}$; Avoid use of mifepristone$^{\downarrow\downarrow}$"
6. Box 6 connects to Box 7, in the shape of a hexagon, asks the question: "Does patient present with CMI and symptoms consistent with FMS?*"
    a. If the answer is "Yes" to Box 7, then Box 8, in the shape of a rectangle: "In addition to the treatments in Box 6:" and the bulleted list, "Consider emotion-focused therapy$^{\uparrow}$; Consider yoga, tai chi, manual acupuncture, or physical exercise$^{\uparrow}$; Consider a trial of SSRIs or PGB$^{\uparrow}$; Avoid NSAIDs for chronic pain related to CMI$^{\downarrow}$"
        i. Box 8 connects to Box 9
    b. If the answer is "No" to Box 7, then Box 9
7. Box 9, in the shape of a hexagon, asks the question: "Does patient present with CMI and symptoms consistent with IBS?*"
    a. If the answer is "Yes" to Box 9, then Box 10, in the shape of a rectangle: "In addition to the treatments in Box 6:" and the bulleted list, "Consider emotion-focused therapy$^{\uparrow}$; Consider psychodynamic therapies$^{\leftrightarrow}$; Consider trial of TCAs or antispasmodics$^{\leftrightarrow}$; Consider trial of rifaximin for patients without significant constipation$^{\uparrow}$; Consider linaclotide or plecanatide for patients with constipation-predominant IBS and who are not responsive to osmotic laxatives$^{\uparrow}$; for women only, consider lubiprostone$^{\leftrightarrow}$; Consider trial of eluxadoline for

patients with significant diarrhea who do not respond to a trial of anti-diarrheals or low-FODMAP diet$^{\leftrightarrow}$; Avoid alosetron and SSRIs for IBS symptoms$^{\leftrightarrow}$"

i. Box 10 connects to Box 11

b. If the answer is "No" to Box 9, then Box 11

8. Box 11, in the shape of a hexagon, asks the question: "Does patient present with CMI and symptoms consistent with ME/CFS?*"

   a. If the answer is "Yes" to Box 11, then Box 12, in the shape of a rectangle: "In addition to the treatments in Box 6:" and the bulleted list, "Avoid corticosteroids, antivirals, or antibiotics†; Avoid stimulants for fatigue symptoms$^{\downarrow\downarrow}$"

      i. Box 12 connects to Box 13

   b. If the answer is "No" to Box 11, then Box 13

9. Box 13, in the shape of a hexagon, asks the question: "Have symptoms, QoL, or function improved to patient satisfaction?"

   a. If the answer is "Yes" to Box 13, then Box 14, in the shape of a rectangle: "Continue individualized treatment plan and update as needed (see Sidebar 3)"

   b. If the answer is "No" to Box 13, then Box 2

Appendix H: Abbreviations

Abbreviation	Definition
AEX	aerobic exercise
CDC	U.S. Centers for Disease Control and Prevention
CI	confidence intervals
CMI	chronic multisymptom illness
COR	contracting officer's representative
CPGs	clinical practice guidelines
DoD	U.S. Department of Defense
EBPWG	Evidence-Based Practice Work Group
FDA	U.S. Food and Drug Administration
FMS	fibromyalgia syndrome
FODMAP	fermentable oligo-, di-, mono-saccharides, and polyols
g	grams
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GWI	Gulf War Illness
GWV	Gulf War Veteran
HRQoL	health-related quality of life
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome-constipation
IBS-D	irritable bowel syndrome-diarrhea
IBS-M	irritable bowel syndrome-mixed
IOM	Institute of Medicine
KQs	key questions
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
mg	milligrams
MSK	musculoskeletal
NAM	National Academy of Medicine
NICE	National Institute for Health and Care Excellence
NSAID	nonsteroidal anti-inflammatory drug
PGB	pregabalin
PICOTS	population, intervention, comparison, outcome, timing and setting
QoL	quality of life
RCT	randomized controlled trial
SNRI	serotonin-norepinephrine reuptake inhibitor
SOC	standard of care
SR	systematic review
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
U.S.	United States

Abbreviation	Definition
USPSTF	U.S. Preventive Services Task Force
VA	U.S. Department of Veterans Affairs
VHA	Veterans Health Administration

Appendix I: Pharmacologic Agents for CMI

The Work Group suggests providers use discretion when stopping and starting these medications. In addition, providers should refer to the individual product prescribing information for information pertaining to warnings and precautions, renal and hepatic impairment dosing, and use in special populations including geriatrics and pregnancy.

Table I-1. Pharmacotherapy

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Escitalopram[†‡§]	• 10 – 20 mg/d; titrate up from 10 mg/d to 20 mg/d after 1 month • Adequate trial: 12 weeks	Global	• Headache • Nausea • Nasopharyngitis • Insomnia • Sexual dysfunction • Suicidal ideation • QTc prolongation • Serotonin syndrome	• Improved somatic symptom severity, depression, pain, anxiety • Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Citalopram (20 – 40 mg/d) may be a reasonable substitute for escitalopram
Fluoxetine[†‡§]	• 10 – 80 mg/d; titrate up from 10 mg/d by 10 mg/d at intervals of at least 1 week • Adequate trial: 6 – 12 weeks • Hepatic impairment: Use lower doses or less frequent dosing	• Global* • Pain	• Nausea • Headache • Insomnia • Nervousness • Anxiety • Somnolence • Asthenia • Diarrhea • Anorexia • Suicidal ideation • Serotonin syndrome • QTc prolongation • Sexual dysfunction • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated within five weeks of discontinuing fluoxetine • 2D6 substrate, potentially significant interactions may exist requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy • Contraindicated with pimozide or thioridazine; avoid with other QTc prolonging drugs • Consider long elimination half-life during dosage titration and drug discontinuation

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Sertraline[†‡§]	• 25 – 200 mg/d; titrate up from 25 mg/d by 50 mg/d at intervals of at least one week • Adequate trial: 12 weeks • Reduce dose to 50% of usual dose with mild (Child-Pugh Class A) hepatic impairment; some experts recommend maximum dose of 100 mg/d • Use not recommended in moderate to severe hepatic impairment	Global*	• Nausea • Somnolence • Dry mouth • Constipation • Dizziness • Sexual dysfunction • Suicidal ideation • Serotonin syndrome • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Conditional risk of QTc prolongation[†]
Paroxetine controlled release[†‡§]	• 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 one week • Adequate trial: 12 weeks • Use lower doses in the elderly	Pain	• Drowsiness • Nausea • Insomnia • Headache • Dizziness • Diaphoresis • Weakness • Constipation • Diarrhea • Dry mouth • Akathisia • Suicidal ideation • Serotonin syndrome • Sexual dysfunction • Discontinuation syndrome	• Also available in immediate-release tablets (20 – 60 mg/d) • Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Most sedating SSRI • Potent anticholinergic effects • 2D6 substrate, potentially significant interactions may exist requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy
Citalopram[†‡§]	• 20 – 40 mg/d; titrate up at intervals of at least one week • Adequate trial: 8 – 16 weeks • The maximum recommended dose in patients with hepatic impairment is 20 mg/d due to decreased clearance and risk of QT prolongation • For patients >60 years of age the maximum recommended dose is 20 mg/d due to risk of QT prolongation	Pain	• Nausea • Dry mouth • Somnolence • Insomnia • Hyperhidrosis • Suicidal ideation • Serotonin syndrome • QTc prolongation • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Avoid using citalopram with other QTc prolonging drugs

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Venlafaxine IR and ER[‡§]	• IR: 37.5 – 375 mg/d; titrate up from 37.5 mg/d by 37.5 – 75 mg/d at intervals of at least one week • ER: 75 – 225 mg/d; titrate up by 75 mg/d at intervals of at least one week • Adequate trial: 12 weeks	Global*	• Nausea • Headache • Fatigue • Dizziness • Constipation • Tremor • Dry mouth • Elevated blood pressure • Sexual dysfunction • Suicidal ideation • Serotonin syndrome • QTc prolongation • Discontinuation syndrome	• Improved pain, anxiety, QoL but not somatic symptom severity • Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Patients treated with a therapeutic dose of venlafaxine IR may be switched to venlafaxine ER at the nearest equivalent dose (mg/day); following the formulation switch, individual dosage adjustments may be necessary
Mirtazapine[‡§]	• 15 – 60 mg/d; titrate up from 15 mg/d by 15 mg/d at intervals of at least 1 – 2 weeks • Adequate trial: 12 weeks	Global*	• Somnolence • Dizziness • Dry mouth • Increased appetite • Weight gain • Constipation • Increased cholesterol • Suicidal ideation • Serotonin syndrome • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • High incidence of somnolence (>50%) • Low doses may be useful for insomnia • Conditional risk of QTc prolongation[¥]
Duloxetine[‡§]	• 60 – 120 mg/d; titrate up from 20 –30 mg by 20 – 30 mg/d over two weeks • Adequate trial: 12 weeks • Avoid use in hepatic impairment • Not recommended in patients with severe renal impairment (CrCl <30 mL/min)	• Pain • Fatigue	• Nausea • Headache • Dry mouth • Fatigue • Somnolence • Constipation • Insomnia • Urinary retention • Serotonin syndrome • Suicidal ideation • Hepatotoxicity • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated within 5 days of discontinuing duloxetine • Doses above 60 mg/d have no evidence of additional benefit and increase the risk of AEs • Do not ordinarily use in patients with hepatic insufficiency

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Milnacipran[‡§]	• 100 mg/d (100 – 200 mg/d) in two divided doses; titrate up from 12.5 mg/d by 12.5 – 50 mg/d per week over 3 – 4 weeks • Adequate trial: 12 weeks • Do not ordinarily use in patients with substantial alcohol use or chronic liver disease • Not recommended in patients with ESRD • Dose in patients with severe renal impairment (5 – 29 mL/min): 50 – 100 mg/d in two divided doses	• Pain • Fatigue	• Nausea • Headache • Constipation • Insomnia • Dizziness • Hot flashes • Serotonin syndrome • Suicidal ideation • Increased blood pressure and heart rate • Urinary retention • Hepatotoxicity • Withdrawal symptoms • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • MAOIs contraindicated within 5 days of discontinuing milnacipran • Contraindicated in patients with uncontrolled narrow-angle glaucoma
Amitriptyline[†‡§]	• 10 – 50 mg/d • Adequate trial: 6 – 8 weeks • Use lower doses in the elderly • No dosage adjustments for hepatic impairment provided in manufacturers labeling. Some experts recommend reducing initial and maintenance doses by 50% in patients with hepatic impairment.	• Pain • Fatigue	• Dry mouth • Fatigue • Sedation • Vasovagal reaction • Orthostatic hypotension • Constipation • Urinary retention • QTc prolongation; conduction abnormalities • Suicidal ideation • Discontinuation syndrome	• Contraindicated with MAOIs and within 14 days of starting or stopping MAOIs • Contraindicated with cisapride • Avoid use with QTc prolonging drugs, anticholinergics • Use with caution in patients with cardio- or cerebrovascular disease • There is currently no evidence to support the use of TCAs in patients with ME/CFS; further, there may be an increased risk (i.e., for suicidality) with the use of TCAs depending on a patient's comorbidities

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Pregabalin	• 300 – 450 mg/d divided BID–TID, starting at 150 mg/d and increasing by 150 mg/d every week • Adequate trial: 8 weeks • Adjust dose based on renal function	• Pain	• Dizziness • Somnolence • Headache • Weight gain • Angioedema • Suicidal ideation • Peripheral edema • Withdrawal symptoms • Blurred vision • Visual field loss	• The Work Group evaluated a 600 mg/d dose but found no additional benefit and an increased risk of AEs
Rifaximin	• 550 mg, three times daily for 14 days	IBS, moderate to severe without constipation	• Peripheral edema • Dizziness • Fatigue • Ascites • Nausea • IBS with diarrhea • Headache • Depression • Pruritus • Skin rash • Abdominal pain • Pseudomembranous colitis • Muscle spasms • Nasopharyngitis	• Hypersensitivity reactions have occurred (exfoliative dermatitis, rash, urticaria, flushing, angioneurotic edema, pruritus, anaphylaxis) as early as 15 minutes after drug administration • Prolonged use may result in fungal or bacterial superinfection, including Clostridioides difficile-associated diarrhea (observed >2 months post-antibiotic treatment) and pseudomembranous colitis
Lubiprostone	• 8 mcg taken orally twice daily with food and water • Adequate trial: 6 weeks	IBS with constipation in females >18 years old	• Headache • Nausea • Diarrhea • Edema • Chest discomfort • Chest pain • Dizziness • Fatigue • Abdominal pain • Flatulence • Abdominal distention • Vomiting • Dyspepsia • Xerostomia	• Contraindicated in patients with known or suspected mechanical gastrointestinal obstruction • Syncope/hypotension may occur (some resulting in hospitalization), which generally resolved following discontinuation or before the next dose; reoccurrences have been reported with subsequent doses

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Linaclotide	• 290 mcg taken orally once daily • Adequate trial: 6 weeks	IBS with constipation	• Diarrhea • Headache • Fatigue • Dehydration • Abdominal pain • Flatulence • Abdominal distention • Viral gastroenteritis • Severe diarrhea • Fecal incontinence • GERD • Vomiting • Upper respiratory tract infection	May cause severe diarrhea associated with dizziness, syncope, hypotension, and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or IV fluids
Plecanatide	• 3 mg taken once daily • Adequate trial: 6 weeks	IBS with constipation	• Dizziness • Diarrhea • Abdominal distention • Abdominal tenderness • Flatulence • Urinary tract infection • Increased serum ALT and AST • Upper respiratory tract infection • Nasopharyngitis	May cause diarrhea within the first month of treatment; severe diarrhea may occur within three days of treatment. Consider discontinuation of treatment and rehydration if severe diarrhea occurs.

Agent	Dosage in Adults	Symptom Efficacy	Notable Adverse Effects	Comments
Eluxadoline	• 100 mg taken twice daily, may decrease to 75 mg twice daily in patients unable to tolerate the 100 mg dose • Adequate trial: 6 weeks	IBS with diarrhea	• Dizziness • Fatigue/ drowsiness • Euphoria • Intoxicated feeling • Sedation • Constipation • Nausea • Abdominal pain • Vomiting • Abdominal distension • Flatulence • Viral gastroenteritis • GERD • Increased AST and ALT • Upper respiratory tract infection • Nasopharyngitis • Bronchitis • Asthma • Bronchospasm	• Constipation sometimes requiring hospitalization has been reported; severe cases with intestinal obstruction, perforation, and fecal impaction may also occur • Severe hypersensitivity reactions including anaphylaxis have been reported • May cause pancreatitis, with or without sphincter of Oddi spasm, including serious cases (some fatal) requiring hospitalization • May cause sphincter of Oddi spasm resulting in pancreatitis or elevated hepatic enzymes. Permanently discontinue use in patients who develop biliary duct obstruction or sphincter of Oddi spasms.

* Equivocal efficacy; not compared with placebo

† The Work Group suggests lower starting doses and slow upward dose titration particularly in patients with anxiety who are generally more sensitive to the overstimulation effects of antidepressants

‡ When discontinuing antidepressant treatment that has lasted for >3 weeks, gradually taper the dose (e.g., over 2 – 4 weeks) to minimize discontinuation symptoms and detect reemerging symptoms

§ Boxed warning for suicidal thinking/behavior: antidepressants may increase the risk of suicidal thinking and behavior in children and young adults (18 – 24 years of age) with MDD or other psychiatric disorders

¥ Associated with a 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)

Abbreviations: AE: adverse effect; ALT: alanine transaminase; AST: aspartate transaminase; BID: twice a day; CrCl: creatinine clearance; d: day; ER: extended release; ESRD: end-stage renal disease; GERD: gastroesophageal reflux disease; IBS: irritable bowel syndrome; IR: immediate release; IV: intravenous; MAOIs: monoamine oxidase inhibitors; mcg: micrograms; mg: milligrams; min: minute; mL: milliliters; TID: three times a day

Appendix J: Behavioral Health Interventions for CMI

Class	Intervention	Description
Cognitive Behavioral Therapy	Traditional Cognitive Behavioral Therapy	Cognitive behavioral therapy is a problem-oriented strategy. It focuses on current problems and finding solutions to them. Unlike psychoanalysis, for example, it does not deal primarily with the past. Cognitive behavioral therapy is much more concerned with current problems. Traditional CBT mainly deals with identifying and changing current distressing thought and behavioral patterns.(109)
	Acceptance-based Behavior Therapy	Acceptance-based behavior therapy (ABBT) was developed based on the theory that generalized anxiety disorder is maintained through a reactive and fused relationship with internal experiences and a tendency toward experiential avoidance and behavioral restriction. Acceptance-based behavior therapy specifically targets these elements. The focus of treatment is not on eliminating worry, but rather on decreasing the distress and interference associated with this cognitive activity.(110)
Mindfulness-based Therapy	Mindfulness-based stress reduction	Mindfulness-based stress reduction therapy is a meditation therapy. Although originally designed for stress management, it is being used to treat a variety of illnesses. It employs mindfulness meditation to alleviate suffering associated with physical, psychosomatic, and psychiatric disorders.(111)
	Meditation awareness training	Meditation awareness training is generally delivered over eight weeks and follows a comprehensive approach to meditation whereby mindfulness is an integral part, but does not form the exclusive focus, of the program. In addition to mindfulness, MAT incorporates practices that would traditionally be followed by meditation practitioners including techniques aimed at cultivating generosity, patience, and compassion. Meditation awareness training also integrates techniques that encourage the participant to investigate and come to an understanding of complex concepts such as impermanence and emptiness.(112)
	Mindfulness-based cognitive therapy	Mindfulness-based cognitive therapy incorporates elements of CBT with MBSR into an 8-session group program. It focuses on encouraging patients to adopt a new way of being and relating to their thoughts and feelings, while placing little emphasis on altering or challenging specific cognitions.(113)
Emotion-focused Therapy	Emotional awareness and expression therapy	Emotional awareness and expression therapy is designed to help patients attribute their pain and other symptoms to emotionally-activated central nervous system mechanisms and become aware of, experience, and adaptively express their emotions stemming from adversity, trauma, or conflict.(48)
	Attachment-based compassion therapy	Comprises eight sessions each lasting two and a half hours, and includes exercises of mindfulness training and compassion such as receiving and offering compassion to friends, individuals deemed to be problematic, unknown individuals, and oneself.(50)
Relaxation Therapy	Manual muscular relaxation therapy	Manual muscular relaxation therapy is an auditory relaxation technique, practiced individually and in silence. It focuses on the psychoneuroimmunological link between mind and body, and incorporates guided imagery, muscular relaxation, and breathing exercises, and implies full engagement and autonomy. The stress-related posture is thought to increase muscle tension and influence the nervous and endocrine systems, as well as cause muscle stiffness and dystonic patterns.(51)

Class	Intervention	Description
Relaxation Therapy (cont.)	Functional relaxation therapy	Functional relaxation therapy is a body-oriented psychologic intervention, which was found to be effective particularly for tension headaches, noncardiac chest pain, and psychosomatically-influenced asthmatic diseases. According to Marianne Fuchs, FR is a body-oriented psychotherapy that involves teaching the patient a type of relaxation technique aimed at maintaining equilibrium of the nervous system.(53, 114)
	Autogenic therapy	The AT relaxation approach focuses on relaxing the entire body through breathing and relaxation exercises, by the repetition of verbal formula.(54)
Guided Imagery	Guided imagery relaxation therapy	Guided imagery with relaxation (GIR) is a cognitive behavioral intervention. Guided imagery with relaxation is used to reduce pain based on the biopsychosocial theory of chronic pain. It utilizes guided cognition to increase focus and relaxation. Response imagery is used and involves imagining oneself in a pleasant scene. Verbal suggestions are given to produce a flow of thoughts that focus the individual's attention on imagined visual, auditory, tactile, and/or olfactory sensations.(115)
	Guided affective imagery	Guided affective imagery (GAI) is a type of psychotherapy that involves focusing on mental images to induce relaxation. The principle behind GAI is the interruption of stress-provoking thoughts with a relaxing image, inducing relaxation.(57, 116)
Clinical Hypnosis	Clinical hypnosis	Clinical hypnosis is a group of techniques that utilizes hypnosis to treat health-related conditions. It assumes that through concentration and relaxation processes, the individual may be able to change undesired conditions and behaviors.(117)
Psychodynamic Therapy	Psychodynamic therapy	Psychodynamic therapy seeks to understand the unconscious processes that impact interpersonal relationships and day-to-day functioning. This assists the individual in becoming aware of these processes so they can modify their responses and behaviors.(118, 119)

Abbreviations: ABBT: acceptance-based behavior therapy; AT: autogenic therapy; CBT: cognitive behavioral therapy; FR: functional relaxation therapy; GAI: guided affective imagery; GIR: guided imagery with relaxation; MAT: meditation awareness training; MBSR: mindfulness-based stress reduction

References

1. Evidence based practice work group charter: U.S. Department of Veterans Affairs/Department of Defense Health Executive Committee (HEC); [updated January 9, 2017]. Available from: www.healthquality.va.gov/documents/EvidenceBasedPracticeWGCharter123020161.pdf.
2. 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. 1996;125(5):398-405. Epub 1996/09/01. doi: 10.7326/0003-4819-125-5-199609010-00007. PubMed PMID: 8702091.
3. Jones E, Hodgins-Vermaas R, McCartney H, Everitt B, Beech C, Poynter D, et al. Post-combat syndromes from the Boer War to the Gulf War: A cluster analysis of their nature and attribution. BMJ. 2002;324(7333):321-4. Epub 2002/02/09. doi: 10.1136/bmj.324.7333.321. PubMed PMID: 11834557; PubMed Central PMCID: PMCPMC65292.
4. Two definitions for chronic multisymptom illness afflicting Gulf War Veterans should guide VA treatment and research [Internet]. Institute of Medicine. 2014.
5. Greco M. The classification and nomenclature of 'medically unexplained symptoms': Conflict, performativity and critique. Soc Sci Med. 2012;75(12):2362-9. Epub 2012/10/10. doi: 10.1016/j.socscimed.2012.09.010. PubMed PMID: 23043902.
6. Kroenke K. Physical symptom disorder: A simpler diagnostic category for somatization-spectrum conditions. J Psychosom Res. 2006;60(4):335-9. Epub 2006/04/04. doi: 10.1016/j.jpsychores.2006.01.022. PubMed PMID: 16581354.
7. Johansen ML, Risor MB. What is the problem with medically unexplained symptoms for GPs? A meta-synthesis of qualitative studies. Patient Educ Couns. 2017;100(4):647-54. Epub 2016/11/30. doi: 10.1016/j.pec.2016.11.015. PubMed PMID: 27894609.
8. Fukuda K, Nisenbaum R, Stewart G, Thompson WW, Robin L, Washko RM, et al. Chronic multisymptom illness affecting Air Force Veterans of the Gulf War. JAMA. 1998;280(11):981-8. Epub 1998/09/28. doi: 10.1001/jama.280.11.981. PubMed PMID: 9749480.
9. 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. 2000;152(10):992-1002. Epub 2000/11/25. doi: 10.1093/aje/152.10.992. PubMed PMID: 11092441.
10. Institute of Medicine. Chronic multisymptom illness in Gulf War Veterans: Case definitions reexamined. Washington, DC: The National Academies Press; 2014. 130 p.
11. U.S. Government Accountability Office. Gulf War Illness: Improvements needed for VA to better understand, process, and communicate decisions on claims. GAO-17-511. 2017.
12. McAndrew LM, Helmer DA, Phillips LA, Chandler HK, Ray K, Quigley KS. Iraq and Afghanistan Veterans report symptoms consistent with chronic multisymptom illness one year after deployment. J Rehabil Res Dev. 2016;53(1):59-70. Epub 2016/03/24. doi: 10.1682/jrrd.2014.10.0255. PubMed PMID: 27006173.
13. Porter B, Long K, Rull RP, Dursa EK. Prevalence of chronic multisymptom illness/Gulf War Illness over time among millennium cohort participants, 2001 to 2016. J Occup Environ Med. 2020;62(1):4-10. Epub 2019/10/19. doi: 10.1097/jom.0000000000001716. PubMed PMID: 31626064.
14. Mohanty AF, McAndrew LM, Helmer D, Samore MH, Gundlapalli AV. Chronic multisymptom illness among Iraq/Afghanistan-deployed US Veterans and their healthcare utilization within the Veterans Health Administration. J Gen Intern Med. 2018;33(9):1419-22. Epub 2018/05/26. doi: 10.1007/s11606-018-4479-6. PubMed PMID: 29797218; PubMed Central PMCID: PMCPMC6109005.
15. Haller H, Cramer H, Lauche R, Dobos G. Somatoform disorders and medically unexplained symptoms in primary care. Dtsch Arztebl Int. 2015;112(16):279-87. Epub 2015/05/06. doi: 10.3238/arztebl.2015.0279. PubMed PMID: 25939319; PubMed Central PMCID: PMCPMC4442550.

16. U.S. Department of Veteran Affairs, Department of Defense. Guideline for guidelines: Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup; 2019 [updated January 29, 2019]. Available from: http://www.healthquality.va.gov/policy/index.asp.

17. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. JAMA. 2013;309(2):139-40. Epub 2013/01/10. doi: 10.1001/jama.2012.156703. PubMed PMID: 23299601.

18. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE Guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. Journal of clinical epidemiology. 2013;66(7):726-35. Epub 2013/04/11. doi: 10.1016/j.jclinepi.2013.02.003. PubMed PMID: 23570745.

19. Andrews JC, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE Guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. Journal of clinical epidemiology. 2013;66(7):719-25. Epub 2013/01/15. doi: 10.1016/j.jclinepi.2012.03.013. PubMed PMID: 23312392.

20. Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. Health research policy and systems / BioMed Central. 2006;4:22. Epub 2006/12/07. doi: 10.1186/1478-4505-4-22. PubMed PMID: 17147811; PubMed Central PMCID: PMCPmc1697808.

21. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE Guidelines: 2. Framing the question and deciding on important outcomes. Journal of clinical epidemiology. 2011;64(4):395-400. Epub 2011/01/05. doi: 10.1016/j.jclinepi.2010.09.012. PubMed PMID: 21194891.

22. Newberry SJ, Ahmadzai N, Motala A, Tsertsvadze A, Maglione M, Ansari MT, et al. AHRQ methods for effective health care. Surveillance and identification of signals for updating systematic reviews: Implementation and early experience. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.

23. U.S. Preventive Services Task Force. Standards for guideline development. June 2018.

24. National Institute for Health and Care Excellence. The guidelines manual. London: National Institute for Health and Care Excellence, 2012.

25. Martinez Garcia L, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. Implementation science : IS. 2014;9:72. Epub 2014/06/13. doi: 10.1186/1748-5908-9-72. PubMed PMID: 24919856; PubMed Central PMCID: PMCPmc4067507.

26. Institute of Medicine Committe on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Washington, DC: The National Academies Press, 2011.

27. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: Definitions and applications to improve outcomes. Journal of the American Academy of Nurse Practitioners. 2008;20(12):600-7. Epub 2009/01/06. doi: 10.1111/j.1745-7599.2008.00360.x. PubMed PMID: 19120591.

28. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, et al. The impact of patient-centered care on outcomes. J Fam Pract. 2000;49(9):796-804. Epub 2000/10/14. PubMed PMID: 11032203.

29. Institute of Medicine. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: The National Academies Press, 2001.

30. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. Medical decision making : an international journal of the Society for Medical Decision Making. 1992;12(2):149-54. Epub 1992/04/01. PubMed PMID: 1573982.

31. U.S. Centers for Disease Control and Prevention. Vital signs: Overdoses of prescription opioid pain relievers-United States, 1999-2008. MMWR Morb Mortal Wkly Rep. 2011;60(43):1487-92. Epub 2011/11/04. PubMed PMID: 22048730.

32. Golier JA, Caramanica K, Michaelides AC, Makotkine I, Schmeidler J, Harvey PD, et al. A randomized, double-blind, placebo-controlled, crossover trial of mifepristone in Gulf War Veterans with chronic multisymptom illness. Psychoneuroendocrinology. 2016;64:22-30. Epub 2015/11/26. doi: 10.1016/j.psyneuen.2015.11.001. PubMed PMID: 26600007.

33. Donta ST, Clauw DJ, Engel CC, Jr., Guarino P, Peduzzi P, Williams DA, et al. Cognitive behavioral therapy and aerobic exercise for Gulf War Veterans' illnesses: A randomized controlled trial. JAMA. 2003;289(11):1396-404. Epub 2003/03/15. doi: 10.1001/jama.289.11.1396. PubMed PMID: 12636462.

34. Bernardy K, Klose P, Welsch P, Häuser W. Efficacy, acceptability and safety of cognitive behavioural therapies in fibromyalgia syndrome - a systematic review and meta-analysis of randomized controlled trials. Eur J Pain. 2018;22(2):242-60. Epub 2017/10/07. doi: 10.1002/ejp.1121. PubMed PMID: 28984402.

35. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Comparative efficacy of psychological therapies for improving mental health and daily functioning in irritable bowel syndrome: A systematic review and meta-analysis. Clin Psychol Rev. 2017;51:142-52. Epub 2016/11/22. doi: 10.1016/j.cpr.2016.11.001. PubMed PMID: 27870997.

36. Li L, Xiong L, Zhang S, Yu Q, Chen M. Cognitive-behavioral therapy for irritable bowel syndrome: A meta-analysis. J Psychosom Res. 2014;77(1):1-12. Epub 2014/06/11. doi: 10.1016/j.jpsychores.2014.03.006. PubMed PMID: 24913335.

37. Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of myalgic encephalomyelitis/chronic fatigue syndrome: A systematic review for a National Institutes of Health Pathways to Prevention workshop. Ann Intern Med. 2015;162(12):841-50. Epub 2015/06/16. doi: 10.7326/m15-0114. PubMed PMID: 26075755.

38. Wiborg JF, van Bussel J, van Dijk A, Bleijenberg G, Knoop H. Randomised controlled trial of cognitive behaviour therapy delivered in groups of patients with chronic fatigue syndrome. Psychother Psychosom. 2015;84(6): 368-76. Epub 2015/09/25. doi: 10.1159/000438867. PubMed PMID: 26402868.

39. Janse A, Worm-Smeitink M, Bleijenberg G, Donders R, Knoop H. Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: Randomised controlled trial. Br J Psychiatry. 2018;212(2):112-8. Epub 2018/02/14. doi: 10.1192/bjp.2017.22. PubMed PMID: 29436329.

40. Pérez-Aranda A, Feliu-Soler A, Montero-Marín J, García-Campayo J, Andrés-Rodríguez L, Borràs X, et al. A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: The EUDAIMON study. Pain. 2019;160(11):2508-23. Epub 2019/07/30. doi: 10.1097/j.pain.0000000000001655. PubMed PMID: 31356450.

41. Van Gordon W, Shonin E, Dunn TJ, Garcia-Campayo J, Griffiths MD. Meditation awareness training for the treatment of fibromyalgia syndrome: A randomized controlled trial. Br J Health Psychol. 2017;22(1):186-206. Epub 2016/11/26. doi: 10.1111/bjhp.12224. PubMed PMID: 27885763.

42. Henrich JF, Gjelsvik B, Surawy C, Evans E, Martin M. A randomized clinical trial of mindfulness-based cognitive therapy for women with irritable bowel syndrome-effects and mechanisms. J Consult Clin Psychol. 2020;88(4): 295-310. Epub 2020/03/07. doi: 10.1037/ccp0000483. PubMed PMID: 32134291.

43. 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. Epub 2013/08/31. doi: 10.1371/journal.pone.0071834. PubMed PMID: 23990997; PubMed Central PMCID: PMCPMC3753315.

44. Windthorst P, Mazurak N, Kuske M, Hipp A, Giel KE, Enck P, et al. Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study. J Psychosom Res. 2017;93:6-13. Epub 2017/01/22. doi: 10.1016/j.jpsychores.2016.11.014. PubMed PMID: 28107894.

45. Reneau M. Heart rate variability biofeedback to treat fibromyalgia: An integrative literature review. Pain Manag Nurs. 2020;21(3):225-32. Epub 2019/09/11. doi: 10.1016/j.pmn.2019.08.001. PubMed PMID: 31501080.

46. Goldenberg JZ, Brignall M, Hamilton M, Beardsley J, Batson RD, Hawrelak J, et al. Biofeedback for treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2019;2019(11). Epub 2019/11/13. doi: 10.1002/14651858.CD012530.pub2. PubMed PMID: 31713856; PubMed Central PMCID: PMCPMC6848969.

47. Clar C, Tsertsvadze A, Court R, Hundt GL, Clarke A, Sutcliffe P. Clinical effectiveness of manual therapy for the management of musculoskeletal and non-musculoskeletal conditions: Systematic review and update of UK evidence report. Chiropr Man Therap. 2014;22(1):12. Epub 2014/04/01. doi: 10.1186/2045-709x-22-12. PubMed PMID: 24679336; PubMed Central PMCID: PMCPMC3997823.

48. Lumley MA, Schubiner H, Lockhart NA, Kidwell KM, Harte SE, Clauw DJ, et al. Emotional awareness and expression therapy, cognitive behavioral therapy, and education for fibromyalgia: A cluster-randomized controlled trial. Pain. 2017;158(12):2354-63. Epub 2017/08/11. doi: 10.1097/j.pain.0000000000001036. PubMed PMID: 28796118; PubMed Central PMCID: PMCPMC5680092.

49. Thakur ER, Holmes HJ, Lockhart NA, Carty JN, Ziadni MS, Doherty HK, et al. Emotional awareness and expression training improves irritable bowel syndrome: A randomized controlled trial. Neurogastroenterol Motil. 2017;29(12). Epub 2017/06/24. doi: 10.1111/nmo.13143. PubMed PMID: 28643436; PubMed Central PMCID: PMCPMC5690851.

50. Montero-Marín J, Navarro-Gil M, Puebla-Guedea M, Luciano JV, Van Gordon W, Shonin E, et al. Efficacy of "attachment-based compassion therapy" in the treatment of fibromyalgia: A randomized controlled trial. Front Psychiatry. 2017;8:307. Epub 2018/02/02. doi: 10.3389/fpsyt.2017.00307. PubMed PMID: 29387020; PubMed Central PMCID: PMCPMC5775966.

51. Amirova A, Cropley M, Theadom A. The effectiveness of the Mitchell Method Relaxation Technique for the treatment of fibromyalgia symptoms: A three-arm randomized controlled trial. International Journal of Stress Management. 2017;24(1).

52. Tomas-Carus P, Branco JC, Raimundo A, Parraca JA, Batalha N, Biehl-Printes C. Breathing exercises must be a real and effective intervention to consider in women with fibromyalgia: A pilot randomized controlled trial. J Altern Complement Med. 2018;24(8):825-32. Epub 2018/04/14. doi: 10.1089/acm.2017.0335. PubMed PMID: 29653069.

53. Lahmann C, Röhricht F, Sauer N, Noll-Hussong M, Ronel J, Henrich G, et al. Functional relaxation as complementary therapy in irritable bowel syndrome: A randomized, controlled clinical trial. J Altern Complement Med. 2010;16(1):47-52. Epub 2010/01/13. doi: 10.1089/acm.2009.0084. PubMed PMID: 20064018.

54. Shinozaki M, Kanazawa M, Kano M, Endo Y, Nakaya N, Hongo M, et al. Effect of autogenic training on general improvement in patients with irritable bowel syndrome: A randomized controlled trial. Appl Psychophysiol Biofeedback. 2010;35(3):189-98. Epub 2009/12/10. doi: 10.1007/s10484-009-9125-y. PubMed PMID: 19997775.

55. Onieva-Zafra MD, Parra-Fernández ML, Fernandez-Martinez E. Benefits of a home treatment program using guided imagery relaxation based on audio recordings for people with fibromyalgia. Holist Nurs Pract. 2019; 33(2):111-20. Epub 2019/02/13. doi: 10.1097/hnp.0000000000000317. PubMed PMID: 30747780.

56. Zech N, Hansen E, Bernardy K, Häuser W. Efficacy, acceptability and safety of guided imagery/hypnosis in fibromyalgia - a systematic review and meta-analysis of randomized controlled trials. Eur J Pain. 2017;21(2): 217-27. Epub 2016/11/30. doi: 10.1002/ejp.933. PubMed PMID: 27896907.

57. Boltin D, Sahar N, Gil E, Aizic S, Hod K, Levi-Drummer R, et al. Gut-directed guided affective imagery as an adjunct to dietary modification in irritable bowel syndrome. J Health Psychol. 2015;20(6):712-20. Epub 2015/06/03. doi: 10.1177/1359105315573450. PubMed PMID: 26032788.

58. Shahbazi K, Solati K, Hasanpour-Dehkordi A. Comparison of hypnotherapy and standard medical treatment alone on quality of life in patients with irritable bowel syndrome: A randomized control trial. J Clin Diagn Res. 2016;10(5):OC01-4. Epub 2016/07/21. doi: 10.7860/jcdr/2016/17631.7713. PubMed PMID: 27437261; PubMed Central PMCID: PMCPMC4948437.

59. Phillips-Moore JS, Talley NJ, Jones MP. The mind-body connection in irritable bowel syndrome: A randomised controlled trial of hypnotherapy as a treatment. Health Psychol Open. 2015;2(1):2055102914564583. Epub 2015/01/28. doi: 10.1177/2055102914564583. PubMed PMID: 28070348; PubMed Central PMCID: PMCPMC5193306.

60. Schaefert R, Klose P, Moser G, Häuser W. Efficacy, tolerability, and safety of hypnosis in adult irritable bowel syndrome: Systematic review and meta-analysis. Psychosom Med. 2014;76(5):389-98. Epub 2014/06/06. doi: 10.1097/psy.0000000000000039. PubMed PMID: 24901382.

61. Welsch P, Bernardy K, Derry S, Moore RA, Häuser W. Mirtazapine for fibromyalgia in adults. Cochrane Database Syst Rev. 2018;8(8):CD012708. Epub 2018/08/07. doi: 10.1002/14651858.CD012708.pub2. PubMed PMID: 30080242; PubMed Central PMCID: PMCPMC6513659.

62. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for fibromyalgia in adults. Cochrane Database of Systematic Reviews. 2015(7).

63. Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Cochrane Database Syst Rev. 2015;2015(6):CD011735. Epub 2015/06/06. doi: 10.1002/14651858.cd011735. PubMed PMID: 26046493; PubMed Central PMCID: PMCPMC4755337.

64. Nüesch E, Häuser W, Bernardy K, Barth J, Jüni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: Network meta-analysis. Ann Rheum Dis. 2013; 72(6):955-62. Epub 2012/06/29. doi: 10.1136/annrheumdis-2011-201249. PubMed PMID: 22739992.

65. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database Syst Rev. 2018;2(2):CD010292. Epub 2018/03/01. doi: 10.1002/14651858. CD010292.pub2. PubMed PMID: 29489029; PubMed Central PMCID: PMCPMC5846183.

66. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database Syst Rev. 2017;1(1):CD012188. Epub 2017/01/04. doi: 10.1002/14651858.CD012188.pub2. PubMed PMID: 28045473; PubMed Central PMCID: PMCPMC6465053.

67. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2016;9(9):CD011790. Epub 2016/09/30. doi: 10.1002/14651858.CD011790. pub2. PubMed PMID: 27684492; PubMed Central PMCID: PMCPMC6457745.

68. Derry S, Wiffen PJ, Häuser W, Mücke M, Tölle TR, Bell RF, et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Cochrane Database Syst Rev. 2017;3(3):CD012332. Epub 2017/03/30. doi: 10.1002/ 14651858.CD012332.pub2. PubMed PMID: 28349517; PubMed Central PMCID: PMCPMC6464559.

69. Aminoshariae A, Kulild JC, Donaldson M. Short-term use of nonsteroidal anti-inflammatory drugs and adverse effects: An updated systematic review. J Am Dent Assoc. 2016;147(2):98-110. Epub 2015/11/13. doi: 10.1016/ j.adaj.2015.07.020. PubMed PMID: 26562732.

70. Theadom A, Cropley M, Smith HE, Feigin VL, McPherson K. Mind and body therapy for fibromyalgia. Cochrane Database Syst Rev. 2015(4):CD001980. Epub 2015/04/10. doi: 10.1002/14651858.CD001980.pub3. PubMed PMID: 25856658.

71. Zhou C, Zhao E, Li Y, Jia Y, Li F. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. Neurogastroenterol Motil. 2019;31(2):e13461. Epub 2018/09/21. doi: 10.1111/nmo.13461. PubMed PMID: 30232834.

72. Wang C, Schmid CH, Fielding RA, Harvey WF, Reid KF, Price LL, et al. Effect of tai chi versus aerobic exercise for fibromyalgia: Comparative effectiveness randomized controlled trial. BMJ. 2018;360:k851. Epub 2018/03/23. doi: 10.1136/bmj.k851. PubMed PMID: 29563100; PubMed Central PMCID: PMCPMC5861462.

73. Maddali Bongi S, Paoletti G, Calà M, Del Rosso A, El Aoufy K, Mikhaylova S. Efficacy of rehabilitation with tai ji quan in an Italian cohort of patients with fibromyalgia syndrome. Complement Ther Clin Pract. 2016;24:109-15. Epub 2016/08/10. doi: 10.1016/j.ctcp.2016.05.010. PubMed PMID: 27502810.

74. Mist SD, Firestone KA, Jones KD. Complementary and alternative exercise for fibromyalgia: A meta-analysis. J Pain Res. 2013;6:247-60. Epub 2013/04/10. doi: 10.2147/jpr.s32297. PubMed PMID: 23569397; PubMed Central PMCID: PMCPMC3616139.

75. Wong A, Figueroa A, Sanchez-Gonzalez MA, Son WM, Chernykh O, Park SY. Effectiveness of tai chi on cardiac autonomic function and symptomatology in women with fibromyalgia: A randomized dontrolled trial. J Aging Phys Act. 2018;26(2):214-21. Epub 2017/06/29. doi: 10.1123/japa.2017-0038. PubMed PMID: 28657825.

76. Zhang XC, Chen H, Xu WT, Song YY, Gu YH, Ni GX. Acupuncture therapy for fibromyalgia: A systematic review and meta-analysis of randomized controlled trials. J Pain Res. 2019;12:527-42. Epub 2019/02/23. doi: 10.2147/jpr.s186227. PubMed PMID: 30787631; PubMed Central PMCID: PMCPMC6365227.

77. Garrido-Ardila EM, González-López-Arza MV, Jiménez-Palomares M, García-Nogales A, Rodríguez-Mansilla J. Effectiveness of acupuncture vs. core stability training in balance and functional capacity of women with fibromyalgia: A randomized controlled trial. Clin Rehabil. 2020;34(5):630-45. Epub 2020/03/25. doi: 10.1177/0269215520911992. PubMed PMID: 32204612.

78. Wang T, Xu C, Pan K, Xiong H. Acupuncture and moxibustion for chronic fatigue syndrome in traditional Chinese medicine: A systematic review and meta-analysis. BMC Complement Altern Med. 2017;17(1):163. Epub 2017/03/25. doi: 10.1186/s12906-017-1647-x. PubMed PMID: 28335756; PubMed Central PMCID: PMCPMC5363012.

79. Zheng H, Chen R, Zhao X, Li G, Liang Y, Zhang H, et al. Comparison between the effects of acupuncture relative to other controls on irritable bowel syndrome: A meta-analysis. Pain Res Manag. 2019;2019:2871505. Epub 2019/12/10. doi: 10.1155/2019/2871505. PubMed PMID: 31814859; PubMed Central PMCID: PMCPMC6877908.

80. Yuan SL, Matsutani LA, Marques AP. Effectiveness of different styles of massage therapy in fibromyalgia: A systematic review and meta-analysis. Man Ther. 2015;20(2):257-64. Epub 2014/12/03. doi: 10.1016/j.math.2014.09.003. PubMed PMID: 25457196.

81. Field T. Massage therapy research review. Complement Ther Clin Pract. 2016;24:19-31. Epub 2016/08/10. doi: 10.1016/j.ctcp.2016.04.005. PubMed PMID: 27502797; PubMed Central PMCID: PMCPMC5564319.

82. U.S. Department of Veterans Affairs. Massage therapy in VA - fact sheet. U.S. Department of Veterans Affairs, Office of Public Health; 2020.

83. TRICARE. List of covered services: Massage 2020 [October 3, 2020]. Available from: https://www.tricare.mil/CoveredServices/IsItCovered/Massage?p=1.

84. Castro-Sánchez AM, Matarán-Peñarrocha GA, Granero-Molina J, Aguilera-Manrique G, Quesada-Rubio JM, Moreno-Lorenzo C. Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med. 2011;2011:561753. Epub 2011/01/15. doi: 10.1155/2011/561753. PubMed PMID: 21234327; PubMed Central PMCID: PMCPMC3018656.

85. Castro-Sánchez AM, Matarán-Peñarrocha GA, Arroyo-Morales M, Saavedra-Hernández M, Fernández-Sola C, Moreno-Lorenzo C. Effects of myofascial release techniques on pain, physical function, and postural stability in patients with fibromyalgia: A randomized controlled trial. Clin Rehabil. 2011;25(9):800-13. Epub 2011/06/16. doi: 10.1177/0269215511399476. PubMed PMID: 21673013.

86. Kerr K, Morse G, Graves D, Zuo F, Lipowicz A, Carpenter DO. A detoxification intervention for Gulf War Illness: A pilot randomized controlled trial. Int J Environ Res Public Health. 2019;16(21). Epub 2019/10/31. doi: 10.3390/ijerph16214143. PubMed PMID: 31661809; PubMed Central PMCID: PMCPMC6862571.

87. 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. 2002;19(6):665-74. Epub 2002/11/14. doi: 10.1093/fampra/19.6.665. PubMed PMID: 12429672.

88. Brosseau L, Wells GA, Tugwell P, Egan M, Wilson KG, Dubouloz CJ, et al. Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: Part 1. Phys Ther. 2008; 88(7):857-71. Epub 2008/05/24. doi: 10.2522/ptj.20070200. PubMed PMID: 18497301.

89. Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: A systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(2):117-31. Epub 2019/12/21. doi: 10.1016/s2468-1253(19)30324-3. PubMed PMID: 31859183.

90. Xie C, Tang Y, Wang Y, Yu T, Wang Y, Jiang L, et al. Efficacy and safety of antidepressants for the treatment of irritable bowel syndrome: A Meta-Analysis. PLoS One. 2015;10(8):e0127815. Epub 2015/08/08. doi: 10.1371/journal.pone.0127815. PubMed PMID: 26252008; PubMed Central PMCID: PMCPMC4529302.

91. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: A systematic review and meta-analysis. Am J Gastroenterol. 2018;113(3):329-38. Epub 2018/01/31. doi: 10.1038/ajg.2017.495. PubMed PMID: 29380823; PubMed Central PMCID: PMCPMC7213047.

92. Atluri DK, Chandar AK, Bharucha AE, Falck-Ytter Y. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): A systematic review and meta-analysis. Neurogastroenterol Motil. 2014;26(4):499-509. Epub 2013/12/20. doi: 10.1111/nmo.12292. PubMed PMID: 24351035.

93. Li F, Fu T, Tong WD, Liu BH, Li CX, Gao Y, et al. Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: A systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2016;91(4):456-68. Epub 2016/04/06. doi: 10.1016/j.mayocp.2016.01.015. PubMed PMID: 27046523.

94. Black CJ, Burr NE, Camilleri M, Earnest DL, Quigley EM, Moayyedi P, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: Systematic review and network meta-analysis. Gut. 2020;69(1):74-82. Epub 2019/04/19. doi: 10.1136/gutjnl-2018-318160. PubMed PMID: 30996042.

95. Nagarajan N, Morden A, Bischof D, King EA, Kosztowski M, Wick EC, et al. The role of fiber supplementation in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2015;27(9):1002-10. Epub 2015/07/07. doi: 10.1097/meg.0000000000000425. PubMed PMID: 26148247.

96. Creed F, Fernandes L, Guthrie E, Palmer S, Ratcliffe J, Read N, et al. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. Gastroenterology. 2003;124(2):303-17. Epub 2003/01/31. doi: 10.1053/gast.2003.50055. PubMed PMID: 12557136.

97. Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. Gastroenterology. 1991;100(2):450-7. Epub 1991/02/01. doi: 10.1016/0016-5085(91)90215-7. PubMed PMID: 1985041.

98. Zijdenbos IL, de Wit NJ, van der Heijden GJ, Rubin G, Quartero AO. Psychological treatments for the management of irritable bowel syndrome. Cochrane Database Syst Rev. 2009(1):CD006442. Epub 2009/01/23. doi: 10.1002/14651858.CD006442.pub2. PubMed PMID: 19160286.

99. Shapiro DA, Rees A, Barkham M, Hardy G, Reynolds S, Startup M. Effects of treatment duration and severity of depression on the maintenance of gains after cognitive-behavioral and psychodynamic-interpersonal psychotherapy. J Consult Clin Psychol. 1995;63(3):378-87. Epub 1995/06/01. doi: 10.1037//0022-006x.63.3.378. PubMed PMID: 7608350.

100. Svedlund J, Sjödin I, Ottosson JO, Dotevall G. Controlled study of psychotherapy in irritable bowel syndrome. Lancet. 1983;2(8350):589-92. Epub 1983/09/10. doi: 10.1016/s0140-6736(83)90678-5. PubMed PMID: 6136745.

101. Arnold LM, Blom TJ, Welge JA, Mariutto E, Heller A. A randomized, placebo-controlled, double-blinded trial of duloxetine in the treatment of general fatigue in patients with chronic fatigue syndrome. Psychosomatics. 2015;56(3):242-53. Epub 2015/02/11. doi: 10.1016/j.psym.2014.12.003. PubMed PMID: 25660434.

102. Montoya JG, Anderson JN, Adolphs DL, Bateman L, Klimas NG, Levine SM, et al. KPAX 002 as a treatment for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A prospective, randomized trial. Int J Clin Exp Med. 2018;11(3):2890-900. Epub 2018/03/15.

103. Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug overdose deaths involving cocaine and psychostimulants with abuse potential - United States, 2003-2017. MMWR Morb Mortal Wkly Rep. 2019;68(17):388-95. Epub 2019/05/03. doi: 10.15585/mmwr.mm6817a3. PubMed PMID: 31048676; PubMed Central PMCID: PMCPMC6541315.

104. FDA. Medication Guide Ritalin. 2013.

105. Institute of Medicine. Chronic multisymptom illness in Gulf War Veterans: Case definitions reexamined. Washington, DC: The National Academies Press; 2014.

106. National Institutes of Health. NINDS Common Data Elements 2020 [December 16, 2020]. Available from: https://www.commondataelements.ninds.nih.gov/.

107. Congressionally Directed Medical Research Programs. GWI Common Data Elements initiative: Department of Defense; 2019 [December 16, 2020]. Available from: https://cdmrp.army.mil/gwirp/research_highlights/19gwi_cde_initiative_highlight.aspx.

108. Agency for Health Research and Quality. The effective health care program stakeholder guide Appendix C: Research questions & PICO(TS) 2011. Available from: https://www.ahrq.gov/research/findings/evidence-based-reports/stakeholderguide/appendixc.html.

109. InformedHealth.org. Cognitive behavioral therapy. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006 September 8, 2016.

110. Zargar F, Farid AA, Atef-Vahid MK, Afshar H, Omidi A. Comparing the effectiveness of acceptance-based behavior therapy and applied relaxation on acceptance of internal experiences, engagement in valued actions and quality of life in generalized anxiety disorder. J Res Med Sci. 2013;18(2):118-22. Epub 2013/08/06. PubMed PMID: 23914213; PubMed Central PMCID: PMCPMC3724371.

111. Niazi AK, Niazi SK. Mindfulness-based stress reduction: A non-pharmacological approach for chronic illnesses. N Am J Med Sci. 2011;3(1):20-3. Epub 2011/01/01. doi: 10.4297/najms.2011.320. PubMed PMID: 22540058; PubMed Central PMCID: PMCPMC3336928.

112. Shonin E, Van Gordon W, Griffiths MD. Meditation awareness training (MAT) for improved psychological well-being: A qualitative examination of participant experiences. J Relig Health. 2014;53(3):849-63. Epub 2013/02/05. doi: 10.1007/s10943-013-9679-0. PubMed PMID: 23377964.

113. Sipe WE, Eisendrath SJ. Mindfulness-based cognitive therapy: Theory and practice. Can J Psychiatry. 2012;57(2):63-9. Epub 2012/02/22. doi: 10.1177/070674371205700202. PubMed PMID: 22340145.

114. Loew TH, Tritt K, Siegfried W, Bohmann H, Martus P, Hahn EG. Efficacy of 'functional relaxation' in comparison to terbutaline and a 'placebo relaxation' method in patients with acute asthma. A randomized, prospective, placebo-controlled, crossover experimental investigation. Psychother Psychosom. 2001;70(3):151-7. Epub 2001/05/08. doi: 10.1159/000056241. PubMed PMID: 11340417.

115. Baird CL, Murawski MM, Wu J. Efficacy of guided imagery with relaxation for osteoarthritis symptoms and medication intake. Pain Manag Nurs. 2010;11(1):56-65. Epub 2010/03/09. doi: 10.1016/j.pmn.2009.04.002. PubMed PMID: 20207328.

116. Eller LS. Guided imagery interventions for symptom management. Annu Rev Nurs Res. 1999;17:57-84. Epub 1999/07/27. PubMed PMID: 10418653.

117. Riera R, Braga VL, Rocha L, Bernardo DD, Andrade LAF, Hsu JC, et al. What do Cochrane systematic reviews say about new practices on integrative medicine? Sao Paulo Med J. 2018;136(3):251-61. Epub 2018/06/28. doi: 10.1590/1516-3180.2018.0172170418. PubMed PMID: 29947699.

118. de Maat S, de Jonghe F, Schoevers R, Dekker J. The effectiveness of long-term psychoanalytic therapy: A systematic review of empirical studies. Harv Rev Psychiatry. 2009;17(1):1-23. Epub 2009/02/12. doi: 10.1080/10673220902742476. PubMed PMID: 19205963.

119. Sankar A, Melin A, Lorenzetti V, Horton P, Costafreda SG, Fu CHY. A systematic review and meta-analysis of the neural correlates of psychological therapies in major depression. Psychiatry Res Neuroimaging. 2018;279:31-9. Epub 2018/08/07. doi: 10.1016/j.pscychresns.2018.07.002. PubMed PMID: 30081291.