VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT AND REHABILITATION OF POST-ACUTE MILD TRAUMATIC BRAIN INJURY

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 – June 2021

Prepared by:

The Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury 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 – June 2021

Based on evidence reviewed through April 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) 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 February 2016, the VA and DoD published a CPG for the Management of Concussion-mild Traumatic Brain Injury (2016 VA/DoD mTBI CPG), which was based on evidence reviewed through March 2015. Since the release of that CPG, a growing body of literature has expanded the evidence base and understanding of mild traumatic brain injury (mTBI). Consequently, a recommendation to update the 2016 VA/DoD mTBI CPG was initiated in 2019.

This CPG provides an evidence-based framework for the management and rehabilitation of patients with symptoms attributed to mTBI toward improving clinical outcomes. Successful implementation of this CPG may facilitate:

- Assessing the patient's condition and collaborating with the patient, family, and caregivers to determine optimal management of patient care
- Emphasizing the use of patient-centered care using individual risk factors and event history
- Minimizing preventable complications and morbidity
- Optimizing individual health outcomes and quality of life

II. Background

A traumatic brain injury (TBI) is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force. It is diagnosed by new onset or worsening of at least one of the following clinical signs immediately following the event:(2, 3)

- Any period of loss of or a decreased level of consciousness
- Any loss of memory for events immediately before or after the injury (post-traumatic amnesia)
- Any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking, alteration of consciousness/mental state)
- Neurological deficits (e.g., weakness, loss of balance, change in vision, apraxia, paresis/plegia, sensory loss, visual-spatial neglect, aphasia) that may or may not be transient
- An intracranial lesion

External forces may include any of the following events: the head being struck by an object, the head striking an object, the brain undergoing an acceleration or deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events (e.g., a blast or explosion), or other forces.

The above criteria define the event of a TBI. Not all individuals exposed to an external force will sustain a TBI, but any person who has a history of such an event with immediate manifestation of any of the above signs and symptoms can be said to have had a TBI.

The most recent U.S. Centers for Disease Control and Prevention (CDC) statistics estimate that approximately 2,500,000 emergency department visits, 288,000 hospitalizations, and 56,800 deaths occurred due to TBI of any severity in 2014.(4) The Defense Health Agency Traumatic Brain Injury Center of Excellence (TBICoE) reports that 336,203 Service Members were diagnosed with a first, lifetime TBI between 2007 through September 30, 2020, with 282,268 of those being classified as mTBI.(5) This data is obtained from multiple sources, including the Armed Forces Health Surveillance Branch (which operates the Defense Medical Surveillance System) and the Theater Medical Data Store (a web-based application used to track, analyze and manage a Service Member's medical treatment information recorded on the battlefield). A TBI case, for routine surveillance and reporting, is defined based on the DoD Standard Surveillance Case Definition for TBI used by the Armed Forces Health Surveillance Branch.(6)

In 2007, VA developed and implemented the TBI Screening and Evaluation Program in its medical facilities. All Veterans from Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND) who present to the VA for care are screened for possible TBI during their initial visit to enhance identification and treatment of TBI and any related physical, cognitive, and emotional problems. From April 13, 2007, through September 30, 2020, 1,437,957 OEF/OIF/OND Veterans were screened for possible mTBI. Of these Veterans, 267,404 screened positive for possible mTBI with current symptoms and were referred for comprehensive TBI evaluations; 103,802 of those Veterans were later diagnosed with having sustained mTBI and received appropriate care.(7) Veterans who initially screened positive and subsequently were determined not to have TBI were referred for medical follow-up as appropriate for their condition. In fiscal year 2020, 97,894 Veterans with TBI of any severity were treated across the VA.

To determine the TBI severity, clinicians should use the criteria displayed in Table 1.

Table 1. Classification of TBI Severity[a] (3)

Criteria	Mild	Moderate	Severe
Structural imaging (see Recommendation 4)	Normal[b]	Normal or abnormal	Normal or abnormal
Loss of consciousness	0-30 min	>30 min and <24 hours	>24 hours
Alteration of consciousness/mental state[c]	up to 24 hours	>24 hours; severity based on other criteria	
Post-traumatic amnesia	0-1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best available score in first 24 hours)[d]	13-15	9-12	<9

[a] If a patient meets criteria in more than one category of severity, the higher severity level is assigned.

[b] No clinically relevant findings.

[c] Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and/or being unable to describe events immediately before or after the trauma injury event.

[d] In April 2015, the DoD released a memorandum recommending against the use of Glasgow Coma Scale scores to diagnose TBI. See the memorandum for additional information.(3)

Abbreviations: TBI: traumatic brain injury

A. Terminology Conventions within this Guideline

This CPG focuses only on mTBI. Within this CPG, the terms "mTBI" and "concussion" are used interchangeably. The term "symptoms," is used most frequently; however, other studies and publications may use the terms "difficulties," "problems," and "dysfunction," and these are synonymous with "symptoms." Patients are also referred to as "patients with symptoms attributed to mTBI," "patients with a history of mTBI," or "patients with a history of concussion" to denote patients that are beyond the immediate period of injury and have been previously diagnosed with a TBI of mild severity. The use of the phrase "patients with mTBI," although widely used in clinical practice, is discouraged in this document because the accepted clinical case definition of mTBI refers only to those symptoms and signs that occur in the immediate injury period and thus should never be used to refer to ongoing symptoms that persist and are attributed to the TBI injury event after the immediate period.

The Work Group acknowledges that there is not standard terminology regarding the periods following mTBI; however, the following construct of terms is used within this CPG and was arrived at by Work Group consensus. The terms used within this CPG to delineate post-injury periods following mTBI are outlined below:

- Acute period refers to 0 – 7 days post-injury
- Post-acute period refers to 1 – 12 weeks post-injury
- Chronic refers to >12 weeks post-injury

When communicating with patients on the diagnosis of an mTBI, the terms "concussion" or "history of mTBI" are preferred, indicating a transient condition. Providers should avoid using the terms "brain damage" or "brain injury" which may inadvertently reinforce misattribution of symptoms or insecurities about recovery.

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through April 28, 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.

A. Guideline Audience

This CPG is intended for use by VA and DoD primary care providers (PCPs) including physicians, nurse practitioners, physician assistants, nurses, pharmacists, psychologists, social workers, and others involved in the healthcare team caring for patients with symptoms attributed to mTBI. Additionally, this guideline is intended for those in community practice involved in the care of Service Members or Veterans with symptoms attributed to mTBI.

B. Guideline Population

The patient population of interest for this CPG is patients with symptoms attributed to mTBI in the post-acute phase who are eligible for care in the VA or DoD healthcare delivery systems, and those who receive care from community-based clinicians. It includes Veterans as well as deployed and non-deployed active duty Service Members, National Guard, Reserve members, Reserve Officer Training Corps (ROTC) Cadets,

those in military academies, and their dependents. Regardless of care setting, any patient in the VA and DoD healthcare system should have access to this CPG's recommended interventions.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The current document is an update to the 2016 VA/DoD mTBI CPG. The following significant updates make it important that health care clinicians review this guideline:

- More user-friendly management algorithms
- Greater specificity in recommendations related to assessment, recovery prognostication, and symptom management
- Clearer delineation of relevance to patient sub-populations
- Expanded review of integrative health approaches
- Use of the most up-to-date, peer-reviewed sources
- Highlights of key research directions

The 2021 VA/DoD mTBI 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 mTBI CPG is the second update to this CPG. It provides clinical practice recommendations for the care of patients with symptoms attributed to mTBI (see Recommendations). In addition, the Algorithm incorporates the recommendations in the context of the flow of patient care. This CPG also includes Research Priorities, which 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: David X. Cifu, MD and Blessen C. Eapen, MD, FAAPMR, from the VA and Maj Thomas J. Bayuk, DO and Katharine C. Stout, PT, DPT, NCS, MBA from the DoD.

The Work Group comprised individuals with the following areas of expertise: neurology, neuropsychology, nursing, occupational therapy, pharmacy, physical medicine and rehabilitation, physical therapy, primary care, psychology, social work, and speech-language pathology. See Table 2 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 2. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	**David X. Cifu, MD (Champion)**
	Blessen C. Eapen, MD, FAAPMR (Champion)
	Jennifer Burton, DPT
	Margaret Daggett, MSN, FNP-BC, CRRN
	Ruby Diaz, LCSW
	Dorene Doi, OTR/L
	Robin A. Hurley, MD
	Tracy Kretzmer, PhD, ABPP-CN
	Linda M. Picon, MCD, CCC-SLP
	Ronald G. Riechers, II, MD
	Kathryn Tortorice, PharmD, BCPS
Department of Defense	**Maj Thomas J. Bayuk, DO (Champion)**
	Katharine C. Stout, PT, DPT, NCS, MBA (Champion)
	Amy O. Bowles, MD
	Lt Col Andrew W. Bursaw, DO
	CDR Stephanie Felder, PhD, LCSW, LCAS-A, BCD
	LTC Carrie W. Hoppes, PT, PhD, NCS, OCS, ATC
	Adam Edward Lang, PharmD, BCACP
	R. Kevin Manning, PhD, CCC-SLP
	Danielle D. Murray, PhD
	CAPT Scott W. Pyne, MD
VA Evidence Based Practice, Office of Quality and Patient Safety ***Veterans Health Administration***	M. Eric Rodgers, PhD, FNP-BC
	James Sall, PhD, FNP-BC
	René Sutton, BS, HCA
Office of Evidence Based Practice ***Defense Health Agency***	Corinne K. B. Devlin, MSN, RN, FNP-BC
	Lisa D. Jones, BSN, RN, MHA, CPHQ

Organization	Names*
The Lewin Group	Cliff Goodman, PhD
	Erika Beam, MS
	Ben Agatston, JD, MPH
	Charlie Zachariades, MSc
	Olivia Samson, MPH
	Inveer Nijjar, BS
ECRI	James Reston, PhD
	Amy Tsou, MD
	Michele Datko, MS
	Jessica Gontarek, MSLIS
	Linnea Hermanson, MA
	Kariann Hudson, MEd
	Nancy Sullivan, BA
Sigma Health Consulting	Frances M. Murphy, MD, MPH
	James G. 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.(8) The *Guideline for Guidelines* is available at http://www.healthquality.va.gov/policy/index.asp. This CPG also aligns with the National Academy of Medicine's (NAM) 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 (SR), and external review).(9) 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):(10)

- 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.(11) 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).

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 standard of care 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 3).

Table 3. 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.(12, 13) 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 2016 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.(14) 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.(15)

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).(16, 17) Table 4 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 2016 VA/DoD mTBI CPG's recommendation categories.

Table 4. 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) (16) and Garcia et al. (2014) (17)

[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*.(8) 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),(18) 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).(8) 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).

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.(12, 19) 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 26, 2020. The focus group aimed to gain insights into patients with symptoms attributed to mTBI 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 nine people. The Work Group acknowledges this convenience sample is not representative of all patients with symptoms attributed to mTBI within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see Appendix B. Patient focus group participants were 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. The organizations that provided feedback on this CPG include: American Physical Therapy Association, Indiana University School of Medicine Department of Physician Medicine & Rehabilitation, Louisiana State University Health Sciences Center, National Center for Medical Rehabilitation Research, University of North Carolina at Chapel Hill, University of Texas Health Science Center at San Antonio, University of Texas Southwestern Medical Center.

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 symptoms attributed to mTBI. 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, Stepped Care and a "Whole Health" Orientation

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/holistic health approach (i.e., individualized treatment based

on patient needs, values, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being. Values and preferences can be affected by a wide range of characteristics and life experiences (e.g., age, sex, race, ethnicity).

A "stepped care" approach preserves the patient-centered nature of care as the patient moves through levels of increasing complexity of needs, to include involvement of specialty services. The "next step" in care becomes a seamless extension of their care to the next level of complexity and specialization in care, rather than being the experience of leaving their team when they are "referred to the specialist."

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.(20, 21) 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 with their patients. Shared decision making was emphasized in *Crossing the Quality Chasm,* an Institute of Medicine (IOM) (now NAM) report, in 2001.(22) 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.

C. Patients with Co-occurring Conditions

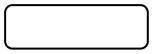
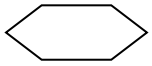
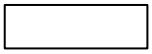
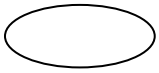
Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management and rehabilitation of mTBI. Many Veterans, Service Members, and their families have one or more co-occurring conditions. Because mTBI is sometimes accompanied by co-occurring conditions, it is often best to manage mTBI collaboratively with other care providers. 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
(see Algorithm Sidebar 5: Relevant VA/DoD CPGs).

VIII. Algorithm

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

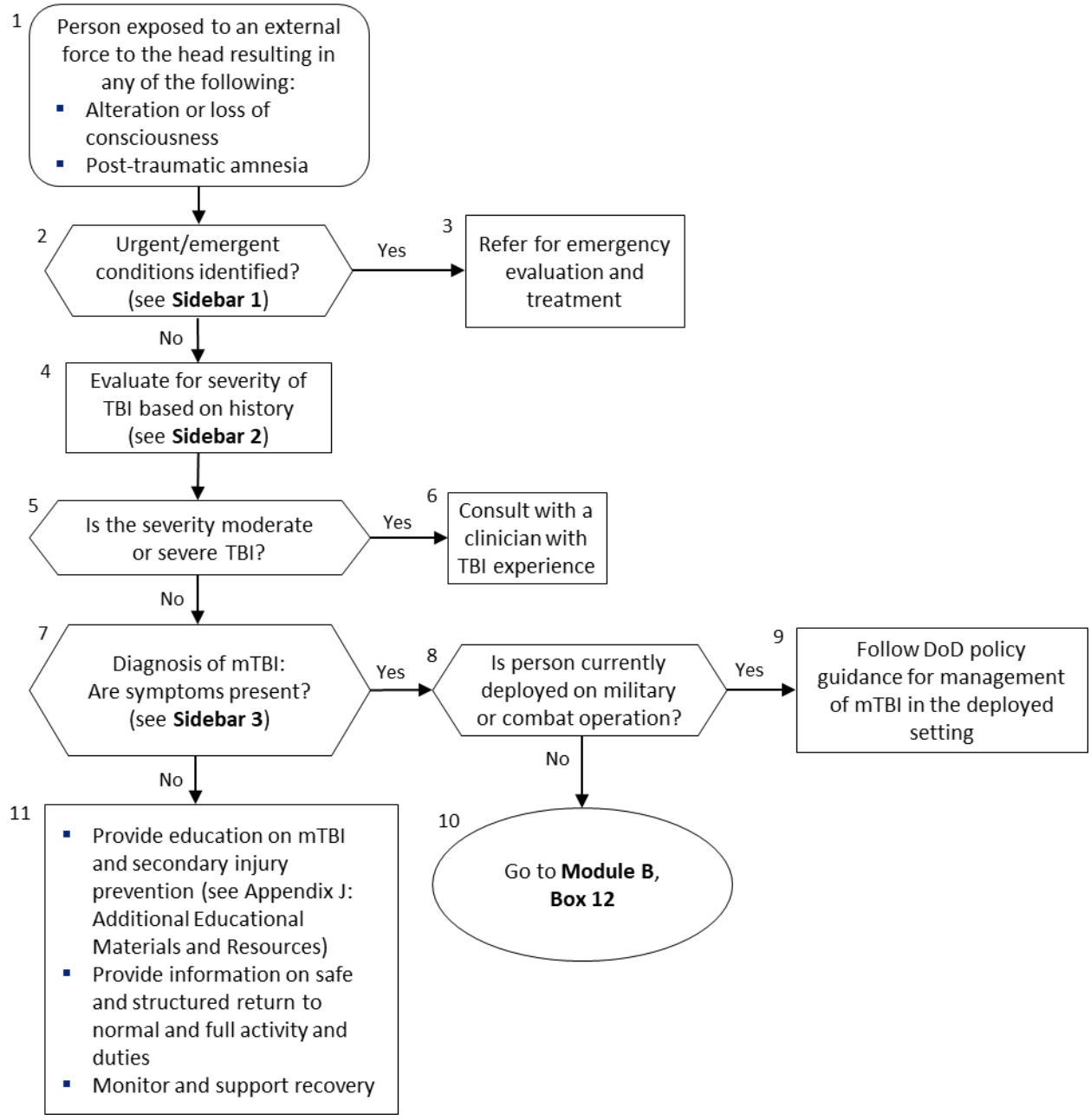
- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

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.(23) 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

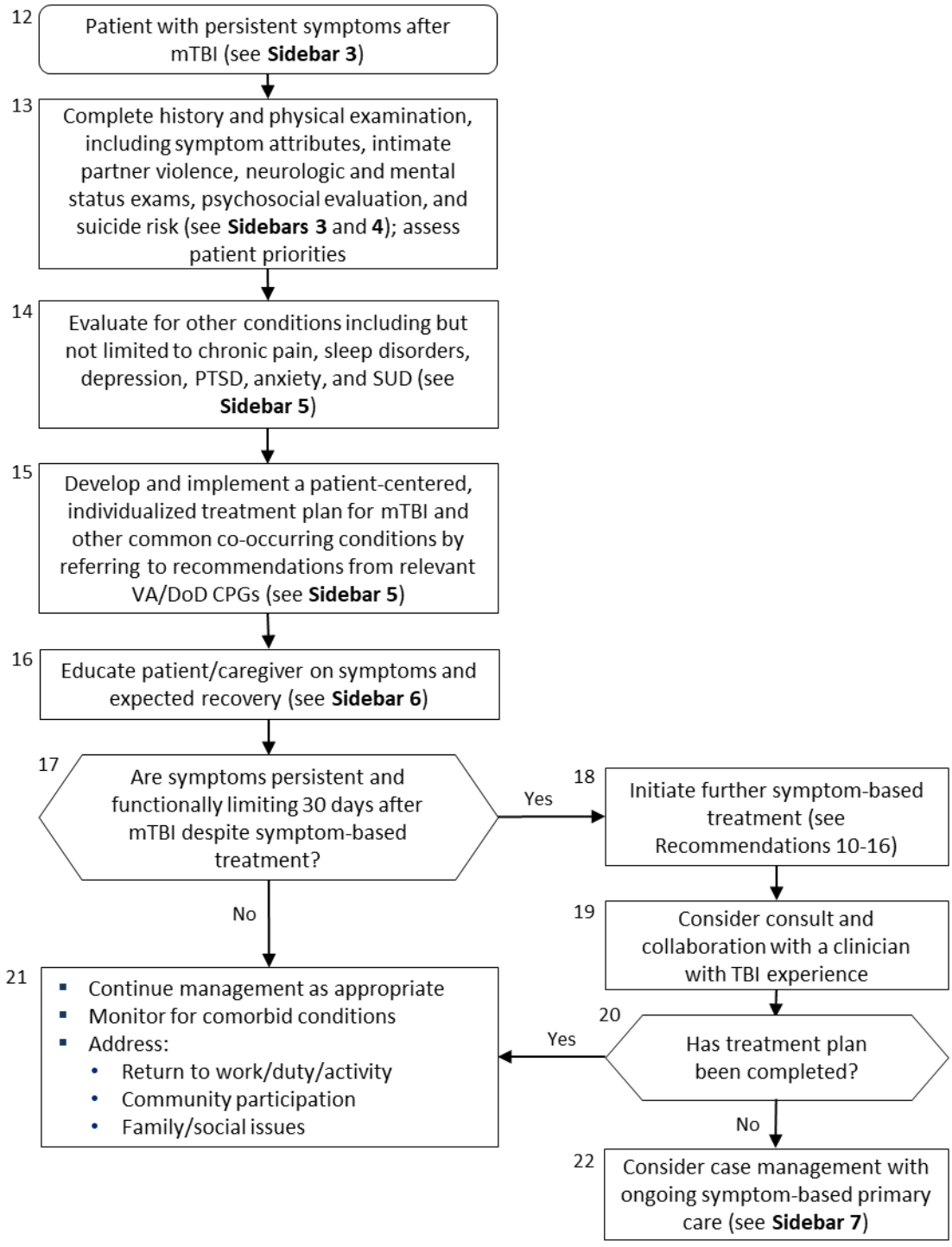
Appendix K contains alternative text descriptions of the algorithm modules.

A. Module A: Initial Presentation (>7 Days Post-injury)



Abbreviations: DoD: Department of Defense; mTBI: mild traumatic brain injury; TBI: traumatic brain injury

B. Module B: Management of Symptoms Persisting >7 Days After Mild Traumatic Brain Injury



Abbreviations: CPG: clinical practice guideline; DoD: Department of Defense; TBI: traumatic brain injury; mTBI: mild traumatic brain injury; PTSD: posttraumatic stress disorder; SUD: substance use disorder; VA: Department of Veterans Affairs

Sidebar 1: Potential Indicators for Immediate Referral
• Declining level of consciousness/impaired alertness • Declining neurological exam/focal neurological symptoms • Pupillary asymmetry • Seizures • Repeated vomiting • Motor or sensory deficits • Double vision • Worsening headache • Slurred speech • Marked change in behavior or orientation

Sidebar 2: Classification of TBI Severity[a]			
Criteria	**Mild**	**Moderate**	**Severe**
Structural imaging (see Recommendation 4)	Normal[b]	Normal or abnormal	Normal or abnormal
Loss of consciousness	0 – 30 min	>30 min and <24 hours	>24 hours
Alteration of consciousness/mental state[c]	up to 24 hours	>24 hours; severity based on other criteria	
Post-traumatic amnesia	0 – 1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best available score in first 24 hours)[d]	13 – 15	9 – 12	<9

[a] If patient meets criteria in more than one category of severity, the higher severity level is assigned.

[b] No clinically relevant findings.

[c] Alteration of mental status must be immediately related to the trauma to the head. Typical symptoms would be: looking and feeling dazed and uncertain of what is happening, confusion, difficulty thinking clearly or responding appropriately to mental status questions, and/or being unable to describe events immediately before or after the injury event.

[d] In April 2015, the DoD released a memorandum recommending against the use of Glasgow Coma Scale scores to diagnose TBI. See the memorandum for additional information(3)

Abbreviations: TBI: traumatic brain injury

Sidebar 3: Possible Post-Concussion Symptoms[a,b]		
Physical Symptoms	**Cognitive Symptoms**	**Behavior/Emotional Symptoms**
• Headache • Dizziness/vertigo • Balance problems • Nausea • Fatigue • Sleep disturbance • Visual disturbance • Sensitivity to light • Hearing difficulties/loss • Tinnitus • Sensitivity to noise	Problems with: • Attention • Concentration • Memory • Speed of processing • Judgment • Executive functions • Speech and language • Visual-spatial function	• Depression • Anxiety • Agitation • Irritability • Impulsivity • Aggression

[a] Symptoms that may develop within 30 days post-injury

[b] Symptoms can be monitored with instruments such as the Neurobehavioral Symptom Inventory (NSI) or Rivermead Post-Concussion Questionnaire (RPCQ).

Abbreviations: mTBI: mild traumatic brain injury

Sidebar 4: Symptom Attributes

- Duration, onset, and location of symptom
- Previous episodes, treatment, and response
- Patient perception of symptom
- Impact on functioning
- Factors that exacerbate or alleviate symptom

Sidebar 5: Relevant VA/DoD CPGs

- VA/DoD Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp
- VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. Available at: https://www.healthquality.va.gov/guidelines/MH/mdd/
- VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/
- 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/
- VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders. Available at: https://www.healthquality.va.gov/guidelines/MH/sud/
- VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache. Available at: https://www.healthquality.va.gov/guidelines/Pain/headache/
- VA/DoD Clinical Practice Guideline for the Management of Chronic Multisymptom Illness. Available at: https://www.healthquality.va.gov/guidelines/MR/cmi/
- VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. Available at: https://www.healthquality.va.gov/guidelines/MH/srb/

Sidebar 6: Early Intervention

- Integrate patient and caregiver needs and preferences into assessment and treatment
- Provide information and education on symptoms and expected recovery
- Provide reassurance on expectation of positive recovery
- Educate about prevention of further injury
- Empower patient for self-management
- Consider teaching relaxation and stress management techniques as needed
- Recommend limiting use of caffeine/nicotine/alcohol
- Encourage monitored progressive return to normal duty/work/activity/exercise[a]
- Discuss need for consistency with healthy nutrition, exercise, and sleep habits
- Provide information regarding the National Suicide Prevention Lifeline (1-800-273-8255) if appropriate

[a] Provider resources for progressive return to activity (PRA) are available at: https://www.health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Provider-Resources

Sidebar 7: Case Management

Case managers may:

- Provide coordination of care as outlined in the individualized treatment plan (referrals, authorizations, appointments/reminders)
- Provide advocacy and support for Veteran/Service Member and caregivers
- Reinforce early interventions and education
- Address psychosocial issues (financial, family, housing, or school/work)
- Connect patient to available resources

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).

The target population for these recommendations is patients with symptoms attributed to mTBI in the post-acute phase (see Guideline Population).

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Setting of Care		1.	We suggest a primary care (as opposed to specialty care), symptom-focused approach in the evaluation and management of the majority of patients with symptoms attributed to mild traumatic brain injury.	Weak for	Reviewed, Amended
		2.	There is insufficient evidence to recommend for or against specialized treatment programs to improve morbidity, function, and return to work in patients with persistent symptoms attributed to mild traumatic brain injury.	Neither for nor against	Reviewed, New-replaced
Diagnosis and Assessment		3.	For patients with new symptoms that develop more than 30 days after mild traumatic brain injury, we suggest a symptom-specific evaluation for non-mild traumatic brain injury etiologies.	Weak for	Not reviewed, Amended
		4.	We suggest against using the following tests to establish the diagnosis of mild traumatic brain injury or direct the care of patients with symptoms attributed to mild traumatic brain injury: a. Neuroimaging b. Serum biomarkers c. Electroencephalogram	Weak against	Reviewed, Amended
		5.	We suggest against using computerized post-concussive screening batteries[a] for routine diagnosis and care of patients with symptoms attributed to mild traumatic brain injury.	Weak against	Reviewed, New-replaced
		6.	We suggest against performing comprehensive neuropsychological/cognitive testing during the first 30 days following mild traumatic brain injury.	Weak against	Reviewed, New-replaced

[a] E.g., Automated Neuropsychological Assessment Metrics (ANAM), Neuro-Cognitive Assessment Tool (NCAT), and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Mild Traumatic Brain Injury and Future Neurocognitive Decline		7.	When counseling patients about the long-term effects of mild traumatic brain injury, there is insufficient evidence to state that single or repeated mild traumatic brain injury increases their risk of future neurocognitive decline.	Neither for nor against	Reviewed, New-added
		8.	When counseling patients about the long-term effects of mild traumatic brain injury, there is insufficient evidence to state that demographic, injury-related clinical, and management factors increase the risk of future neurocognitive decline in patients with symptoms attributed to single or repeated mild traumatic brain injury.	Neither for nor against	Reviewed, New-added
Effects of Mild Traumatic Brain Injury Etiology on Treatment		9.	We suggest against adjusting outcome prognosis and treatment strategy based on mechanism of injury.	Weak against	Reviewed, New-replaced
Symptom-based Treatments of Mild Traumatic Brain Injury	*a. Cognitive Symptoms*	10.	We suggest that patients with symptoms attributed to mild traumatic brain injury who present with memory, attention, or executive function problems despite appropriate management of other contributing factors (e.g., sleep, pain, behavioral health, headache, disequilibrium) should be referred for a short trial of clinician-directed cognitive rehabilitation services.	Weak for	Reviewed, Amended
		11.	We suggest against the use of self-administered computer training programs for the cognitive rehabilitation of patients with symptoms attributed to mTBI.	Weak against	Reviewed, New-added
	b. Behavioral Symptoms	12.	We suggest that patients with symptoms attributed to mild traumatic brain injury who present with behavioral health conditions, including posttraumatic stress disorder, substance use disorders, and mood disorders, be evaluated and managed the same whether they have had mild traumatic brain injury or not, according to the relevant existing VA/DoD clinical practice guidelines.	Weak for	Reviewed, New-replaced

Topic	Sub-topic	#	Recommendation	Strength[a]	Category[b]
Symptom-based Treatments of Mild Traumatic Brain Injury (cont.)	*c. Vestibular and Proprioceptive Symptoms*	13.	We suggest that patients with persistent symptoms of dizziness and imbalance attributed to mild traumatic brain injury be offered a trial of specific vestibular rehabilitation and proprioceptive therapeutic exercise.	Weak for	Reviewed, New-replaced
	d. Visual Symptoms	14.	There is insufficient evidence to suggest for or against the use of any particular modality for the treatment of visual symptoms attributed to mild traumatic brain injury such as diplopia, accommodation or convergence deficits, visual tracking deficits and/or photophobia.	Neither for nor against	Reviewed, Amended
	e. Tinnitus	15.	There is no evidence to suggest for or against the use of any particular modality for the treatment of tinnitus attributed to mild traumatic brain injury.	Neither for nor against	Reviewed, Amended
	f. Exertion-induced Symptoms	16.	There is insufficient evidence to recommend for or against treatments for exertion-induced symptoms/symptom clusters attributed to mild traumatic brain injury.	Neither for nor against	Reviewed, New-added
Interventions with Insufficient Evidence	*a. Complementary and Integrative Health*	17.	There is insufficient evidence to recommend for or against the use of any of the following interventions for the treatment of patients with symptoms attributed to mild traumatic brain injury: a. Acupuncture b. Tai chi c. Meditation d. Mindfulness e. Yoga f. Massage g. Chiropractic therapy h. Cranial electrotherapy stimulation (CES) i. Sensory deprivation tanks	Neither for nor against	Reviewed, New-added
	b. Hyperbaric Oxygen Therapy	18.	We recommend against the use of hyperbaric oxygen therapy for the treatment of patients with symptoms attributed to mild traumatic brain injury.	Strong against	Reviewed, New-added
	c. Repetitive Transcranial Magnetic Stimulation	19.	We suggest against the use of repetitive transcranial magnetic stimulation for the treatment of patients with symptoms attributed to mild traumatic brain injury.	Weak against	Reviewed, New-added

[a] For additional information, see Grading Recommendations.

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

A. Setting of Care

Recommendation

1. We suggest a primary care (as opposed to specialty care), symptom-focused approach in the evaluation and management of the majority of patients with symptoms attributed to mild traumatic brain injury.
   (Weak for | Reviewed, Amended)

Discussion

Based on studies included in the 2016 VA/DoD mTBI CPG systematic evidence review, Snell et al. (2009),(24) and Bell et al. (2008),(25) the Work Group determined that evaluation and management of the majority of patients with symptoms attributed to mTBI should be driven by primary care. The benefits of this approach outweigh the harms and burdens.

Symptoms attributed to mTBI are nonspecific, and many of these symptoms are present in people without a history of mTBI. It is often difficult to determine the exact etiology, especially when symptoms involve multiple domains (e.g., psychological, neurological, neuroendocrine symptoms) or when patients present at times distant from their original injury event. There is currently insufficient evidence regarding the long-term sequelae of concussive events.

The presumption that all presenting symptoms are attributed to the mTBI event may lead to the consideration that all are "mTBI symptoms." This misattribution may lead to the patient being considered a lifelong patient with symptoms attributed to mTBI and, as a result, subjected to repeated evaluations that are unlikely to be helpful and may be potentially harmful (e.g., needless repeated exposure to radiation).

Approaching these symptoms in a manner consistent with the treatment of chronic, multisystem conditions commonly managed in the primary care model is preferred when developing a comprehensive and personalized treatment plan. Building a solid therapeutic patient-provider alliance is essential to the proper management of patients with symptoms attributed to mTBI. Providers should acknowledge symptoms (i.e., not label them as psychogenic) and reinforce normalcy and wellness rather than impairment and self-labeling.

Regularly scheduled primary care appointments with the same team providing longitudinal care are advised rather than as-needed appointments. PCPs should protect patients from unnecessary tests or consultations that could potentially put them at risk (e.g., medication interactions prescribed from different providers, radiation exposure) or lead to more negative illness expectations. Specialty consultation is appropriate if clinically indicated but should be conducted prudently and judiciously. This symptom-driven, primary care approach validates the patient's experience, minimizes misattribution and labeling, maintains vigilance regarding new symptoms that may arise, and decreases the use of expensive and labor-intensive specialty consultation and evaluations.

The Work Group systematically reviewed evidence related to Recommendation 1, but no identified studies were included due to very low quality and a focus on the moderate/severe TBI population. The Work Group also considered the assessment of the evidence put forth in the 2016 VA/DoD mTBI CPG.(24, 25)

Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including lack of concealed allocation or blinding of outcome assessors, more than 20% attrition, no intention-to-treat analysis, and drop-out rates differed between groups. The benefits of a consistent primary care approach outweighed the potential harms of causing undue panic or worry to patients (e.g., negative expectations) when referring to specialists. Patient values and preferences were somewhat varied due to uncertainty regarding the best place to get their care (see Appendix B). PCPs may lack confidence in managing symptoms that may be related to mTBI, and mTBI specialty clinics may lack confidence in PCP capabilities or fail to support the PCPs in providing this care. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

2. There is insufficient evidence to recommend for or against specialized treatment programs to improve morbidity, function, and return to work in patients with persistent symptoms attributed to mild traumatic brain injury.
   (Neither for nor against | Reviewed, New-replaced)

Discussion

Patients with persistent symptoms attributed to mTBI are often best treated in the primary care setting (see Recommendation 1). However, some patients who present with chronic, persistent symptoms and co-occurring conditions may benefit from an individualized treatment plan for symptom management developed through an interdisciplinary, team-based approach. The interdisciplinary team often includes a clinician with TBI experience, physical therapist, occupational therapist, psychologist (rehabilitation/neuropsychology), speech-language pathologist, and/or case manager.

Scheenen et al. (2017), the only study that met criteria for inclusion in the systematic evidence review, compared telephone counseling to cognitive behavioral therapy (CBT) and found no clinically significant difference in return to work outcomes, function, depression, or anxiety measures.(26)

The Work Group systematically reviewed evidence related to this recommendation (26) and considered the assessment of the evidence put forth in the 2016 VA/DoD mTBI 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 in terms of time, travel, copays, and potential stigma of mental health treatment. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

B. Diagnosis and Assessment

Recommendation

3. For patients with new symptoms that develop more than 30 days after mild traumatic brain injury, we suggest a symptom-specific evaluation for non-mild traumatic brain injury etiologies.
   (Weak for | Not reviewed, Amended)

Discussion

The anticipated outcome for most patients with symptoms attributed to mTBI is full recovery within weeks to months, without residual deficits. Symptoms related to concussion are nonspecific, making it difficult to definitively attribute new symptoms to the concussive injury. However, with patients that are initially asymptomatic and then develop new symptoms 30 days or more following mTBI, these symptoms are

unlikely to be the result of the mTBI; therefore, the work-up and management should not focus on the initial mTBI, but rather on alternative etiologies. Consequently, symptom-focused evaluation and treatment are recommended, particularly when the time since injury is greater than 30 days.

The supporting evidence for this recommendation (27) was not reviewed in either 2016 or the current update, but was carried forward from the 2009 VA/DoD mTBI CPG. Considering this literature, the Work Group determined the benefits of a symptom-focused diagnostic workup outweigh the harm of unnecessary testing. Despite general consistency in the literature supporting focused diagnostic work-up specific to new symptoms, there is some variability in patient preferences regarding this treatment approach; some patients value diagnostic tests, while others are not interested.(27)

Patient focus group participants noted a desire for providers to use individualized treatment approaches (see Appendix B). Furthermore, patient focus group participants perceived a lack of adequate expertise and training in the early identification and diagnosis of mTBI within the military culture. They believed this contributed to their mTBIs being diagnosed and treated long after the point of injury, often years later.

The Work Group did not systematically review new evidence related to this recommendation and considered the assessment of the evidence put forth in the 2009 VA/DoD mTBI CPG.(27) Therefore, this is a *Not Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations, including significant selection bias and risk for false positive results.(27) The benefits of a focused diagnostic workup outweighed the potential harm of unnecessary testing. Patient values and preferences were varied, as some patients may value testing and explanations, while others may not want to come in for testing. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

4. We suggest against using the following tests to establish the diagnosis of mild traumatic brain injury or direct the care of patients with symptoms attributed to mild traumatic brain injury:
   a. Neuroimaging
   b. Serum biomarkers
   c. Electroencephalogram

   (Weak against | Reviewed, Amended)

Discussion

Mild TBI continues to be a clinical diagnosis based on the VA/DoD criteria outlined above (see Background). There is a tremendous effort within the mTBI clinical and research community to achieve objective measures of mTBI for diagnosis and prognosis. However, because of the significant clinical and pathophysiologic heterogeneity of mTBI, no definitive objective test exists. Currently, evidence does not support the use of laboratory, imaging, or physiologic testing for diagnosing mTBI or directing the care of patients with symptoms attributed to mTBI.

The systematic evidence review of neuroimaging found four cross-sectional studies (28-31) and one cohort study.(32) Weak associations were seen between diffusion tensor imaging (DTI) and outcomes related to symptom severity and return to work.(28-30, 32) No correlation could be made between white matter hyperintensities seen on MRI utilizing T2 fluid-attenuated inversion recovery (FLAIR) sequences and

neuropsychological testing or self-reported fatigue.(31) The confidence in the quality of the evidence was very low with significant limitations such as small sample size with mixed-severity TBI. Neuroimaging research continues to make advances; however, there is inadequate evidence to recommend any particular neuroimaging modality or technique for routine clinical use that may aid in the diagnosis and/or direction of care for patients with symptoms attributed to mTBI.

Similar to neuroimaging biomarkers, there is substantial interest in the prognostic value of serum biomarkers for mTBI. Literature regarding serum biomarkers in the post-acute period (>7 days) is growing, adding to an already established body of evidence for use in the acute period. Unfortunately, current evidence regarding the use of such in routine clinical practice following the acute period is limited and weak.

An SR by Mercier et al. (2018) assessed the predictive value of the serum protein S100β collected 3 – 6 hours after mTBI and found no significant association with persistent post-concussion symptoms (≥3 months) or return to work at six months.(33) This study illustrates the poor clinical utility of S100β in identifying patients at risk for persistent symptoms related to mTBI. Three other cross-sectional studies on serum biomarkers: exosomal tau, phosphorylated-tau (p-tau), plasma tau, amyloid beta 42 (Aβ42), and serum cytokines,(34-36) as well as supporting literature from the 2016 VA/DoD mTBI CPG,(37) were reviewed; however, the evidence from these additional studies had significant limitations including mixed-severity TBI samples and poor methodological quality. Because of this, the Work Group suggests against the use of serum biomarkers to establish the diagnosis of mTBI or direct the care for patients with symptoms attributed to mTBI. These serum biomarkers include: S100β, exosomal tau, exosomal p-tau, plasma tau, Aβ42, glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), neuron specific enolase (NSE), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide, serum cytokines including interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10, IL-12, chemokine ligand 2 (CCL2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α).

Electroencephalography (EEG) is an objective neurophysiologic test that is gaining interest as a potential biomarker for the diagnosis of mTBI and management of symptoms related to mTBI. Unfortunately, there were no studies identified in this systematic evidence review to support the use of EEG for diagnosis and/or prognosis in post-acute mTBI.

The Work Group systematically reviewed evidence related to this recommendation (28-36) and considered the assessment of the evidence put forth in the 2016 VA/DoD mTBI CPG.(37) Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. Evidence did not support or show a potential benefit from the routine clinical use of neuroimaging, laboratory, or neurophysiologic testing to establish a diagnosis of mTBI or direct the care of patients with symptoms attributed to mTBI. The harms outweighed the benefits given the risk of potential harm in the form of patient anxiety/apprehension from unnecessary testing, mismanaged patient expectations, and inappropriate utilization of healthcare resources. Patient values and preferences were somewhat varied as some patients favor diagnostic testing such as imaging, while others may have apprehension with additional tests. Thus, the Work Group decided on a *Weak against* recommendation.

Recommendations

5. We suggest against using computerized post-concussive screening batteries[a] for routine diagnosis and care of patients with symptoms attributed to mild traumatic brain injury.
   (Weak against | Reviewed, New-replaced)

6. We suggest against performing comprehensive neuropsychological/cognitive testing during the first 30 days following mild traumatic brain injury.
   (Weak against | Reviewed, New-replaced)

Discussion

The Work Group acknowledges that the sports community widely utilizes baseline and acute post-injury neuropsychological testing.(38) In the subacute period, however, the performance of routine testing is not supported by the evidence.

There are consistent findings of cognitive deficits especially in the first 48 hours after concussion in domains including memory, complex attention, working memory, and processing speed.(39, 40) These abnormalities usually resolve after a few hours or days to weeks,(39-41) and there is no clear correlation between self-reported cognitive symptoms and findings on formal neuropsychological testing beyond the initial 7 – 30 days.(42) If in doubt, consider a virtual or in-person brain injury consultation.

There were no studies identified in the 2009, 2016, or 2020 systematic evidence reviews for this CPG regarding the use of computerized post-concussion screening batteries in the post-acute period that addressed the outcomes of interest. Therefore, the Work Group considered other risks and benefits of using this testing routinely outside of the first week following concussion. Among the harms the Work Group identified were unnecessary resource use, particularly when systems are put in place to obtain widespread baseline testing. Thus, the Work Group suggests against the routine use of automated screening tools like the Automated Neuropsychological Assessment Metrics (ANAM), Neuro-Cognitive Assessment Tool (NCAT), and the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) for patients who present to care with symptoms or complaints potentially related to concussion in the post-acute period, including patients identified by post-deployment screening.

Two studies identified utilized more comprehensive neuropsychological testing, but there was no evidence to support the use of this strategy to routinely diagnose mTBI, guide treatment decisions, or improve outcomes in the post-acute period.(43, 44) While such testing may be useful in some situations, it is not recommended for routine use in all patients. Thus, the Work Group recommends against routine comprehensive neuropsychological testing in this population within the first 30 days. As discussed in Recommendation 10, comprehensive neuropsychological testing may be helpful at other points in the care of some post-concussion patients beyond the initial period.

For both recommendations, the confidence in the quality of the evidence was very low. In addition, the Work Group determined that the potential harms of routine testing outweighed the potential benefits. A significant concern was the unnecessary resource use, particularly in the context of obtaining widespread

[a] E.g., Automated Neuropsychological Assessment Metrics (ANAM), Neuro-Cognitive Assessment Tool (NCAT), and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

baseline data. There is some variability in patient preferences. While some patients desire formal testing and a lengthy evaluation process, other patients do not feel it is necessary. Some types of testing are widely available in the community, and some tests may be directly marketed to consumers (e.g., automated computerized screening tests). Comprehensive neuropsychological testing is more limited in its availability and is resource intensive. In addition, it is not clear how the data obtained from this burdensome testing leads to better outcomes for these patients. Other potential harms include unnecessary appointments for the patient, promotion of negative illness expectations, and increased utilization of clinical resources that could be applied elsewhere. In addition, rather than providing reassurance, normal testing in the face of subjective complaints can sometimes leave patients convinced that more testing is needed and undermine their confidence in the medical system.

The Work Group systematically reviewed evidence related to Recommendation 5. No studies were found that evaluated the use of automated computerized post-concussion screening tests in the post-acute period. The Work Group also considered the assessment of the evidence put forth in the 2016 VA/DoD mTBI CPG.(44) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. Patient values and preferences were somewhat varied. This recommendation was revised to remove the qualifying text regarding situations in which patients may be identified (e.g., post-deployment screening), as that was deemed unnecessary and was not specified in the literature. The potential harms of routine testing (e.g., unnecessary appointments for the patient, promotion of negative illness expectations, increased utilization of clinical resources that could be applied elsewhere) outweighed the potential benefits. Thus, the Work Group decided upon a *Weak against* recommendation.

The Work Group systematically reviewed evidence related to Recommendation 6 (43) and considered the assessment of the evidence put forth in the 2016 VA/DoD mTBI CPG.(44) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was very low. Patient values and preferences were somewhat varied. The potential harms, particularly the promotion of negative illness expectations, outweighed any benefits. Thus, the Work Group decided upon a *Weak against* recommendation.

C. Mild Traumatic Brain Injury and Future Neurocognitive Decline

Recommendations

7. When counseling patients about the long-term effects of mild traumatic brain injury, there is insufficient evidence to state that single or repeated mild traumatic brain injury increases their risk of future neurocognitive decline.
   (Neither for nor against | Reviewed, New-added)

8. When counseling patients about the long-term effects of mild traumatic brain injury, there is insufficient evidence to state that demographic, injury-related clinical, and management factors increase the risk of future neurocognitive decline in patients with symptoms attributed to single or repeated mild traumatic brain injury.
   (Neither for nor against | Reviewed, New-added)

Discussion

In communicating with patients with a single or repeated mTBI, there is insufficient high-quality evidence to answer questions on future neurocognitive decline after mTBI(s). The Work Group reviewed the current medical literature meeting criteria for inclusion in a systematic evidence review on neurocognitive decline after single or repeated mTBI and on any injury-related clinical or management factors that might affect the future development of neurocognitive decline. To date, there is very limited published research (one SR (45) and six prognostic studies (46-51) to inform any risk of future neurocognitive decline after single or repeated mTBI. Only one study focused on injury-related clinical or management factors, and that study did not distinguish between levels of TBI (e.g. mild, moderate, severe).(46)

The SR did not provide enough patient-specific data to link mTBI to delayed neurocognitive decline.(45) There were large inconsistencies between the six prognostic studies.(46-51) The largest of the prognostic studies reported that Veterans with two or more TBIs had a significantly higher risk of developing a neurocognitive disorder.(46) The study also noted that individuals taking beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) plus a statin, or ACEI plus metformin may have a lower risk of neurocognitive decline after TBI(s). However, the authors did not identify the severity of TBI and used financial claims data for the analysis, as opposed to neuropsychological testing via a blinded interviewer. Both of these study elements greatly decrease the ability to ascertain if mTBI is a risk factor for future neurocognitive decline or if the effects of the medications were in individuals with mild, moderate, or severe TBI. Methodological inconsistencies across the other studies included missing measures of exposure, poor study design, unclear blinding, and lack of comparison groups. These studies did not address injury-related clinical or management factors.(47-51)

Given the lack of high-quality evidence on the risk of neurocognitive decline after mTBI or effects of any injury-related clinical or management factors, the Work Group determined the benefits and harms to be balanced. These recommendations might lead to avoidance of unnecessary neuropsychological testing, but do not alleviate possible anxieties for predicting one's future. There is some variation among patient preferences regarding knowledge of future decline in neurocognitive function. Some patients ask their providers whether or not they are at risk for dementia, especially given media attention to this topic. While some patients may want to know this information, others may not. However, it is critical to the provider-patient relationship to acknowledge the patient's concern and be able to answer questions regarding the lack of evidence supporting future decline. General healthy living and foundational self-care strategies taking into consideration the patient's current medical issues, plus history and their life goals (e.g., complementary and integrative approaches including tobacco cessation, moderation of alcohol consumption, appropriate management of chronic disease states [e.g., hypertension, diabetes], exercise, sleep hygiene) may benefit all patients. However, evidence was not specifically reviewed on these strategies in general nor is there data in the context of mTBI to know if these or other strategies will affect neurocognitive decline in this population.

The Work Group systematically reviewed evidence related to Recommendation 7 (45, 47-51) and Recommendation 8.(46) Therefore, these are *Reviewed, New-added* recommendations. The Work Group's confidence in the quality of the evidence for both recommendations was very low. The body of evidence had many limitations that prevented the Work Group from concluding whether a single or repeated mTBI can increase risk of neurocognitive decline or if any injury-specific or management factors can influence

any neurocognitive decline after mTBI. These limitations included different subject and comparator groups among studies, inadequate classification of severity of the TBI examined, lack of rater blinding, different instruments of evaluation, and possible selection bias. The Work Group acknowledges this topic's critical importance, particularly to Service Members and Veterans who have experienced mTBI and their families. The benefits slightly outweighed harms as unnecessary neurocognitive testing may be avoided. Patient values and preferences were somewhat varied as patients desire some level of certainty for the future. An additional factor is the implication of media portrayal of mTBI and public opinion. Thus, the Work Group decided upon *Neither for nor against* recommendations.

D. Effects of Mild Traumatic Brain Injury Etiology on Treatment

Recommendation

9. We suggest against adjusting outcome prognosis and treatment strategy based on mechanism of injury.
   (Weak against | Reviewed, New-replaced)

Discussion

Adjusting outcome prognosis or treatment strategy based on mechanism of injury (e.g., blast, fall, motor vehicle accident, sports injury, assault) has poor empirical support. This CPG's systematic evidence review identified two studies examining differences in mechanism of injury as related to treatment effectiveness and health outcome prognosis. Nathan et al. (2016) found no significant difference between blast and non-blast related mTBI on a patient survey of health outcomes.(52) A retrospective study by Janak et al. (2017) examining differences in treatment outcomes for post-concussive and posttraumatic stress symptoms found no differences in symptom reduction when comparing blast to non-blast related mechanism of injury in participants with a history of mTBI.(53) Neither study identified treatment-specific benefit or harm unique to mechanism of injury. However, history of blast injury may be associated with higher levels of combat exposure and, therefore, increased risk of developing co-occurring posttraumatic stress symptoms.(54-56) In addition, patients with symptoms attributed to mTBI associated with domestic or interpersonal violence should be provided referral to appropriate agencies and domestic violence (DV)/intimate partner violence (IPV) programs to ensure safety and reduce risk of further injury. Given the lack of available evidence to suggest a difference in mTBI outcomes, treatment strategies or outcome prognosis should not be modified based on mechanism of injury at this time.

Development of specialized care plans based on mechanism of injury may be resource-intensive despite the lack of evidence supporting it. Patient preferences may vary regarding treatment strategy based on mechanism of injury. The patient focus group participants emphasized the importance of individualized care plans, education, and the need for greater knowledge about their injury (see Appendix B).

The Work Group systematically reviewed evidence related to this recommendation.(52-54) 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 significant limitations including observational study design, sampling bias, and poor confound control. No significant differences were found across treatment prognosis or outcome when mechanism of injury (blast versus non-blast) was compared. Other considerations included the impact of resource use that may be required to adjust treatment plans based

on mechanism of injury, without evidence of necessity. In assessing the balance of potential benefits and harms, there was no evidence of benefit and a potential burden of unnecessarily adjusting treatment strategy. Patients may have some variation in their preferences. Thus, the Work Group decided upon a *Weak against* recommendation.

E. Symptom-based Treatments of Mild Traumatic Brain Injury

a. Cognitive Symptoms

Recommendation

10. We suggest that patients with symptoms attributed to mild traumatic brain injury who present with memory, attention, or executive function problems despite appropriate management of other contributing factors (e.g., sleep, pain, behavioral health, headache, disequilibrium) should be referred for a short trial of clinician-directed cognitive rehabilitation services.
    (Weak for | Reviewed, Amended)

Discussion

The systematic evidence review found that specialized, interdisciplinary, and comprehensive cognitive rehabilitation interventions were effective at reducing cognitive symptoms when targeting impaired memory, attention, or executive functions.(57-62) These comprehensive cognitive rehabilitation services included various interventions, such as compensatory cognitive training,(57) clinician-directed computer-based practices,(59, 62) and therapist-assisted virtual reality.(61) Similarly, there is support for interdisciplinary, integrated interventions that combine cognitive interventions with supported employment.(63, 64) A positive impact on behavioral symptoms was also noted.(65)

Studies included in the systematic evidence review further support the superiority of cognitive interventions that address a range of cognitive symptoms over usual care (i.e., general education on concussion or no treatment in individuals with persistent complaints following a concussion.(57-62, 65) However, the literature neither promotes the effectiveness of one particular cognitive intervention nor suggests these interventions will be effective for all patients. Therefore, a short trial of treatment (dependent on patient response) is suggested as a practical means of determining if a patient will benefit from ongoing cognitive rehabilitation treatment. Interventions that are not achieving improvements or continue despite a plateau in improvements may foster negative expectations (i.e., “sick role”).

These interventions present a significant burden in that cognitive rehabilitation often requires several weekly appointments for multiple weeks. This can be challenging for the patient (e.g., time, usually requires in-person treatment, transportation, cost) and may be of limited availability given the lack of trained cognitive rehabilitation specialists.

The Work Group systematically reviewed evidence related to this recommendation (57-62, 65) and considered the assessment of the evidence carried forward from the 2016 VA/DoD mTBI CPG.(63, 64) Therefore, this is a *Reviewed, Amended* recommendation. The Work Group’s confidence in the quality of the evidence was very low. The body of evidence had limitations including assessor blinding,(61) high risk of selection and performance bias,(58) attrition bias,(58) and unclear methods for randomization and allocation concealment.(57, 61) Additionally, most randomized control trials (RCTs) reviewed had serious imprecision, and one RCT had serious indirectness (e.g., inclusion of head injuries other than mTBI).(58)

The benefits (e.g., short-term treatment, some cognitive, behavioral, and general symptom improvement with symptom-specific cognitive intervention) outweighed the potential harms (e.g., prolonged or ineffective treatments fostering negative expectations or "sick role"). Patient values and preferences were somewhat varied, as patients are accepting of a wide range of interventions and have varying degrees of acceptance of cognitive services. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

11. We suggest against the use of self-administered computer training programs for the cognitive rehabilitation of patients with symptoms attributed to mTBI.
    (Weak against | Reviewed, New-added)

Discussion

In a large comparative effectiveness RCT of cognitive rehabilitation in Service Members with a history of mTBI, those who received specialized, clinician-directed treatments demonstrated and sustained superior cognitive, behavioral, and emotional outcomes on the Paced Auditory Serial Attention Test (PASAT) and the Key Behaviors Change Inventory (KBCI) over those who participated in psychoeducation or self-administered computerized brain training alone.(59, 66) Similarly, in Hwang et al. (2020), self-managed, computerized cognitive training did not result in meaningful or sustained improvement in cognitive function over usual care (no care).(67) Cooper et al. (2017) and Vanderploeg et al. (2018) found that cognitive rehabilitation consisting of primarily self-directed computer training tasks was not only less effective than clinician-directed services, but was also associated with worse cognitive and neurobehavioral outcomes (e.g., Global Distress Index [GSI] subscale of Symptom Checklist-90-Revised [SCL-90-R]).(59, 66)

In contrast, RCTs examining computer-assisted and virtual reality interventions when provided as components of comprehensive cognitive rehabilitation have demonstrated improvements in cognitive (e.g., cognitive flexibility, processing speed), behavioral (e.g., anxiety, depression), balance (e.g., Tinetti balance), and functional (e.g., return to work) outcomes. Specifically, Caplain et al. (2019) and De Luca et al. (2019) demonstrated that computer and virtual reality-based cognitive training that is part of a holistic, comprehensive, clinician-directed cognitive rehabilitation program resulted in significant functional improvement (e.g., symptom reduction, increased return to work rate) compared to usual care (e.g., psychoeducation or paper and pencil tasks) in individuals with concussion-related cognitive symptoms.(61, 62) In addition, two studies examined the overall efficacy of clinician-directed cognitive rehabilitation across a range of patient populations, some of which included computer-supported interventions as part of comprehensive cognitive rehabilitation services. Both of these studies demonstrated improved outcomes when compared to usual care.(58, 60)

The Work Group systematically reviewed evidence related to this recommendation.(58-62, 66, 67) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations, including imprecision (59, 61, 62, 66, 67) and study quality/risk of bias.(61) The benefits of clinician-directed interventions (e.g., improved functional outcomes, patient-centric, holistic care) outweighed the potential harms (e.g., time, transportation, limited availability of specialized clinicians). Furthermore, the Work Group noted potential harms of self-administered computer training (e.g., worsened neurobehavioral

outcomes) compared with evidence-based, clinician-directed rehabilitation. Patient values and preferences were somewhat varied since there may be a lack of credibility and risk of abandonment of computerized training for those who favor clinician-directed rehabilitation. On the other hand, commercially available computer programs and applications may have game-like appeal and more public recognition than specialized cognitive rehabilitation services. Other considerations included costs, data privacy threats, and the variability of cognitive services, settings, and training programs. Thus, the Work Group decided upon a *Weak against* recommendation.

b. Behavioral Symptoms

Recommendation

12. We suggest that patients with symptoms attributed to mild traumatic brain injury who present with behavioral health conditions, including posttraumatic stress disorder, substance use disorders, and mood disorders, be evaluated and managed the same whether they have had mild traumatic brain injury or not, according to the relevant existing VA/DoD clinical practice guidelines. **(Weak for| Reviewed, New-replaced)**

Discussion

Depression, anxiety, and irritability are common, co-occurring behavioral symptoms after mTBI. Substance use disorders are also common among individuals with symptoms attributed to mTBI. The emergence of psychiatric symptoms and substance use disorders after mTBI can depend on many factors, including pre-injury psychosocial function and/or pre-existing mental illness, genetic predisposition to mental illness, injury factors, and post-injury psychosocial factors.(68-71) The nature and severity of symptoms (including any presence of suicidal ideation and/or suicide risk), as ascertained in a thorough medical history, is necessary to choose appropriate treatments. Given the association of depression, posttraumatic stress disorder (PTSD), and other mental health disorders with a history of mTBI and other injuries, providers should assess for these conditions and consult related VA/DoD CPGs (e.g., major depressive disorder [MDD][b], PTSD[c], Patients at Risk for Suicide[d], substance use disorder [SUD][e]). Moreover, providers should consider the underlying diagnoses, patient preferences, co-occurring conditions, and available treatment modalities.

The standard of care for psychological and behavioral symptoms following mTBI includes psychotherapeutic and pharmacologic treatment modalities. In the 2016 VA/DoD mTBI CPG, there was no high-quality evidence for any specific therapy for irritability and other behavioral symptoms (such as impulsivity) following mTBI. To date, there are no medications specifically approved by the U.S. Food and Drug Administration (FDA) for the treatment of post-mTBI psychiatric/behavioral symptoms.

[b] See the VA/DoD Clinical Practice Guideline for the Management 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 Assessment and Management of Patients at Risk for Suicide. Available at: https://www.healthquality.va.gov/guidelines/MH/srb/

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

Since the 2016 VA/DoD mTBI CPG, two SRs addressing pharmacologic treatment (i.e., sertraline versus placebo) have been published, providing very low quality evidence.(72, 73) The two SRs found no difference between sertraline and placebo in quality of life (QoL), depression (Hamilton Depression Rating Scale [HAM-D]), anxiety, aggression, or dizziness after 24 weeks, and MDD treatment response at 12 weeks.(72, 73) Reyes et al. (2019) found a significant improvement in post-TBI depression (Patient Health Questionnaire-9 [PHQ-9]) with sertraline versus placebo at 24 weeks.(73) Both SRs included the same three RCTs. However, the SRs used different primary outcomes, which impacted the results of each.

An RCT by Jak et al. (2019) examined integrated interventions (i.e., Symptom Management and Rehabilitation Therapy cognitive processing therapy [SMART-CPT] versus traditional CPT) for Veterans with co-occurring PTSD and a history of mild to moderate TBI with cognitive symptoms.(74) While both interventions provided clinically significant reductions in post-concussive symptom (PCS) severity (Neurobehavioral Symptom Inventory [NSI]) and PTSD symptoms (PTSD Checklist-specific trauma [PCL-S]), hybrid SMART-CPT provided no significant benefit over CPT at six months in Veterans with a history of mTBI and PCS. This is primarily because the patients in both groups experienced improvement in symptoms and QoL. No significant differences were reported for improvement in QoL (Quality of Life Interview-Brief Version [QOLI-B] General Life Satisfaction). The authors noted that 47% of patients did not complete all treatment sessions; however, this may have indicated adequate symptom improvement for these individuals.(74)

Another RCT examined the effectiveness of five sessions of a newly developed CBT intervention compared to telephonic counseling (TC) in at-risk patients with symptoms attributed to mTBI (patients with high reports of early complaints).(26) The study demonstrated no significant differences concerning return to work, with 65% of patients receiving the CBT intervention and 67% of patients receiving the TC reporting a return to work at previous level.(26) However, patients in the TC group reported fewer complaints at three months (eight versus six complaints; p=0.010) and 12 months post-injury (nine versus five complaints; p=0.006), and more patients in the TC group showed a full recovery 12 months post-injury compared to the CBT intervention group (62% versus 39%). The study outcomes may have been impacted by the possibility that patients may require more than five CBT sessions to experience a positive benefit and the lack of a control group receiving usual care. Additionally, this was a small trial with only 39 patients in the CBT intervention group and 45 patients in the TC group.

The Work Group systematically reviewed evidence related to this recommendation.(26, 72-74) 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 selective reporting, high attrition, and lack of blinding of participants and study personnel.(72, 73) The benefits of treatment strongly outweighed the harms of leaving underlying co-occurring behavioral symptoms untreated. Patient values and preferences largely varied due to challenges with patient preference for medications and attending treatment, as well as the stigma associated with behavioral health conditions. Thus, the Work Group decided upon a *Weak for* recommendation.

c. Vestibular and Proprioceptive Symptoms

Recommendation

13. We suggest that patients with persistent symptoms of dizziness and imbalance attributed to mild traumatic brain injury be offered a trial of specific vestibular rehabilitation and proprioceptive therapeutic exercise.
    (Weak for | Reviewed, New-replaced)

Discussion

Dizziness is one of the most common presenting symptoms attributed to mTBI in the primary care setting.(75, 76) Patients with dizziness may struggle to return to functional activities and work duties given the severity of symptoms. The Work Group reviewed two RCTs that suggested specific vestibular and proprioceptive therapeutic exercises may help reduce dizziness symptom severity and improve functional independence in the short term.(77, 78) However, there were serious limitations (i.e., high risk of bias,(77) small sample size (77, 78)), which led to concerns about the precision of the estimates reported.

Benefits slightly outweighed harms/burdens with participation in specific vestibular therapy. Vestibular/balance therapy should be encouraged in patients with unresolved symptoms of dizziness or imbalance that persist beyond the acute phase (see the Algorithm, Module A: Initial Presentation (>7 Days Post-Injury). Although recently reviewed evidence for vestibular rehabilitation was limited in the mTBI population, vestibular and balance rehabilitation programs have demonstrated efficacy in patients with vestibular disorders in general.(79) Patients may respond favorably when a treatment plan is specifically designed to address deficits identified by a detailed vestibular/balance evaluation. Possible deficits related to symptoms of dizziness and imbalance that could be addressed during therapy include, but are not limited to:

1. Poor gaze stabilization/vestibular-ocular reflex (VOR) adaptation
2. Increased motion sensitivity
3. Poor functional balance and gait measures
4. Cervicogenic dysfunction
5. Poor sensory integration related to postural stability

Reporting of adverse events during vestibular rehabilitation in small studies is limited. There is low risk of harm with participation in vestibular rehabilitation. However, the Work Group discourages a prolonged course of therapy in the absence of patient improvement to mitigate negative illness expectations. To minimize the potential negative effects of protracted, ineffective treatment, the Work Group suggests goal-based, functional re-assessment to determine treatment responsiveness by a vestibular rehabilitation provider (i.e., physical therapist or occupational therapist). It is preferred that the rehabilitation provider has acquired post-graduate training specific to vestibular rehabilitation.

When initiating a vestibular rehabilitation program, providers should consider patient preferences, which likely vary. Provocation of symptoms to a moderate level should be expected by patients participating in vestibular rehabilitation. Some patients may dislike the unpleasant nature of vestibular rehabilitation with the possible transient provocation of symptoms during therapy sessions. While patients may be willing to

engage in treatment, they may have trouble adhering to a prescribed program with transient symptom provocation and/or lack of significant improvement. It is important that providers try to change patient perception of vestibular rehabilitation to recognize that symptom provocation, under the direction of a vestibular provider, may help to improve outcomes.

There are several highly sophisticated vestibular programs and services across the VA and DoD that are part of comprehensive specialized programs. In addition, most physical therapists have basic vestibular/balance rehabilitation training making this intervention available to most VA/DoD patients; however, when possible, patients should be referred to providers with additional continuing post-graduate vestibular-specific rehabilitation training.

The Work Group systematically reviewed evidence related to this recommendation.(77, 78) 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 the high risk of bias (77) and small sample size in both studies reviewed.(77, 78) The potential benefits of decreased severity of dizziness symptoms and improvement of functional independence slightly outweighed the potential harms of transient provocation of symptoms during treatment. Patient values and preferences were varied. Thus, the Work Group decided upon a *Weak for* recommendation.

d. Visual Symptoms

Recommendation

14. There is insufficient evidence to suggest for or against the use of any particular modality for the treatment of visual symptoms attributed to mild traumatic brain injury such as diplopia, accommodation or convergence deficits, visual tracking deficits and/or photophobia. **(Neither for nor against | Reviewed, Amended)**

Discussion

There is limited evidence for the current treatment of visual symptoms associated with mTBI (e.g., diplopia, accommodation/convergence/tracking deficits, photophobia). Only one study met the inclusion criteria for the systematic evidence review carried out for this guideline update. An RCT by Berryman et al. (2020) compared six eye exercises (SEE) to the standard of care (i.e., activities and occupations integrating eye movements, including scanning and reading) in 20 patients.(80) The treatments were intensive with 30-minute sessions occurring five days per week for four weeks. The results demonstrated a greater average improvement in post-TBI visual symptoms in the SEE group than the standard of care group on multiple measures, including Delis-Kaplan Executive Function System (visual scanning speed and accuracy), King-Devick Test (saccadic speed and accuracy), Nelson-Denny Reading Test (reading speed and accuracy), Vestibular Ocular Reflex test, and Vision Symptom Scale (standardized measure of visual symptoms). The confidence in the quality of the evidence was very low. An intention-to-treat (ITT) analysis was not performed and there was notable attrition, with only 14 total patients completing the study (eight in SEE and six in the standard of care group), which the authors attributed to fatigue. There were also concerns about the generalizability of this evidence to the mTBI population, as the study did not specify the severity of the TBI for those enrolled.

The Work Group also considered the high resource use requirements of this treatment, as it would require daily, in-person visits with a therapist. The intervention's specialized nature and the limited availability of specifically trained therapists also raised concerns about accessibility to this treatment. The Work Group determined there would be some variability in patient engagement with this treatment, which may exacerbate other symptoms such as headache or dizziness. Lastly, any prolonged treatment may foster negative expectations for disease recovery and leave the patient in a "sick role."

The Work Group systematically reviewed evidence related to this recommendation.(80) Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence had some limitations including the small sample size and significant methodological concerns. The potential benefits of such therapy (e.g., improved scanning/saccadic speed, reading speed, visual symptoms) only slightly outweighed the potential harms (e.g., exacerbation of other mTBI related symptoms, fostering negative expectations). There were significant resource utilization and feasibility concerns. Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

e. Tinnitus

Recommendation

15. There is no evidence to suggest for or against the use of any particular modality for the treatment of tinnitus attributed to mild traumatic brain injury.
    (Neither for nor against | Reviewed, Amended)

Discussion

The systematic evidence review carried out as part of this guideline update found no new studies that addressed the use of any particular modality for the treatment of tinnitus in patients with symptoms attributed to mTBI.

The patient focus group participants reported mixed preferences for home or technology-based treatments such as using a smartphone-based application to deliver white noise to reduce tinnitus symptoms (see Appendix B). Patient focus group participants identified tinnitus among other prominent symptoms they experience that impact their daily life. They expressed interest in individualized treatment approaches and the value of education to understand and address their symptoms.

The Work Group reviewed the evidence related to this recommendation; however, no evidence that met inclusion criteria was identified. Therefore, this is a *Reviewed, Amended* recommendation. The potential harm of treatment (e.g., repetitive transcranial magnetic stimulation [rTMS], see Recommendation 19) slightly outweighed the potential benefit of reducing tinnitus symptoms. Patient values and preferences were somewhat varied. The Work Group also considered the burden of travel time and frequency to receive treatment, as well as the availability of equipment and experienced providers across the VA and DoD. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

f. Exertion-induced Symptoms

Recommendation

16. There is insufficient evidence to recommend for or against treatments for exertion-induced symptoms/symptom clusters attributed to mild traumatic brain injury.
    (Neither for nor against | Reviewed, New-added)

Discussion

The Work Group reviewed the evidence for mTBI-related exertion-induced symptoms in patients with a history of mTBI. The systematic evidence review identified limited advances in this emerging area for adult patients.(81) Overall, the evidence on interventions for treating symptoms or symptom clusters exacerbated by exertion is sparse. The confidence in the quality of the evidence was very low, but captured the following measures: daily step count, self-reported fatigue, exertional test improvement, return to activity/duty/work/sports, and community reintegration.(81)

There was limited discussion on exertional symptoms and related treatment from the patient focus group participants (see Appendix B). Patient focus group participants disliked burdensome or time-consuming treatments. Therefore, providers should weigh treatment burdens and their potential effects when developing treatment plans for patients with exertion-induced symptoms attributed to mTBI. Providers may consider offering interested patients a trial-based, graded treatment program to address specific symptoms exacerbated by exertion.

The Work Group systematically reviewed evidence related to this recommendation.(81) 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 study groups of mixed TBI severity and limited impact of treatment on various outcomes. The Work Group acknowledges that there is research on exertional testing as a measure of recovery after TBI, including mTBI; however, there is very limited literature looking at treatment to address symptoms exacerbated by exertion. The benefits and harms were balanced. Patients may benefit from participation in therapy to decrease exertion-induced symptoms, but potential harm may be caused by fostering negative illness expectations should symptoms not improve with participation in therapy. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

F. Interventions with Insufficient Evidence

a. Complementary and Integrative Health

Recommendation

17. There is insufficient evidence to recommend for or against the use of any of the following interventions for the treatment of patients with symptoms attributed to mild traumatic brain injury:
    a. Acupuncture
    b. Tai chi
    c. Meditation
    d. Mindfulness
    e. Yoga

f. Massage
g. Chiropractic therapy
h. Cranial electrotherapy stimulation (CES)
i. Sensory deprivation tanks

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

Discussion

Several patient focus group participants reported responding best to complementary therapies for their mTBI symptoms (see Appendix B). Based on this feedback, the Work Group sought to ensure that, as part of this guideline update, evidence was reviewed for complementary and integrative health (CIH) interventions including acupuncture, tai chi, meditation, mindfulness, yoga, massage, chiropractic therapy, cranial electrotherapy stimulation (CES), and sensory deprivation.

The confidence in the quality of the evidence for acupuncture to improve outcomes in patients with symptoms attributed to mTBI is very low. The systematic evidence review found one small RCT (n=29) comparing auricular acupuncture (AA) and traditional Chinese acupuncture (TCA) to treatment as usual care, with mixed results reported at six weeks.(82) Auricular acupuncture was associated with improvements in headache impact and headache-related pain, while TCA was associated with improvements in headache pain only.(82) Neither type of acupuncture showed significant benefits for sleep, depression, and QoL.(82) There were a small number of adverse events in both AA and TCA groups. Given the very low quality of evidence and mixed results, there was insufficient evidence to recommend for or against acupuncture. The VA/DoD Headache CPG (2020)[f] also independently reviewed the use of acupuncture in the general headache population and found insufficient evidence to recommend for or against acupuncture for the treatment of headache.

Patient preferences regarding this treatment were found to be somewhat varied. While some patients may not have an interest in pursuing acupuncture due to dislike or fear of needles, the patient focus group participants were interested in pursuing acupuncture as a CIH treatment (see Appendix B). The potential benefits of acupuncture are unclear, and the potential harms are minimal. One study not included in the evidence base, White et al. (2001), reported less than 5% risk of discomfort, tiredness, drowsiness, dizziness, nausea, or an exacerbation of symptoms, as well as low risk of local infections (0.01%).(83) Thus, the Work Group determined the benefits and harms to be balanced. Acupuncture treatment availability varies widely within the VA and DoD. Also, since acupuncture treatment likely requires multiple in-person treatments, adherence could be challenging for Veterans and Service Members living in rural areas.

Tai chi is an ancient Chinese martial art that utilizes the principles of mind-body practices and is becoming increasingly popular among civilians and Service Members. Tai chi utilizes whole body movements in slow and rhythmic patterns while integrating mindfulness and breathing techniques to improve overall well-being. It is commonly referred to as "meditation-in-motion." Tai chi may improve muscle strength, flexibility, proprioception, and balance.(84) There was only one study that met the inclusion criteria for the systematic evidence review carried out as part of this guideline update. An RCT by Hwang et al. (2020) studied 90 participants over the age of 55 with mild, moderate, and severe TBI and found no effect on

[f] See the VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache. Available at: https://www.healthquality.va.gov/guidelines/Pain/headache/

cognitive function or QoL.(67) There was also a high attrition rate (21% across usual care and tai chi intervention arms).

The patient focus group participants expressed an interest in alternative treatment modalities for the treatment of mTBI symptoms (see Appendix B). The risk of participation in tai chi is low and there is a potential for additional benefits (e.g., increased self-awareness, self-regulation, and relaxation). The Work Group also considered the potential that outcome variability will depend on patient willingness to learn different tai chi movements and techniques.

A variety of CIH and integrative health interventions were considered as potential interventions for patients with symptoms attributed to mTBI. Meditation, mindfulness, and yoga are accessible to patients because they can be practiced in the privacy of one's own home, while massage and chiropractic therapy typically require travel to a trained provider's location. CES devices are available for in-home use but need to be prescribed and supervised by healthcare providers. Similarly, sensory deprivation requires specialized equipment that is not yet feasible for wide-spread, in-home use. Thus, these interventions can vary significantly in suitability and accessibility from patient to patient.

The systematic evidence review found no studies that met inclusion criteria for these CIH interventions. There is insufficient evidence for or against the use of such treatments currently. This remains a growing area of interest for multiple medical problems; therefore, the Work Group hopes that additional research in this area can inform more definitive recommendations in the future.

The Work Group systematically reviewed evidence related to this recommendation.(67, 82) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. No evidence was identified on meditation, mindfulness, yoga, massage, chiropractic therapy, CES, and sensory deprivation. The body of evidence on acupuncture had some limitations, including inconsistency of results related to outcomes, imprecision, and small sample size.(82) The benefits and harms of acupuncture treatment were balanced. Patient values and preferences were varied; some patients often have interest in acupuncture and other CIH treatments while others may have no interest in this type of treatment. There was a limited body of evidence on tai chi with several limitations, including small sample size, variation in brain injury severity, and an older population.(67) The potential benefits of tai chi slightly outweighed the limited burden from use of time and resources. Patient values and preferences were somewhat varied. The benefits of meditation, mindfulness, yoga, massage, chiropractic therapy, CES, and sensory deprivation were determined to slightly outweigh the potential harms/burdens for all interventions except chiropractic and CES therapies, for which harms may slightly outweigh the benefits. Patient values and preferences were somewhat varied as there is general interest in CIH interventions, but preferences may vary by patient and type of intervention. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

b. Hyperbaric Oxygen Therapy

Recommendation

18. We recommend against the use of hyperbaric oxygen therapy for the treatment of patients with symptoms attributed to mild traumatic brain injury.
    (Strong against | Reviewed, New-added)

Discussion

The Work Group recommends against the use of hyperbaric oxygen therapy (HBOT) for patients with symptoms attributed to mTBI. An SR (85) of five RCTs and one long-term follow-up RCT (86) found no evidence of improved symptom severity and only a mixed effect on QoL. When HBOT was compared to sham intervention, HBOT was associated with decreased QoL at long-term follow-up at two and three years.(85, 86)

In addition to lack of patient improvement, the use of HBOT after mTBI may have harmful impacts, including seizures.(87) Emerging treatments are often marketed to patients struggling with chronic symptoms, and providers need to understand the potential negative impact that referrals for unfounded treatments can have on the provider-patient relationship. When treatments do not work, it may lead to disappointment, damage to a patient's trust, an increase in the likelihood of the patient taking on a "sick role," and even harm to the patient.

Despite the lack of evidence supporting HBOT for mTBI and symptoms related to mTBI, there is some variability in patient preferences. There is limited availability of providers and HBOT treatment centers, and multiple treatments are often required. This may be inconvenient and can place a significant financial burden on patients, as it is not an approved service through VA eligibility or insurances, including Tricare. Given the evidence of harm in the literature (85, 86) and the FDA findings,(87) currently, HBOT is not an effective or safe treatment after mTBI.

The Work Group systematically reviewed evidence related to this recommendation.(85, 86) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was low. The harms of HBOT were significant and outweighed any potential benefits, which were minimal. Patient focus group participant perspectives included distrust in the medical system, fostering negative illness expectations, and Veteran frustration with attempting to obtain funding through VA for travel costs. Furthermore, there was a decreased QoL at two and three years post-treatment.(86) The Work Group also considered the current lack of FDA approval for the use of HBOT in patients with TBI.(87) There was some variation in patient values and preferences to try HBOT, but patients who do try HBOT are subsequently often disappointed when outcomes are not as expected. Thus, the Work Group decided upon a *Strong against* recommendation.

c. Repetitive Transcranial Magnetic Stimulation

Recommendation

19. We suggest against the use of repetitive transcranial magnetic stimulation for the treatment of patients with symptoms attributed to mild traumatic brain injury.
    (Weak against| Reviewed, New-added)

Discussion

Based on three small RCTs (i.e., ≤30 patients) comparing rTMS to sham treatment, the Work Group suggests against the use of rTMS in patients with symptoms attributed to mTBI.(88-90)

In patients with symptoms attributed to mTBI, there was no difference in post-concussion symptoms between those who received true or sham rTMS at four months (90) or six months.(89) Similarly, there was no difference in headache symptoms between those who received true or sham rTMS at six months.(89) Leung et al. (2017) found that rTMS was associated with improvement in debilitating headache (measured by multiplying average duration of headache exacerbation by average frequency of episodes per week) at one month.(88) However, this is not a validated means of measuring change in headache symptom severity. Additionally, there were no differences in performance on a battery of neuropsychological tests between patients with a history of mTBI and post-traumatic headache who received true or sham rTMS at one month.(88) Finally, there was no difference in Quality of Life after Brain Injury Questionnaire scores in patients with a history of mTBI and post-traumatic headache who received true or sham rTMS at six months.(89) However, Stilling et al. (2020) reported that patients receiving rTMS were more likely to return to work than patients receiving sham treatment.(89)

The potential harm and burden of rTMS slightly outweighs the potential benefits of improvement in debilitating headache or return to work. The FDA identified a risk for seizure with the use of rTMS (91) which is a concern for patients with a history of mTBI. None of the reviewed studies noted seizure as an adverse event; however, all three studies excluded individuals with a history of seizures.(88-90) Evidence also indicated some potential harm associated with rTMS, particularly headache.(89, 90) Other side effects included worsening mood, dizziness, stimulation site discomfort, insomnia, face tightness, and toothache.(90) Stilling et al. (2020) also noted scalp discomfort, toothache, and dizziness.(89) Additionally, patients noted a burden of time and travel associated with attending treatment sessions.(90)

There is likely some variability in patient values and preferences for rTMS treatment. Patient focus group participants noted they want providers to use individualized treatment approaches, which is possible with use of rTMS (see Appendix B). However, rTMS may be burdensome because it requires frequent visits. Travel time for rTMS treatment may also be a concern. Further, there is limited access to this treatment since it is still experimental for the treatment of mTBI. Many sites will not have the equipment or trained personnel needed to administer rTMS treatment.

The Work Group systematically reviewed evidence related to this recommendation.(88-90) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was very low. Only three small RCTs comparing rTMS to sham treatment were included in the systematic evidence review carried out as part of this guideline update.(88-90) The body of evidence had some limitations, including small sample sizes. The potential harms (e.g., seizure, headache) outweighed the potential benefits (e.g., improvement in debilitating headache, return to work). Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Weak against* recommendation.

X. Research Priorities

During the development of the 2021 mTBI CPG, the Work Group identified numerous areas in which well-designed studies (in the military/Veteran population) are needed in the future. These include areas that require stronger evidence to support current recommendations as well as those that require evidence to inform new recommendations in future CPGs. After assessing the currently available evidence, the Work Group identified the following important topics for future research:

A. Setting of Care

- On the setting of care (e.g., inpatient, outpatient)
- To identify subpopulations that may benefit from mTBI specialty care
- For sham-control RCTs examining mode of delivery, dosage, and timing of primary care and rehabilitation-based programs (e.g., telemedicine versus in-person treatment)

B. Diagnosis and Assessment

- To achieve objective measures of mTBI for diagnosis and prognosis; because of the significant clinical and pathophysiologic heterogeneity of mTBI, no definitive objective test exists
- To identify the relevance and clinical utility of biomarkers in individuals with post-acute to chronic mTBI for diagnosis, prognosis, management, and return to duty/work decision making
- On which neuroimaging modality or technique for routine clinical use may aid in the diagnosis and/or direction of care for patients with symptoms attributed to mTBI
- To determine the point in time (or under what circumstances) neuropsychological testing improves mTBI outcomes or improves cost-effectiveness of care
- To identify the role and value of computer-based cognitive screening/testing for evaluating cognitive function at baseline and after mTBI to improve mTBI outcomes or cost-effectiveness of care in military populations
- To confirm the validity and effectiveness of diagnostic work-ups of new symptoms that develop after the initial 30 days following injury
- Into diagnosis and assessment tools focused on helping clinicians determine the most appropriate symptom-based treatments

C. Mild Traumatic Brain Injury and Future Neurocognitive Decline

- To determine if there is a relationship between mTBI and neurocognitive decline over time
- On injury-related clinical or management factors and neurocognitive decline over time
- To identify neuroimaging correlates for the persistence of symptoms or neurocognitive decline over time
- On personal factors (to include experiencing adverse events prior to injury) and their effect on long-term mTBI sequela

- To consider the presence and management of co-morbidities, injury-related clinical factors, and lifestyle factors (such as weight management, smoking, physical activity, and diet) in the design of future longitudinal studies for the treatment of mTBI sequela
- To determine if there are any adverse effects of lifetime/career-long exposure to repetitive, low-level blasts

D. Effects of Mild Traumatic Brain Injury Etiology on Treatment

- To determine if the mechanism or frequency of injury correlates with the persistence of symptoms or neurocognitive decline over time

E. Symptom-based Treatments of Mild Traumatic Brain Injury

- For targeted research on return to duty outcomes

a. Cognitive Symptoms

- To identify subpopulations who may benefit from specific cognitive rehabilitation interventions
- On the safety, efficacy, and effectiveness of a range of technology-supported activities, including virtual-reality interventions, as part of comprehensive, clinician-directed cognitive rehabilitation services for individuals with symptoms attributed to mTBI, including combat-related injury
- On efficacy and comparative effectiveness of interventions for mTBI sequela to identify which treatments or components of treatment are most effective
    - Efficacy of tele-rehabilitation (remote) delivery and in-person cognitive treatment delivery
    - Comparative effectiveness of tele-rehabilitation (remote) delivery versus in-person cognitive treatment delivery
    - Efficacy and safety of self-administered computer-exercises and computer-assisted cognitive rehabilitation
    - Comparative effectiveness of self-administered computer-exercises versus computer-assisted cognitive rehabilitation
    - Efficacy of virtual reality assessments/interventions and traditional cognitive assessments/interventions
    - Comparative effectiveness of virtual reality assessments/interventions versus traditional cognitive assessments/interventions
    - Comparative effectiveness of comprehensive cognitive rehabilitation interventions versus integrated cognitive and mental health interventions
    - Effectiveness of specific elements (distinct parts) of assistive technology
- On exploring what factors in comprehensive cognitive interventions are predictors of positive functional outcomes

b. Behavioral Symptoms

- On the efficacy of pharmacologic, behavioral health, and combination therapies (e.g., pharmacologic plus behavioral health) for adults with mTBI and co-morbidities (e.g., PTSD, SUD, mood disorders)
- On the comparative effectiveness of pharmacologic, behavioral health, and combination therapies (e.g., pharmacologic plus behavioral health) for adults with mTBI and co-morbidities (e.g., PTSD, SUD, mood disorders)
- To define primary behavioral health conditions and symptoms secondary to mTBI (somatic, cognitive, functional, and QoL)
- On suicidal ideation in adults with mTBI

c. Vestibular and Proprioceptive Symptoms

- To determine if specific vestibular rehabilitation interventions improve symptoms in individuals with symptoms attributed to mTBI and complaints of dizziness and imbalance
- To be able to identify subpopulations who may benefit from vestibular rehabilitation
- For vestibular/proprioceptive rehabilitation exercises in individuals with symptoms attributed to mTBI
    - Group versus individual treatment
    - Virtual reality interventions versus traditional (low-technology) interventions
    - Vestibular rehabilitation versus integrated vestibular rehabilitation and mental health treatments
    - Specific elements (distinct parts) of assistive technology
    - Specificity of provider specialty and level of expertise

d. Visual Symptoms

- To evaluate the effects of specific visual treatments on visual symptoms after mTBI in high-quality RCTs
- To determine what treatment interventions are effective for improving visual dysfunction following mTBI
- To determine if visual rehabilitation interventions improve functional outcomes
- To focus on functional outcomes in larger clinical trials with appropriate methodology

e. Tinnitus and Auditory Perception

- On the incidence and prevalence of isolated tinnitus following mTBI, including tinnitus that is bothersome and persistent
- To establish the incidence and prevalence of other co-occurring symptoms in individuals with a history of mTBI (e.g., vision and vestibular symptoms, mental health conditions, decreased sound tolerance, hearing loss, etc.) that overlap with tinnitus-like symptoms

- On comparative effectiveness of tinnitus management agents/modalities for individuals with mTBI etiology of tinnitus versus individuals with non-TBI etiology tinnitus
- To develop a standardized definition for Central Auditory Processing Disorder separate from mTBI
- To determine if a correlation exists between mTBI and a diagnosis of Central Auditory Processing Disorder
- To determine the effects of mechanism of injury (i.e., blunt, blast, other) on the assessment, prognosis, and treatment of individuals with symptoms attributed to mTBI who report problems with auditory perception

f. Exertion-induced Symptoms

- To identify effective treatments for exertion-induced symptoms in individuals with symptoms attributed to mTBI
- To evaluate the impact of exertional-related treatment protocols for symptoms worsened by exertion
- To determine if symptom clusters inform treatment timing, response, and outcomes in individuals with a history of mTBI with complaints of exertion-induced symptoms

g. Neuroendocrine Disorder-related Symptoms

- On assessment/identification of neuroendocrine disorders in adults with mTBI
- To identify effective treatments for neuroendocrine-related symptoms in adults with mTBI

F. Interventions with Insufficient Evidence

a. Complementary and Integrative Health

- On CIH interventions (e.g., meditation, mindfulness, CES) for treatment of symptoms attributed to mTBI
- On the comparative effectiveness research of multimodal and combination complementary and integrative health therapies
- To identify which individuals with symptoms attributed to mTBI would benefit from acupuncture (responders versus non-responders)
- On how to best administer the acupuncture treatment (e.g., time since injury, location, dosage)
- On longer-term outcomes for acupuncture in individuals with symptoms attributed to mTBI as it relates not only to symptom severity but also QoL
- To determine if auricular acupuncture (including battlefield acupuncture) is effective in improving acute or chronic mTBI symptoms
- To determine the effectiveness of CES (e.g., Alpha-Stim) utilizing sham-control RCTs
- To determine barriers to the delivery of complementary and integrative health therapies in military and Veteran populations

b. Repetitive Transcranial Stimulation

- On the safety and effectiveness of rTMS for individuals with symptoms attributed to mTBI
- To identify which individuals with symptoms attributed to mTBI would benefit from rTMS (responders versus non-responders)
- On how to best administer the rTMS treatment (e.g., time since injury, location, dosage)
- On which location(s) should be targeted during rTMS for specific symptoms and individuals

c. Hyperbaric Oxygen Therapy

No further research is needed on HBOT given the literature (85, 86) and FDA findings (87) determining that HBOT is not an effective or safe treatment after mTBI.

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 key questions (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 (92)

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)

The key questions are specific to adults 18 years or older who have mTBI with or without other health conditions. For key questions 2 through 12, patients must have had mTBI for 1 week or longer.

- Key Question 1: Adult patients who are being evaluated for concussion/head injury exposure or care.
- Key Questions 2 and 9: Adults with any persistent symptoms attributable to mTBI.
- Key Question 3: Adults with symptoms of dizziness, that persists for a week or more after an mTBI.

- Key Question 4: Adults with mTBI and symptom clusters and/or concussion subtypes from exertion that persist for a week or more after an mTBI.
- Key Question 5: Adults with tinnitus, a week or more after an mTBI.
- Key Question 6: Adults with visual impairment, such as diplopia, visual tracking deficits, and/or photophobia, a week or more after an mTBI.
- Key Question 7: Adult patients with mTBI for at least a week or longer.
- Key Question 8: Adults with symptoms of impaired attention, impaired concentration, or impaired memory, a week or more after an mTBI.
- Key Question 10: Adults with one or more mTBI.
- Key Question 11: Adults with mTBI for at least a week or longer.
- Key Question 12: Adults with mTBI and comorbidities for at least a week or longer.

b. Interventions

- Key Question 1:
    - Multi-modal assessment tools (Military Acute Concussion Evaluation, Military Acute Concussion Evaluation 2, Sport Concussion Assessment Tool, Vestibular/Ocular Motor Screening)
    - Neuroimaging (diffusion tensor imaging, magnetic resonance imaging, single-photon emission computed tomography)
    - Electrophysiologic imaging
    - Neuropsychological testing
    - Visual, hearing, smell tests
    - Eye tracking or ocular motor tests
    - EEG
    - Gait and balance assessment
    - Computerized posturography testing
    - Biomarkers (biofluids)
    - Effort validity testing
    - Focused neurologic exam
- Key Question 2: Exposure:
    - Low-level, repetitive blast
    - Single medium/high-level blast
    - Blunt trauma
    - Acceleration/deceleration injury (whiplash)

- Key Question 3: Specialized vestibular rehabilitation exercises or each of their components, including:
    - Habituation
    - Gaze stability
    - Balance and gait
    - Walking or aerobic
    - Canalith repositioning maneuvers
    - Benign paroxysmal positional vertigo
    - Cervicogenic rehabilitation
    - Manual therapy
- Key Question 4
    - Skilled physical therapy
    - Aerobic exercise
    - Medication therapy
- Key Question 5: Specific tinnitus interventions, such as:
    - White noise generator
    - Medications
    - rTMS
    - CBT
    - Other specific interventions
- Key Question 6: Visual/vestibular/ocular rehabilitation/convergence insufficiency
- Key Question 7: CIH and other interventions:
    - Meditation
    - Massage
    - Mindfulness
    - Yoga
    - Tai chi
    - Acupuncture
    - Chiropractic/manual therapy
    - HBOT
    - rTMS

- Key Question 8
    - Automated (computer-based apps or software): Cognitive exercises, cognitive games, cognitive training, brain games, cognitive apps, brain fitness programs, brain training (e.g., Lumosity, Posit Science/BrainHQ, Cogmed, Brain Age)
    - Clinician-based/skilled/in person: Cognitive rehabilitation, cognitive interventions, cognitive therapy (addressing memory, attention, concentration, learning, executive functions, problem solving, information processing/speed)
    - NOT included: Interventions addressing behavioral health (i.e., cognitive processing therapy, cognitive behavioral therapy)
- Key Question 9: Early patient referral to specialty rehabilitative and treatment services (physical therapy, occupational therapy, speech language therapy, neuro-optometry, physical medicine and rehabilitation, neurology, neurosurgery, behavioral health, audiology, vision therapy/rehabilitation, cognitive rehabilitation, vestibular rehabilitation, ocular rehabilitation, tinnitus interventions, cervical therapies)
- Key Question 10: Exposure: adults with one or more mTBI
- Key Question 11: Programs:
    - Intensive multidisciplinary program
    - Comprehensive program
    - Integrated program
    - Outpatient program
    - Intensive outpatient program
    - Mental health program
    - Residential rehabilitation program
    - Multidisciplinary inpatient program
    - Telehealth program
- Key Question 12
    - Behavioral health
    - Case management
    - Pharmacologic interventions

c. Comparators

- Key Question 1: mTBI diagnostic criteria by history and physical examination
- Key Question 2: Each other
- Key Question 3: Usual care; no intervention; each component of vestibular rehabilitation exercises compared to the other(s)
- Key Question 4: Usual care; no intervention; education only

- Key Question 5: Stress management strategies or other behavioral interventions
- Key Question 6: Usual care; no intervention
- Key Question 7: Usual care
- Key Question 8: Usual care; no intervention; clinician-based services
- Key Question 9: Usual care with delayed specialty referral
- Key Question 10: mTBI without multiple brain injuries (mTBI resulting from a single brain injury)
- Key Question 11: Another mTBI treatment program
- Key Question 12: Usual care

d. Outcomes

- Key Question 1
    - Critical outcomes: Predictive value for outcomes; predictive value versus a gold standard; symptom improvement (Neurobehavioral Symptom Inventory [NSI], Rivermead Post-Concussion Questionnaire [RPCQ]); return to activity/duty/work/sports; community reintegration
    - Important outcomes: Functional independence/quality of life (Mayo-Portland Adaptability Inventory [MPAI-4], Satisfaction with Life Scale [SWLS])
- Key Question 2
    - Critical outcomes: Symptom improvement (NSI, RPCQ)
    - Important outcomes: Functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
- Key Question 3
    - Critical outcomes: Symptom improvement (NSI, RPCQ); severity of dizziness (Dizziness Handicap Inventory); balance/disequilibrium symptoms (Activities-specific Balance Confidence Scale, Balance Error Scoring System, Balance Evaluation Systems Test, Four Square Step Test, Dynamic Gait Index), visual acuity (Dynamic Visual Acuity Test); proprioceptive symptoms (joint position error test)
    - Important outcomes: Functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
- Key Question 4
    - Critical outcomes: Return to activity/duty/work/sports; community reintegration; exertional test improvement (several instruments)
- Key Question 5
    - Critical outcomes: Symptom improvement (NSI, RPCQ); severity of tinnitus (questionnaire)
    - Important outcomes: Functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration

- Key Question 6
  - Critical outcomes: Symptom improvement (NSI, RPCQ); visual symptoms (diplopia, tracking deficits, photophobia, eye tracking, reading)
  - Important outcomes: Functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration; driving
- Key Question 7
  - Critical outcomes: Symptom improvement (NSI, RPCQ); functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
- Key Question 8
  - Critical outcomes: Symptom improvement (NSI, RPCQ); functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
  - Important outcomes: Functional attention, concentration, or memory (validated tools)
- Key Question 9
  - Critical outcomes: Symptom improvement (NSI, RPCQ); functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
- Key Question 10
  - Critical outcomes: Neurodegenerative disorders (dementia, chronic traumatic encephalopathy, mild cognitive impairment, Parkinson's); other neurocognitive function loss
- Key Question 11
  - Critical outcomes Functional independence/quality of life (MPAI-4, SWLS); return to activity/duty/work/sports; community reintegration
  - Important outcomes: Symptom improvement (NSI, RPCQ)
- Key Question 12
  - Critical outcomes: Symptom improvement (NSI, RPCQ); functional independence/quality of life (MPAI-4, SWLS)
  - Important outcomes: return to activity/duty/work/sports; community reintegration

e. Timing

- Key Questions 1, 2 and 9: >7 days post-mTBI
- Key Questions 3, 4, 7, 8, 10-12: ≥1 month follow-up
- Key Questions 5 and 6: ≥3 months follow-up

f. Settings

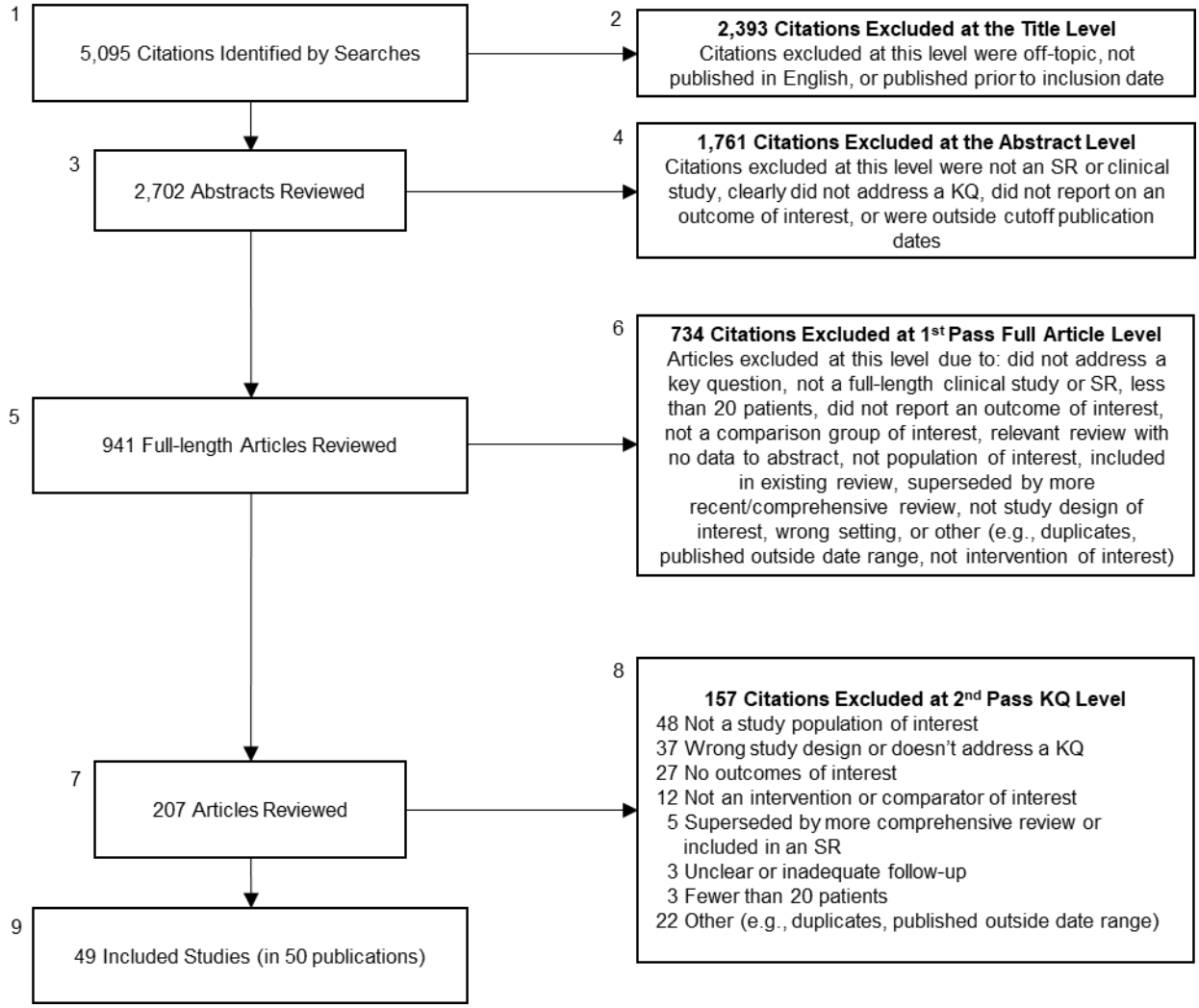
- Key Question 1: Primary care or emergency department setting
- Key Questions 2 and 6: Outpatient setting
- Key Questions 3-5, 7-12: Any setting

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 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: 5,095 citations identified by searches
    a. Right to Box 2: 2,393 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: 2,702 abstracts reviewed
    a. Right to Box 4: 1,761 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: 941 full-length articles reviewed
    a. Right to Box 6: 734 citations excluded at 1st pass full article level
        i. Articles excluded at this level due to: did not address a key question, not a full-length clinical study or SR, less than 20 patients, did not report an outcome of interest, not a comparison group of interest, relevant review with no data to abstract, not population of interest, included in existing review, superseded by more recent/comprehensive review, not study design of interest, wrong setting, or other (e.g., duplicates, published outside date range, not intervention of interest)
    b. Down to Box 7
4. Box 7: 207 articles reviewed
    a. Right to Box 8: 157 citations excluded at 2nd pass KQ level
        i. 48 Not a study population of interest
        ii. 37 Wrong study design or doesn't address a KQ
        iii. 27 No outcomes of interest
        iv. 12 Not an intervention or comparator of interest
        v. 5 Superseded by more comprehensive review or included in an SR
        vi. 3 Unclear or inadequate follow-up
        vii. 3 Fewer than 20 patients
        viii. 22 Other (e.g., duplicates, published outside date range)
    b. Down to Box 9
5. Box 9: 49 included studies (in 50 publications)

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	For adults who are being evaluated for concussion/head injury exposure or care, is there a single or set of specialized tests that improve treatment decision-making?	1 SR and 9 prognostic studies (3 cohort, 6 cross-sectional)
2	In adults with persistent symptoms after mTBI, what is the evidence that mechanism of injury should affect treatment strategies or impact treatment effectiveness and long-term outcomes?	2 cohort studies
3	In adults with mTBI and impairments due to dizziness (vertigo, disequilibrium, spatial disorientation symptoms or proprioceptive disorders including cervicogenic), what interventions improve outcomes?	2 RCTs
4	In adults with mTBI that experience symptoms or symptom clusters due to exertion, are treatments effective in improving outcomes?	1 RCT
5	In adults with mTBI and persistent tinnitus, what is the comparative effectiveness and safety of tinnitus interventions, such as white noise generators, medications, repetitive transcranial magnetic stimulation (rTMS), or other interventions on reducing symptoms when compared to stress management strategies as measured using standardized tinnitus questionnaires, at 3 months or more after initiation of intervention?	2 RCTs
6	In adults with persistent, post-concussive, visual symptoms, such as diplopia, tracking deficits and/or photophobia, do visual rehabilitation interventions durably (>3 months after treatments completed) improve outcomes?	1 RCT
7	In adults with mTBI, what is the effectiveness of complementary and integrative health (CIH) interventions in improving outcomes?	1 SR and 7 RCTs
8	a) In adults with mTBI and post-concussive symptoms of impaired attention, concentration and/or memory, what is the evidence that automated (computer-based) cognitive rehabilitation has equal or superior efficacy compared to clinician-based services in improving chronic symptoms at 1 month or more after initiation of the intervention? b) In adults with persistent cognitive symptoms or functional cognitive complaints, do specific cognitive rehabilitation interventions improve outcomes?	1 SR and 7 RCTs (in 8 publications)
9	For individuals with persistent symptoms attributable to mTBI, what is the evidence supporting the optimal timing for referral from a primary care clinician to a TBI/symptom specialist?	4 cohort studies
10	Are adults with mTBI and multiple brain injuries at increased risk of neurocognitive decline? a) What are demographic and clinical and management factors that may alter risks of these conditions?	1 SR and 6 prognostic studies (1 cohort, 5 cross-sectional)
11	What is the comparative effectiveness of mTBI treatment programs to improve morbidity, function, and return to work?	1 RCT
12	In adults with mTBI and co-morbidities (PTSD, SUD, and mood disorders), what interventions are effective for improving outcomes?	2 SRs and 1 RCT
	Total Evidence Base	**49 studies (in 50 publications)**

Abbreviations: RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

All studies included as evidence, must have been published in English on or after March 1, 2015 to April 28, 2020.

Publications must have been a full text clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.

Systematic reviews 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 ratings used by the Evidence-based Practice Centers for the Agency for Healthcare Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed judgment of the overall risk of bias, consistency, directness, and precision of evidence. Existing reviews were not used as evidence if unable to assess the overall quality of the evidence in the review.

Each study must have enrolled a patient population in which at least 85% of patients had mTBI, with identifiable data for the population of interest (i.e., patients with mTBI could be identifiable in the dataset). For some KQs with limited evidence, the threshold was lowered as appropriate.

Only studies assessing the efficacy of drugs that have received U.S. Food and Drug Administration's (FDA) approval for marketing in the United States were included in this review.

Each study must have enrolled at least 20 patients (10 per study group).

Each study must have reported on an outcome of interest.

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

Studies addressing KQ 3 through 8, 11, and 12 must have been a systematic review of randomized controlled trials or a randomized controlled trial. Observational studies were not considered as evidence for these questions. Randomized crossover trials were included only if data from the first period (prior to treatment crossover) was reported separately. Post-hoc and non-systematic pooled analyses were only included if they addressed a subpopulation or outcome not covered or reported in the original study.

For KQ 1, systematic reviews of acceptable study designs, randomized controlled trials and prospective diagnostic cohort or other prospective non-randomized studies that reported on diagnostic characteristics or other outcomes from instruments assessed in the question were accepted as evidence. Retrospective studies were only accepted if evidence from other study designs was not identified.

For KQ 2, 9 and 10, systematic reviews of acceptable study designs, randomized controlled trials and non-randomized controlled studies (controlled cohort, case-control, or prognostic studies) were accepted as evidence. Retrospective studies were only accepted if evidence from other study designs was not identified.

For KQ 8, short-term antibiotic use was defined as 10 days or less.

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
Bibliographic Databases	EMBASE (Excerpta Medica)	March 11, 2015 to April 28, 2020	Elsevier
	MEDLINE PreMEDLINE (National Library of Medicine)	March 11, 2015 to April 28, 2020	Elsevier
	PsycINFO (American Psychological Association)	March 11, 2015 to April 28, 2020	Wolters Kluwer
	PubMed (Inprocess, Publisher records, and PubMedNotMedline records)	March 11, 2015 to April 28, 2020	National Library of Medicine
Grey Literature	Agency for Healthcare Research and Quality (AHRQ) website	March 11, 2015 to April 28, 2020	AHRQ
	Department of Veterans Affairs. Evidence Synthesis Program Reports	March 11, 2015 to April 28, 2020	VA

C. Developing Evidence-based Recommendations

In consultation with the VA 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 August 10-13, 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 2016 VA/DoD mTBI CPG as necessary (see Categorization of 2016 Clinical Practice Guideline Recommendations). The Work Group also developed new recommendations not included in the 2016 VA/DoD mTBI 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:(10)

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.(12, 13)

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).(10)

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 QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). 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: 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
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 A-4.

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 mTBI; 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 carried forward 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 2016 VA/DoD mTBI 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 period (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 EBPWG approved the final CPG and toolkit products in June 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.

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. 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.

B. Patient Focus Group Findings

a. Participants noted the most prominent symptoms they experience(d) include sleep disturbance/insomnia, headaches, difficulties in learning/cognition/memory, light sensitivity, tinnitus, and behavioral symptoms and conditions such as depression and excessive anger.

- Participants noted a variety of symptoms stemming from their injury. Some participants also noted personality changes compared to before their injury.
- Some participants recalled being easily overwhelmed and overstimulated following their injury.

b. Participants noted their symptoms impact multiple aspects of their lives, including basic functioning, quality of life, family life, and the ability to pursue further education and professional advancement.

- Participants stated their mTBI has had a significant impact on work, deployment, and schooling.
- Participants reflected on the problems their mTBI caused in their personal relationships.

c. Participants described the military culture and perceived a lack of adequate expertise and training in the early identification and diagnosis of mTBI. As a result, participants reported their mTBIs were diagnosed and treated long after the point of injury, often years later.

- Participants noted that the fast paced and demanding military environment, stigma associated with a history of mTBI, and the prioritization of returning to duty can be barriers to recognizing mTBI.
- Participants noted difficulty in obtaining a diagnosis for their mTBI at the time of injury. Sometimes, physical and visible injuries were prioritized for treatment.
- Some participants could not easily trace the cause of their symptoms to one specific event but instead to multiple events and injuries.
- Participants felt symptoms were sometimes not taken seriously.

d. Participants described success with non-pharmacologic treatments and less success with pharmacologic treatments. Participants thought pharmacologic treatments were prescribed too readily, in excess, and often without adequate discussion of risks and side effects. Participants' opinions varied on the importance of self-management or at-home treatments/therapies.

- Participants described success with isolation tanks, CES devices, neurofeedback, and physical, vision, talk, and family therapies.
- Participants described including family members in treatment/therapy as important and beneficial.
- Participants expressed frustration with prescription medications and perceived them as an overused quick fix.
- Participants had mixed feelings on the importance of take-home treatment/therapies/machines and technology solutions or apps.
- Participants had mixed feelings on the quality of treatment received from the VA and DoD.

e. Participants described their mTBI treatment course as a long and confusing process, in part related to the difficulty in distinguishing mTBI symptoms from those related to co-occurring symptoms/disorders. Participants want providers to use individualized treatment approaches, maintain an open dialogue, and participate in shared decision making.

- Participants noted the difficulty in distinguishing the underlying cause of their symptoms when they had overlapping medical issues.
- Participants wanted more tailored treatment options (e.g., support groups for women only).

f. Participants emphasized the importance of education and the need for greater knowledge on mTBI so patients can learn about their injury, develop self-awareness, and feel empowered and included in their treatment plan.

- Participants noted that developing self-awareness and an ability to anticipate triggers helps them manage their symptoms attributed to mTBI.
- Participants noted education on mTBI can be beneficial for themselves and the larger community around them.

Appendix C: Evidence Table

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

Recommendation	2016 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
1. We suggest a primary care (as opposed to specialty care), symptom-focused approach in the evaluation and management of the majority of patients with symptoms attributed to mild traumatic brain injury (mTBI).	Weak for, Weak against	(24, 25)	Weak for	Reviewed, Amended
2. There is insufficient evidence to recommend for or against specialized treatment programs to improve morbidity, function, and return to work in patients with persistent symptoms attributed to mTBI.	Neither for nor against	(26)	Neither for nor against	Reviewed, New-replaced
3. For patients with new symptoms that develop more than 30 days after mTBI, we suggest a symptom-specific evaluation for non-mild traumatic brain injury etiologies.	Weak for	(27)	Weak for	Not reviewed, Amended
4. We suggest against using the following tests to establish the diagnosis of mTBI or direct the care of patients with symptoms attributed to mTBI: a. Neuroimaging b. Serum biomarkers c. Electroencephalogram	Weak against	(28-37)	Weak against	Reviewed, Amended

[a] 2016 Strength of Recommendation column: The 2016 VA/DoD mTBI CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2016 strength of recommendation indicates that more than one 2016 VA/DoD mTBI CPG recommendation is covered by the 2021 recommendation. "Not applicable" indicates that the 2021 VA/DoD mTBI CPG recommendation was a new recommendation, and therefore does not have an associated 2016 strength of recommendation. "Neither for nor against" represents updated language for "N/A" used in the 2016 VA/DoD mTBI CPG.

[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 mTBI 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	2016 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
5. We suggest against using computerized post-concussive screening batteries* for routine diagnosis and care of patients with symptoms attributed to mTBI.	Strong against	(44) **Additional references:** (38-42)	Weak against	Reviewed, New-replaced
6. We suggest against performing comprehensive neuropsychological/cognitive testing during the first 30 days following mTBI.	Strong against	(43, 44) **Additional references**: (38-42)	Weak against	Reviewed, New-replaced
7. When counseling patients about the long-term effects of mTBI, there is insufficient evidence to state that single or repeated mTBI increases their risk of future neurocognitive decline.	Not applicable	(45, 47-51)	Neither for nor against	Reviewed, New-added
8. When counseling patients about the long-term effects of mTBI, there is insufficient evidence to state that demographic, injury-related clinical, and management factors increase the risk of future neurocognitive decline in patients with symptoms attributed to single or repeated mTBI.	Not applicable	(46)	Neither for nor against	Reviewed, New-added
9. We suggest against adjusting outcome prognosis and treatment strategy based on mechanism of injury.	Strong against, Strong against	(52-54) **Additional references:** (55, 56)	Weak against	Reviewed, New-replaced
10. We suggest that patients with symptoms attributed to mTBI who present with memory, attention, or executive function problems despite appropriate management of other contributing factors (e.g., sleep, pain, behavioral health, headache, disequilibrium) should be referred for a short trial of clinician-directed cognitive rehabilitation services.	Weak for	(57-65)	Weak for	Reviewed, Amended
11. We suggest against the use of self-administered computer training programs for the cognitive rehabilitation of patients with symptoms attributed to mTBI.	Not applicable	(58-62, 66, 67)	Weak against	Reviewed, New-added

Recommendation	2016 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
12. We suggest that patients with symptoms attributed to mTBI who present with behavioral health conditions, including posttraumatic stress disorder, substance use disorders, and mood disorders, be evaluated and managed the same whether they have had mTBI or not, according to the relevant existing VA/DoD clinical practice guidelines.	Strong for	(26, 72-74) **Additional references:** (68-71)	Weak for	Reviewed, New-replaced
13. We suggest that patients with persistent symptoms of dizziness and imbalance attributed to mild traumatic brain injury be offered a trial of specific vestibular rehabilitation and proprioceptive therapeutic exercise.	Weak for	(77, 78) **Additional references:** (75, 76, 79)	Weak for	Reviewed, New-replaced
14. There is insufficient evidence to suggest for or against the use of any particular modality for the treatment of visual symptoms attributed to mTBI such as diplopia, accommodation or convergence deficits, visual tracking deficits and/or photophobia.	Neither for nor against	(80)	Neither for nor against	Reviewed, Amended
15. There is no evidence to suggest for or against the use of any particular modality for the treatment of tinnitus attributed to mTBI.	Neither for nor against	None	Neither for nor against	Reviewed, Amended
16. There is insufficient evidence to recommend for or against treatments for exertion-induced symptoms/symptom clusters attributed to mTBI.	Not applicable	(81)	Neither for nor against	Reviewed, New-added
17. There is insufficient evidence to recommend for or against the use of any of the following interventions for the treatment of patients with symptoms attributed to mild traumatic brain injury: a. Acupuncture b. Tai chi c. Meditation d. Mindfulness e. Yoga f. Massage g. Chiropractic therapy h. Cranial electrotherapy stimulation (CES) i. Sensory deprivation tanks	Not applicable	(67, 82) **Additional references:** (83, 84)	Neither for nor against	Reviewed, New-added

Recommendation	2016 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
18. We recommend against the use of hyperbaric oxygen therapy for the treatment of patients with symptoms attributed to mild traumatic brain injury.	Not applicable	(85, 86) **Additional references:** (87)	Strong against	Reviewed, New-added
19. We suggest against the use of repetitive transcranial magnetic stimulation for the treatment of patients with symptoms attributed to mild traumatic brain injury.	Not applicable	(88-90) **Additional references:** (91)	Weak against	Reviewed, New-added

* E.g., Automated Neuropsychological Assessment Metrics (ANAM), Neuro-Cognitive Assessment Tool (NCAT), and Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT)

Appendix D: 2016 Recommendation Categorization Table

Table D-1. 2016 mTBI CPG Recommendation Categorization Table[a,b,c,d,e,f]

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
1	We suggest using the terms "history of mild traumatic brain injury (mTBI)" or "concussion" and to refrain from using the terms "brain damage" or "patients with mTBI" in communication with patients and the public.	Weak for	Not reviewed, Amended	Not reviewed, Deleted	–
2	We recommend evaluating individuals who present with symptoms or complaints potentially related to brain injury at initial presentation.	Strong for	Not reviewed, Amended	Reviewed, Deleted	–
3	Excluding patients with indicators for immediate referral, for patients identified by post-deployment screening or who present to care with symptoms or complaints potentially related to brain injury, we suggest ***against*** using the following tests to establish the diagnosis of mTBI or direct the care of patients with a history of mTBI: a. Neuroimaging b. Serum biomarkers, including S100 calcium-binding protein B (S100-B), glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal esterase L1 (UCH-L1), neuron specific enolase (NSE), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) peptide c. Electroencephalogram (EEG)	Weak against	Reviewed, New-replaced	Reviewed, Amended	4

[a] 2016 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2016 VA/DoD mTBI CPG.

[b] 2016 CPG Recommendation Text column: This contains the wording of each recommendation from the 2016 VA/DoD mTBI CPG.

[c] 2016 CPG Strength of Recommendation column: The 2016 VA/DoD mTBI CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2016 VA/DoD mTBI CPG were: Strong for, Weak for, N/A, Weak against, or Strong against. "Neither for nor against" represents updated language for "N/A" used in the 2016 VA/DoD mTBI CPG.

[d] 2016 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2016 VA/DoD mTBI 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 mTBI 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 2016 VA/DoD mTBI CPG, this column indicates the new recommendation(s) to which they correspond.

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
4	We recommend ***against*** performing comprehensive neuropsychological/cognitive testing during the first 30 days following mTBI. For patients with symptoms persisting after 30 days, see Recommendation 17.	Strong against	Not reviewed, Amended	Reviewed, New replaced	6
5	For patients identified by post-deployment screening or who present to care with symptoms or complaints potentially related to brain injury, we recommend ***against*** using the following tests in ***routine*** diagnosis and care of patients with symptoms attributed to mTBI: a. Comprehensive and focused neuropsychological testing, including Automated Neuropsychological Assessment Metrics (ANAM), Neuro-Cognitive Assessment Tool (NCAT), or Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT).	Strong against	Not reviewed, Amended	Reviewed, New replaced	5
6	For patients with new symptoms that develop more than 30 days after mTBI, we suggest a focused diagnostic work-up specific to those symptoms only.	Weak for	Not reviewed, Amended	Not reviewed, Amended	3
7	We recommend assessing patients with symptoms attributed to mTBI for psychiatric symptoms and comorbid psychiatric disorders including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), substance use disorders (SUD) and suicidality. Consult appropriate VA/DoD clinical practice guidelines.	Strong for	Not reviewed, Amended	Reviewed, Deleted	–
8	We suggest considering, and offering as appropriate, a primary care, symptom-driven approach in the evaluation and management of patients with a history of mTBI and persistent symptoms.	Weak for	Not reviewed, Amended	Reviewed, Amended	1
9	We recommend ***not*** adjusting treatment strategy based on mechanism of injury.	Strong against	Reviewed, New-added	Reviewed, New-replaced	9
10	We recommend ***not*** adjusting outcome prognosis based on mechanism of injury.	Strong against	Reviewed, New-added	Reviewed, New-replaced	9

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
11	We suggest that the treatment of headaches should be individualized and tailored to the clinical features and patient preferences. The treatment may include: a. Headache education including topics such as stimulus control, use of caffeine/tobacco/alcohol and other stimulants b. Non-pharmacologic interventions such as sleep hygiene education, dietary modification, physical therapy (PT), relaxation and modification of the environment (for specific components for each symptom, see Appendix B: Clinical Symptom Management) c. Pharmacologic interventions as appropriate both for acute pain and prevention of headache attacks	Weak for	Reviewed, New-replaced	Reviewed, Deleted	–
12	In individuals with a history of mTBI who present with functional impairments due to dizziness, disequilibrium, and spatial disorientation symptoms, we suggest that clinicians offer a short-term trial of specific vestibular, visual, and proprioceptive therapeutic exercise to assess the individual's responsiveness to treatment. Refer to occupational therapy (OT), physical therapy (PT) or other vestibular trained care provider as appropriate. ***A prolonged course of therapy in the absence of patient improvement is strongly discouraged.***	Weak for	Reviewed, Amended	Reviewed, New-replaced	13
13	There is no evidence to suggest for or against the use of any particular modality for the treatment of tinnitus after mTBI.	Neither for nor against	Reviewed, New-added	Reviewed, Amended	15
14	There is no evidence to suggest for or against the use of any particular modality for the treatment of visual symptoms such as diplopia, accommodation or convergence disorder, visual tracking deficits and/or photophobia after mTBI.	Neither for nor against	Reviewed, New-added	Reviewed, Amended	14

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
15	We suggest that treatment of sleep disturbance be individualized and tailored to the clinical features and patient preferences, including the assessment of sleep patterns, sleep hygiene, diet, physical activities and sleep environment. The treatment may include, in order of preference: a. Sleep education including education about sleep hygiene, stimulus control, use of caffeine/tobacco/alcohol and other stimulants b. Non-pharmacologic interventions such as cognitive behavioral therapy specific for insomnia (CBTi), dietary modification, physical activity, relaxation and modification of the sleep environment (for specific components for each symptom, see Appendix B: Clinical Symptom Management) c. Pharmacologic interventions as appropriate to aid in sleep initiation and sleep maintenance	Weak for	Reviewed, Amended	Not Reviewed, Deleted	–
16	We recommend that the presence of psychological or behavioral symptoms following mTBI should be evaluated and managed according to existing evidence-based clinical practice guidelines, and based upon individual factors and the nature and severity of symptoms.	Strong for	Reviewed, Amended	Reviewed, New-replaced	12
17	We suggest that patients with a history of mTBI who report cognitive symptoms that do not resolve within 30-90 days and have been refractory to treatment for associated symptoms (e.g., sleep disturbance, headache) be referred as appropriate for a structured cognitive assessment or neuropsychological assessment to determine functional limitations and guide treatment.	Weak for	Not reviewed, Amended	Reviewed, Deleted	-
18	We suggest that individuals with a history of mTBI who present with symptoms related to memory, attention or executive function problems that do not resolve within 30-90 days and have been refractory to treatment for associated symptoms should be referred as appropriate to cognitive rehabilitation therapists with expertise in TBI rehabilitation. We suggest considering a short-term trial of cognitive rehabilitation treatment to assess the individual patient responsiveness to strategy training, including instruction and practice on use of memory aids, such as cognitive assistive technologies (AT). ***A prolonged course of therapy in the absence of patient improvement is strongly discouraged.***	Weak for	Reviewed, New-replaced	Reviewed, Amended	10

2016 CPG Recommendation #	2016 CPG Recommendation Text	2016 CPG Strength of Recommendation	2016 CPG Recommendation Category	2021 CPG Recommendation Category	2021 CPG Recommendation #
19	We suggest ***against*** offering medications, supplements, nutraceuticals or herbal medicines for ameliorating the neurocognitive effects attributed to mTBI.	Weak against	Not reviewed, Amended	Not reviewed, Deleted	–
20	We suggest ***against routine*** referral to specialty care in the majority of patients with a history of mTBI.	Weak against	Reviewed, Amended	Reviewed, Amended	1
21	If the patient's symptoms do not resolve within 30-90 days and are refractory to initial treatment in primary care and significantly impact activities of daily living (ADLs), we suggest consultation and collaboration with a locally designated TBI or other applicable specialist.	Weak for	Reviewed, Amended	Reviewed, Deleted	–
22	For patients with persistent symptoms that have been refractory to initial psychoeducation and treatment, we suggest referral to case managers within the primary care setting to provide additional psychoeducation, case coordination and support.	Weak for	Reviewed, Amended	Not reviewed, Deleted	–
23	There is insufficient evidence to recommend for or against the use of interdisciplinary/multidisciplinary teams in the management of patients with chronic symptoms attributed to mTBI.	Neither for nor against	Reviewed, New-replaced	Reviewed, New-replaced	2

Appendix E: Participant List

Maj Thomas J. Bayuk, DO (Champion)
Neurology
United States Air Force, Medical Corps
National Intrepid Center of Excellence
Walter Reed National Military Medical Center
Bethesda, MD

Amy O. Bowles, MD
Physical Medicine and Rehabilitation
Brooke Army Medical Center
Fort Sam Houston, TX

Lt Col Andrew W. Bursaw, DO
General and Vascular Neurology
Neurology Element Chief
U.S. Air Force Academy Medical Clinic
Air Force Academy, CO

Jennifer Burton, DPT
Physical Therapy
George E. Wahlen VA Medical Center
Salt Lake City, UT

David X. Cifu, MD (Champion)
Physical Medicine and Rehabilitation
Senior TBI Specialist, Department of Veterans Affairs
Associate Dean of Innovation and System Integration
Herman J. Flax, MD Professor and Chair, Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University School of Medicine
Richmond, VA

Margaret Daggett, MSN, FNP-BC, CRRN
Rehabilitation Nursing
Transition Care Management Program
Polytrauma/TBI Program Nurse Practitioner
Active Duty Military Clinic Nurse Practitioner
Syracuse VA Medical Center
Syracuse, NY

Ruby Diaz, LCSW
Social Work
Edward Hines, Jr. VA Hospital
Hines, IL

Dorene Doi, OTR/L
Occupational Therapy
Tibor Rubin VA Medical Center
Long Beach, CA

Blessen C. Eapen, MD, FAAPMR (Champion)
Physical Medicine and Rehabilitation Service
VA Greater Los Angeles Healthcare System
Associate Professor
Division of Physical Medicine and Rehabilitation
David Geffen School of Medicine at UCLA
Los Angeles, CA

CDR Stephanie Felder, PhD, LCSW, LCAS-A, BCD
Clinical Social Work
Traumatic Brain Injury Center of Excellence
Defense Health Agency Research and Development (J-9)
Silver Spring, MD

LTC Carrie W. Hoppes, PT, PhD, NCS, OCS, ATC
Physical Therapy
Army-Baylor University Doctoral Program in Physical Therapy
U.S. Army Medical Center of Excellence
Fort Sam Houston, TX

Robin A. Hurley, MD
Physical Medicine & Rehabilitation
Salisbury VA Medical Center Associate Chief of Staff, Research and Academic Affairs
Professor, Wake Forest School of Medicine
Departments of Psychiatry and Radiology
Senior Liaison for VA Affairs, Office of the Dean
VISN 6 MIRECC Associate Director, Education
VISN 6 Academic Affiliations Officer
Salisbury, NC

Tracy Kretzmer, PhD, ABPP-CN
Neuropsychology
Mental Health and Behavioral Sciences
Inpatient Polytrauma, Rehabilitation, Post-Deployment Rehabilitation and Evaluation Program (PREP)
James A. Haley Veterans' Hospital
Tampa, FL

Adam Edward Lang, PharmD, BCACP
Clinical Pharmacy
Internal Medicine, Troop Medical Services
McDonald Army Health Center
Fort Eustis, VA

R. Kevin Manning, PhD, CCC-SLP
Speech Language Pathology
Brain Injury Rehabilitation Service (BIRS)
San Antonio Military Medical Center - North
Fort Sam Houston, TX

Danielle D. Murray, PhD
Psychology
Brain Injury Rehabilitation Service
Brooke Army Medical Center
Fort Sam Houston, TX

Linda M. Picon, MCD, CCC-SLP
Speech Language Pathology
Rehabilitation and Prosthetic Services
Patient Care Services
Veterans Health Administration
Washington, DC

CAPT Scott W. Pyne, MD
Family Medicine/Sports Medicine
Division Chief
Traumatic Brain Injury Center of Excellence
Defense Health Agency Research and Development (J-9)
Silver Spring, MD

Ronald G. Riechers, II, MD
Neurology
Chief, Department of Neurology
Medical Director, Polytrauma Team
Cleveland VA Medical Center
Associate Professor, Department of Neurology
Case Western Reserve University
Cleveland, OH

Katharine C. Stout, PT, DPT, NCS, MBA (Champion)
Director of Clinical Affairs Division
Traumatic Brain Injury Center of Excellence
Defense Health Agency Research and Development (J-9)
Silver Spring, MD

Kathryn Tortorice, PharmD, BCPS
National Pharmacy Benefits Management (PBM)
Clinical Pharmacy Program Manager, Neurology and Solid Organ Transplant
National PBM Services
U.S. Department of Veterans Affairs
Hines, IL

Appendix F: Literature Review Search Terms and Strategy

Table F-1. mTBI Search Strategy for EMBASE with EMBASE.com syntax

KQ	Set #	Concept	Strategy
KQ 1 – For adults being evaluated for concussion/head injury exposure or care, is there a single or set of specialized tests that improve treatment decision-making?	1	Adult patients who are being evaluated for concussion/head injury exposure or care	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Specialized diagnostic approaches General/cross-cutting terms	'brain injury assessment'/exp/mj OR 'brain mapping'/mj OR 'clinical assessment'/mj OR 'clinical assessment tool'/mj OR 'clinical decision making'/mj OR 'clinical evaluation'/mj OR 'decision support system'/exp/mj OR 'functional status assessment'/mj OR 'learning and memory test'/exp/mj OR (assessment* OR batteries OR battery OR decision* OR diagnos* OR 'functional status' OR inventory OR inventories OR index OR measur* OR scale* OR score* OR screen* OR test* OR tool OR tools):ti
	3	Specialized diagnostic approaches Multi-modal assessment tools (MACE, MACE2, SCAT, VOMS)	('brain concussion'/mj AND diagnosis/lnk) OR 'screening test'/mj OR (((concussion OR multi-modal OR multimodal) NEAR/2 (assessment OR diagnos* OR evaluation OR screen* OR test*)) OR 'military acute concussion evaluation' OR MACE* OR 'sport concussion assessment tool' OR SCAT* OR (vestibular* NEXT/3 screen*) OR VOMS):ti
	4	Neuroimaging	'diagnostic imaging'/exp/mj OR echoencephalography/mj OR neuroimaging/exp/mj OR radiodiagnosis/exp/mj OR ('brain scan*' OR 'computed tomography' OR CT OR 'diffus* tensor' OR echoencephalogra* OR fMRI OR 'functional imaging' OR 'magnetic resonance' OR magnetoencephalogra* OR MRI* OR (('multi modal' OR multimodal) NEXT/1 (imaging OR neuroimaging)) OR 'single photon emission' OR SPECT OR 'x-ray*' OR imaging OR neuroimaging OR neuroradio* OR radiolog* OR radiograph*):ti
	5	Electrophysiologic imaging, EEG	'brain electrophysiology'/exp/mj OR electroencephalogram/exp/mj OR electroencephalography/exp/mj OR electrophysiology/mj OR (electroencephalogra* OR electrophysiolog* OR EEG OR EEGs):ti
	6	Neuropsychological testing; effort (symptom) validity testing	'neuropsychological test'/exp/mj OR ('sensory dysfunction'/exp/mj AND diagnosis/lnk) OR 'task performance'/mj OR ((effort OR performance OR symptom*) NEXT/2 (test* OR validity)) OR ((auditory OR cognitive OR hearing OR 'neuro-cognitive' OR 'neuro-psych*' OR neuropsyc* OR olfactory OR smell OR vision OR visual) NEXT/2 (assessment* OR diagnos* OR evaluation OR screen* OR test*))):ti
	7	Eye tracking or ocular motor tests	(('eye movement disorder'/exp/mj OR 'visual system parameters'/exp/mj) AND diagnosis/lnk) OR ('eye tracking' OR (('eye movement*' OR ocular OR oculo-motor OR oculomotor OR saccad*) NEAR/3 (assessment* OR control OR evaluation OR screen* OR test*)) OR 'king-devick'):ti
	8	Gait, balance assessment	(('balance disorder'/exp/mj OR 'gait disorder'/mj OR 'neurologic gait disorder'/mj) AND 'diagnosis'/lnk) OR 'exercise test'/exp/mj OR 'motor dysfunction assessment'/exp/mj OR stabilograph/mj OR stabilography/mj OR (CDP OR posturograph* OR stabilograph*):ti OR ((gait OR balance OR equilibrium OR vestibular) AND (assessment* OR control OR evaluation OR screen* OR test*)):ti

KQ	Set #	Concept	Strategy
KQ 1 (cont.)	9	Biomarkers (including concepts listed in the PICOTS table)	'biological marker'/mj OR 'genome wide association study'/de OR 'interleukin 6'/mj OR 'interleukin 10'/mj OR orexin/mj OR 'protein s100b'/mj OR 'tau protein'/mj OR 'tumor necrosis factor'/mj OR vasculotropin/mj OR ('amyloid β40' OR 'amyloid β42' OR 'amyloid beta40' OR 'amyloid beta42' OR (amyloid NEXT/1 (β OR beta) NEXT/1 (40 OR 42)) OR 'c reactive protein' OR 'epi-genetic*' OR epigenetic* OR 'genome wide association' OR (inflammat* NEXT/2 (biomarker* OR marker*)) OR 'IL-6' OR 'interleukin-6' OR 'IL-10' OR 'interleukin-10' OR 'neurofilament light chain' OR (protein NEAR/1 s100b) OR 'tumor necrosis factor alpha' OR 'tnf-alpha' OR 'vascular endothelial growth factor' OR 'UCH-L1' OR UCHL1 OR VEGF OR assay* OR biomarker* OR GFAP OR marker* OR neuromarker* OR ((blood OR fluid* OR plasma OR serum OR saliva*) AND (analys* OR evaluation OR level OR levels OR screen* OR test*)) OR mRNA OR RNA OR tau):ti
	10	Focused neurologic exam	'functional assessment'/mj OR 'neurologic disease assessment'/mj OR 'neurologic examination'/mj OR 'patient assessment'/mj OR ((neurologic* OR physical) NEXT/2 (exam OR exams OR examination*)):ti,ab
	11	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
	12	Refocus results	#11 AND ('diagnostic procedure'/exp OR diagnosis/lnk OR (assess* OR diagnos* OR decision OR evaluat* OR identif* OR measur* OR predict* OR prognos* OR screen* OR test*):ti) AND (((brain OR head) AND (damage* OR contusion* OR injur* OR trauma)) OR concuss* OR postconcuss*):ti
	13	Apply general hedges	See General Hedges at the end of this table
	14	Limit to systematic reviews and diagnostic studies	See Study Type Hedges at the end of this table
KQ 2 – In adults with persistent symptoms after mTBI, what is the evidence that mechanism of injury should affect treatment strategies or impacts treatment effectiveness and long-term outcomes?	1	Adults with any symptoms attributed to mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Mechanism of injury	acceleration/mj OR 'battle injury'/mj OR 'blast injury'/mj OR 'contrecoup injury'/mj OR deceleration/mj OR explosion/mj OR 'military deployment'/mj OR 'whiplash injury'/mj OR (accelerat* OR blast* OR 'blunt trauma' OR bomb* OR closed OR collision* OR combat* OR coup OR contrecoup OR crash* OR decelerat* OR deploy* OR explod* OR explosi* OR nonblast* OR nondeploy* OR polytrauma* OR undeploy* OR whiplash):ti OR 'source of injury':ti,ab OR ((caus* OR characteristics OR factors OR mechanism* OR type*) NEAR/2 injury):ti,ab OR (mechanism* NEXT/2 ('brain injur*' OR 'traumatic brain injur*')):ti,ab
	3	Combine population and mechanism of injury sets	#1 AND #2
	4	Treatment strategy	'disease management':lnk OR 'rehabilitation':lnk OR therapy/exp OR 'therapy'/lnk OR (approach* OR decision* OR intervention* OR manag* OR pathway* OR program* OR rehabilitat* OR retrain* OR strateg* OR therap* OR train* OR treat*):ti

KQ	Set #	Concept	Strategy
KQ 2 (cont.)	5	Treatment effectiveness and outcomes	'treatment outcome'/exp OR (associated OR association* OR efficac* OR effective* OR outcome* OR perform* OR predict* OR prognos* OR recover* OR symptom*):ti
	6	Combine treatment and outcome sets	#4 OR #5
	7	Combine all sets	#3 AND #6
	8	Apply general hedges	See General Hedges at the end of this table
	9	Limit to systematic reviews, RCTs, and non-RCTs/ observational studies	See Study Type Hedges at the end of this table
KQ 3 – In adults with mTBI and impairments due to dizziness (vertigo, disequilibrium, spatial disorientation symptoms or proprioceptive disorders including cervicogenic), what interventions improve outcomes?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Dizziness	'balance disorder'/exp OR 'cervicogenic dizziness'/de OR dizziness/de OR 'positional dizziness'/de OR 'vestibular disorder'/exp OR 'vestibular function'/exp OR 'vestibular system'/exp OR (balance OR canalith* OR cervicogenic OR disequilibrium OR dizziness OR dizzy* OR dysequilibrium OR equilibrium OR gait OR imbalanc* OR 'inner ear*' OR instability OR labyrinth* OR perceptual OR positional OR positioning OR postural OR stability OR unbalanc* OR unstead* OR vertigo OR vestibular):ti,ab
	3	Combine population sets	#1 AND #2
	4	Specialized vestibular rehabilitation exercises General terms	rehabilitation/exp OR 'vestibular test'/exp OR 'vestibular testing equipment'/exp OR 'disease management':lnk OR 'rehabilitation':lnk OR 'therapy'/lnk OR (exercis* OR intervention* OR manag* OR program* OR rehabilitat* OR retrain* OR therap* OR train* OR treat*):ti OR ('cawthorne-cooksey' OR 'vestibular adaptation' OR 'vestibular rehab*'):ti,ab
	5	Visual exercises	((eye OR eyes OR focus* OR gaz* OR refocus* OR saccadic OR 'smooth-pursuit' OR visual OR vision OR visuospatial) NEAR/3 (exercise* OR feedback OR stabili* OR retrain* OR train*)):ti,ab
	6	Proprioceptive exercises	proprioception/de OR 'proprioceptive feedback'/de OR ((kinaesthe* OR kinesthe* OR propriocept*) NEAR/3 (exercis* OR feedback OR retrain* OR train*)):ti,ab
	7	Balance and physical exercises	exercise/exp OR kinesiotherapy/exp OR 'physical activity'/de OR physiotherapy/exp OR walking/exp OR ((balance NEAR/3 (exercis* OR feedback OR retrain* OR train*)) OR 'aerobic exercise*' OR kinesi* OR physiother* OR 'physical therapy' OR walking):ti,ab
	8	Manual therapy and repositioning maneuvers	'manipulative medicine'/exp OR ((manipulat* NEXT/1 (medicine OR therap* OR treatment*)) OR (manual NEXT/2 therapy) OR ((spinal OR spine) NEAR/2 manipulat*) OR chiropract* OR epley OR liberatory OR maneuver* OR manoeuver* OR reposition* OR semont):ti,ab OR manipulat*:ti
	9	Combine intervention sets	#4 OR #5 OR #6 OR #7 OR #8

KQ	Set #	Concept	Strategy
KQ 3 (cont.)	10	Combine population and intervention sets	#3 AND #9
	11	Apply general hedges	See General Hedges at the end of this table
	12	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
KQ 4 – In adults with mTBI that experience symptoms or symptom clusters due to exertion, are treatments effective in improving outcomes?	1	Adults with any symptoms attributed to mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Symptom clusters and/or concussion subtypes from exertion	'postconcussion syndrome'/de OR (((cluster* OR complex*) NEAR/3 symptom*) OR (concussion NEAR/1 (sub-type* OR subtype*)) OR (constellation AND symptoms) OR exertion* OR 'group* of symptoms' OR (neurosensory NEXT/3 (deficit* OR dysfunction* OR function* OR sequelae OR symptom*)) OR (persisten* NEAR/2 symptom*) OR ((post-concuss* OR postconcuss*) NEXT/1 (headache* OR dizziness OR symptoms OR syndrome))):ti,ab,kw
	3	Combine population sets	#1 AND #2
	4	Skilled physical therapy and aerobic exercise	exercise/exp OR kinesiotherapy/exp OR rehabilitation/exp OR rehabilitation/lnk OR 'physical activity'/exp OR physiotherapy/exp OR 'return to sport'/de OR 'return to work'/de OR sport/exp OR 'treatment outcome'/exp OR ('aerobic exercise*' OR 'physical therapy' OR physiotherap* OR (return* NEXT/2 (duty OR play OR sport* OR work))):ti,ab OR (approach* OR exercis* OR intervention* OR manag* OR neurorehabilitat* OR outcome* OR program* OR rehabilitat* OR therap* OR train* OR treat*):ti
	5	Medication therapy	'drug therapy'/exp OR 'drug therapy'/lnk OR 'antimigraine agent'/exp OR 'benzodiazepine derivative'/exp OR 'beta adrenergic receptor blocking agent'/exp OR 'calcium channel blocking agent'/exp OR central nervous system agents/exp OR 'dopamine receptor affecting agent '/exp OR melatonin/de OR ((anti NEXT/1 (anxiety OR depress* OR convuls* OR epileptic OR hypertensive)) OR antianxiety OR antidepress* OR anticonvuls* OR antiepileptic* OR antihypertensive* OR anxiolytic OR drug OR drugs OR medication* OR pharmacologic* OR pharmacotherap*):ti,ab
	6	Combine intervention sets	#4 OR #5
	7	Combine population and intervention sets	#3 AND #6
	8	Apply general hedges	See General Hedges at the end of this table
	9	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 5 - In adults with mTBI and persistent tinnitus, what is the comparative effectiveness and safety of tinnitus interventions, such as white noise generators, medications, repetitive transcranial magnetic stimulation (rTMS), or other interventions on reducing symptoms when compared to stress management strategies as measured using standardized tinnitus questionnaires, at 3 months or more after initiation of intervention?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Tinnitus	'tinnitus'/de OR tinnitus:ti,ab,kw OR ((acoustic:ti,ab OR audiologic*:ti,ab OR auditory:ti,ab OR cochlear:ti,ab OR ear:ti,ab OR ears:ti,ab OR hear*:ti,ab) AND (buzz*:ti,ab OR click*:ti,ab OR hiss*:ti,ab OR hum:ti,ab OR humming:ti,ab OR noise*:ti,ab OR pulsing:ti,ab OR pulsat*:ti,ab OR ring*:ti,ab OR roar*:ti,ab OR rush*:ti,ab OR sound*:ti,ab OR whistl*:ti,ab))
	3	Combine population sets	#1 AND #2
	4	Specific tinnitus interventions	((acoustic* OR auditory) NEXT/2 (mask* OR stimulat*)):ti,ab,kw OR 'auditory masking'/exp OR 'auditory stimulation'/de OR 'anxiolytic agent'/de OR antianxiety:ti,ab,kw OR 'anti anxiety':ti,ab,kw OR 'antidepressant agent'/de OR antidepressant*:ti,ab,kw OR 'anti depressant*':ti,ab,kw OR antidepressive*:ti,ab,kw OR 'anti-depressive*':ti,ab,kw OR 'benzodiazepine derivative'/exp OR benzodiazepine*:ti,ab,kw OR 'cochlea prosthesis'/exp OR (cochlea* NEXT/1 (implant* OR prosthes*)):ti,ab,kw OR 'cortical stimulat*':ti,ab,kw OR 'transcranial direct current stimulation'/de OR 'transcranial direct current':ti,ab,kw OR 'drug therapy'/exp OR drug*:ti,ab OR 'drug therapy'/lnk OR 'hearing aid'/exp OR 'hearing aid*':ti,ab,kw OR masker:ti,ab,kw OR masking:ti,ab,kw OR medicat*:ti,ab OR 'neuromodulation'/de OR neuromodulat*:ti,ab,kw OR 'neuro modulat*':ti,ab,kw OR 'pharmacology'/de OR pharmacolog*:ti,ab,kw OR 'residual inhibition':ti,ab,kw OR retrain*:ti,ab,kw OR (sound* NEAR/2 (mask* OR therap*)):ti,ab,kw OR 'sound machine*':ti,ab,kw OR stimulat*:ti,ab OR 'transcranial magnetic stimulation'/de OR 'transcranial magnetic stimulat*':ti,ab,kw OR rTMS:ti,ab,kw OR 'tinnitus masker'/exp OR 'tinnitus mask*':ti,ab,kw OR treat*:ti,ab,kw OR 'vagus nerve stimulat*':ti,ab,kw OR 'white noise'/exp OR 'white noise*':ti,ab,kw
	5	Comparative interventions (behavioral and stress management)	'alternative medicine'/de OR 'alternative medicine*':ti,ab OR 'autogenic training'/de OR 'autogenic train*':ti,ab,kw OR 'behavior therapy'/exp OR 'behavior* therap*':ti,ab,kw OR 'behaviour* therap*':ti,ab,kw OR 'biofeedback'/exp OR biofeedback:ti,ab,kw OR 'bio feedback':ti,ab,kw OR 'breathing exercise'/exp OR 'breathing exercise*':ti,ab,kw OR 'cognitive behavioral therapy'/exp OR (cognitive NEXT/2 therap*):ti,ab,kw OR 'cognitive rehabilitation'/exp OR 'cognitive rehabilitation':ti,ab,kw OR 'counseling'/de OR counsel*:ti,ab,kw OR 'desensitization'/de OR desensiti*:ti,ab,kw OR 'exercise'/exp OR exercise*:ti,ab,kw OR 'guided imagery'/de OR 'guided imag*':ti,ab,kw OR holistic:ti,ab,kw OR homeopathic:ti,ab,kw OR intervention*:ti,ab,kw OR maintenance:ti,ab,kw OR 'meditation'/exp OR meditat*:ti,ab,kw OR 'mindfulness'/exp OR mindful*:ti,ab,kw OR 'progressive tinnitus management':ti,ab,kw OR ptm:ti,ab,kw OR 'tele ptm':ti,ab,kw OR relax*:ti,ab,kw OR rehabilitation*:ti,ab,kw OR reprocessing:ti,ab,kw OR 'psychiatric treatment'/de OR psychiatric:ti,ab,kw OR 'psychology'/de OR psychological:ti,ab,kw OR psychotherapy:ti,ab,kw OR stress*:ti OR 'stress management'/exp OR (stress NEAR/2 manag*):ti,ab,kw OR 'telehealth'/exp OR telehealth:ti,ab,kw OR 'therapy'/de OR therap*:ti,ab,kw OR visuali*:ti,ab,kw OR 'yoga'/exp OR yoga:ti,ab,kw

KQ	Set #	Concept	Strategy
KQ 5 (cont.)	6	Measurement/ questionnaires	'assessment of humans'/exp OR assess*:ti,ab,kw OR 'functional index*':ti,ab,kw OR 'glasgow outcome scale'/exp OR 'glasgow outcome':ti,ab,kw OR 'measurement'/exp OR measur*:ti,ab,kw OR 'rating scale'/exp OR rating:ti,ab,kw OR 'severity of illness index'/exp OR 'severity of illness':ti,ab,kw OR 'questionnaire'/exp OR questionnaire*:ti,ab,kw
	7	Combine intervention sets	#4 OR #5 OR #6
	8	Combine population and intervention sets	#3 AND #7
	9	Apply general hedges	See General Hedges at the end of this table
	10	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
KQ 6 – In adults with persistent, post-concussive, visual symptoms, such as diplopia, tracking deficits and/or photophobia, do visual rehabilitation interventions durably (>3 months after treatments completed) improve outcomes?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Visual symptoms (controlled terms)	'accommodation disorder'/de OR 'eye movement disorder'/exp OR photophobia/de OR 'photosensitivity disorder'/exp OR 'visual disorder'/exp OR accommodation/de OR 'eye fixation'/de OR 'eye movement'/exp OR 'fixation failure'/de OR vision/exp OR 'visual adaptation'/exp OR 'visual orientation'/de OR reading/de
	3	Visual symptoms (free-text terms)	((binocular OR eye OR eyes OR eyesight OR gaze OR ocular OR oculo* OR reading OR saccad* OR sight OR pursuit* OR spatial OR stereopsis OR vision OR visual* OR 'visuo-spatial' OR visuospatial) NEAR/2 (acuity OR alignment OR blur* OR convergence OR defect* OR deficien* OR deficit* OR difficult* OR disorder* OR disorient* OR double* OR disparity OR dysfunction* OR fatigue OR fixation OR headache* OR impair* OR loss* OR motility OR movement* OR orient* OR navigat* OR percept* OR problem* OR processing OR reduc* OR sensitiv* OR symptom* OR task* OR track* OR trauma)):ab,ti OR ((binocular OR eye OR eyes OR eyesight OR gaze OR ocular OR oculo* OR reading OR saccad* OR sight OR pursuit* OR spatial OR stereopsis OR vision OR visual* OR 'visuo-spatial' OR visuospatial) AND (acuity OR alignment OR blur* OR convergence OR defect* OR deficien* OR deficit* OR difficult* OR disorder* OR disorient* OR double* OR disparity OR dysfunction* OR fatigue OR fixation OR headache* OR impair* OR loss* OR motility OR movement* OR orient* OR navigat* OR percept* OR problem* OR processing OR reduc* OR sensitiv* OR symptom* OR task* OR track* OR trauma)):ti OR (accommodation OR akinetopsia OR 'convergence insufficiency' OR (depth AND (discriminat* OR percept*)) OR diplopia OR hemianopia OR hemianopsia OR nystagmus OR oscillopsia OR phoria* OR photophobia* OR photosensitiv* OR stereoacuity OR vergence OR 'visual field' OR 'visuo spatial' OR visuospatial):ti,ab
	4	Combine population sets	#1 AND (#2 OR #3)
	5	Interventions (broad terms)	kinesiotherapy/exp OR rehabilitation/exp OR rehabilitation/lnk OR (approach* OR assistive OR exercis* OR intervention* OR manag* OR learning OR neurorehabilitat* OR program* OR rehabilitat* OR relearning OR retrain* OR technique* OR technolog* OR therap* OR train* OR treat*):ti

KQ	Set #	Concept	Strategy
KQ 6 (cont.)	6	Interventions (specific terms)	'hyperbaric oxygen therapy'/de OR neuroophthalmology/de OR 'ophthalmological therapeutic device'/exp OR prism/exp OR 'video game'/de OR ((oculomotor OR vision OR visual) NEAR/2 (rehabilitation OR therap* OR training OR treatment*)):ti,ab OR (computer* OR gam* OR 'hyperbaric oxygen therapy' OR 'neuro-ophthalmol*' OR 'neuro-optomet*' OR neuroop* OR neurostimulat* OR stimulat* OR video*):ti,ab
	7	Combine intervention sets	#5 OR #6
	8	Combine population and intervention sets	#4 AND #7
	9	Apply general hedges	See General Hedges at the end of this table
	10	Limit to systematic reviews, RCTs, and non-RCTs/ observational studies	See Study Type Hedges at the end of this table
KQ 7 – In adults with mTBI, what is the effectiveness of complementary and integrative health (CIH) interventions in improving outcomes?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Complementary and integrative health (CIH) interventions General terms	'alternative medicine'/exp OR 'integrative medicine'/de OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR medicine OR modalit* OR therapies OR therapy OR treatment*)):ti,ab
	3	VA list (meditation, massage, mindfulness, yoga, tai chi, acupuncture, cranial electrotherapy, isolation chamber)	'acupuncture'/exp OR 'meditation'/de OR 'mindfulness'/de OR 'relaxation training'/de OR 'tai chi'/de OR 'yoga'/de OR (acupunctur* OR massage OR meditat* OR 'mind-body' OR mindbody OR mindfulness OR relaxation OR 'tai chi' OR taichi OR 'tai ji' OR taiji OR yoga):ti,ab OR alphastim* OR 'alpha stim*' OR electrostimulation/de OR electrotherapy/exp OR 'transcranial electrical stimulation'/exp OR ((electrical OR electro) NEXT/2 (neurostimulat* OR stimulat*)) OR electrostim* OR electrotherapy):ti,ab OR neuromodulation/de OR neuromodulat*:ti,ab OR ((flotation OR isolation OR 'sensory deprivation') AND (chamber* OR tank OR tanks)):ti,ab OR 'restricted environmental stimulation therapy':ti,ab
	4	Chiropractic/manual therapy, HBOT, rTMS	'hyperbaric oxygen therapy'/de OR 'manipulative medicine'/exp OR 'repetitive transcranial magnetic stimulation'/de OR (chiropract* OR 'hyperbaric oxygen therapy' OR (manipulat* NEXT/1 (medicine OR therap* OR treatment*)) OR (manual NEXT/2 therapy) OR 'repetitive transcranial magnetic stimulation' OR rTMS OR ((spinal OR spine) NEAR/2 manipulat*)):ti,ab OR manipulat*:ti
	5	Combine population and intervention sets	#1 AND (#2 OR #3 OR #4)
	6	Apply general hedges	See General Hedges at the end of this table
	7	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 8 – a) In adults with mTBI and post-concussive symptoms of impaired attention, concentration and/or memory, what is the evidence that automated (computer-based) cognitive rehabilitation has equal or superior efficacy compared to clinician-based services in improving chronic symptoms at 1 month or more after initiation of the intervention? b) In adults with persistent cognitive symptoms or functional cognitive complaints, do specific cognitive rehabilitation interventions improve outcomes?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR 'OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Symptoms of impaired attention, impaired concentration, or impaired memory	((cognition/exp OR (attention OR attentive OR cognition OR cognitive OR concentrat* OR executive OR memories OR memory OR reasoning OR recall* OR remember* OR recognition):ti,ab) AND (declin* OR defect* OR deficien* OR deficit* OR difficult* OR disorder* OR disorient* OR dysfunction* OR function* OR impair* OR loss* OR problem* OR processing OR symptom*):ab,ti) OR amnesia/exp OR 'concentration loss'/de OR 'memory disorder'/de OR (amnes* OR forget* OR 'post-concussion syndrome' OR 'postconcussion syndrome' OR 'problem solving'):ti,ab OR ('cognitive communication' OR ((language OR reading) AND comprehension) OR 'meta-cognitive' OR metacognitive OR 'pragmatic language'):ti,ab OR 'cognitive function test'/exp OR 'mental function assessment'/ exp
	3	Combine population sets	#1 AND #2
	4	Cognitive rehabilitation (broad terms)	'cognitive rehabilitation'/de OR 'cognitive therapy'/exp OR 'occupational therapy' OR ('cognitive rehab*' OR 'cognitive therapy' OR 'cognitive training' OR (intensive NEXT/2 (rehabilitation OR treatment*))):ti,ab OR (approach* OR exercis* OR intervention* OR manag* OR program* OR rehabilitat* OR remediation OR retrain* OR strateg* OR therap* OR train* OR treat*):ti
	5	Cognitive rehabilitation (specific terms)	'cognitive therapy software'/de OR 'group therapy'/de OR ('attention process training' OR automat* OR 'brain training' OR brainhq* OR cogsmart* OR 'compensatory strategy*' OR computer* OR 'errorless learning' OR game* OR gaming OR 'group therapy' OR lumosity* OR online OR software OR technolog* OR video*):ti,ab OR group:ti
	6	Combine intervention sets	#4 OR #5
	7	Combine population and intervention sets	#3 AND #6
	8	Apply general hedges	See General Hedges at the end of this table
	9	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 9 – For individuals with persistent symptoms attributable to mTBI, what is the evidence supporting the optimal timing for referral from a primary care clinician to a TBI/symptom specialist? Search 1	1	Individuals with persistent symptoms attributable to mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti,ab
	2	Referral (narrow approach)	(('clinical pathway'/de OR 'integrated care':de OR 'integrated health care system'/de OR 'integrated care pathway':de OR 'medical specialist'/de OR 'outpatient care'/de OR 'patient referral'/de OR 'rehabilitation'/de OR 'transition of care':de) AND (collaborat* OR consult* OR interdisciplinary OR 'inter disciplinary' OR integrated OR multidisciplinary OR 'multi disciplinary' OR outpatient* OR paths OR pathway* OR refer OR referr* OR specialist* OR specialt* OR team* OR transition* OR transfer*):ti) OR ('integrated care' OR 'integrated healthcare' OR 'integrated health care' OR 'levels of care' OR 'pathway* for' OR 'pathway* to' OR 'refer to' OR 'referr* to' OR 'second opinion*' OR 'specialized care' OR 'symptom specialist*' OR 'transition* of care'):ti,ab OR ((hospital OR prehospital) NEXT/2 rehab*):ti,ab OR ((neurorehabilitation OR 'neuro rehabilitation*') NEAR/2 (consult* OR refer* OR special*)):ti,ab OR ((paths OR pathway*) NEAR/2 (care OR rehab*)):ti,ab OR (patient* NEAR/2 refer*):ti,ab OR ((time OR timing) NEAR/2 (collaborat* OR consult* OR refer OR referr* OR specialist* OR specialt*)):ti,ab OR ((refer* OR transition* OR transfer*) NEXT/2 (care OR rehab* OR special* OR treatment*)):ti,ab
	3	Referral (broad approach)	'clinical pathway'/de OR 'integrated care':de OR 'integrated health care system'/de OR 'integrated care pathway':de OR 'medical specialist'/de OR 'outpatient care'/de OR 'patient referral'/de OR 'rehabilitation'/de OR 'transition of care':de OR (collaborat* OR consult* OR interdisciplinary OR 'inter disciplinary' OR multidisciplinary OR 'multi disciplinary' OR outpatient* OR 'paths to' OR 'pathway* for' OR 'pathway* to' OR rehab* OR specialist* OR specialt* OR team* OR therap* OR transition* OR transfer* OR treatment*):ti OR ('care pathway*' OR 'clinical pathway*' OR 'consult* with' OR 'integrated care' OR 'integrated healthcare' OR 'integrated health care' OR 'levels of care' OR refer OR referr* OR 'rehabilitation specialist*' OR 'second opinion*' OR 'specialized care' OR 'symptom specialist*' OR ((transition* OR transfer*) NEXT/3 (care OR rehab* OR special* OR treatment*))):ti,ab

KQ	Set #	Concept	Strategy
KQ 9 – Search 1 (cont.)	4	Specialty rehabilitative and treatment services	'audiologist'/de OR 'audiology'/de OR 'behavior therapy'/exp OR 'case management'/de OR 'case manager'/de OR 'cognitive rehabilitation'/de OR 'cognitive therapy'/exp OR 'manipulative medicine'/exp OR 'manual therapist'/exp OR 'neurologist'/de OR 'neurology'/de OR 'neuropsychology'/de OR 'neurorehabilitation'/de OR 'neuroophthalmology'/de OR 'occupational therapist'/de OR 'occupational therapy'/de OR 'physical medicine'/de OR 'physical rehabilitation':de OR 'physiotherapist'/de OR 'physiotherapy'/de OR 'psychiatrist'/de OR 'psychiatry'/de OR 'psychologist'/de OR 'psychology'/de OR 'rehabilitation medicine'/de OR 'speech language pathologist'/de OR 'speech and language rehabilitation'/exp OR 'social worker'/de OR 'tinnitus therapy':de OR 'vestibular rehabilitation':de OR 'vocational rehabilitation'/de OR (audiolog* OR 'behavior* therap*' OR 'case manage*' OR 'case worker*' OR ((cervical OR spine) NEXT/1 therap*) OR (cognitive NEXT/2 (rehab* OR specialist* OR treatment* OR therap*)) OR counsel* OR (exercise NEXT/1 (rehab* OR therap*)) OR 'manual therap*' OR 'manipulative medicine' OR (neck NEAR/2 (rehab* OR therap*)) OR neuroopthalmolog* OR 'neuro opthalmolog*' OR neurolog* OR neuropsycholog* OR 'neuro psycholog*' OR neurooptometr* OR 'neuro optometr*' OR neurorehab* OR 'neuro* rehab*' OR neurosurg* OR neurotrauma* OR 'occupational therap*' OR (pain NEXT/1 (clinic OR management)) OR physiatrist* OR 'physical medicine' OR (physical NEXT/2 (rehab* OR therap*)) OR physiotherap* OR 'physio therap*' OR psychiatr* OR psycholog* OR ((speech OR language) NEXT/1 (patholog* OR rehab* OR therap*)) OR 'social worker*' OR (tinnitus NEAR/2 (treatment* OR therap*)) OR 'vestibular rehab*' OR ((vision OR ocular) NEXT/2 (therap* OR rehab*)) OR 'vocation* rehabilitation'):ti,ab,kw
	5	Combine large referral with specialized set	#3 AND #4
	6	Combine population with narrow referral set	#1 AND #2
	7	Combine population with combined referral and specialized terms sets	#1 AND #5
	8	Combine all sets	#6 OR #7
	9	Apply general hedges	See General Hedges at the end of this table
	10	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 9 – Search 2	1	Individuals with persistent symptoms attributable to mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti,ab
	2	Referral (narrow approach)	(('clinical pathway'/de OR 'integrated care':de OR 'integrated health care system'/de OR 'integrated care pathway':de OR 'medical specialist'/de OR 'outpatient care'/de OR 'patient referral'/de OR 'rehabilitation'/de OR 'transition of care':de) AND (collaborat* OR consult* OR interdisciplinary OR 'inter disciplinary' OR integrated OR multidisciplinary OR 'multi disciplinary' OR outpatient* OR paths OR pathway* OR refer OR referr* OR specialist* OR specialt* OR team* OR transition* OR transfer*):ti) OR ('integrated care' OR 'integrated healthcare' OR 'integrated health care' OR 'levels of care' OR 'pathway* for' OR 'pathway* to' OR 'refer to' OR 'referr* to' OR 'second opinion*' OR 'specialized care' OR 'symptom specialist*' OR 'transition* of care'):ti OR ((hospital OR prehospital) NEXT/2 rehab*):ti OR ((neurorehabilitation OR 'neuro rehabilitation*') NEAR/2 (consult* OR refer* OR special*)):ti OR ((paths OR pathway*) NEAR/2 (care OR rehab*)):ti OR (patient* NEAR/2 refer*):ti OR ((time OR timing) NEAR/2 (collaborat* OR consult* OR refer OR referr* OR specialist* OR specialt*)):ti OR ((refer* OR transition* OR transfer*) NEXT/2 (care OR rehab* OR special* OR treatment*)):ti
	3	Referral (broad approach)	'clinical pathway'/de OR 'integrated care':de OR 'integrated health care system'/de OR 'integrated care pathway':de OR 'medical specialist'/de OR 'outpatient care'/de OR 'patient referral'/de OR 'rehabilitation'/de OR 'transition of care':de OR (collaborat* OR consult* OR interdisciplinary OR 'inter disciplinary' OR multidisciplinary OR 'multi disciplinary' OR outpatient* OR 'paths to' OR 'pathway* for' OR 'pathway* to' OR rehab* OR specialist* OR specialt* OR team* OR therap* OR transition* OR transfer* OR treatment*):ti OR ('care pathway*' OR 'clinical pathway*' OR 'consult* with' OR 'integrated care' OR 'integrated healthcare' OR 'integrated health care' OR 'levels of care' OR refer OR referr* OR 'rehabilitation specialist*' OR 'second opinion*' OR 'specialized care' OR 'symptom specialist*' OR ((transition* OR transfer*) NEXT/3 (care OR rehab* OR special* OR treatment*))):ti

KQ	Set #	Concept	Strategy
KQ 9 – Search 2 (cont.)	4	Specialty rehabilitative and treatment services	'audiologist'/de OR 'audiology'/de OR 'behavior therapy'/exp OR 'case management'/de OR 'case manager'/de OR 'cognitive rehabilitation'/de OR 'cognitive therapy'/exp OR 'manipulative medicine'/exp OR 'manual therapist'/exp OR 'neurologist'/de OR 'neurology'/de OR 'neuropsychology'/de OR 'neurorehabilitation'/de OR 'neuroophthalmology'/de OR 'occupational therapist'/de OR 'occupational therapy'/de OR 'physical medicine'/de OR 'physical rehabilitation':de OR 'physiotherapist'/de OR 'physiotherapy'/de OR 'psychiatrist'/de OR 'psychiatry'/de OR 'psychologist'/de OR 'psychology'/de OR 'rehabilitation medicine'/de OR 'speech language pathologist'/de OR 'speech and language rehabilitation'/exp OR 'social worker'/de OR 'tinnitus therapy':de OR 'vestibular rehabilitation':de OR 'vocational rehabilitation'/de OR (audiolog* OR 'behavior* therap*' OR 'case manage*' OR 'case worker*' OR ((cervical OR spine) NEXT/1 therap*) OR (cognitive NEXT/2 (rehab* OR specialist* OR treatment* OR therap*)) OR counsel* OR (exercise NEXT/1 (rehab* OR therap*)) OR 'manual therap*' OR 'manipulative medicine' OR (neck NEAR/2 (rehab* OR therap*)) OR neuroopthalmolog* OR 'neuro opthalmolog*' OR neurolog* OR neuropsycholog* OR 'neuro psycholog*' OR neurooptometr* OR 'neuro optometr*' OR neurorehab* OR 'neuro* rehab*' OR neurosurg* OR neurotrauma* OR 'occupational therap*' OR (pain NEXT/1 (clinic OR management)) OR physiatrist* OR 'physical medicine' OR (physical NEXT/2 (rehab* OR therap*)) OR physiotherap* OR 'physio therap*' OR psychiatr* OR psycholog* OR ((speech OR language) NEXT/1 (patholog* OR rehab* OR therap*)) OR 'social worker*' OR (tinnitus NEAR/2 (treatment* OR therap*)) OR 'vestibular rehab*' OR ((vision OR ocular) NEXT/2 (therap* OR rehab*)) OR 'vocation* rehabilitation'):ti,ab
	5	Combine large referral with specialized set	#3 AND #4
	6	Combine population with narrow referral set	#1 AND #2
	7	Combine population with combined referral and specialized terms sets	#1 AND #5
	8	Combine all sets	#6 OR #7
	9	Apply general hedges	See General Hedges at the end of this table
	10	Limit to non-RCTs/ observational studies	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 10 – Are adults with mTBI and multiple brain injuries at increased risk of neurocognitive decline? a. What are demographic and clinical and management factors that may alter risks of these conditions?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Multiple brain injuries	(('cumulative effect*' OR multiple OR recurrent OR repeat* OR repetitive) NEXT/4 (injur* OR trauma* OR mtbi* OR tbi*)):ti,ab,kw
	3	Neurocognitive decline/ neurodegenerative diseases (broad approach)	'alzheimer disease'/mj OR alzheimer*:ti,ab OR 'amyotrophic lateral sclerosis'/mj OR 'amyotrophic lateral sclerosis':ti,ab OR als:ti OR 'dementia'/mj OR dementia*:ti,ab OR 'parkinson disease'/mj OR parkinson*:ti,ab OR 'mild cognitive impairment'/mj OR 'cognitive impairment*':ti,ab OR MCI:ti OR ((cognition OR cognitive OR mental OR neurocognitive OR 'neuro cognitive' OR neurodegenerat* OR 'neuro degenerat*' OR neurological OR neuropsychological OR 'neuro psychological') NEAR/2 (associated OR association* OR defect* OR declin* OR deficit* OR degenerat* OR deteriorat* OR diagnos* OR disease* OR disorder* OR efficac* OR effective* OR impair* OR loss* OR outcome* OR perform* OR prognos* OR symptom*)):ti,ab
	4	Neurocognitive decline/ neurodegenerative diseases (narrow approach)	alzheimer*:ti OR 'amyotrophic lateral sclerosis':ti OR als:ti OR dementia*:ti OR MCI:ti OR parkinson*:ti OR ((cognition OR cognitive OR mental OR neurocognitive OR 'neuro cognitive' OR neurodegenerat* OR 'neuro degenerat*' OR neurological OR neuropsychological OR 'neuro psychological') NEAR/2 (defect* OR declin* OR deficit* OR degenerat* OR deteriorat* OR diagnos* OR disease* OR disorder* OR impair* OR loss* OR perform* OR symptom*)):ti
	5	Combine broad population with narrow set	#1 AND #4
	6	Combine narrow population with broad set	#1 AND #2 AND #3
	7	Combine all sets	#5 OR #6
	8	Apply general hedges	See General Hedges at the end of this table
	9	Limit to systematic reviews, RCTs, and non-RCTs/ observational studies	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 11 – What is the comparative effectiveness of mTBI treatment programs to improve morbidity, function, and return to work?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti
	2	Treatment programs (key terms)	'health program'/de OR 'program evaluation'/exp OR 'rehabilitation center'/de OR 'residential care'/de OR 'telerehabilitation'/de OR ((intensive NEXT/3 rehabilitation):ti,ab) OR telerehabilitation:ti,ab
	3	Treatment programs (additional terms)	'community program'/de OR 'education program'/de OR ((telehealth/exp OR (home OR online OR remote OR tele*):ti) AND program*:ti,ab) OR (((comprehensive OR 'in patient' OR inpatient OR integrated OR (intensive NOT 'intensive care') OR 'inter disciplinary' OR interdisciplinary OR 'multi disciplinary' OR multidisciplinary OR 'out patient' OR outpatient):ti OR (program* OR residential OR session*):ti,ab) AND (rehabilitation/exp OR 'return to work'/de OR therapy/exp OR 'disease management':lnk OR rehabilitation:lnk OR therapy/lnk OR (return* NEXT/2 (duty OR play OR sport* OR work)):ti OR (intervention* OR manag* OR rehabilitat* OR therap* OR train* OR treat*):ti))
	4	Combine population and intervention sets	#1 AND (#2 OR #3)
	5	Apply general hedges	See General Hedges at the end of this table
	6	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
KQ 12 – In adults with mTBI and co-morbidities (PTSD, SUD, mood disorders) what interventions are effective for improving outcomes?	1	Adults with mTBI	'acquired brain injury'/de OR 'brain concussion'/de OR 'brain contusion'/de OR 'brain damage'/de OR 'brain injury'/de OR 'brain stem injury'/de OR 'cerebellum injury'/de OR concussion/de OR 'diffuse brain injury'/exp OR 'head injury'/de OR 'postconcussion syndrome'/de OR 'traumatic brain injury'/exp OR ('brain damag*' OR ((brain OR craniocerebral OR 'cranio-cerebral' OR head) NEAR/3 (contusion* OR injur* OR trauma*)) OR concuss* OR mTBI OR postconcuss* OR TBI):ti,ab
	2	PTSD	'acute stress disorder'/de OR 'posttraumatic stress disorder'/de OR psychotrauma/exp OR ('post-traumatic' OR posttraumatic OR 'combat disorder*' OR 'combat stress' OR 'operational stress' OR ptsd OR 'psychological trauma' OR 'stress disorder*' OR 'psychological stress' OR 'trauma syndrome*' OR 'traumatic stress'):ti,ab
	3	Substance use disorders	'drug abuse'/exp OR 'drug dependence'/exp OR (alcoholism OR 'alcohol use disorder' OR addiction* OR 'drug abuse' OR 'drug dependence' OR 'substance abuse' OR 'substance use disorder*'):ti,ab OR (dependence OR dependency OR 'use disorder'):ti
	4	Mood disorders	'mood disorder'/exp OR (affective OR bipolar OR depression OR depressive OR dysphor* OR irritability OR mania OR manic OR MDD OR mood OR ((neurobehavior* OR neuropsychiatric) NEXT/1 (deficit* OR dysfunction* OR disorder* OR function* OR sequelae OR symptom*)) OR neuroses OR neurosis OR neurotic OR psychopathology* OR psychosis OR psychoses OR psychotic):ti,ab
	5	Combine population sets	#1 AND (#2 OR #3 OR #4)

KQ	Set #	Concept	Strategy
KQ 12 (cont.)	6	Behavioral health interventions and case management	'case management'/de OR counseling/exp OR psychotherapy/exp OR ('12-step*' OR (acceptance NEXT/2 commitment) OR 'addiction focused' OR ((behavior* OR behaviour* OR cognitive) NEXT/1 (intervention* OR therap* OR treat*)) OR 'behav* activation' OR 'brief eclectic' OR 'case management' OR 'cognitive processing' OR 'cognitive restructuring' OR (couples NEXT/1 (counseling OR therapy)) OR counseling OR exposure OR 'eye movement desensiti*' OR 'family therapy' OR 'interpersonal therapy' OR meditation OR mindfulness OR 'motivational interviewing' OR (('neuro-psych*' OR neuropsych* OR psychiatric OR psychological) NEXT/1 (intervention* OR therap* OR treatment*)) OR ('problem-solving' NEXT/1 (therapy OR treatment)) OR psychotherap* OR reintegration OR 'self-management' OR 'social skills' OR 'trauma-focused' OR 'twelve step*'):ti,ab OR coping:ti
	7	Pharmacologic interventions	'benzodiazepine derivative'/exp OR 'central depressant agent'/exp OR 'central stimulant agent'/exp OR 'drug therapy'/exp OR 'drug therapy'/lnk OR 'drugs used in the treatment of addiction'/exp OR 'psychotropic agent'/exp OR ((anti NEXT/1 (anxiety OR depress* OR convuls* OR epileptic OR hypertensive)) OR antianxiety OR antidepress* OR anticonvuls* OR antiepileptic* OR antihypertensive* OR anxiolytic OR neuroleptic* OR (serotonin NEAR/2 (reuptake OR uptake) NEAR/1 inhibitor*) OR SNRI* OR SSRI* OR tricyclic*):ti,ab OR (drug OR drugs OR medication* OR pharmacologic* OR pharmacotherap*):ti
	8	Combine intervention sets	#6 OR #7
	9	Combine population and intervention sets	#5 AND #8
	10	Apply general hedges	See General Hedges at the end of this table
	11	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
General Hedges Applied to Each Search		Exclude animal and experimental studies	NOT (([animals]/lim NOT [humans]/lim) OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine OR pig OR pigs OR piglet* OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
		Exclude studies focusing on children	NOT ((adolescen* OR baby OR babies OR boys OR child* OR girls OR infancy OR infant* OR juvenile* OR neonat* OR newborn* OR NICU OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*):ti NOT adult*:ti)
		Limit to English language publications and to results with abstracts	AND [english]/lim AND [abstracts]/lim
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR ('a case' OR 'a patient' OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR ('case report' OR comment OR protocol):ti)
		Limit to results added to the database since the prior literature search (March 11, 2015)	AND [11-3-2015]/sd NOT [29-4-2020]/sd

KQ	Set #	Concept	Strategy
Study Type Hedges Applied as Needed (per KQ specific criteria provided earlier in this report)		SRs	AND ('meta analysis'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de OR (EMBASE OR 'meta analysis' OR 'meta analytic' OR metaanaly* OR pooled OR pooled OR pooling OR RCTs OR 'research synthesis' OR search* OR (systematic NEXT/3 review)):ti,ab OR ('critical review' OR 'evidence based' OR systematic*):ti OR [cochrane review]/lim)
		RCTs	AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR (random* OR RCT):ti,ab)
		Non-RCTs/ observational studies	AND ((‘cohort analysis’/de OR 'comparative study'/exp OR 'controlled study'/exp OR ‘evaluation study’/de OR ‘longitudinal study’/de OR ‘major clinical study’/de OR ‘observational study’/de OR ‘prospective study’/de OR ‘retrospective study’/de OR ‘treatment outcome’/de) OR (‘between groups’ OR 'case control*' OR cohort* OR compar* OR 'control group*' OR 'controlled study' OR 'controlled trial' OR 'cross over' OR crossover OR 'double blind' OR 'double blinded' OR longitudinal OR 'matched controls' OR (observational NEXT/3 study) OR placebo* OR prospective OR retrospective OR sham):ti,ab OR (versus OR vs):ti)
		Diagnostic studies (e.g., diagnostic cohort, diagnostic accuracy)	AND (‘diagnostic accuracy’/de OR ‘diagnostic test accuracy study’/de OR 'predictive validity'/de OR ‘predictive value’/de OR ‘sensitivity and specificity’/de OR ((‘area under’ AND curve) OR AUC OR ‘diagnostic accuracy’ OR ‘diagnostic odds ratio’ OR (false NEXT/1 (positive* OR negative*)) OR ‘likelihood function*’ OR ‘likelihood ratio*’ OR PPV OR ‘predictive value*’ OR ‘ROC curve*’ OR sensitiv* OR specific*):ti,ab OR (usefulness OR utility OR value):ti OR ‘cohort analysis’/de OR 'comparative study'/exp OR 'controlled study'/exp OR ‘major clinical study’/de OR 'prospective study'/de OR (‘between groups’ OR cohort* OR compar* OR 'control group*' OR 'controlled study' OR 'controlled trial' OR 'cross over' OR crossover OR 'double blind' OR 'double blinded' OR 'matched controls' OR prospective):ti,ab)

Table F-2. mTBI Search Strategy for PsycINFO with OVID syntax

KQ	Set #	Concept	Strategy
KQ 10 – Are adults with mTBI and multiple brain injuries at increased risk of neurocognitive decline? a. What are demographic and clinical and management factors that may alter risks of these conditions?	1	Adults with mTBI	exp brain injuries/ OR exp head injuries/ OR "brain damage" OR "brain damaged" OR (((brain OR craniocerebral OR "cranio cerebral" OR head) AND (contusion$ OR injur$ OR trauma$)) OR concuss$ OR mTBI OR postconcuss$ OR TBI).ti,ab
	2	Terms for multiple	(("cumulative effect" OR "cumulative effects" OR multiple OR recurrent OR repeat$ OR repetitive) ADJ4 (injur$ OR trauma$ OR mtbi$ OR tbi$)).ti,ab
	3	Neurocognitive decline/ neurodegenerative diseases (broad)	exp alzheimer disease/ OR exp amyotrophic lateral sclerosis/ OR exp dementia/ OR exp parkinsons disease/ OR exp cognitive impairment/ OR alzheimer$.ti,ab. OR "amyotrophic lateral sclerosis".ti,ab. OR als.ti. OR dementia$.ti,ab. OR parkinson$.ti,ab. OR "cognitive impairment".ti,ab. OR "cognitive impairments".ti,ab. OR MCI.ti. OR ((cognition OR cognitive OR mental OR neurocognitive OR "neuro cognitive" OR neurodegenerat$ OR "neuro degenerative" OR "neuro degenerating" OR neurological OR neuropsychological OR "neuro psychological") ADJ2 (associated OR association$ OR defect$ OR declin$ OR deficit$ OR degenerat$ OR deteriorat$ OR diagnosed OR diagnosis OR disease$ OR disorder$ OR efficac$ OR effective$ OR impair$ OR loss$ OR outcome$ OR perform$ OR prognos$ OR symptom$)).ti,ab
	4	Neurocognitive decline, etc. (narrow)	Alzheimer$.ti. OR "amyotrophic lateral sclerosis".ti. OR als.ti. OR dementia$.ti. OR MCI.ti. OR Parkinson$.ti. OR ((cognition OR cognitive OR mental OR neurocognitive OR "neuro cognitive" OR neurodegenerat$ OR "neuro degenerate" OR "neuro degenerating" OR "neuro degenerative" OR neurological OR neuropsychological OR "neuro psychological") ADJ2 (defect$ OR declin$ OR deficit$ OR degenerat$ OR deteriorat$ OR disease$ OR disorder$ OR impair$ OR loss$ OR perform$ OR symptom$)).ti
	5	Broad population with narrow terms	1 AND 4
	6	Narrow population with broad terms	1 AND 2 AND 3
	7	Combine sets	5 OR 6
	8	Apply general hedges	See General Hedges at the end of this table
	9	Limit to systematic reviews, RCTs, and non-RCTs/ observational studies	See Study Type Hedges at the end of this table

KQ	Set #	Concept	Strategy
KQ 11 – What is the comparative effectiveness of mTBI treatment programs to improve morbidity, function, and return to work?	1	Population Adults with any symptoms attributed to mTBI	exp brain injuries/ OR exp head injuries/ OR "brain damage" OR "brain damaged" OR (((brain OR craniocerebral OR 'cranio-cerebral' OR head) AND (contusion$ OR injur$ OR trauma$)) OR concuss$ OR mTBI OR postconcuss$ OR TBI).ti,ab
	2	Interventions Treatment programs (key terms)	mental health programs/ OR program evaluation/ OR program development/ OR rehabilitation centers/ OR residential care institutions/ OR telerehabilitation/ OR ((intensive ADJ3 rehabilitation) OR telerehabilitation).ti,ab
	3	Treatment programs (additional terms)	(exp telemedicine/ OR (in-patient OR inpatient OR inter-disciplinary OR interdisciplinary OR multi-disciplinary OR multidisciplinary OR out-patient OR outpatient).ti. OR (program$ OR residential OR session$).ti,ab.) AND (reemployment/ OR exp rehabilitation/ OR exp treatment/ OR (intervention$ OR manag$ OR rehabilitat* OR (return$ ADJ2 work) OR therap$ OR train$ OR treat$).ti.)
	4	Combine population and intervention sets	#1 AND (#2 OR #3)
	5	Apply general hedges	See General Hedges at the end of this table
	6	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
KQ 12 – In adults with mTBI and co-morbidities (PTSD, SUD, mood disorders) what interventions are effective for improving outcomes?	1	Population Adults with any symptoms attributed to mTBI	exp brain injuries/ OR exp head injuries/ OR "brain damage" OR "brain damaged" OR (((brain OR craniocerebral OR 'cranio-cerebral' OR head) AND (contusion$ OR injur$ OR trauma$)) OR concuss$ OR mTBI OR postconcuss$ OR TBI).ti,ab
	2	PTSD	exp "stress and trauma related disorders"/ OR ("post-traumatic" OR posttraumatic OR "combat disorder*" OR "combat stress" OR "operational stress" OR ptsd OR "psychological trauma" OR "stress disorder*" OR "psychological stress" OR "trauma syndrome*" OR "traumatic stress").ti,ab
	3	Substance use disorders	exp "substance use disorder"/ OR (alcoholism OR "alcohol use disorder" OR addiction* OR "drug abuse" OR "drug dependence" OR "substance abuse" OR "substance use disorder" OR "substance use disorders").ti,ab. OR (dependence OR dependency OR "use disorder").ti
	4	Mood disorders	exp affective disorders/ OR (affective OR bipolar OR depression OR depressive OR dysphor* OR irritability OR mania OR manic OR MDD OR ((neurobehavior* OR neuropsychiatric) ADJ1 (deficit* OR dysfunction* OR disorder* OR function* OR sequelae OR symptom*)) OR "mood disorder" OR "mood disorders" OR neuroses OR neurosis OR neurotic OR psychopathology* OR psychosis OR psychoses OR psychotic).ti,ab
	5	Combine population sets	1 AND (2 OR 3 OR 4)

KQ	Set #	Concept	Strategy
KQ 12 (cont.)	6	Behavioral health interventions	exp counseling/ OR exp psychotherapy/ OR exp "substance use treatment"/ OR ("12-step" OR "12 steps" OR (acceptance ADJ2 commitment) OR "addiction focused" OR ((behavior* OR behaviour* OR cognitive) ADJ1 (intervention* OR therap* OR treat*)) OR (behav* ADJ1 activation) OR "brief eclectic" OR "cognitive processing" OR "cognitive restructuring" OR (couples ADJ1 (counseling OR therapy)) OR counseling OR exposure OR ("eye movement" ADJ1 desensiti*) OR "family therapy" OR "group therapy" OR "interpersonal therapy" OR meditation OR mindfulness OR "motivational interviewing" OR (("neuro psychiatric" OR "neuro psychological" OR neuropsych* OR psychiatric OR psychological) ADJ1 (intervention* OR therap* OR treatment*)) OR ("problem-solving" ADJ1 (therapy OR treatment)) OR psychotherap* OR reintegration OR "self management" OR "social skills" OR "trauma-focused" OR "twelve step" OR "twelve steps").ti,ab. OR coping.ti.
	7	Pharmacologic interventions	exp analgesic drugs/ OR exp anticonvulsive drugs/ OR exp antidepressant drugs/ OR antihypertensive drugs/ OR exp benzodiazepines/ OR exp mood stabilizers/ OR narcotic antagonists/ OR exp narcotic drugs/ OR exp sedatives/ OR exp serotonin agonists/ OR exp tranquilizing drugs/ OR "drug therapy"/ OR exp psychopharmacology/ OR ((anti ADJ1 (anxiety OR depress* OR convuls* OR epileptic* OR hypertensive*)) OR antianxiety OR antidepress* OR anticonvuls* OR antiepileptic* OR antihypertensive* OR anxiolytic* OR neuroleptic* OR (serotonin ADJ2 (reuptake OR uptake) ADJ1 inhibitor*) OR SNRI* OR SSRI* OR tricyclic*).ti,ab. OR (drug OR drugs OR medication* OR pharmacologic* OR pharmacotherap*).ti.
	8	Combine intervention sets	6 OR 7
	9	Combine population and intervention sets	5 AND 8
	10	Apply general hedges	See General Hedges at the end of this table
	11	Limit to systematic reviews and RCTs	See Study Type Hedges at the end of this table
General Hedges Applied to Each Search		Exclude animal and experimental studies	NOT (animal$ OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine OR pig OR pigs OR piglet$ OR rabbit$ OR rat OR rats OR rodent$ OR sheep OR swine).ti
		Exclude studies focusing on children	NOT ((adolescen$ OR baby OR babies OR boys OR child$ OR girls OR infancy OR infant$ OR juvenile$ OR neonat$ OR newborn$ OR NICU OR paediatric$ OR pediatric$ OR preschool$ OR school OR schools OR teen$ OR toddler$ OR youth$).ti. NOT adult$.ti.)
		Limit to English language publications and to results with abstracts	AND English.lg
		Limit to English language publications and to results with abstracts	Limit # to abstracts
		Remove undesired publication and study types (e.g., case reports, conferences, editorials)	NOT ((chapter OR "column/opinion" OR comment OR "comment/reply" OR dissertation OR editorial OR letter OR review-book).dt. OR (book OR encyclopedia OR "dissertation abstract").pt. OR ("case report" OR "a case" OR "a patient" OR "year-old").ti,ab.)
		Limit to results added to the database since the prior literature search (March 11, 2015)	limit # to yr="2015 - 2020"

KQ	Set #	Concept	Strategy
Study Type Hedges Applied as Needed (per KQ specific criteria provided earlier in this report)		SRs	AND (meta analysis/ OR ("meta analysis" OR "meta analytic" OR metaanaly$ OR pooled OR pooling OR RCTs OR "research synthesis" OR search$ OR (systematic ADJ3 review)).ti,ab. OR ("critical review" OR "evidence based" OR systematic).ti.) OR cochrane.jw.)
		RCTs	AND (random sampling/ OR (random* OR RCT).ti,ab.)
		Non-RCTs/ observational studies	AND ((cohort analysis/ OR longitudinal studies/ OR prospective studies/ OR retrospective studies/ OR treatment outcomes/) OR ("between groups" OR "case control" OR cohort* OR compar* OR "control group" OR "control groups" OR "controlled study" OR "controlled trial" OR "cross over" OR crossover OR "double blind" OR "double blinded" OR "evaluation study" OR longitudinal OR "matched controls" OR (observational ADJ3 study) OR placebo* OR prospective OR retrospective OR sham).ti,ab. OR (versus OR vs).ti.)

Appendix G: Clinical Symptom Management

A. Appendix Contents

This appendix serves as a reference guide for symptoms most commonly occurring after a history of mTBI. VA/DoD CPGs on many of these symptoms are available to help guide providers (available at www.healthquality.va.gov). Symptom treatment is not based on the underlying mechanism of injury; instead, it is based on standardized clinical practice for that disorder or diagnosis. Given the complexities of war-related injury, there can be many co-occurring conditions. There is a lack of RCTs to guide assessment and treatment of these conditions; therefore, providers must use clinical judgment and refer to other VA/DoD CPGs.

B. Introduction

The emergence of behavioral symptoms after mTBI can depend on many factors including pre-injury psychosocial function and/or pre-existing illnesses or conditions, genetic predisposition to neurobehavioral disorders, injury factors, and post-injury psychosocial and health factors. The nature and severity of symptoms, as ascertained in a thorough medical history, should be determined to optimally choose appropriate treatments. A comprehensive treatment plan that integrates psychosocial and pharmacologic interventions is recommended, as there is a paucity of strong evidence for a singular treatment that specifically targets symptoms in this population.

There is a complex relationship among symptoms attributed to mTBI (e.g., headache, sleep disturbances, cognition, mood). It is clinically reasonable to expect that alleviating and improving one symptom may lead to an improvement in other symptoms and symptom clusters. The presence of co-occurring mental health problems (e.g., MDD, anxiety disorders, PTSD, SUD), that may or may not be etiologically related to the mTBI, should be comprehensively managed.

There are no specific FDA-approved pharmaceutical agents for the treatment of post-concussive neurological or behavioral symptoms. Management of behavioral and mental health conditions following mTBI should be guided by CPGs for behavioral conditions (with or without mTBI) and the guidance from the mental health field.

See guidance such as:

- VA/DoD Clinical Practice Guidelines Homepage - www.healthquality.va.gov
- VA National Center for PTSD: Traumatic Brain Injury and PTSD - https://www.ptsd.va.gov/professional/treat/cooccurring/tbi_ptsd_vets.asp
- Psychological Health Center of Excellence (PHCoE) VA/DoD Clinical Practice Guidelines and Clinical Support Tools - https://www.pdhealth.mil/clinical-guidance/clinical-practice-guidelines-and-clinical-support-tools
- VA Health Services Research and Development: Evidence-based Synthesis Program - www.hsrd.research.va.gov/publications/esp/

The Work Group neither reviewed nor endorses the accuracy or clinical utility of other provider resources.

C. Medication

Treatments for difficulties that arise proximately to a concussion should be symptom-based and not specific to the historical traumatic event. Sound clinical judgment with a thorough clinical history, targeted physical exam, and any needed laboratory testing appropriate to the condition are always prudent before prescribing any treatment. If pharmacologic intervention is being considered, following established recommended dosing guidelines for the specific symptoms or conditions is prudent.

Considerations in using medication for treatment of symptoms after brain injury include:

- Avoid medications that lower the seizure threshold (e.g., bupropion, traditional antipsychotic medications) or those that can cause confusion (e.g., lithium, benzodiazepines, anticholinergic agents).
- Before prescribing medications, rule out social factors (e.g., abuse, neglect, caregiver conflict, environmental issues).
- Unless side effects prevail, give full therapeutic trials at maximal tolerated doses before discontinuing a medication trial. Under-treatment is common.
- Some patients with symptoms attributed to mTBI can be more sensitive to side effects. Watch closely for toxicity and drug-drug interactions. Assess regularly for side effects.
- Limit quantities of medications with high risk for suicide. The suicide rate in individuals who have sustained a TBI is higher than in the general population.
- Educate patients and family/caregivers to avoid the use of alcohol or other illicit drugs with the medications.
- Minimize caffeine and avoid herbal or dietary supplements such as “energy” products, as some contain agents that cross-react with prescribed medications (e.g., use with certain psychiatric medications may lead to a hypertensive crisis).

D. Co-occurring Conditions

a. Clinical Guidance

Assess individuals in a primary care setting. Typical screening instruments for co-occurring mental health diagnoses or symptoms include the Columbia Suicide Severity Rating Scale (C-SSRS), Patient Health Questionnaire (PHQ-2 or PHQ-9), the Generalized Anxiety Disorder Scale (GAD-2 or GAD-7), Alcohol Use Disorders Identification Test-Concise (AUDIT-C), and the PTSD Checklist (PCL-5). While these instruments do not diagnose individuals with MDD, anxiety, SUD, or PTSD, they serve to identify individuals who require further assessment. Many of these screening instruments have links to access them within the electronic health record.

It is always critical that the evaluation of individuals with persistent symptoms attributed to mTBI includes an assessment for suicidal and homicidal ideations. If an individual’s history or current distress suggests any suicidal ideas, intent, past attempts, or worsening psychiatric symptoms, consider consulting with, or referring to, a behavioral health provider. Many institutions have mental health teams embedded in primary care for same-day access or have a fast-track referral system for immediate interventions. For

individuals who present with an existing and chronic psychiatric disorder, refer to behavioral health services for further follow-up/treatment if indicated.

Individuals with persistent symptoms attributed to mTBI should be re-evaluated for emerging or worsening co-occurring mental health disorders, as clinically indicated.

In individuals with persistent post-concussive symptoms that have been refractory to treatment, consideration should be given to other factors that may be contributing, including unidentified mental health disorders, lack of psychosocial support, negative illness expectations, and compensation/litigation issues. Clinicians should be very careful with any communications with patients regarding possible attributions of physical symptoms to any of these causes and should follow clinical guidelines for the management of persistent unexplained symptoms.

The VA/DoD CPG website has the following guidelines to assist with the management of co-occurring mental health symptoms:

- Suicide[a]
- MDD[b]
- PTSD[c]
- SUD[d]

E. Headache

a. Background

Post-traumatic headaches (PTH) are very common, occurring in 25-78% of individuals following mTBI.(93) They are more frequent in individuals with mild versus moderate or severe TBI,(94) including having a negative correlation between the duration of unconsciousness and incidence of headache in moderate to severe TBI.(95) Posttraumatic headache most frequently resembles tension-type or migraine headaches and can be exacerbated by very mild physical or mental exertion.

For a much more detailed analysis of PTH and guidance on how to manage patients, see the VA/DoD CPG for the Primary Care Management of Headache (2019).[e]

[a] See the VA/DoD Clinical Practice Guideline for the Assessment and Management of Patients at Risk for Suicide. Available at: https://www.healthquality.va.gov/guidelines/MH/srb/

[b] See the VA/DoD Clinical Practice Guideline for the Management 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 Disorder. Available at: https://www.healthquality.va.gov/guidelines/MH/sud/

[e] See the VA/DoD Clinical Practice Guideline for the Primary Care Management of Headache. Available at: https://www.healthquality.va.gov/guidelines/Pain/headache/

F. Dizziness and Disequilibrium

a. Background

Dizziness and disequilibrium are common symptoms that individuals present with in the primary care settings and may be related to mTBI. They have a range of causes and can be broadly organized into the following disorders: inner ear disorders (peripheral vestibular disorders), central nervous system disorders, psychological disorders, musculoskeletal disorders, and (commonly) idiopathic disorders.

b. Assessment

1. Physical Examination

In individuals with symptoms attributed to mTBI, a description and characterization of their dizziness (e.g., vertigo, lightheadedness, syncope, disequilibrium, confusion), temporal pattern (e.g., seconds, minutes, hours, days), and symptom-provoking activities (e.g., rolling over in bed, bending over, head movement) provides valuable information in establishing a working differential diagnosis. Primary care assessment for vestibular disorders should be done before referring for further vestibular examination and rehabilitation. Observation and patient interview are key elements to the examination and often guide the clinician in determining the plan of care. Evaluation should include a thorough examination of the following:

- Neurologic function
- Orthostatics
- Vision (acuity, monocular confrontation fields, pupils, eye movements, nystagmus)
- Auditory (hearing screen, otoscopic exam)
- Sensory (sharp touch, light touch, proprioception, vibration)
- Motor (strength, coordination)
- Cervical (range of motion)
- Vestibular (static and dynamic visual acuity, positional testing)

Evaluation of functional activities should include sitting and standing balance (e.g., Romberg with eyes open/closed, single-leg stance) and gait (e.g., walking, tandem walking, walking with head turns, and whole-body turning). Once the initial assessment is completed and other causes are eliminated (e.g., vertebral basilar insufficiency, orthostatic hypotension, polypharmacy), referral to a vestibular rehabilitation specialist (i.e., physical therapy or occupational therapy) is recommended for symptom management.

2. Medication Review

A detailed medication history is warranted as numerous medications include dizziness as a potential side effect. The following classes of medications are particularly important to consider: stimulants, benzodiazepines, tricyclics, monoamine oxidase inhibitors, tetracyclics, neuroleptics, anticonvulsants, selective serotonin agonists, beta blockers, and cholinesterase inhibitors. The temporal relationship to the onset of dizziness and the initiation and dosing of these medications should be investigated.

c. Treatment

1. Pharmacologic Treatment

Initiating vestibular suppressants for dizziness may delay central compensation or promote counterproductive compensation;(96, 97) and, while vestibular suppressants may be helpful during the acute period of several vestibular disorders, they are not recommended after concussion.(98) Medications should only be considered if symptoms are severe enough to significantly limit functional activities. Trials of medications should be brief (optimally less than a week), and particular attention should be paid to dosing and titration due to the effects on arousal, cognition, and memory, and the potential addictive qualities of these medications.(99) Meclizine is the preferred agent, followed by scopolamine and dimenhydrinate. The use of clonazepam, diazepam, or lorazepam is discouraged due to the sedating and addictive qualities of those agents.

2. Non-Pharmacologic Treatment

Non-pharmacologic interventions for posttraumatic dizziness may be useful as an alternative to or in conjunction with pharmacotherapies, although the effectiveness of such interventions is not fully established with mTBI.(100) The efficacy of vestibular and balance rehabilitation has been shown in different, non-TBI populations.(101-103) Patients with vestibular disorders who received customized programs showed greater improvement than those who received generic exercises.(102) Studies utilizing vestibular exercises have shown up to an 85% success rate in reducing symptoms and improving function in the population with peripheral vestibular disorders.(102, 104)

With mTBI, recovery of vestibular lesions is often limited or protracted due to the coexistence of central or psychological disorders.(105) Evidence is limited regarding the benefits of specific vestibular exercises for patients with a history of mTBI and psychological co-occurring symptoms.

Knowledge of canalith repositioning and liberatory maneuvers for the treatment of benign paroxysmal positional vertigo (BPPV) is beneficial for primary care physicians.(106) Clinicians should perform the Dix-Hallpike and supine roll tests to assess for BPPV; radiographic imaging, vestibular testing, and routinely treating BPPV with vestibular suppressant medications is not recommended.(107) In addition, patients with history and clinical examination consistent with BPPV, whose symptoms do not fully resolve after one trial of a canalith repositioning maneuver, may also be sent to a vestibular rehabilitation therapist for further specialized BPPV assessment and treatment.

In cases of persistent dizziness and disequilibrium, a vestibular rehabilitation therapist may also be utilized to execute a more comprehensive vestibular and balance evaluation and treatment program. The types of specialized assessment tools, maneuvers, and exercises to treat dizziness and disequilibrium are beyond the scope of this guideline. Patients with central, functional, and psychological disorders need a coordinated team effort to address the underlying impairments and activity limitations in order to maximize the outcome of vestibular rehabilitation.

If an individual appears to be at fall risk due to symptoms of dizziness and disequilibrium, referral for home evaluation for adaptive equipment should also be considered as a compensatory strategy to limit further injury.

The Office of the Surgeon General (OTSG) Army Toolkit and TBICoE may also provide guidance regarding symptoms of dizziness and vestibular rehabilitation.[f] While these resources may assist PCPs, the Work Group did not review the information contained in these documents.
(See Appendix J: Additional Educational Materials and Resources.)

G. Visual Symptoms

a. Background

Vision symptoms, including sensitivity to light, eye fatigue, difficulty focusing, and blurry vision occur acutely in some individuals who sustain mTBI. Most vision symptoms resolve within minutes or hours; however, for those with persistent difficulties, targeted assessments to guide symptom management during the first few weeks after mTBI are most effective.

PCPs need to be aware of reasons for an urgent referral to an eye care provider, including: vision loss or decline, diplopia, abnormal pupils, abnormal external eye exam (e.g., evidence of infection or hemorrhage), abnormal visual behavior (e.g., unexpectedly bumping into things), abnormal eye movements (e.g., nystagmus), or acute ocular symptoms (e.g., evidence of trauma, severe eye pain, flashes and/or floaters, severe photophobia). If visual symptoms persist and impact daily function, providers should refer patients to optometry, ophthalmology, neuro-ophthalmology, neurology, and/or vision rehabilitation team.

Higher-order cognitive symptoms (e.g. visual-spatial issues, spatial bias) may be mistaken by either the Veteran, or the clinician, for ocular or vision issues, especially because these cognitive symptoms are usually associated with unawareness of deficit (anosognosia). Occupational therapy vision assessment, or behavioral neurology assessment, may be very helpful in ruling out these symptoms.

b. Assessment and Treatment

In response to persistent vision symptoms, primary care clinicians or others should inquire about how the vision impairment has impacted the individual's daily functioning by asking questions such as, "how have your vision problems impacted school or work such as reading and/or using a computer?" If functional complaints or impairments are evident, the clinician should proceed with a basic eye/vision exam which should include visual acuity (distant and near), monocular confrontational fields, pupils (size/equality/ response), eye movements, an external exam (direct illumination of anterior segment), and nystagmus (primary position and gaze evoked). The clinician should also perform a slit lamp exam, if available.

Medications should be evaluated. Drugs that may be associated with vision symptoms include antihistamines, anticholinergics, digitalis derivatives, antimalarial drugs, corticosteroids, erectile dysfunction drugs, phenothiazines, chlorpromazine, indomethacin, and others. Other co-occurring symptoms (e.g., migraines, sleep disturbances, chronic pain, mood disorders, PTSD) may be contributing factors or the source of the vision dysfunction.

If the vision problem is impacting function over time, a referral to a specialist trained in specialized oculomotor assessment (e.g., neuro-ophthalmology, polytrauma blind rehabilitation outpatient specialist,

[f] Hearing Center of Excellence. Available at: https://hearing.health.mil/For-Providers/Standards-and-Clinical-Practice-Guidelines/COMMON-DIZZINESS-AND-BALANCE-DISORDERS-IN-MILITARY-POPULATIONS

low vision therapist, occupational therapist) should be made to complete a vision screen and functional assessment. If indicated, an eye care provider can complete a comprehensive vision assessment and together with the rehabilitation team can develop a treatment intervention to address the individual's visual complaints and functional deficits.

The types of specialized vision rehabilitation assessment tools and interventions (e.g., vision exercises) to address visual dysfunction related to mTBI are beyond the scope of this guideline. Patients benefit from a coordinated team effort to address the underlying impairments and maximize vision rehabilitation. Additional resources to support vision care and vision disorders after mTBI can be found through the TBICoE[g] and Vision Center of Excellence[h] websites.

H. Fatigue

a. Background

Fatigue is one of the most common symptoms following mTBI. Fatigue can be a primary effect related to central nervous system dysfunction or a secondary effect of common coexisting disorders in mTBI (e.g., depression, chronic pain, sleep disturbances). Medications, substance use, and unhealthy lifestyle habits may also contribute to fatigue.

b. Assessment and Treatment

A detailed pre- and post-injury history of physical activity, cognitive function, and mental health is important to determine the effects of fatigue in temporal relation to the injury. It is important to review current medications and supplements for possible side effects. Multiple self-assessment scales for fatigue exist, many of which have been studied in other populations. Common fatigue assessment tools used in TBI include the Multidimensional Assessment of Fatigue (MAF), Fatigue Impact Scale (FIS), and the Fatigue Assessment Instrument (FAI). Objective testing (e.g., laboratory evaluation), to exclude other medical conditions contributing to fatigue, should be considered when clinically indicated.

Education is an important component in the management of fatigue. Educational efforts should be focused on the modification of lifestyle factors including a healthy diet, regular exercise, and sleep hygiene. Cognitive behavioral therapy may be a useful management approach for post-traumatic fatigue. Exercise routines should be individualized to maximize benefit and promote a proper ratio of activity and rest.

I. Sleep Disturbance

a. Background

Sleep disturbance is a common complaint of individuals with a history of mTBI.(108) Assessment and treatment of sleep disturbances is similar to individuals without a history of mTBI. In an individual with a history of mTBI, co-occurring conditions (e.g., anxiety, depression, PTSD, chronic pain, headache) can complicate the clinical picture, as many of these conditions can also negatively impact sleep.

[g] Available at: https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Provider-Resources

[h] Available at: https://vce.health.mil/Clinicians-and-Researchers/Clinical-Practice-Recommendations

See the VA/DoD 2019 CPG on the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea for more detailed recommendations on assessment and treatment of chronic complaints for sleep disturbance.[i]

b. Assessment

Assessing individuals with reported sleep disturbance and its underlying causes is an essential component of the clinical work-up. It is important to attribute symptoms correctly and to identify and treat any co-occurring conditions.

c. Treatment

Treatment will be dependent upon specific sleep disorder diagnosis and etiological cause. For chronic insomnia, the use of non-pharmacologic therapies should be considered a first-line treatment. Pharmacologic treatment of sleep disturbance following mTBI may be complex. For all pharmacologic interventions, providers should weigh the risk-benefit profiles, including toxicity and abuse potential.

J. Cognitive Symptoms

a. Background

Cognitive symptoms are common after mTBI. While symptoms improve within days to several weeks in most situations, cognitive problems in attention, thinking speed, memory, and executive functions may persist for several months or years for some. For those reporting cognitive symptoms for more than 30 days following mTBI, a time-limited trial of cognitive rehabilitation with a focus on psychoeducation and strategies for daily function may facilitate recovery. Persons with persistent or late-emerging cognitive symptoms (e.g., months to years following TBI) may benefit from an integrated and holistic approach to cognitive symptom management, particularly when co-occurring conditions and associated refractory symptoms are present.(109) Because problems with speech and language or spatial function (e.g. spatial neglect) can be mistaken for problems with memory, concentration, or executive function, specific screening for these issues, especially in Veterans with co-occurring stroke risk factors, is important.

Since 2009, the term “polytrauma triad” has been used to describe the higher rate of chronic pain and mental health disorders in those with a history of military-related TBI.(110) These factors can impact daily functioning across multiple domains (i.e., cognitive, emotional, behavioral) and require referral for appropriate management to maximize effectiveness of cognitive rehabilitation. Recent evidence demonstrating that physical (e.g., pain, headache, fatigue),(111) psychological (e.g., PTSD, anxiety, depression),(111) and sleep conditions (112, 113) are significant contributors to cognitive symptoms following mTBI further supports the need for integrated, interdisciplinary management of functional cognitive complaints, including cognitive rehabilitation, particularly in patients with chronic or late-emerging symptoms.

In 2020, Belanger et al. reported “self-efficacy” (i.e., one’s personal perception of one’s abilities and capabilities) as the most potent predictor of cognitive rehabilitation response in a study of Service Members and Veterans following mTBI.(114) As such, developing a therapeutic alliance, establishing

[i] See the VA/DoD Clinical Practice Guideline for Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp

positive but realistic expectations, and providing quick wins early in treatment may be critical components of effective, clinician-directed, cognitive rehabilitation. Psychoeducation that is centered on validation of symptoms and understanding their impact on function should include information about the potential contributions of coexisting conditions, and medication side effects, on cognitive dysfunction.

b. Clinical Guidance

A comprehensive evaluation that combines objective, self-report, and ecologically-relevant measures may be necessary to capture the functional impact of cognitive symptoms following mTBI.(115) Practices such as motivational interviewing (116) and goal attainment scaling (117, 118) have been shown to facilitate the development of meaningful treatment goals and plans that align with patient values, preferences, functional needs, and limitations. Assessments and guided interventions that promote active engagement in the treatment process and self-management techniques empower patients to co-manage their recovery and contribute to self-efficacy. Short-term trials of evidence-based cognitive rehabilitation (e.g., 4 – 6 sessions) may provide sufficient information to determine potential benefit from further cognitive rehabilitation. Prolonged treatment trials that are not resulting in improved activity participation, and that perpetuate dependence and a "sick role," are strongly discouraged.

Compensatory training as an individualized, functional intervention can involve adaptive strategies such as environmental modifications to facilitate attention and establishing and practicing new techniques (e.g., organization, note-taking) to support daily functioning, work, and school activities. Compensatory strategy training requires selection of appropriate targets, building skills based on prior knowledge, and training of sufficient intensity and complexity to ensure transfer of learned skills and habits to everyday situations.(119) Cognitive assistive technologies may range from a wristwatch with an alarm function to a multi-function device (e.g., smartphone, tablet). Familiar and commercially available devices are easier to learn and may lead to less abandonment than customized devices. Successful long-term utilization of compensatory strategies and devices ultimately requires specialized evaluation to select the appropriate technique or device (for the person and the situation) and sufficient practice in meaningful, real-life contexts.(120, 121)

Treatment approaches for executive functions that promote self-reflection and self-regulation are suggested to support generalization of treatment gains to community-based activities that lead to functional independence. Mobile applications (e.g., Concussion Coach, PTSD Coach, CBTi) may be beneficial when used in support of a comprehensive treatment approach focused on self-management and real-world benefit. For example, assistive devices and apps for self-management, self-advocacy, health monitoring or journaling, can increase self-awareness and reduce the impact of memory dysfunction on accurate symptom self-monitoring and reporting to medical providers.

K. Persistent Pain

(See also discussion of Headache.)

a. Background

Approximately 40-50% of individuals with a history of mTBI may experience chronic pain.(122) Pain management is similar to individuals without a history of mTBI. However, in individuals with a history of

mTBI, the complaint of chronic pain is sometimes interwoven with co-occurring conditions such as sleep disorders, anxiety, MDD, or PTSD.

b. Assessment

Providers may also consult the VA/DoD CPG for Opioid Therapy for Chronic Pain[j] for assessment of persistent pain. Pain management is a priority and thus all individuals presenting with a history of mTBI and complaints of pain should be thoroughly assessed. The underlying cause of the pain should be determined and treated, if possible.

c. Treatment

The use of non-pharmacologic therapies should be considered as first-line. Rehabilitation therapies may be beneficial for the management of pain in individuals with a history of mTBI. The use of opioid agents in chronic pain conditions should be avoided until other avenues of pain control have been given appropriate treatment trials.

Providers may also consult the VA/DoD CPG for the Management of Chronic Multisymptom Illness[k] or the VA/DoD CPG for Opioid Therapy for Chronic Pain[l] for additional strategies to manage persistent pain.

L. Hearing Difficulties

a. Background

Hearing difficulties, including altered acuity and sensitivity to noise, can occur acutely in over half of the individuals who sustain a blast-related mTBI.(123) Hearing difficulties may include tinnitus, sensorineural hearing loss, conductive hearing loss, hyperacusis, and/or central auditory dysfunction.(124) In Operation Iraqi Freedom, in Veterans who experienced blast-related injuries, 38% experienced tinnitus and 62% experienced hearing loss.(124) If not diagnosed, these issues can hinder successful mTBI-related treatment and rehabilitation outcomes for patients.[m] Co-occurring conditions, specifically depression,[n] anxiety, and insomnia,[o] are associated with tinnitus and proper management of these conditions can help improve symptoms of tinnitus.(124)

True abnormalities in central auditory acuity or processing are extremely rare with mTBI. Other causes of problems are also extremely rare and often not related directly to the concussion injury. Pre-injury hearing deficits are common and should be ruled out.

---

[j] See the VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/

[k] See the VA/DoD Clinical Practice Guideline for Management of Chronic Multisymptom Illness. Available at: https://www.healthquality.va.gov/guidelines/MR/cmi/

[l] See the VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/

[m] Available at: https://hearing.health.mil/Resources/Education/Conditions-and-Concerns/TBI-and-Hearing-Loss

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

[o] See the VA/DoD Clinical Practice Guideline for Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp

b. Assessment and Treatment

1. Perform an otologic examination.
2. Review medications for agents that may cause ototoxicity.
3. Refer to audiology for testing as part of an interdisciplinary assessment.

M. Other Symptoms

a. Smell (Olfactory Deficits)

1. Background

Posttraumatic olfactory deficits (anosmia) are not common in individuals who sustain an mTBI.(125) Treatments have limited effect and are usually aimed at flavoring/spicing food to enhance taste and providing specific safety education (e.g., particular attention to working smoke detectors for patients who may not smell smoke). Other causes are also extremely rare and often not related directly to the concussion injury. Depression, common among those with persistent symptoms following mTBI, has been associated with perceptual biases in olfaction that may drive patient complaints of changes in smell and taste.(126) Pre-injury causes of anosmia need to be ruled out.(76)

2. Assessment and Treatment

1. Perform a nasal and oropharyngeal examination. Screen for depression.
2. Refer to ear, nose, and throat specialist (ENT) for further evaluation, if needed.
3. If neurologic status is stable and there are no objective findings, reassurance and monitoring are appropriate.
4. For depressed patients, treatment with psychotherapy may improve olfaction.(127)
5. Increase spicing of foods (with or without dietary referral). Monitor weight. Provide specific safety education.
6. Smoking cessation as a possible treatment for loss of smell.

b. Nausea

1. Background

Occasionally, posttraumatic nausea occurs acutely after mTBI, most often in combination with dizziness, as a secondary effect of medications (pain), or due to an exacerbation of underlying gastroesophageal reflux disease (GERD) and gastrointestinal (GI) dysfunction. This symptom may also be associated with psychological stressors.

2. Assessment and Treatment

1. Define triggers and patterns of nausea.
2. Assess medication lists for agents that may cause or worsen GI symptoms.
3. The initial focus should be on the rapid management of dizziness and return to activity. Formal assessment should be limited.

3. Changes in Appetite

While changes in appetite can occur, these are not a primary effect of mTBI but rather are the result of secondary issues. When a change in appetite is noted, it may be related to mood, medications, smell, or other factors and will likely resolve as these factors are addressed.

c. Numbness

Numbness following mTBI in the absence of peripheral nerve injury is atypical and may be associated with psychological stressors. A sensory examination may be performed to assess the symptom.

Appendix H: Mechanism of Injury

Figure H-1. DoD TBI Diagnoses from 2002-2009 (128)

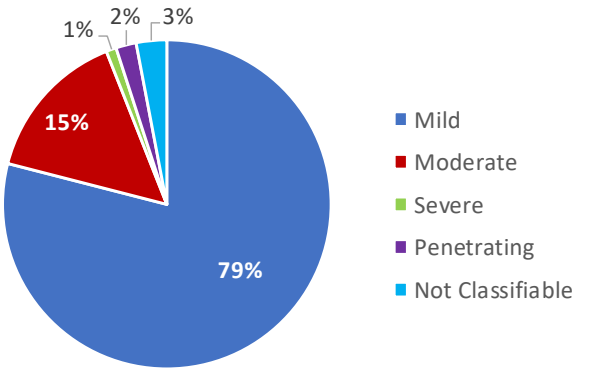
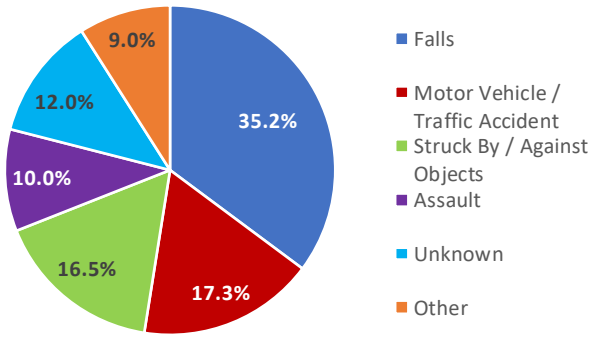


Figure H-2. Leading Causes of mTBI (128)



In both blast and non-blast etiologies, primary injury occurs at the time of the initial injury and can involve neurons, neuroglia, and vascular structures.(129) A multitude of diffuse and dynamic processes also can contribute to secondary injury to include hypoxia and hypotension. The result of this secondary process is the release of inflammatory cytokines, initiation of an excitotoxic cascade, development of cerebral edema, and apoptotic signaling. The effects of free radical oxygen species, excitatory amino acids, and fluctuations in ion gradients such as calcium, alterations in neurotransmitters such as glutamate, receptor activation, lipid peroxidation, and mitochondrial uncoupling all result in increased neurologic injury.(130)

While the extent of such processes may be limited within the mTBI spectrum, the disturbances in brain metabolism and network connectivity associated with mTBI are related more to the complex cascade of ionic, metabolic, and physiologic events rather than to structural injury or damage. The unique molecular activation and intracellular processes associated with individual mTBI etiologies require continued investigation. In addition, the effect of these physiologic responses needs to be studied over a variety of acute, sub-acute, and chronic time points in order to identify the underlying pathophysiology associated with mTBI and its association with the development of chronic neurodegenerative changes in a subpopulation of at-risk individuals.

An individual blast produces a complex mechanical profile consisting of a primary shock wave, followed immediately by a period of negative pressure, generation of a supersonic blast wind, and a delayed period of dissipating elevated pressure.(131) However, depending on multiple blast and environmental variables this profile is quickly modified. Primary blast injury originates from early time point interactions between the blast-induced shock wave and the regional parenchyma and extra parenchymal tissues. This may result in a diffuse traumatic injury that precedes the onset of any linear or rotational acceleration injury. Passage of the shock wave through the tissues generates a combination of mechanical stresses which engage the neurons, glial cells, extracellular matrix, vascular structures, and cerebrospinal fluid-containing structures. These forces include spalling, shearing, mean and deviatoric stress, pressure, and volumetric tension.

Secondary blast injury is related to objects which are displaced by the blast overpressure and blast wind. Secondary injuries may include a combination of both penetrating and blunt trauma. Tertiary blast injury occurs when an individual is thrown by the blast, sustaining blunt trauma such as a closed brain injury. Quaternary blast injuries, such as burns, chemical exposure, and asphyxia are directly related to the blast,

but cannot be classified as a primary, secondary, or tertiary injury. Physical effects of the primary blast on an individual depend not only on blast characteristics but also on the physical relationship to the blast, such as the distance from the blast and exposure in an open environment versus an enclosed structure.

While isolated head trauma does occur, oftenly, blast-related mechanisms of mTBI are associated with multi-system polytrauma and complicated by factors known to exacerbate secondary injuries such as hypotension, hypoxia, and hypothermia. Primary blast effects on an individual likely do not often occur in the absence of secondary or tertiary blast effects, due to the narrower radius of primary blast dispersion compared with more widespread dispersion of blast fragment. The neurometabolic cascade following TBI is diverse and dynamic. The contribution of any particular physiologic response varies based on the magnitude of the forces involved, environmental features, and an individual's unique characteristics at the time of the event. Potential modifiers include, but are not limited to, genetic profile and epigenetic response to a blast or non-blast stimulus, a history of previous TBI, general medical conditions, sleep deprivation, increased levels of stress hormone, and nutritional and hydration status.

Non-blast injuries are associated with focal, multifocal, and diffuse injury. Coup-contrecoup injury is the result of a mismatch in brain and skull movement. When the skull moves faster than the brain, the brain will strike the inner table of the calvarium causing a focal contusion, then, after the skull and brain have stopped their initial direction of movement, the brain may rebound in the opposite direction and impact the calvarium a second time. The orbitofrontal and anterior temporal lobes are most often affected as these are the most common sites of impact from motor vehicle accidents and sports-related injuries. The secondary effects of an acceleration/deceleration injury include edema and hemorrhage.

Depending on the individual forces transmitted during an event, white matter injury through axonal stretch may play a prominent role in the pathology and clinical sequelae associated with both blast and non-blast mechanisms of TBI. With increased energy transfer, acceleration/deceleration is the primary etiology associated with diffuse axonal injury (DAI) and can occur as a primary mechanism of injury in closed brain injury or as a secondary force associated with blast exposure. A complex interrelationship exists between impact location, linear and rotational acceleration, and concussion as a primary or secondary effect of acceleration/deceleration forces. To what extent the addition of shock wave propagation plays in modulation of biomechanical properties and what, if any, distinct physiologic effects are generated from the cumulative effects of blast plus acceleration, rather than either primary mechanism of injury in isolation, is currently unknown.

Given the limited evidence base and lack of evidence to suggest a difference in mTBI symptoms caused by mechanism of injury, treatment programs and outcomes should not be modified.(132-136)

Appendix I: Reference Guide for Providers, Veterans, and Families: Accessing Mental Health Services after Traumatic Brain Injury

Table I-1. Reference Guide for Providers, Veterans, Families: Accessing Mental Health Services after Traumatic Brain Injury

Note: This table was developed by the Mental Health Workgroup of the VHA Committee on the Care of Veterans with Traumatic Brain Injury, February 2021.

Question or Mental Health Need	Mental Health Reference Materials and Websites to Learn More
Military Culture Training	**Military Culture Training for Health Care Professionals: Treatment Resources, Prevention & Treatment** VA TMS 2.0 course # 19335 (*internal VA training site*)
Current suicidal ideations with patient in provider's office	Immediately phone mental health provider in your VA or engage PCMHI in your clinic for assistance in evaluating the patient straightaway. Do not leave the patient unattended while accessing mental health care. Additional guidance can be obtained by calling the Veterans Crisis Line at 1-800-273-8255.
Learning more about how to **evaluate for suicidal ideas** and general warning signs	https://www.mirecc.va.gov/visn19/education/products.asp
Lethal Means Safety and Suicide prevention	Preventing suicide or self-directive violence is critical in the prevention of suicide in Veterans. One aspect is the prevention of lethal means. https://www.mirecc.va.gov/lethalmeanssafety/index.asp
Lethal Means Safety Training for providers	Learning how to discuss lethal means safety with Veterans and their families is critical to the prevention of suicide. This site provides training in how to have these critical discussions. https://www.mirecc.va.gov/visn19/lethalmeanssafety/counseling/
Suicide Risk Screening and Evaluation for providers	Preventing suicide and evaluation for risk is critical. This website describes VHA efforts towards screening evaluation, risk assessment, and education on different levels of risk stratification with evidence-based tools. https://dvagov.sharepoint.com/sites/ECH/srsa (internal Sharepoint site for VA staff)
To refer a Veteran in clinic for treatment of mental health symptoms beyond the comfort/scope of primary care interventions	PACT providers should turn first to their PCMHI, if available. If not, consultation to the mental health Service Line for referrals.
General Facts on TBI exposures in OIF/OEF/OND Veterans: includes information on assessments and treatment recommendations	https://www.polytrauma.va.gov/understanding-tbi/
Neuropsychiatric Manifestations after TBI	The website contains information for Veterans, families, and providers. https://www.mirecc.va.gov/visn6/TBI_education.asp
Substance Use after TBI and Risk Reduction	https://www.mirecc.va.gov/visn19/education/products.asp

Question or Mental Health Need	Mental Health Reference Materials and Websites to Learn More
Teaching Tools for trainees on understanding neuroanatomy and neuropsychiatry	https://www.mirecc.va.gov/visn6/Tools-Tips.asp
PTSD Guides and references for providers	https://www.ptsd.va.gov/professional/index.asp
PTSD Guides and references for Veterans and families	https://www.ptsd.va.gov/family/effects_ptsd.asp
Common Post-deployment **Symptom Education Guides** for patients	https://www.mirecc.va.gov/visn6/Readjustment.asp
Overview of PTSD and violence towards others	https://www.ptsd.va.gov/professional/treat/cooccurring/research_violence.asp
Evaluating risk of violence towards others in context of PTSD	https://www.ptsd.va.gov/professional/treat/cooccurring/assessing_risk_violence.asp
Epidemiological Data on Common Diagnoses and numbers of Veterans treated post-deployment	https://www.publichealth.va.gov/epidemiology/reports/oefoifond/health-care-utilization/index.asp
PTSD Consultation Services with the National Center for PTSD	PTSDconsult@va.gov
General Facts on Chronic Pain in OIF/OEF/OND Veterans	TMS 2.0 (internal VA training site) Course # 13260: chronic pain
Caregiver Education Facts and handouts on multiple medical conditions	This site provides extensive education for caregivers of Veterans with many chronic disease processes. https://www.caregiver.va.gov/publications_resources_topic.asp
Military-Veteran Caregiver and Family Education	This site provides extensive resources for Veteran caregivers and families on a wide variety of psychosocial and medical issues. https://psycharmor.org/caregivers/
CPG for **Patients at Risk for Suicide**	https://www.healthquality.va.gov/guidelines/MH/srb/
CPG for **PTSD**	https://www.healthquality.va.gov/guidelines/MH/ptsd/
CPG for **mild TBI**	https:https://www.healthquality.va.gov/guidelines/Rehab/mtbi/
CPG for **Opioid Therapy for Chronic Pain**	https://www.healthquality.va.gov/guidelines/Pain/cot/
Consensus Conference Recommendations for Treating patients with mild TBI, PTSD, and Pain	https://www.mirecc.va.gov/docs/visn6/Report_Consensus_Conf_Practice_Recommend_TBI_PTSD_Pain.pdf
VA Mobile Phone **APPs**	Apps for the management of multiple mental health conditions and TBI- related symptoms, including the new COVID coach app. https://mobile.va.gov/appstore

Question or Mental Health Need	Mental Health Reference Materials and Websites to Learn More
Website supports for managing stress in providers, Veterans, community, and families in times of infectious disease outbreaks	https://www.cstsonline.org/resources/resource-master-list/coronavirus-and-emerging-infectious-disease-outbreaks-response https://www.ptsd.va.gov/covid/index.asp
Managing general stress in times of COVID-19	This website has resources for managing stress in the pandemic. It contains guidance for the general public, for health care workers, and for employers and community leaders. https://www.ptsd.va.gov/covid/index.asp
Managing PTSD in the context of the COVID-19 pandemic	This website contains recorded lectures from the National Center for PTSD on managing PTSD in the COVID-19 pandemic. https://www.ptsd.va.gov/professional/consult/lecture_series.asp
Coping strategies for building resilience in COVID-19	This Center for Disease Control (CDC) website contains multiple resources for identifying and managing the mental health toll of COVID-19. It includes resources for personal life and for the workplace. https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/stress-coping/index.html

Abbreviations: CDC: Centers for Disease Control and Prevention; CPG: clinical practice guideline; COVID-19: coronavirus disease 2019; OEF: Operation Enduring Freedom; OIF: Operation Iraqi Freedom; OND: Operation New Dawn; PACT: patient-aligned care team; PCMHI: Primary Care Mental Health Integration Team; PTSD: posttraumatic stress disorder; TBI: traumatic brain injury; TMS: Talent Management System; VA: Department of Veterans Affairs; VHA: Veterans Health Administration

Appendix J: Additional Educational Materials and Resources

For additional information on mTBI, there are several topic-specific resources published and offered by TBICoE that pertain to the content described in this CPG.[a] These resources may offer additional information about numerous topics in the care and management of patients with symptoms attributed to mTBI. See the OTSG Army Toolkit[b] and the TBICoE educational materials[c] and publications list[d] for more details. The Work Group has not reviewed the scientific content or quality of any of those materials and is not in a position to endorse them.

[a] See the TBICoE Evidence-Based Resources here: https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Provider-Resources

[b] See the OTSG Army Toolkit here: https://medcoe.army.mil/borden-tb-tbi

[c] See the TBICoE patient and provider educational materials here: https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Patient-and-Family-Resources

[d] See the TBICoE publications list here: https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/Research

Appendix K: Alternative Text Descriptions of Algorithm Modules

A. Module A: Initial Presentation (>7 Days Post-Injury)

1. Module A starts with Box 1, in the shape of a rounded rectangle: "Person exposed to an external force to the head resulting in any of the following: Alteration or loss of consciousness; Post-traumatic amnesia"
2. Box 1 connects to Box 2, in the shape of a hexagon, asks the question: "Urgent/emergent conditions identified? (see Sidebar 1)"
    a. If the answer is "Yes" to Box 2, then Box 3, in the shape of a rectangle: "Refer for emergency evaluation and treatment"
    b. If the answer is "No" to Box 2, then Box 4, in the shape of a rectangle: "Evaluate for severity of TBI based on history (see Sidebar 2)"
3. Box 4 connects to Box 5, in the shape of a hexagon, asks the question: "Is the severity moderate or severe TBI?"
    a. If the answer is "Yes" to Box 5, then Box 6, in the shape of a rectangle: "Consult with a clinician with TBI experience"
    b. If the answer is "No" to Box 5, then Box 7
4. Box 7, in the shape of a hexagon, asks the question: "Diagnosis of mTBI: Are symptoms present? (see Sidebar 3)"
    a. If the answer is "Yes" to Box 7, then Box 8, in the shape of a hexagon, asks the question: "Is person currently deployed on military or combat operation?"
        i. If the answer is "Yes" to Box 8, then Box 9, in the shape of a rectangle: "Follow DoD policy guidance for management of mTBI in the deployed setting"
        ii. If the answer is "No" to Box 8, then Box 10, in the shape of an oval: "Go to Module B, Box 12"
    b. If the answer is "No" to Box 7, then Box 11, in the shape of a rectangle: "Provide education on mTBI and secondary injury prevention (see Appendix J: Additional Educational Materials and Resources); Provide information on safe and structured return to normal and full activity and duties; Monitor and support recovery"

B. Module B: Management of Symptoms Persisting >7 Days After Mild Traumatic Brain Injury

1. Module B starts with Box 12, in the shape of a rounded rectangle: "Patient with persistent symptoms after mTBI (see Sidebar 3)"
2. Box 12 connects to Box 13, in the shape of a rectangle: "Complete history and physical examination, including symptom attributes, intimate partner violence, neurologic and mental status exams, psychosocial evaluation, and suicide risk (see Sidebars 3 and 4); assess patient priorities"

3. Box 13 connects to Box 14, in the shape of a rectangle: "Evaluate for other conditions including but not limited to chronic pain, sleep disorders, depression, PTSD, anxiety, and SUD (see Sidebar 5)"
4. Box 14 connects to Box 15, in the shape of a rectangle: "Develop and implement a patient-centered, individualized treatment plan for mTBI and other common co-occurring conditions by referring to recommendations from relevant VA/DoD CPGs (see Sidebar 5)"
5. Box 15 connects to Box 16, in the shape of a rectangle: "Educate patient/caregiver on symptoms and expected recovery (see Sidebar 6)"
6. Box 16 connects to Box 17, in the shape of a hexagon, asks the question: "Are symptoms persistent and functionally limiting 30 days after mTBI despite symptom-based treatment?"
    a. If the answer is "Yes" to Box 17, then Box 18, in the shape of a rectangle: "Initiate further symptom-based treatment (see Recommendations 10-16)"
        i. Box 18 connects to Box 19, in the shape of a rectangle: "Consider consult and collaboration with a clinician with TBI experience"
        ii. Box 19 connects to Box 20, in the shape of a hexagon, asks the question: "Has treatment plan been completed?"
            1. If the answer is "Yes" to Box 20, then Box 21, in the shape of a rectangle: "Continue management as appropriate; Monitor for comorbid conditions; Address: Return to work/duty/activity, Community participation, Family/social issues"
            2. If the answer is "No" to Box 20, then Box 22, in the shape of a rectangle: "Consider case management with ongoing symptom-based primary care (see Sidebar 7)"
    b. If the answer is "No" to Box 17, then Box 21, in the shape of a rectangle: "Continue management as appropriate; Monitor for comorbid conditions; Address: Return to work/duty/activity, Community participation, Family/social issues".

Appendix L: Abbreviations

Abbreviation	Definition
AA	auricular acupuncture
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor peptide
ANAM	Automated Neuropsychological Assessment Metrics
AT	assistive technologies
CAPD	central auditory processing disorder
CBT	cognitive behavioral therapy
CBTi	cognitive behavioral therapy for insomnia
CDC	Centers for Disease Control and Prevention
CES	cranial electrotherapy stimulation
CIH	complementary and integrative health treatment
COR	Contracting Officer's Representative
COVID-19	coronavirus disease 2019
CPG	clinical practice guideline
DoD	Department of Defense
DV	domestic violence
EBPWG	Evidence-Based Practice Work Group
EEG	electroencephalogram
FDA	U.S. Food and Drug Administration
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GFAP	glial fibrillary acidic protein
GRADE	Grading of recommendations assessment, development and evaluation
HAM-D	Hamilton Depression Rating Scale
HBOT	hyperbaric oxygen therapy
HEC	Health Executive Committee
ImPACT	Immediate Post-Concussion Assessment and Cognitive Testing
IOM	Institute of Medicine
IPV	intimate partner violence
KQ	key question
MDD	major depressive disorder
MHS	Military Health System
MPAI-4	Mayo-Portland Adaptability Inventory
mTBI	mild traumatic brain injury
NAM	National Academy of Medicine
NCAT	Neuro-Cognitive Assessment Tool
NICE	National Institute for Health and Care Excellence
NSE	neuron specific enolase
NSI	Neurobehavioral Symptom Inventory

Abbreviation	Definition
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
OTSG	Office of the Surgeon General
PACT	patient-aligned cared team
PBM	pharmacy benefits management
PCL-S	PTSD Checklist-specific trauma
PCMHI	Primary Care Mental Health Integration Team
PCP	primary care provider
PCS	post-concussive symptoms
PHCoE	Psychological Health Center of Excellence
PHQ-9	Patient Health Questionnaire-9
PRA	progressive return to activity
PREP	Post-Deployment Rehabilitation and Evaluation Program
PTH	posttraumatic headache
PTSD	posttraumatic stress disorder
QoL	quality of life
QOLI-B	Quality of Life Interview-Brief Version
RCT	randomized controlled trial
ROTC	Reserve Officers' Training Corps
RPCQ	Rivermead Post-Concussion Questionnaire
rTMS	repetitive transcranial magnetic stimulation
S100β	S100 calcium-binding protein B
SCL-90-R	Symptom Checklist-90-Revised
SEE	six eye exercises
SMART-CPT	symptom management and rehabilitation therapy cognitive processing therapy
SR	systematic review
SUD	substance use disorder
SWLS	Satisfaction with Life Scale
TBI	traumatic brain injury
TBICoE	Traumatic Brain Injury Center of Excellence
TC	telephonic counseling
TCA	traditional Chinese acupuncture
TMS	Talent Management System
UCH-L1	ubiquitin carboxyl-terminal esterase L1
US	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs
VHA	Veterans Health Administration
VOR	vestibular-ocular reflex

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. Centers for Disease Control Prevention. Report to congress on traumatic brain injury in the United States: Epidemiology and rehabilitation. National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention. 2015:1-72.
3. Assistant Secretary of Defense. Traumatic brain injury: Updated definition and reporting. Washington, DC: Department of Defense 2015. Available from: https://www.health.mil/Reference-Center/Policies/2015/04/06/Traumatic-Brain-Injury-Updated-Definition-and-Reporting.
4. Peterson AB, Xu L, Daugherty J, Breiding MJ. Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths. 2014.
5. DoD TBI worldwide numbers: Traumatic Brain Injury Center of Excellence (TBICoE). Available from: https://health.mil/About-MHS/OASDHA/Defense-Health-Agency/Research-and-Development/Traumatic-Brain-Injury-Center-of-Excellence/DoD-TBI-Worldwide-Numbers.
6. Defense Health Agency. DoD standard surveillance case definition for TBI adapted for AFHSB use 2019. Available from: https://cms.health.mil//Reference-Center/Publications/2015/12/01/Traumatic-Brain-Injury.
7. VA TBI screening and evaluation: Veterans Health Administration (VHA) Support Service Center Capital Assets Database. Available from: http://vssc.med.va.gov/tbireports/comprehensivetbi.aspx.
8. U.S. Department of Veteran Affairs, Department of Defense. Guideline for guidelines: Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup [updated January 29, 2019]. Available from: http://www.healthquality.va.gov/policy/index.asp.
9. 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.
10. 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. J Clin Epidemiol. 2013;66(7):726-35. Epub 2013/04/11. doi: 10.1016/j.jclinepi.2013.02.003. PubMed PMID: 23570745.
11. Andrews J, 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. J Clin Epidemiol. 2013; 66(7):719-25. Epub 2013/01/15. doi: 10.1016/j.jclinepi.2012.03.013. PubMed PMID: 23312392.
12. Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. Health Res Policy Syst. 2006;4:22. Epub 2006/12/07. doi: 10.1186/1478-4505-4-22. PubMed PMID: 17147811; PubMed Central PMCID:PMC1697808.
13. 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. J Clin Epidemiol. 2011;64(4):395-400. Epub 2011/01/05. doi: 10.1016/ j.jclinepi.2010.09.012. PubMed PMID: 21194891.
14. 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.
15. U.S. Preventive Services Task Force. Standards for guideline development. June 2018.

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

17. Martinez GL, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. Implement Sci. 2014;9:72. Epub 2014/06/13. doi: 10.1186/1748-5908-9-72. PubMed PMID: 24919856; PubMed Central PMCID:PMC4067507.

18. Comper P, Bisschop SM, Carnide N, Tricco A. A systematic review of treatments for mild traumatic brain injury. Brain Inj. 2005;19(11):863-80. Epub 2005/11/22. doi: 10.1080/02699050400025042. PubMed PMID: 16296570.

19. Clinical practice guidelines we can trust. Washington, DC: National Academies Press, 2011.

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

21. 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.

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

23. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. Med Decis Making. 1992;12(2):149-54. Epub 1992/04/01. PubMed PMID: 1573982.

24. Snell DL, Surgenor LJ, Hay-Smith EJ, Siegert RJ. A systematic review of psychological treatments for mild traumatic brain injury: An update on the evidence. J Clin Exp Neuropsychol. 2009;31(1):20-38. Epub 2008/07/09. doi: 10.1080/13803390801978849. PubMed PMID: 18608646.

25. Bell KR, Hoffman JM, Temkin NR, Powell JM, Fraser RT, Esselman PC, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: A randomised trial. J Neurol Neurosurg Psychiatry. 2008;79(11):1275-81. Epub 2008/05/13. doi: 10.1136/jnnp.2007.141762. PubMed PMID: 18469027.

26. Scheenen ME, Visser-Keizer AC, de Koning ME, van der Horn HJ, van de Sande P, van Kessel M, et al. Cognitive behavioral intervention compared to telephone counseling early after mild traumatic brain injury: A randomized trial. J Neurotrauma. 2017;34(19):2713-20. Epub 2017/03/25. doi: 10.1089/neu.2016.4885. PubMed PMID: 28335664.

27. Mooney G, Speed J, Sheppard S. Factors related to recovery after mild traumatic brain injury. Brain Inj. 2005; 19(12):975-87. Epub 2005/11/03. doi: 10.1080/02699050500110264. PubMed PMID: 16263640.

28. Ware JB, Biester RC, Whipple E, Robinson KM, Ross RJ, Nucifora PG. Combat-related mild traumatic brain injury: Association between baseline diffusion-tensor imaging findings and long-term outcomes. Radiology. 2016;280(1):212-9. Epub 2016/03/30. doi: 10.1148/radiol.2016151013. PubMed PMID: 27022770.

29. Delano-Wood L, Bangen KJ, Sorg SF, Clark AL, Schiehser DM, Luc N, et al. Brainstem white matter integrity is related to loss of consciousness and postconcussive symptomatology in veterans with chronic mild to moderate traumatic brain injury. Brain Imaging Behav. 2015;9(3):500-12. Epub 2015/08/08. doi: 10.1007/s11682-015-9432-2. PubMed PMID: 26248618.

30. Miller DR, Hayes JP, Lafleche G, Salat DH, Verfaellie M. White matter abnormalities are associated with chronic postconcussion symptoms in blast-related mild traumatic brain injury. Hum Brain Mapp. 2016;37(1):220-9. Epub 2015/10/27. doi: 10.1002/hbm.23022. PubMed PMID: 26497829; PubMed Central PMCID:PMC4760357.

31. Berginström N, Nordström P, Nyberg L, Nordström A. White matter hyperintensities increases with traumatic brain injury severity: Associations to neuropsychological performance and fatigue. Brain Inj. 2020;34(3):415-20. Epub 2020/02/11. doi: 10.1080/02699052.2020.1725124. PubMed PMID: 32037894.

32. Veeramuthu V, Narayanan V, Kuo TL, Delano-Wood L, Chinna K, Bondi MW, et al. Diffusion tensor imaging parameters in mild traumatic brain injury and its correlation with early neuropsychological impairment: A longitudinal study. J Neurotrauma. 2015;32(19):1497-509. Epub 2015/05/09. doi: 10.1089/neu.2014.3750. PubMed PMID: 25952562; PubMed Central PMCID:PMC4589266.

33. Mercier E, Tardif PA, Cameron PA, Batomen Kuimi BL, Émond M, Moore L, et al. Prognostic value of s-100β protein for prediction of post-concussion symptoms after a mild traumatic brain injury: Systematic review and meta-analysis. J Neurotrauma. 2018;35(4):609-22. Epub 2017/10/04. doi: 10.1089/neu.2017.5013. PubMed PMID: 28969486.

34. Kenney K, Qu BX, Lai C, Devoto C, Motamedi V, Walker WC, et al. Higher exosomal phosphorylated tau and total tau among veterans with combat-related repetitive chronic mild traumatic brain injury. Brain Inj. 2018; 32(10):1276-84. Epub 2018/06/12. doi: 10.1080/02699052.2018.1483530. PubMed PMID: 29889559.

35. Lippa SM, Yeh PH, Gill J, French LM, Brickell TA, Lange RT. Plasma tau and amyloid are not reliably related to injury characteristics, neuropsychological performance, or white matter integrity in service members with a history of traumatic brain injury. J Neurotrauma. 2019;36(14):2190-9. Epub 2019/03/06. doi: 10.1089/neu. 2018.6269. PubMed PMID: 30834814; PubMed Central PMCID:PMC6909749.

36. Sun Y, Bai L, Niu X, Wang Z, Yin B, Bai G, et al. Elevated serum levels of inflammation-related cytokines in mild traumatic brain injury are associated with cognitive performance. Front Neurol. 2019;10:1120. Epub 2019/11/12. doi: 10.3389/fneur.2019.01120. PubMed PMID: 31708858; PubMed Central PMCID:PMC6819507.

37. Dambinova SA, Shikuev AV, Weissman JD, Mullins JD. Ampar peptide values in blood of nonathletes and club sport athletes with concussions. Mil Med. 2013;178(3):285-90. Epub 2013/05/28. doi: 10.7205/milmed-d-12-00368. PubMed PMID: 23707115.

38. Iverson GL, Schatz P. Advanced topics in neuropsychological assessment following sport-related concussion. Brain Inj. 2015;29(2):263-75. Epub 2014/10/15. doi: 10.3109/02699052.2014.965214. PubMed PMID: 25313596.

39. Belanger HG, Curtiss G, Demery JA, Lebowitz BK, Vanderploeg RD. Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. J Int Neuropsychol Soc. 2005;11(3):215-27. Epub 2005/05/17. doi: 10.1017/s1355617705050277. PubMed PMID: 15892898.

40. Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: A meta-analysis. J Int Neuropsychol Soc. 2005;11(4):345-57. Epub 2005/10/08. doi: 10.1017/s1355617705050411. PubMed PMID: 16209414.

41. Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. Int Rev Psychiatry. 2003;15(4):341-9. Epub 2004/07/28. doi: 10.1080/09540260310001606728. PubMed PMID: 15276955.

42. Stulemeijer M, Vos PE, Bleijenberg G, van der Werf SP. Cognitive complaints after mild traumatic brain injury: Things are not always what they seem. J Psychosom Res. 2007;63(6):637-45. Epub 2007/12/07. doi: 10.1016/ j.jpsychores.2007.06.023. PubMed PMID: 18061755.

43. Caplain S, Blancho S, Marque S, Montreuil M, Aghakhani N. Early detection of poor outcome after mild traumatic brain injury: Predictive factors using a multidimensional approach a pilot study. Front Neurol. 2017;8:666. Epub 2018/01/10. doi: 10.3389/fneur.2017.00666. PubMed PMID: 29312112; PubMed Central PMCID:PMC5732974.

44. Pape TL, High WM, Jr., St Andre J, Evans C, Smith B, Shandera-Ochsner AL, et al. Diagnostic accuracy studies in mild traumatic brain injury: A systematic review and descriptive analysis of published evidence. PM&R. 2013;5(10):856-81. Epub 2013/10/29. doi: 10.1016/j.pmrj.2013.06.007. PubMed PMID: 24160300.

45. Alsalaheen B, Stockdale K, Pechumer D, Giessing A, He X, Broglio SP. Cumulative effects of concussion history on baseline computerized neurocognitive test scores: Systematic review and meta-analysis. Sports Health. 2017;9(4):324-32. Epub 2017/07/01. doi: 10.1177/1941738117713974. PubMed PMID: 28661827; PubMed Central PMCID:PMC5496709.

46. Li M, Reisman J, Morris-Eppolito B, Qian SX, Kazis LE, Wolozin B, et al. Beneficial association of angiotensin-converting enzyme inhibitors and statins on the occurrence of possible alzheimer's disease after traumatic brain injury. Alzheimers Res Ther. 2020;12(1):33. Epub 2020/03/30. doi: 10.1186/s13195-020-00589-3. PubMed PMID: 32220235; PubMed Central PMCID:PMC7102441.

47. List J, Ott S, Bukowski M, Lindenberg R, Flöel A. Cognitive function and brain structure after recurrent mild traumatic brain injuries in young-to-middle-aged adults. Front Hum Neurosci. 2015;9:228. Epub 2015/06/09. doi: 10.3389/fnhum.2015.00228. PubMed PMID: 26052275; PubMed Central PMCID:PMC4440350.

48. Ivanov I, Fernandez C, Mitsis EM, Dickstein DL, Wong E, Tang CY, et al. Blast exposure, white matter integrity, and cognitive function in Iraq and Afghanistan combat Veterans. Front Neurol. 2017;8:127. Epub 2017/05/10. doi: 10.3389/fneur.2017.00127. PubMed PMID: 28484418; PubMed Central PMCID:PMC5399028.

49. Merritt VC, Jurick SM, Crocker LD, Sullan MJ, Sakamoto MS, Davey DK, et al. Associations between multiple remote mild TBIs and objective neuropsychological functioning and subjective symptoms in combat-exposed Veterans. Arch Clin Neuropsychol. 2020;35(5):491-505. Epub 2020/03/05. doi: 10.1093/arclin/acaa006. PubMed PMID: 32128559.

50. Mattson EK, Nelson NW, Sponheim SR, Disner SG. The impact of PTSD and mTBI on the relationship between subjective and objective cognitive deficits in combat-exposed veterans. Neuropsychology. 2019;33(7):913-21. Epub 2019/06/14. doi: 10.1037/neu0000560. PubMed PMID: 31192654; PubMed Central PMCID:PMC6763389.

51. Cooper DB, Curtiss G, Armistead-Jehle P, Belanger HG, Tate DF, Reid M, et al. Neuropsychological performance and subjective symptom reporting in military service members with a history of multiple concussions: Comparison with a single concussion, posttraumatic stress disorder, and orthopedic trauma. J Head Trauma Rehabil. 2018;33(2):81-90. Epub 2018/03/09. doi: 10.1097/htr.0000000000000375. PubMed PMID: 29517589.

52. Nathan DE, Bellgowan JF, Oakes TR, French LM, Nadar SR, Sham EB, et al. Assessing quantitative changes in intrinsic thalamic networks in blast and nonblast mild traumatic brain injury: Implications for mechanisms of injury. Brain Connect. 2016;6(5):389-402. Epub 2016/03/10. doi: 10.1089/brain.2015.0403. PubMed PMID: 26956452.

53. Janak JC, Cooper DB, Bowles AO, Alamgir AH, Cooper SP, Gabriel KP, et al. Completion of multidisciplinary treatment for persistent postconcussive symptoms is associated with reduced symptom burden. J Head Trauma Rehabil. 2017;32(1):1-15. Epub 2015/12/29. doi: 10.1097/htr.0000000000000202. PubMed PMID: 26709579.

54. Belanger HG, Kretzmer T, Yoash-Gantz R, Pickett T, Tupler LA. Cognitive sequelae of blast-related versus other mechanisms of brain trauma. J Int Neuropsychol Soc. 2009;15(1):1-8. Epub 2009/01/09. doi: 10.1017/s1355617708090036. PubMed PMID: 19128523.

55. Ryan-Gonzalez C, Kimbrel NA, Meyer EC, Gordon EM, DeBeer BB, Gulliver SB, et al. Differences in post-traumatic stress disorder symptoms among post-9/11 Veterans with blast- and non-blast mild traumatic brain injury. J Neurotrauma. 2019;36(10):1584-90. Epub 2018/12/05. doi: 10.1089/neu.2017.5590. PubMed PMID: 30511882.

56. Kennedy JE, Leal FO, Lewis JD, Cullen MA, Amador RR. Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non-blast-related mild TBI. NeuroRehabilitation. 2010;26(3):223-31. Epub 2010/05/08. doi: 10.3233/nre-2010-0558. PubMed PMID: 20448312.

57. Storzbach D, Twamley EW, Roost MS, Golshan S, Williams RM, O'Neil M, et al. Compensatory cognitive training for operation enduring freedom/operation iraqi freedom/operation new dawn Veterans with mild traumatic brain injury. J Head Trauma Rehabil. 2017;32(1):16-24. Epub 2016/03/30. doi: 10.1097/htr.0000000000000228. PubMed PMID: 27022961.

58. Kumar KS, Samuelkamaleshkumar S, Viswanathan A, Macaden AS. Cognitive rehabilitation for adults with traumatic brain injury to improve occupational outcomes. Cochrane Database Syst Rev. 2017;6(6):Cd007935. Epub 2017/06/21. doi: 10.1002/14651858.CD007935.pub2. PubMed PMID: 28631816; PubMed Central PMCID:PMC6481568

59. Cooper DB, Bowles AO, Kennedy JE, Curtiss G, French LM, Tate DF, et al. Cognitive rehabilitation for military service members with mild traumatic brain injury: A randomized clinical trial. J Head Trauma Rehabil. 2017; 32(3):E1-e15. Epub 2016/09/08. doi: 10.1097/htr.0000000000000254. PubMed PMID: 27603763.

60. Rytter HM, Westenbaek K, Henriksen H, Christiansen P, Humle F. Specialized interdisciplinary rehabilitation reduces persistent post-concussive symptoms: A randomized clinical trial. Brain Inj. 2019;33(3):266-81. Epub 2018/12/01. doi: 10.1080/02699052.2018.1552022. PubMed PMID: 30500267.

61. De Luca R, Maggio MG, Maresca G, Latella D, Cannavò A, Sciarrone F, et al. Improving cognitive function after traumatic brain injury: A clinical trial on the potential use of the semi-immersive virtual reality. Behav Neurol. 2019;2019:9268179. Epub 2019/09/05. doi: 10.1155/2019/9268179. PubMed PMID: 31481980; PubMed Central PMCID:PMC6701422 of this article.

62. Caplain S, Chenuc G, Blancho S, Marque S, Aghakhani N. Efficacy of psychoeducation and cognitive rehabilitation after mild traumatic brain injury for preventing post-concussional syndrome in individuals with high risk of poor prognosis: A randomized clinical trial. Front Neurol. 2019;10:929. Epub 2019/09/26. doi: 10.3389/fneur.2019.00929. PubMed PMID: 31551902; PubMed Central PMCID:PMC6737662.

63. Twamley EW, Jak AJ, Delis DC, Bondi MW, Lohr JB. Cognitive symptom management and rehabilitation therapy (CogSMART) for veterans with traumatic brain injury: Pilot randomized controlled trial. J Rehabil Res Dev. 2014;51(1):59-70. Epub 2014/05/09. doi: 10.1682/jrrd.2013.01.0020. PubMed PMID: 24805894.

64. Twamley EW, Thomas KR, Gregory AM, Jak AJ, Bondi MW, Delis DC, et al. CogSMART compensatory cognitive training for traumatic brain injury: Effects over 1 year. J Head Trauma Rehabil. 2015;30(6):391-401. Epub 2014/07/18. doi: 10.1097/htr.0000000000000076. PubMed PMID: 25033034.

65. Bell KR, Fann JR, Brockway JA, Cole WR, Bush NE, Dikmen S, et al. Telephone problem solving for service members with mild traumatic brain injury: A randomized, clinical trial. J Neurotrauma. 2017;34(2):313-21. Epub 2016/09/01. doi: 10.1089/neu.2016.4444. PubMed PMID: 27579992; PubMed Central PMCID:PMC6436019.

66. Vanderploeg RD, Cooper DB, Curtiss G, Kennedy JE, Tate DF, Bowles AO. Predicting treatment response to cognitive rehabilitation in military service members with mild traumatic brain injury. Rehabil Psychol. 2018; 63(2):194-204. Epub 2018/06/08. doi: 10.1037/rep0000215. PubMed PMID: 29878826.

67. Hwang HF, Chen CY, Wei L, Chen SJ, Yu WY, Lin MR. Effects of computerized cognitive training and tai chi on cognitive performance in older adults with traumatic brain injury. J Head Trauma Rehabil. 2020;35(3):187-97. Epub 2019/09/04. doi: 10.1097/htr.0000000000000533. PubMed PMID: 31479083.

68. Booker J, Sinha S, Choudhari K, Dawson J, Singh R. Description of the predictors of persistent post-concussion symptoms and disability after mild traumatic brain injury: The SHEFBIT cohort. Br J Neurosurg. 2019;33(4):367-75. Epub 2019/04/10. doi: 10.1080/02688697.2019.1598542. PubMed PMID: 30964349.

69. Hart T, Benn EKT, Bagiella E, Arenth P, Dikmen S, Hesdorffer DC, et al. Early trajectory of psychiatric symptoms after traumatic brain injury: Relationship to patient and injury characteristics. J Neurotrauma. 2014;31(7):610-7. Epub 01/10. doi: 10.1089/neu.2013.3041. PubMed PMID: 24237113.

70. Stein MB, Ursano RJ, Campbell-Sills L, Colpe LJ, Fullerton CS, Heeringa SG, et al. Prognostic indicators of persistent post-concussive symptoms after deployment-related mild traumatic brain injury: A prospective longitudinal study in U.S. Army soldiers. J Neurotrauma. 2016;33(23):2125-32. Epub 04/08. doi: 10.1089/neu.2015.4320. PubMed PMID: 26905672.

71. Yue JK, Cnossen MC, Winkler EA, Deng H, Phelps RRL, Coss NA, et al. Pre-injury comorbidities are associated with functional impairment and post-concussive symptoms at 3- and 6-months after mild traumatic brain injury: A TRACK-TBI study. Frontiers in Neurology. 2019;10(343). doi: 10.3389/fneur.2019.00343. PubMed PMID: 31024436; PubMed Central PMCID:PMC6465546.

72. Gao C, Fu Q, Chen P, Liu Z, Zhou Q. The influence of sertraline on depressive disorder after traumatic brain injury: A meta-analysis of randomized controlled studies. Am J Emerg Med. 2019;37(9):1778-83. Epub 2019/07/22. doi: 10.1016/j.ajem.2019.06.050. PubMed PMID: 31326198.

73. Reyes NGD, Espiritu AI, Anlacan VMM. Efficacy of sertraline in post-traumatic brain injury (post-TBI) depression and quality of life: A systematic review and meta-analysis of randomized controlled trials. Clin Neurol Neurosurg. 2019;181:104-11. Epub 2019/04/29. doi: 10.1016/j.clineuro.2019.03.024. PubMed PMID: 31030031.

74. Jak AJ, Jurick S, Crocker LD, Sanderson-Cimino M, Aupperle R, Rodgers CS, et al. SMART-CPT for veterans with comorbid post-traumatic stress disorder and history of traumatic brain injury: A randomised controlled trial. J Neurol Neurosurg Psychiatry. 2019;90(3):333-41. Epub 2018/12/17. doi: 10.1136/jnnp-2018-319315. PubMed PMID: 30554135.

75. Cicerone KD, Kalmar K. Persistent postconcussion syndrome: The structure of subjective complaints after mild traumatic brain injury. The Journal of Head Trauma Rehabilitation. 1995;10(3):1-17. PubMed PMID: 00001199-199506000-00002.

76. Terrio H, Brenner LA, Ivins BJ, Cho JM, Helmick K, Schwab K, et al. Traumatic brain injury screening: Preliminary findings in a U.S. Army brigade combat team. J Head Trauma Rehabil. 2009;24(1):14-23. Epub 2009/01/23. doi: 10.1097/HTR.0b013e31819581d8. PubMed PMID: 19158592.

77. Jafarzadeh S, Pourbakht A, Bahrami E, Jalaie S, Bayat A. Effect of early vestibular rehabilitation on vertigo and unsteadiness in patients with acute and sub-acute head trauma. Iran J Otorhinolaryngol. 2018;30(97):85-90. Epub 2018/03/30. PubMed PMID: 29594074; PubMed Central PMCID:PMC5866486.

78. Kleffelgaard I, Soberg HL, Tamber AL, Bruusgaard KA, Pripp AH, Sandhaug M, et al. The effects of vestibular rehabilitation on dizziness and balance problems in patients after traumatic brain injury: A randomized controlled trial. Clin Rehabil. 2019;33(1):74-84. Epub 2018/07/31. doi: 10.1177/0269215518791274. PubMed PMID: 30056743.

79. Hall CD, Herdman SJ, Whitney SL, Cass SP, Clendaniel RA, Fife TD, et al. Vestibular rehabilitation for peripheral vestibular hypofunction: An evidence-based clinical practice guideline: From the American Physical Therapy Association Neurology Section. J Neurol Phys Ther. 2016;40(2):124-55. doi: 10.1097/NPT.0000000000000120. PubMed PMID: 26913496.

80. Berryman A, Rasavage K, Politzer T, Gerber D. Oculomotor treatment in traumatic brain injury rehabilitation: A randomized controlled pilot trial. Am J Occup Ther. 2020;74(1):7401185050p1-p7. Epub 2020/02/23. doi: 10.5014/ajot.2020.026880. PubMed PMID: 32078510; PubMed Central PMCID:PMC7018460.

81. Kolakowsky-Hayner SA, Bellon K, Toda K, Bushnik T, Wright J, Isaac L, et al. A randomised control trial of walking to ameliorate brain injury fatigue: A NIDRR TBI model system centre-based study. Neuropsychol

Rehabil. 2017;27(7):1002-18. Epub 2016/10/14. doi: 10.1080/09602011.2016.1229680. PubMed PMID: 27733079.

82. Jonas WB, Bellanti DM, Paat CF, Boyd CC, Duncan A, Price A, et al. A randomized exploratory study to evaluate two acupuncture methods for the treatment of headaches associated with traumatic brain injury. Med Acupunct. 2016;28(3):113-30. Epub 2016/07/28. doi: 10.1089/acu.2016.1183. PubMed PMID: 27458496; PubMed Central PMCID:PMC4926228.

83. White A, Hayhoe S, Hart A, Ernst E. Adverse events following acupuncture: Prospective survey of 32 000 consultations with doctors and physiotherapists. BMJ. 2001;323(7311):485-6. Epub 2001/09/05. doi: 10.1136/bmj.323.7311.485. PubMed PMID: 11532840; PubMed Central PMCID:PMC48133.

84. Solloway MR, Taylor SL, Shekelle PG, Miake-Lye IM, Beroes JM, Shanman RM, et al. An evidence map of the effect of tai chi on health outcomes. Syst Rev. 2016;5(1):126. Epub 2016/07/28. doi: 10.1186/s13643-016-0300-y. PubMed PMID: 27460789; PubMed Central PMCID:PMC4962385.

85. Hart BB, Weaver LK, Gupta A, Wilson SH, Vijayarangan A, Deru K, et al. Hyperbaric oxygen for mTBI-associated PCS and PTSD: Pooled analysis of results from Department of Defense and other published studies. Undersea Hyperb Med. 2019;46(3):353-83. Epub 2019/08/09. PubMed PMID: 31394604.

86. Hart BB, Wilson SH, Churchill S, Deru K, Weaver LK, Minnakanti M, et al. Extended follow-up in a randomized trial of hyperbaric oxygen for persistent post-concussive symptoms. Undersea Hyperb Med. 2019;46(3):313-27. Epub 2019/08/09. PubMed PMID: 31394601.

87. U.S. Food and Drug Administration (FDA). Hyperbaric oxygen therapy: Don't be misled. U.S. Food and Drug Administration (FDA), 2013.

88. Leung A, Metzger-Smith V, He Y, Cordero J, Ehlert B, Song D, et al. Left dorsolateral prefrontal cortex rTMS in alleviating mTBI related headaches and depressive symptoms. Neuromodulation. 2018;21(4):390-401. Epub 2017/05/31. doi: 10.1111/ner.12615. PubMed PMID: 28557049.

89. Stilling J, Paxman E, Mercier L, Gan LS, Wang M, Amoozegar F, et al. Treatment of persistent post-traumatic headache and post-concussion symptoms using repetitive transcranial magnetic stimulation: A pilot, double-blind, randomized controlled trial. J Neurotrauma. 2020;37(2):312-23. Epub 2019/09/19. doi: 10.1089/neu.2019.6692. PubMed PMID: 31530227.

90. Rao V, Bechtold K, McCann U, Roy D, Peters M, Vaishnavi S, et al. Low-frequency right repetitive transcranial magnetic stimulation for the treatment of depression after traumatic brain injury: A randomized sham-controlled pilot study. J Neuropsychiatry Clin Neurosci. 2019;31(4):306-18. Epub 2019/04/26. doi: 10.1176/appi.neuropsych.17110338. PubMed PMID: 31018810.

91. U.S. Food and Drug Administration (FDA). Class II special controls guidance document: Repetitive transcranial magnetic stimulation (rTMS) systems U.S. Food and Drug Administration 2011.

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

93. Evans RW. Postconcussion syndrome [cited 2020]. Available from: https://www.uptodate.com/contents/postconcussion-syndrome.

94. Couch JR, Bearss C. Chronic daily headache in the posttrauma syndrome: Relation to extent of head injury. Headache. 2001;41(6):559-64. Epub 2001/07/05. doi: 10.1046/j.1526-4610.2001.041006559.x. PubMed PMID: 11437891.

95. Stovner LJ, Schrader H, Mickeviciene D, Surkiene D, Sand T. Headache after concussion. Eur J Neurol. 2009;16(1):112-20. Epub 2008/12/18. doi: 10.1111/j.1468-1331.2008.02363.x. PubMed PMID: 19087157.

96. Hain TC, Yacovino D. Pharmacologic treatment of persons with dizziness. Neurol Clin. 2005;23(3):831-53, vii. Epub 2005/07/20. doi: 10.1016/j.ncl.2005.01.012. PubMed PMID: 16026678.

97. Pyykkö I, Magnusson M, Schalén L, Enbom H. Pharmacological treatment of vertigo. Acta Otolaryngol Suppl. 1988;455:77-81. Epub 1988/01/01. doi: 10.3109/00016488809125063. PubMed PMID: 3064540.

98. Zee DS. Perspectives on the pharmacotherapy of vertigo. Archives of Otolaryngology. 1985;111(9):609-12. doi: 10.1001/archotol.1985.00800110087009.

99. Arciniegas DB, Anderson CA, Topkoff J, McAllister TW. Mild traumatic brain injury: A neuropsychiatric approach to diagnosis, evaluation, and treatment. Neuropsychiatr Dis Treat. 2005;1(4):311-27. PubMed PMID: 18568112.

100. de Kruijk JR, Leffers P, Meerhoff S, Rutten J, Twijnstra A. Effectiveness of bed rest after mild traumatic brain injury: A randomised trial of no versus six days of bed rest. J Neurol Neurosurg Psychiatry. 2002;73(2):167-72. doi: 10.1136/jnnp.73.2.167. PubMed PMID: 12122176.

101. Herdman SJ, Clendaniel RA, Mattox DE, Holliday MJ, Niparko JK. Vestibular adaptation exercises and recovery: Acute stage after acoustic neuroma resection. Otolaryngol Head Neck Surg. 1995;113(1):77-87. Epub 1995/07/01. doi: 10.1016/s0194-5998(95)70148-6. PubMed PMID: 7603726.

102. Shepard NT, Telian SA. Programmatic vestibular rehabilitation. Otolaryngol Head Neck Surg. 1995;112(1):173-82. Epub 1995/01/01. doi: 10.1016/s0194-59989570317-9. PubMed PMID: 7816453.

103. Yardley L, Beech S, Zander L, Evans T, Weinman J. A randomized controlled trial of exercise therapy for dizziness and vertigo in primary care. Br J Gen Pract. 1998;48(429):1136-40. PubMed PMID: 9667087.

104. Krebs DE, Gill-Body KM, Parker SW, Ramirez JV, Wernick-Robinson M. Vestibular rehabilitation: Useful but not universally so. Otolaryngol Head Neck Surg. 2003;128(2):240-50. Epub 2003/02/26. doi: 10.1067/mhn.2003.72. PubMed PMID: 12601321.

105. Gottshall KR, Gray NL, Drake AI, Tejidor R, Hoffer ME, McDonald EC. To investigate the influence of acute vestibular impairment following mild traumatic brain injury on subsequent ability to remain on activity duty 12 months later. Military Medicine. 2007;172(8):852-7. doi: 10.7205/milmed.172.8.852.

106. Fife TD, Iverson DJ, Lempert T, Furman JM, Baloh RW, Tusa RJ, et al. Practice parameter: Therapies for benign paroxysmal positional vertigo (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2008;70(22):2067-74. Epub 2008/05/29. doi: 10.1212/01.wnl.0000313378.77444.ac. PubMed PMID: 18505980.

107. Bhattacharyya N, Gubbels SP, Schwartz SR, Edlow JA, El-Kashlan H, Fife T, et al. Clinical practice guideline: Benign paroxysmal positional vertigo (update). Otolaryngol Head Neck Surg. 2017;156(3_suppl):S1-s47. Epub 2017/03/02. doi: 10.1177/0194599816689667. PubMed PMID: 28248609.

108. Wickwire EM, Williams SG, Roth T, Capaldi VF, Jaffe M, Moline M, et al. Sleep, sleep disorders, and mild traumatic brain injury. What we know and what we need to know: Findings from a national working group. Neurotherapeutics. 2016;13(2):403-17. Epub 2016/03/24. doi: 10.1007/s13311-016-0429-3. PubMed PMID: 27002812; PubMed Central PMCID:PMC4824019.

109. Lange RT, Lippa SM, Bailie JM, Wright M, Driscoll A, Sullivan J, et al. Longitudinal trajectories and risk factors for persistent postconcussion symptom reporting following uncomplicated mild traumatic brain injury in U.S. Military service members. Clin Neuropsychol. 2020;34(6):1134-55. Epub 2020/04/15. doi: 10.1080/13854046.2020.1746832. PubMed PMID: 32284000.

110. Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: Polytrauma clinical triad. J Rehabil Res Dev. 2009;46(6):697-702. Epub 2010/01/28. doi: 10.1682/jrrd.2009.01.0006. PubMed PMID: 20104399.

111. Lippa SM, French LM, Bell RS, Brickell TA, Lange RT. United States military service members demonstrate substantial and heterogeneous long-term neuropsychological dysfunction after moderate, severe, and penetrating traumatic brain injury. J Neurotrauma. 2020;37(4):608-17. Epub 2019/09/29. doi: 10.1089/neu.2019.6696. PubMed PMID: 31559904.

112. Garcia A, Reljic T, Pogoda TK, Kenney K, Agyemang A, Troyanskaya M, et al. Obstructive sleep apnea risk is associated with cognitive impairment after controlling for mild traumatic brain injury history: A chronic effects of neurotrauma consortium study. J Neurotrauma. 2020. Epub 2020/07/28. doi: 10.1089/neu.2019.6916. PubMed PMID: 32709212.

113. Garcia AM, Vanderploeg R, Wilde L, Kenney K, Pagoda T, Nakase-Richardson R. 0579 obstructive sleep apnea risk is associated with cognitive impairment after controlling for TBI: A chronic effects of neurotrauma consortium study. Sleep. 2019;42(Supplement_1):A230-A1. doi: 10.1093/sleep/zsz067.577.

114. Belanger HG, Vanderploeg RD, Curtiss G, Armistead-Jehle P, Kennedy JE, Tate DF, et al. Self-efficacy predicts response to cognitive rehabilitation in military service members with post-concussive symptoms. Neuropsychol Rehabil. 2020;30(6):1190-203. doi: 10.1080/09602011.2019.1575245.

115. Coelho C, Ylvisaker M, Turkstra LS. Nonstandardized assessment approaches for individuals with traumatic brain injuries. Semin Speech Lang. 2005;26(4):223-41. Epub 2005/11/10. doi: 10.1055/s-2005-922102. PubMed PMID: 16278795.

116. Medley AR, Powell T. Motivational interviewing to promote self-awareness and engagement in rehabilitation following acquired brain injury: A conceptual review. Neuropsychol Rehabil. 2010;20(4):481-508. Epub 2010/02/26. doi: 10.1080/09602010903529610. PubMed PMID: 20182952.

117. Malec JF. Goal attainment scaling in rehabilitation. Neuropsychol Rehabil. 1999;9(3-4):253-75. doi: 10.1080/096020199389365.

118. Grant M, Ponsford J. Goal attainment scaling in brain injury rehabilitation: Strengths, limitations and recommendations for future applications. Neuropsychol Rehabil. 2014;24(5):661-77. Epub 2014/05/03. doi: 10.1080/09602011.2014.901228. PubMed PMID: 24787703.

119. Whyte J, Dijkers MP, Hart T, Van Stan JH, Packel A, Turkstra LS, et al. The importance of voluntary behavior in rehabilitation treatment and outcomes. Arch Phys Med Rehabil. 2019;100(1):156-63. doi: https://doi.org/10.1016/j.apmr.2018.09.111.

120. Bogner J, Dijkers M, Hade EM, Beaulieu C, Montgomery E, Giuffrida C, et al. Contextualized treatment in traumatic brain injury inpatient rehabilitation: Effects on outcomes during the first year after discharge. Arch Phys Med Rehabil. 2019;100(10):1810-7. Epub 2019/02/05. doi: 10.1016/j.apmr.2018.12.037. PubMed PMID: 30716280.

121. Sohlberg M, Turkstra L. Optimizing cognitive rehabilitation: Effective instructional methods. New York, NY: Guilford Publications; 2011.

122. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: A systematic review. JAMA. 2008; 300(6):711-9. Epub 2008/08/14. doi: 10.1001/jama.300.6.711. PubMed PMID: 18698069.

123. Oleksiak M, Smith BM, St Andre JR, Caughlan CM, Steiner M. Audiological issues and hearing loss among Veterans with mild traumatic brain injury. J Rehabil Res Dev. 2012;49(7):995-1004. Epub 2013/01/24. doi: 10.1682/jrrd.2011.01.0001. PubMed PMID: 23341275.

124. Singh T, Seidman MD. Chapter 11 - hearing disorders associated with mild traumatic brain injury (mTBI). In: Hoffer ME, Balaban CD, editors. Neurosensory disorders in mild traumatic brain injury: Academic Press; 2019. p. 149-63.

125. Vanderploeg RD, Cooper DB, Belanger HG, Donnell AJ, Kennedy JE, Hopewell CA, et al. Screening for postdeployment conditions: Development and cross-validation of an embedded validity scale in the

neurobehavioral symptom inventory. J Head Trauma Rehabil. 2014;29(1):1-10. Epub 2013/03/12. doi: 10.1097/HTR.0b013e318281966e. PubMed PMID: 23474880.

126. Naudin M, Carl T, Surguladze S, Guillen C, Gaillard P, Belzung C, et al. Perceptive biases in major depressive episode. PLOS ONE. 2014;9(2):e86832. doi: 10.1371/journal.pone.0086832.

127. Croy I, Symmank A, Schellong J, Hummel C, Gerber J, Joraschky P, et al. Olfaction as a marker for depression in humans. J Affect Disord. 2014;160:80-6. Epub 2014/01/22. doi: 10.1016/j.jad.2013.12.026. PubMed PMID: 24445134.

128. Defense and Veterans Brain Injury Center. TBI awareness and prevention Silver Spring, MD: Defense and Veterans Brain Injury Center 2015 [updated September 8, 2015; cited 2015 September 9]. Available from: https://dvbic.dcoe.mil/about-tbi/about-traumatic-brain-injury?audience[0]=3.

129. Casey KF, Mclntosh T. The role of novel pharmacotherapy in brain injury. The Journal of Head Trauma Rehabilitation. 1994;9(1):82-90.

130. Eapen BC, Allred DB, O'Rourke J, Cifu DX. Rehabilitation of moderate-to-severe traumatic brain injury. Semin Neurol. 2015;35(1):e1-3. Epub 2015/03/31. doi: 10.1055/s-0035-1549094. PubMed PMID: 25816124.

131. Subbarao BS, Tapia RN, Eapen BC. Mild traumatic brain injury rehabilitation. In: Galante JM, Martin MJ, Rodriguez CJ, Gordon WT, editors. Managing dismounted complex blast injuries in military & civilian settings: Springer, Cham; 2018. p. 241-9.

132. Cooper DB, Vanderploeg RD, Armistead-Jehle P, Lewis JD, Bowles AO. Factors associated with neurocognitive performance in OIF/OEF servicemembers with postconcussive complaints in postdeployment clinical settings. J Rehabil Res Dev. 2014;51(7):1023-34. Epub 2014/12/06. doi: 10.1682/jrrd.2013.05.0140. PubMed PMID: 25479335.

133. Mac Donald CL, Johnson AM, Wierzechowski L, Kassner E, Stewart T, Nelson EC, et al. Prospectively assessed clinical outcomes in concussive blast vs nonblast traumatic brain injury among evacuated US military personnel. JAMA Neurol. 2014;71(8):994-1002. Epub 2014/06/18. doi: 10.1001/jamaneurol.2014.1114. PubMed PMID: 24934200.

134. Belanger HG, Proctor-Weber Z, Kretzmer T, Kim M, French LM, Vanderploeg RD. Symptom complaints following reports of blast versus non-blast mild TBI: Does mechanism of injury matter? Clin Neuropsychol. 2011;25(5):702-15. Epub 2011/04/23. doi: 10.1080/13854046.2011.566892. PubMed PMID: 21512958.

135. Cooper DB, Kennedy JE, Cullen MA, Critchfield E, Amador RR, Bowles AO. Association between combat stress and post-concussive symptom reporting in OEF/OIF service members with mild traumatic brain injuries. Brain Inj. 2011;25(1):1-7. Epub 2010/12/02. doi: 10.3109/02699052.2010.531692. PubMed PMID: 21117916.

136. Lingsma HF, Yue JK, Maas AI, Steyerberg EW, Manley GT, Cooper SR, et al. Outcome prediction after mild and complicated mild traumatic brain injury: External validation of existing models and identification of new predictors using the TRACK-TBI pilot study. J Neurotrauma. 2015;32(2):83-94. Epub 2014/07/16. doi: 10.1089/neu.2014.3384. PubMed PMID: 25025611; PubMed Central PMCID:PMC4291219.