RESEARCH REVIEW ON TRAUMATIC BRAIN INJURY AND PTSD

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RELEVANCE TO WARFIGHTER BRAIN HEALTH

Post-traumatic stress disorder is a highly prevalent mental health concern among service members and veterans with a history of traumatic brain injury. Evidence suggests a complex relationship between PTSD and TBI; their overlap in symptoms challenges diagnosis and effective treatment. Comorbid PTSD and TBI can have a substantial impact on function and overall well-being in service members and veterans, with notable effects on cognitive function and other brain health outcomes. Clinicians treating service members and veterans with comorbid PTSD and TBI must carefully weigh treatment options as these patients typically present with more severe or persistent symptoms than individuals diagnosed with only one of these conditions. While studies have consistently shown the high prevalence and impact of comorbid PTSD among service members, continued research and education are needed to:

- Identify and proactively address factors that confer an increased risk for developing PTSD after TBI.
- Confirm the utility of novel strategies for assessing and monitoring comorbid PTSD and TBI, such as blood-based biomarkers and advanced neuroimaging methods that are developed with consideration of military-specific needs (including those that are readily available across clinical settings, ruggedized for operational use, and can interface within the existing technology landscape).
- Validate the use of traditional treatments for PTSD, as well as novel therapeutic strategies, in service members with comorbid PTSD and TBI.

KEY TAKEAWAYS

- Service members and veterans have an increased risk of developing comorbid mild TBI and PTSD.
- Due to overlapping symptomology and reliance on self-report methods, distinguishing between PTSD and mild TBI can be difficult. Patients should be screened for PTSD when being evaluated for mild TBI.
- The environment in which a mild TBI is sustained can impact clinical outcomes.
    - The risk of developing PTSD and severe PTSD symptoms is correlated more with combat-related mild TBI than non-combat related mild TBI.
    - Blast-related mild TBI may be associated with more severe PTSD symptoms than non-blast-related mild TBI.

    - Combat exposure conveys an increased risk of multiple lifetime TBIs, which can also influence PTSD symptom severity.
- Advanced imaging techniques may eventually help clinicians better identify the structural and functional changes in the brain associated with TBI and PTSD and understand the origins of their neuropsychiatric symptoms. However, these techniques are not widely available for clinical use.
- Chronic neuropsychological impairments in domains like learning, memory, and executive function have been linked to PTSD and mild TBI individually. Whether the presence of both mild TBI and PTSD increases the incidence and severity of these impairments remains unclear.
- A holistic treatment plan that includes integrated behavioral health and rehabilitation interventions is recommended when managing service members and veterans with mild TBI and PTSD.
    - Clinicians should consider patient-centered treatment strategies and multidisciplinary coordinated care when treating patients with co-occurring mild TBI and PTSD.
    - Effectively treating PTSD can lead to less severe neurobehavioral outcomes, improved sleep, and decreased pain.
    - Engaging in cognitive rehabilitation may also have a positive impact on other outcomes including emotional regulation and functional performance. Several cognitive processing and behavioral therapies show promise for treating comorbid mild TBI and PTSD.
    - Newer treatments like repetitive transcranial magnetic stimulation are also being explored to treat comorbid symptoms.
    - Retention and compliance are necessary factors to consider when designing successful therapies. It is important for military providers to address barriers, provide psychoeducation, and consider family or significant others' involvement in planning and treatment.
- Nonpharmacological management of mild TBI and PTSD should always be the first choice for treatment.
    - Pharmacological treatment with SSRIs and SNRIs may be used in some cases for alleviating PTSD symptoms.

PURPOSE

The purpose of this research review is to provide an overview of studies on the diagnosis and treatment of comorbid TBI and PTSD, as well as the unique features associated with the presentation of both. This research review focuses specifically on mild TBI, the most common form of TBI, where possible.

BACKGROUND

TBI

In the DOD, TBI is defined as the alteration of brain function that results from exposure of the head to an external force. It is a prevalent public health concern[1]; each year, about 2.5 million civilians visit emergency rooms for TBI-related care.[2] Most TBIs are mild, accounting for 81.8% of the over 515,000 TBIs diagnosed among service members between 2000 and 2024.[3] In the military population, 5%–35% of service members who deployed to Iraq and Afghanistan sustained a mild TBI (also known as concussion) during their deployment.[4] While service members can sustain mild TBIs through many mechanisms, the most common source during the past two decades has been blast exposure.[4] Overpressure waves from explosions can cause a blast-related mild TBI, which accounts for 33% of mild TBIs in deployed service members.[5] Evidence suggests that regardless of the origin, experiencing one mild TBI nearly doubles the risk of sustaining subsequent mild TBIs.[6] This finding has important implications for recovery because people who have had multiple mild TBIs tend to have longer recovery times and more severe health problems.[7]

The diagnostic criteria for mild TBI following trauma to the head currently include loss of consciousness lasting up to 30 minutes and altered consciousness (such as confusion or disorientation) or post-traumatic amnesia that can last up to 24 hours.[8] According to Department of Defense and VA clinical guidelines, mild TBIs should not show abnormalities on standard brain imaging such as CT scans.[8,9] This guidance contrasts with guidelines for diagnosing mild TBI in civilians, which define mild TBIs by a Glasgow Coma Scale score of 13–15, regardless of the presence of CT abnormalities; however, the American Congress of Rehabilitation Medicine Diagnostic Criteria for mild TBI recommend using the qualifier "mild TBI with neuroimaging evidence of structural intracranial injury" when CT shows a TBI-related intracranial abnormality. Mild TBI patients with abnormal CT scan findings are also often described as having complicated mild TBI.[10] Notably, in both military and civilian populations, CT scans are not usually indicated after a concussion. Indications for a CT are typically based on the presence of "red flags" as described in tools for evaluating individuals with a suspected head injury, such as the Military Acute Concussion Evaluation 2,[11] the Canadian CT Head Rule,[12] the New Orleans Criteria,[13] and Traumatic Brain Injury Center of Excellence Clinical Recommendation on Neuroimaging following mild TBI.[14]

In 2025, the National Institutes of Health and National Institute of Neurological Disorders and Stroke published the results of an initiative to develop a new approach for characterizing TBI.[15,16] The proposed classification system, known as the CBI-M framework, is named for the four components it incorporates: clinical assessments (including the GCS),[17] blood-based biomarkers,[18] neuroimaging,[19] and psychosocial and environmental modifiers.[20] The CBI-M model, which can be used for multidimensional TBI characterization within 14 days of injury, aims to provide a more precise and individualized approach to TBI evaluation and could address some limitations of severity-based TBI characterization.[15] However, some aspects of the model, particularly the blood-based biomarker and

neuroimaging components, may be difficult to implement for TBI evaluation in deployed settings and other resource-limited and austere environments.

Mild TBI patients may exhibit somatic, cognitive, or emotional symptoms soon after injury.[21] Somatic symptoms include nausea, dizziness, headache, blurred vision, oculomotor deficits, auditory disturbances, vestibular dysfunction, and fatigue. The most common cognitive symptoms are delayed reaction time and disrupted memory and executive function. Emotional symptoms, such as disinhibition and emotional lability, are also common.[21] In addition, mild TBI may influence the development of long-term cognitive impairments and psychiatric illnesses.[22] There is some evidence that blast-related mild TBIs may be associated with a higher odds of symptoms like tinnitus, headache, and trouble concentrating than impact-related mild TBI.[23]

PTSD

PTSD is a psychological condition resulting from exposure to a traumatic event often involving actual or threatened death, serious injury, or violation.[24] Exposure can include personal experience of these traumatic events or having a close relationship with a victim of an event. The National Comorbidity Survey Replication reported that in 2017, an estimated 3.6% of U.S. adults had PTSD, and the lifetime prevalence of PTSD was 6.8%.[25] The prevalence is higher in the military, and the DOD Health Related Behaviors Survey found that 10.5% of Army, 9.1% of Marines, 9.7% of Navy, and 3.9% of Air Force active duty service members had PTSD in 2015.[26] The prevalence of PTSD in the veteran population is estimated to be between 10% and 15%, with a lifetime prevalence ranging from 12% to 30%.[27] Service members diagnosed with PTSD are prone to self-stigmatization about the disorder, or judgements and beliefs that prevent them from seeking treatment.[28] Thus, cases may be underestimated.

The Diagnostic and Statistical Manual of Mental Disorders fifth edition, text revision (also known as the DSM-5-TR), recognizes PTSD with delayed expression, in which full diagnostic criteria are not met until at least six months post-trauma.[29] If symptoms occur earlier than one month post-trauma, the resulting condition is referred to as acute stress disorder.[30] A diagnosis of PTSD usually occurs when patients experience symptoms from four categories: intrusive thoughts; avoiding reminders; negative thoughts and feelings; and arousal and reactive symptoms. Symptoms associated with the intrusive-thoughts category involve experiencing vivid dreams, flashbacks, or involuntary memories. The avoiding-reminders category involves patients' inclination to actively avoid people, places, activities, or situations that can bring on distressing memories. Avoiding talking or thinking about traumatic events is also common. Patients experiencing negative thoughts and feelings display distorted beliefs about themselves and others, as well as chronic fear, horror, guilt, anger, and shame. Finally, arousal and reactive symptoms include irritability, angry outbursts, engaging in reckless activities, startling easily, inability to concentrate, and sleep disturbances.[30]

The 11th edition of the International Statistical Classification of Diseases and Related Health Problems manual, developed by the World Health Organization, defined a subtype of PTSD not previously characterized in the DSM-5.[31] This subtype, known as complex PTSD, or CPTSD, is believed to differ from PTSD due to its association with chronic or prolonged trauma, which is commonly experienced by service members who were prisoners of war.[32] CPTSD can lead to greater impairment than traditional PTSD.[32] CPTSD shares the same hallmark symptoms of PTSD, as well as additional symptoms that include trouble staying organized, difficulty managing emotions, low self-esteem, and troubled relationships.[33] When a group of veterans was evaluated based on guidelines for distinguishing PTSD from CPTSD, approximately 25–50% met the criteria for CPTSD.[34] A 2024 meta-analysis of studies of active duty service members and veterans reported a prevalence of 5–81%. This large range likely was due to the differences in combat exposure and prior PTSD diagnoses in the groups studied.[35] More research is needed to determine how CPTSD may affect military populations and how this clinical classification could impact diagnosis and treatment of PTSD within the Military Health System.

COMORBID TBI AND PTSD

PTSD is one of the most diagnosed psychiatric disorders associated with mild TBI in both civilians and service members. In fact, one 2023 study reported that PTSD was the third most common comorbidity to be diagnosed at two years post-injury in over 47,000 active duty and reserve service members who sustained a TBI (most of which were mild).[36] A separate study on civilians found that it is the fifth most common comorbidity reported at five years after mild TBI.[37] In a study of over 860,000 service members, among those who sustained a TBI of any severity while in service, PTSD diagnoses nearly doubled after injury.[38] Other studies have similarly reported that the risk of PTSD is elevated two-to-threefold after confirmed or probable mild TBI in veterans, service members, and civilians.[39,40] The origin of PTSD in groups where mild TBI is comorbid is unclear. Experiencing a traumatic event that causes TBI may initiate a constellation of symptoms that secondarily lead to PTSD. However, PTSD can also either predate TBI, arise concurrently or after the onset of post-concussive symptoms, or be related to a separate event or series of events. For example, a retrospective analysis of over 14,000 veterans found that the pre-injury prevalence of PTSD in those who sustained a TBI was nearly sixfold higher than in veterans who did not sustain a TBI.[41] Thus, these findings collectively support a bidirectional relationship between TBI and PTSD, wherein TBI can increase the risk of PTSD while PTSD can also increase the risk of sustaining a TBI.

Symptom Etiology

There is a strong, albeit unclear, relationship between PTSD and post-concussive symptoms. PTSD and mild TBI share some common symptoms, which can complicate PTSD diagnoses in comorbid groups.[42] These common symptoms include insomnia, fatigue, irritability, depression, anxiety, emotional numbing, avoidance, trouble concentrating, memory deficits, and hyperarousal.[43] Evaluating PTSD symptoms can aid in predicting post-concussive

symptom onset and severity. In some studies with military or veteran participants, psychological factors were more predictive of post-concussive symptoms than TBI history.[44] PTSD can also influence treatment and recovery time and increase post-concussive symptom severity.[45,46] This finding is particularly true in service members with PTSD who experience mild TBI, although misattribution of post-concussive symptoms to PTSD also is common in this group.[47] Many studies have shown that this relationship is reciprocal, as PTSD symptoms are also more severe in civilian, military, and veteran groups with probable or diagnosed mild TBI than in those with no history of mild TBI.[48]

Prevalence

The prevalence rates of comorbid PTSD and TBI vary depending on the populations assessed. Some studies report that comorbid TBI and PTSD are significantly more common in service members than in civilians. Across all studies included in one systematic review, 11.0–18.6% of the civilians who sustained a TBI of any severity developed PTSD within two years of injury, while 48.2% of service members and veterans developed PTSD post-TBI.[49] An analysis of studies assessing only those with mild TBI found that 16.8% of civilians developed PTSD within two years of injury, and 48.8% of service members and veterans developed PTSD post-TBI.[49] Similarly, a 2024 meta-analysis reported a pooled prevalence of 11.8% in civilians with mild TBI[50], while another reported a pooled prevalence of 36% in active duty service members with mild TBI.[51]

Risk Factors

Many factors may be associated with an increased likelihood of developing PTSD following TBI. These include psychosocial and environmental factors, military-specific factors, TBI-related factors, psychological and cognitive factors, genetics, and other comorbidities.

Psychosocial and environmental factors associated with increased PTSD risk following TBI of any severity include fewer years of education, being unmarried, and younger age.[52-54] Some studies report a higher risk of PTSD in females than in males following TBI.[37] However, in studies conducted on military populations and controlling for non-deployment related traumas, there are no significant sex differences in the rates of PTSD diagnosis following TBI.[55,56] Regarding other psychosocial and environmental factors, lack of social support may play a role. In one study that was part of the Defense and Veterans Brain Injury Center-Traumatic Brain Injury Center of Excellence's 15 Year Longitudinal Study on TBI, a high proportion of 1,301 service members with TBI of any severity and persisting PTSD symptoms reported a lack of social participation.[57] Additionally, one civilian study that developed a model to predict PTSD risk following TBI (most of which were mild) reported that pre-injury unemployment was among the factors associated with an increased risk.[58] Finally, some studies indicate diet may play a role. One systematic review examined 44 studies on the relationship between dietary glutamate consumption and PTSD after TBI of any severity.[59] The findings revealed that individuals living in countries with a higher dietary consumption of glutamate were 15 times more likely to develop PTSD after TBI.

Characteristics unique to the military could increase the risk of developing PTSD after TBI. As previously mentioned, being a member of the military is itself a risk factor for PTSD diagnosis and greater PTSD symptom severity.[60] The dissonance between civilian and military populations could be attributed to the kinds of trauma each group may be exposed to. Combat exposure among service members is associated with an increased likelihood of sustaining multiple lifetime TBIs, and the combination of these two factors yields greater PTSD symptom severity.[61] It is unclear whether specific military occupations are associated with a higher risk. One study comparing the prevalence and severity of PTSD between special operations forces and conventional forces personnel reported no significant differences in PTSD symptom severity during the 10 years after TBI of any severity.[62] Factors that have been associated with an increased risk include a history of combat deployment and military service for longer than four years. In one study, these two factors significantly increased the likelihood of PTSD diagnosis at one year after moderate to severe TBI.[63]

Several factors related to the TBI itself may be associated with an increased risk of developing PTSD. Most studies indicate that mild TBI is more frequently associated with a higher incidence of PTSD and more severe PTSD symptoms than moderate or severe TBI.[57,62,64,65] It is plausible that the loss of consciousness and amnesia associated with more severe TBIs may protect against developing PTSD.[66] However, some studies dispute this finding, showing that the risk of developing PTSD increases with the severity of deployment-related TBI and blast exposure among those in the military.[67-69] Regarding other TBI-related factors, sustaining multiple TBIs, mild TBIs with extracranial injuries, and TBIs of any severity resulting from violence increase the risk for developing PTSD and more severe PTSD symptoms.[58,70,71] The environment in which a TBI is sustained may also play a role. Rates of PTSD are higher after deployment-related or combat-related TBI of any severity than after nondeployment-related or noncombat TBI.[72,73] Additionally, TBIs of any severity sustained before military service are associated with less severe PTSD symptoms than those sustained during service.[73] The increased risk could be due to blast exposure. Blast-exposed service members can experience an increase in PTSD symptom severity up to five years post-injury, suggesting that an evolving mental health burden is related to this TBI mechanism.[74]

Among the psychological factors associated with the risk of PTSD, morally injurious events have emerged as important to consider and may be a risk factor for post-concussive symptoms in veterans with mild TBI.[75] These events include witnessing, committing, or failing to prevent an action that violates a fundamental moral belief system[76] or an event that produces a sense of betrayal by entrusted authorities.[77] Moral injury is associated with an increased risk of a variety of mental health disorders among service members and veterans with TBI of any severity, including suicidality[78] and PTSD. In one study, veterans who screened positive for current PTSD or depression were more likely to have experienced a potentially morally injurious event.[79] Events involving betrayal or perpetration were linked to a two-to-three times higher chance of having PTSD, depression, or both.[79]

Other psychological and cognitive factors may be associated with an increased risk of PTSD following TBI. These include greater mood fluctuations,[80] difficulty regulating behavior,[81] and

lower distress tolerance,[82] which have each been associated with PTSD incidence and severity in both veterans and active duty service members with TBI of any severity. While these factors have important differences, they each relate to an individual's ability to withstand or regulate shifts in mood or emotion. Reporting higher levels of anger has also been associated with PTSD symptoms in combat veterans and active duty service members.[83] Poorer pre-deployment inhibitory control and sustained attention, as well as poor perception of preparedness for deployment are also potential cognitive risk factors for post-deployment PTSD in military personnel.[84]

Genetic risk factors may moderate the relationship between mild TBI and PTSD. Having the ε4 allele of the apolipoprotein E4 gene is associated with poorer long-term clinical outcomes following all severities of TBI than having the ε2 or ε3 alleles.[85] One study examined the relationship between APOE genotype and neurocognitive function in service members and veterans with a remote history of TBI of any severity. Those with the APOE ε4 allele performed significantly worse on tests of memory than those who did not possess the APOE ε4 allele.[86] However, TBI severity and APOE ε4 status did not show a significant interactive effect on cognitive function, and the authors concluded that one potential reason for this finding is that PTSD symptom severity may play a greater role.[86] However, some studies dispute these findings. One study examining over 130,000 veterans found no association between APOE ε4 genotype and PTSD severity or diagnosis, combat exposure severity, or comorbid TBI and PTSD.[87] Thus, more research is warranted to gain a comprehensive understanding of how APOE gene variants affect PTSD incidence and outcomes.

Multiple genes in addition to APOE may interact to confer an increased risk of PTSD following mild TBI.[50,88,89] Polygenetic risk scores, which are calculated using data from genome-wide association studies, can be used to estimate an individual's overall genetic susceptibility and risk for a disease based on its known risk variants.[90] In one study, investigators found that individuals of European descent who had the highest polygenic risk scores for PTSD had a nearly fourfold higher odds of developing PTSD during the six months after mild TBI than those with the lowest scores.[88] This finding indicates that with further study, an individual's polygenic risk score for PTSD could be used along with other clinical data to predict the need for early intervention to prevent PTSD development following mild TBI.

Finally, having other comorbidities before or after sustaining a TBI plays an important role in the risk of developing PTSD. One of the most common risk factors for developing PTSD after mild TBI is acute stress disorder, which, if diagnosed within 12 months after a mild TBI, doubles the risk of developing PTSD.[91] Other risk factors that increase the likelihood of developing PTSD or more severe PTSD symptoms in veterans included alcohol and substance misuse, smoking, history of chest pain, and chronic pain.[92,93]

Impact

Comorbid mild TBI and PTSD have been associated with a variety of adverse outcomes, including increased pain-related disability, impacting satisfaction with and quality of life.[94] Individuals with comorbid PTSD and TBI (of all severities) report lower quality of life across

all domains of health[95-97] and worse behavioral functioning.[44,97] Additionally, service members with PTSD and those who sustain a deployment-related TBI are significantly more likely to be found "not medically ready" for duty than those without PTSD or TBI.[98] Among service members and veterans with TBI, those with comorbid PTSD symptoms demonstrate lower physical, emotional, and cognitive functioning as well as more depressive symptoms.[57,99,100] Headache, suicidal impulses, dizziness, self-harm, chronic pain, substance use disorder, sleep disturbances, cumulative disease burden, photosensitivity, cardiovascular risk factors, and polypharmacy have also been documented with comorbid TBI and PTSD.[95,101-108]

Comorbid PTSD and TBI may also increase the risk of developing neurodegenerative diseases, such as Parkinson's disease,[109-111] Alzheimer's disease, Lewy body disease, other dementias, and mild cognitive impairment.[112,113] Among veterans with European ancestry, two studies have further demonstrated that the risk of Alzheimer's disease and related dementias is even higher for those with PTSD and TBI who also have the APOE ε4 genotype.[114,115] However, research leveraging neuroimaging or blood biomarkers of neurodegenerative disease have found no association of comorbid PTSD and TBI with neurodegenerative pathologies.[116-118] Thus, additional investigation is required to better understand the long-term impact of comorbid PTSD and TBI.

Comorbid PTSD and mild TBI can have an impact on social outcomes, including reduced psychosocial function, challenges operating a motor vehicle, lower return-to-work rates, and increased incidence of intimate partner violence.[119,120] Relatedly, one study showed that service members who reported being dissatisfied in their relationships with their intimate partners had worse scores on tests for PTSD symptoms of irritability, aggression, situational avoidance, and distressing dreams and flashbacks.[121] Caregivers of service member and veterans are also impacted by co-occurring PTSD and mild TBI.[122] Increased hostility and low emotional self-awareness after TBI can negatively impact caregiver quality of life, relationship satisfaction, and family functioning.[123-125] These outcomes can be partially attributed to challenges with service members reintegrating into the family following deployments.[126]

DIAGNOSTIC AND ASSESSMENT TOOLS

Diagnosis of PTSD and mild TBI based on symptoms alone can be difficult due to considerable symptom overlap and the lack of objective tools for understanding and differentiating symptom etiology. As described above, mild TBI diagnosis requires a clinician's assessment, as well as a precipitating injury that results in a loss of consciousness (up to 30 minutes), altered consciousness, or post-traumatic amnesia.[8] The Neurobehavioral Symptom Inventory and the Rivermead Post-Concussion Symptoms Questionnaire are self-reporting tools that can be used to determine post-concussive symptom severity.[127] Both instruments provide a list of symptoms (22 on the NSI; 16 on the RPQ) and ask respondents to indicate severity on a five-point scale. The NSI also has two items that invite the test-taker to name a symptom and provide a severity rating. Several factor analysis studies have been performed that seek to group symptoms to improve

interpretation of the results.[128,129] The resulting factor structures vary, but one comparative study found that, for the NSI, a three-factor structure including vestibular and somatic, cognitive, and mood and behavioral factors provided the best fit for a sample of Operation Enduring Freedom and Operation Iraqi Freedom veterans.[128] Normative tables have been created for the NSI, which may be useful in comparing post-deployment NSI questionnaires to peer-matched demographics to detect potential medical concerns.[130] However, additional studies have determined that, while the NSI is a reliable metric for determining psychological stress, it does not reliably predict changes in functioning.[131]

Neither the NSI nor the RPQ are diagnostic, in part due to the high base rate of these symptoms among non-injured populations[132] and in part because a number of symptoms on these scales are also associated with PTSD and other psychological conditions. The Clinician-Administered PTSD Scale, or CAPS, is widely used for PTSD diagnosis. The CAPS was updated to reflect revisions to the criteria for PTSD defined in the DSM-5, so the preferred version is the CAPS-5.[133] PTSD checklists for the military and civilians, known as the PCL-M and PCL-C respectively, have also been updated to the PCL-5 to reflect DSM-5 changes and are common tools for assessing symptom severity.[134] To support the analysis of changes in PTSD symptoms over time following the introduction of the PCL-5, investigators at the VA developed a crosswalk to predict PCL-5 scores using data from the PCL-C.[135] A separate study reported that predicted PCL-5 scores obtained using this method had near perfect agreement with observed PCL-5 scores in a sample of service members and veterans with TBI, suggesting this approach is applicable to this population.[136]

The 2023 *VA/DOD Clinical Practice Guideline for Management of Posttraumatic Stress Disorder* recommends that patients should be screened for PTSD annually during deployment cycles and during the first five years following separation from service.[137] The DOD includes screening for PTSD in the Post-Deployment Health Assessment (*DD Form 2796*), Post-Deployment Health Reassessment (*DD Form 2900*), and Deployed Mental Health Assessment (*DD Form 2978*). However, the most commonly used instrument in the VA and DOD is the Primary Care PTSD Screen, or the PC-PTSD-5, which is specifically designed for use in primary care settings.[138] The five questions on the screen relate to avoidance, arousal, vigilance, dissociation, and nightmares. If the patient responds “yes” to any question, the screen is considered positive, and the patient is referred for further assessment. The PC-PTSD-5 has good diagnostic utility and can accurately detect PTSD in the VA primary care setting.[139] However, one civilian study showed that it is less accurate at detecting PTSD in individuals with persistent post-concussive symptoms than the Generalized Anxiety Disorder-7.[140] The study also found that the combined use of the PC-PTSD-5 and the GAD-7 was more accurate at detecting PTSD in this sample of mild TBI patients than the PC-PTSD-5 alone.

Post-concussive and PTSD symptom instruments rely primarily on self-reporting, so most tools for assessing mild TBI and PTSD should be used in conjunction with clinician assessment. In a study using the Minnesota Multiphasic Personality Inventory-2-Restructured Form symptom validity test, many treatment-seeking veterans of Operation Enduring Freedom and Operation Iraqi Freedom were prone to exaggerate cognitive, post-

concussive, and PTSD symptom severity. These self-reported symptoms did not agree with performance on more objective measures.[141] To address this problem, many commonly used tools such as the NSI have additions like the Validity-10 scale that can help identify exaggerated symptom reports in patients with comorbid mild TBI and PTSD or other psychological disorders.[142] As individuals with mild TBI and comorbid psychiatric conditions like PTSD are more likely to fail these validity measures, it is important to take a holistic approach to evaluating their care needs.[143]

Assessments that include structured interviews can help identify lifetime history of mild TBI. The Veterans Health Administration TBI Clinical Reminder is one structured interview developed to support diagnosis of TBI specifically in veterans.[144] In addition to these interviews, researchers are exploring assessments that provide objective data on vestibular and motor function in those with PTSD and mild TBI history.[145]

Biomarkers

Researchers are investigating biomarkers to identify unique indicators of comorbid PTSD and mild TBI occurrence that could aid in the differential diagnosis of their symptoms or predict treatment response.[146] The most commonly studied include brain-derived proteins like tau; neurofilament light chain, or NfL; glial fibrillary acidic protein, or GFAP; and ubiquitin carboxyl-terminal hydrolase L1, or UCH-L1.[147] Notably, UCH-L1 and GFAP are recommended as part of the CBI-M model of acute TBI characterization (0–24 hours post-injury) and are components of common commercially available blood-based assays for TBI like the i-STAT TBI test.[18] One study measured these four proteins in service members with TBI of any severity and healthy controls.[148] The results showed that tau and GFAP levels measured within 12 months of head injury could predict the progression of PTSD symptoms at the follow-up 2 or more years after injury. However, other studies have shown conflicting findings,[149] indicating additional research is required to determine the utility of these biomarkers in predicting PTSD after TBI.

One systematic review evaluated 16 studies on genetic and peripheral biomarkers of comorbid PTSD and TBI, including 15 that specifically evaluated service member or veteran samples.[150] Of all the biomarkers examined, only the inflammatory marker interleukin-6, or IL-6, consistently correlated with comorbid TBI and PTSD status across multiple studies.[150] However, the nonspecific nature of IL-6 function challenges its use in clinical practice. Researchers have also investigated the ability of other biomarkers (including standard clinical blood tests,[151] phospholipids (a key component of cell membranes),[152] RNAs,[153] and vocal biomarkers[154]), as well as technologies like EEG[155] and MEG[156] to characterize subjects with PTSD and mild TBI, but these approaches are still being evaluated for clinical use.

NEUROPSYCHOLOGICAL MANIFESTATIONS OF MILD TBI AND PTSD

Common Neuropsychological and Neurocognitive Tests

Neuropsychological tests are used to evaluate cognition, mood, social functioning, and motivation. Commonly administered computerized neurocognitive assessment tools or NCATs for mild TBI include the Automated Neuropsychological Assessment Metric or ANAM; the Cognigram; and the Immediate Post-Concussion Assessment and Cognitive Testing or ImPACT (Table 1).[157] Of these, the ANAM and ImPACT have been cleared by the FDA specifically as tools to aid in the assessment of individuals with suspected head injury.[158] The ANAM was developed by the DOD to measure processing speed, reaction time, memory, and cognitive efficiency. The DOD requires that the fourth version, ANAM4 TBI-MIL,[159] be performed on service members within one year prior to deployment as a baseline and following a diagnosed mild TBI.[160]

For PTSD, many neurocognitive tests can be used (Table 2). The domains most commonly examined with these tests include verbal learning and memory, working memory, visual processing speed, verbal performance IQ, visual attention and task switching, and executive function.[161] When assessing comorbid occurrence, a battery of tests is used to objectively assess performance in areas affected by both mild TBI and PTSD.[162] The battery should include assessments for subjective cognitive complaints and objective measures of cognitive performance to better understand the impact of trauma-related psychopathology.[162]

Neurocognitive and neuropsychological changes can greatly affect quality of life for those with PTSD or mild TBI.[163] Differentiating cognitive impairment caused by mild TBI from that caused by PTSD is imperative for determining how to target therapeutic interventions to improve performance in comorbid groups. For example, attributing PTSD symptoms to mild TBI can reduce adherence to effective treatment protocols.[164] Neuropsychological testing can determine discrete functional changes associated with each condition. This information can allow clinicians to prescribe differential cognitive or behavioral therapy that addresses both sets of deficits.

Neuropsychological and neurocognitive tests are not indicated for diagnostic purposes; however, they do provide objective evaluations of neuropsychological manifestations of mild TBI, PTSD, and comorbid occurrence. In one study, neuropsychological test performance was found to be more robust than neuroimaging measures in differentiating distinct symptom profiles in active duty service members with mild TBI and PTSD.[165] Objective information on cognitive performance may be important for determining return to duty, treatment benefits, and other decisions. However, it is important to note that there is often discordance between objective and subjective cognitive complaints among individuals with mild TBI and PTSD.[166-169] This finding could be due to the limited sensitivity of some assessments in individuals with milder head injuries. Thus, it is crucial to consider both objective and subjective cognitive and neuropsychological complaints when developing strategies for intervention.[166,168]

Additional neuropsychological assessment tools are being tested to determine how well they evaluate comorbid mild TBI and PTSD symptoms in military samples. For example, a cognitive battery in the iPad-based NIH Toolbox has been used to examine mild TBI and PTSD symptom severity and resulting cognitive deficits in comorbid groups. This tool was able to detect greater cognitive impairment in the comorbid group than in groups with PTSD or mild TBI only.[170] The tool also enables researchers to accurately assess neuropsychological function in large samples and in conditions that require readily available testing and rapid results.[170] Though the NIH Toolbox demonstrates potential for usefulness in the military population, further research is needed to determine clinical utility.

Neuropsychological and Neurocognitive Findings: Mild TBI Only

Within 24 hours of mild TBI, decreases in neuropsychological test performance can occur in the domains of attention, language, memory, visual perception, and executive function.[171] Impairments in attention, language, memory, and executive function can also occur even six months or longer after injury.[172,173] Reaction time impairments on the ANAM appear to be sensitive to mild TBI in the active duty military population.[174] Some studies have reported that service members who have sustained a blast-related TBI show a decline in simple reaction time on the ANAM within days of injury,[175] which is associated with changes in neuroimaging metrics.[176]

Although several other studies also report lasting impairments, mild TBI patients who are months to years post-injury and do not have comorbid psychological health conditions do not consistently demonstrate poorer neuropsychological test performance than those without TBI. However, other studies have found that impairments can arise years following both blast and non-blast mild TBI.[74] These variations in the likelihood of chronic deficits may be attributed to the number of mild TBIs sustained, as a single mild TBI is not generally associated with lasting deficits while multiple mild TBIs may convey a higher risk.[177] One study of over 1,300 service members and veterans with one or more lifetime TBIs observed no significant association between the number of blast-related TBIs sustained and cognitive performance.[178] This finding indicates that factors other than TBI history may also contribute to the likelihood of cognitive decline after TBI. For example, one study reported that cognitive impairment following mild TBI was more common in older service members (25–40 years) than in younger ones (24 years and younger).[179] Thus, additional studies should aim to investigate how various demographic and injury-related factors may interact to contribute to the risk of cognitive impairment after TBI.

While cognitive impairment following TBI can occur, it is important to emphasize that recovery is possible. One study of over 1,000 service members and veterans found that those who sustained a deployment-related mild TBI consistently showed worse cognitive performance across the 5-year study period than those who did not; however, cognitive function did slightly improve by the end of the study period in the TBI group.[180] This finding highlights the value of conducting additional long-term prospective studies to evaluate the evolving and dynamic nature of TBI outcomes and identify factors associated with a higher risk of poor recovery.

Neuropsychological and Neurocognitive Findings: PTSD Only

PTSD alone is associated with decreased neurocognitive performance in several domains, especially verbal learning, processing speed, attention, and working memory, according to a meta-analysis of data from 1,779 PTSD patients including military and civilian trauma survivors.[181] These findings are consistent with neuropsychological studies showing lower performance in veterans with PTSD than in veteran controls without PTSD.[182] PTSD is also associated with impairments in episodic memory and executive function.[183,184] Severe PTSD symptoms and PTSD diagnosis are correlated with higher rates of impaired neuropsychological outcomes, including development of attention deficit hyperactivity disorder.[185,186] Together, these data suggest that PTSD and subclinical PTSD symptoms may be bidirectionally related to the cognitive impairments observed among PTSD patients with mild TBI history. The origin of these impairments cannot be determined from neuropsychological testing, however, so further studies are needed to understand how discrete factors in the constellation of PTSD symptoms can influence cognition.

Neuropsychological and Neurocognitive Findings: Comorbid Group

Several studies have shown that those with a PTSD diagnosis or significant PTSD symptoms in combination with mild TBI history performed significantly worse on neuropsychological tests than those with PTSD only, mild TBI only, or controls. This finding has been reported in service members,[187] veterans,[188] and civilians.[189] One study found that among individuals with PTSD, those with higher low-level blast exposure showed worse performance on tests of immediate and delayed recall than those with less blast exposure.[190] The study also found that PTSD and deployment-related TBI interacted to impact memory and processing speed. Similarly, other studies have shown that among service members who sustain a blast-related mild TBI, the presence of PTSD symptoms is correlated with neuropsychological deficits.[191] Impaired long-term working memory and lower cognitive flexibility have also been associated with probable PTSD in adults with TBI history.[192] In contrast, some studies report no significant neuropsychological differences between those with mild TBI history and PTSD and those with only one condition.[193] These inconsistent findings may be due to the characteristics of study participants, study design, outcomes, or other factors and suggest additional research is needed.

CHANGES IN THE BRAIN ASSOCIATED WITH MILD TBI AND PTSD

Neuroimaging

Imaging techniques provide valuable tools to examine the brain and detect alterations resulting from PTSD and mild TBI, as well as to identify changes unique to their comorbid occurrence.[194] These techniques are not yet routinely used for clinical assessments of patients, as their predictive and diagnostic capabilities require study in larger clinical samples. They do, however, reveal valuable mechanistic and neuroanatomical information that may prove to have clinical utility.

Traditional CT scans and MRI have not been able to differentiate mild TBI alone from mild TBI comorbid with PTSD. However, brain volume measurements show promise for identifying those with comorbid PTSD and mild TBI history.[195] Other imaging approaches that may warrant further study include advanced MRI techniques such as functional MRI; diffusion tensor imaging, or DTI; diffusion kurtosis imaging; and single photon emission computed tomography, or SPECT. Limited evidence shows that SPECT has potential to help evaluate those with PTSD, mild TBI, or both.[196] Fluid-attenuated inversion recovery MRI approaches have been used to characterize white matter hyperintensity in these populations.[197] DTI demonstrates mixed capabilities for matching white matter integrity to symptom severity in comorbid groups; however, it remains promising in its diagnostic and prognostic potential.[198]

MEG is a functional imaging technique that detects the magnetic signal in the grey matter produced by neuronal activity.[199] This technique has shown efficacy in detecting functional changes that occur in specific brain regions after mild TBI and can identify PTSD-specific influences on these changes in the same brain regions.[200] MEG imaging could therefore be a powerful tool for identifying unique functional changes characteristic of comorbid mild TBI and PTSD. While not currently used in routine clinical practice, further research with these techniques will contribute to greater understanding of the brain's response to TBI and PTSD.

Mild TBI Only

Uncomplicated mild TBIs are characterized by the presence of diffuse injuries that cannot be detected on CT. They typically involve areas of damage scattered throughout seemingly intact brain structures. This damage often presents as widespread injury to brain cells, disruption of white matter, and changes in blood vessels, which are difficult to detect with standard imaging methods.[201] DTI and similar techniques can detect diffuse axonal injuries resulting from mild TBI.[202] For example, a meta-analysis of DTI studies performed on patients exposed to blast mild TBI showed persistent changes in white matter integrity in several prominent tracts throughout the brain, as well as cortical thinning.[203] A separate study found that multiple brain regions can show white matter damage after mild TBI.[204] In another study, the extent of white matter damage was also correlated with the severity of post-concussive symptoms.[205] Changes in white matter can greatly alter the connectivity between brain regions, resulting in functional impairments.

Mild TBIs, including those sustained during deployment, can cause changes to the function and structure of the hippocampus.[206,207] Other changes in brain structure and function are thought to contribute to impairments in executive function that are commonly observed in patients with mild TBIs.[208,209] Mild TBI can also damage the thalamus, which is correlated with worse symptoms and poor recovery.[210] The thalamus plays roles in pain, sleep, fatigue, and cognition, which may contribute to post-traumatic headache and disturbances in sleep and cognition following mild TBI.[211]

PTSD Only

Imaging studies have identified brain regions that are altered with PTSD. Three primary brain regions have frequently been investigated, which include the amygdala, hippocampus, and medial prefrontal cortex.

The amygdala is thought to play a role in behavioral and physiological responses to fear, and many studies have indicated that changes in its activity and structure are a hallmark of PTSD. Amygdala volume is decreased in combat veterans with PTSD, which has been linked to hyperresponsiveness and subsequent anxious arousal (a common symptom).[212] Increased or decreased activation of the amygdala does not seem to be uniform across all PTSD patients.[213] Rather, increased or decreased amygdala activity may be associated with specific symptoms.[214]

The hippocampus is primarily responsible for orchestrating normal learning and memory. In PTSD, increased hippocampal activity is associated with reliving symptoms and impaired episodic memory.[213] Structural connectivity between the left and right hippocampus may also be impacted by PTSD.[215] Structural imaging studies have shown that decreased hippocampal volume may also be associated with PTSD.[216] However, one study of veterans with PTSD reported that smaller volume in specific regions of the hippocampus at the beginning of the study was associated with fewer symptoms two years later.[216] This finding was observed even after adjusting for treatment and combat exposure. Thus, more research is needed to understand the relationship between hippocampal structure and PTSD symptoms.

The medial prefrontal cortex is responsible for processing and encoding emotional information and using that information to add context to memories. Reduced activity of the ventromedial prefrontal cortex, which is linked to the experience and regulation of motion, is observed in PTSD.[217] This decrease in activity seems to be an acquired characteristic caused by PTSD.[218] Smaller medial prefrontal cortex volumes are also a hallmark of PTSD.[219]

Comorbid Group

Many studies have aimed to examine the amygdala, hippocampus, and medial prefrontal cortex to determine if key pathological features of mild TBI and PTSD are worsened by comorbid occurrence. A study that explored the impact of PTSD on cortical structural integrity in a group of veterans showed a potential dose-response relationship in individuals with comorbid severe PTSD and deployment-related mild TBI.[220] Notably, however, the study also found a stronger association between age and cortical changes than between PTSD and cortical changes. Decreased cortical thickness has been reported in individuals diagnosed with PTSD with a history of mild TBI.[221] In two studies of veterans, those with comorbid PTSD and TBI exhibited an increase in amygdala volume that was not apparent in the TBI-only group.[195,222] However, other studies have shown that amygdala volume decreases with PTSD alone,[223] which could indicate that comorbid mild TBI and PTSD may have a distinct phenotype detectable through brain imaging. To further distinguish mild TBI

and PTSD, future studies could evaluate differences in imaging metrics within brain regions associated with the cognitive capabilities assessed by neurocognitive tests to identify features unique to comorbid PTSD and TBI.

The current view of how changes in brain structure and function can uniquely underlie symptom manifestation with comorbid PTSD and TBI is that both these conditions alter the ability of networks of brain structures to communicate.[224] This view is partially supported by one systematic review, which found trends suggesting that TBI-related PTSD is associated with disrupted white matter tracts, as well as changes in whole-brain networks or resting-state MEG connectivity.[225] Other studies have also shown widespread changes in white matter integrity in those with mild TBI and PTSD symptoms.[226] White matter integrity changes observed in mild TBI are pivotal, as they alter the connectivity between structures, resulting in a higher likelihood of developing behavioral and cognitive symptoms.[227] These changes occur in white matter tracts that connect regions important for PTSD symptoms, including the corpus callosum and tracts connecting limbic system structures, such as the hippocampus and amygdala.[228] In mild TBI patients, more severe PTSD symptoms are linked to greater damage in these tracts.[229]

There are more regions with changes in white matter integrity in those with comorbid mild TBI and PTSD than in those with PTSD or mild TBI alone.[230] These findings suggest that, while PTSD is associated with overt structural differences, the white matter changes associated with mild TBI are an insidious contributor to increased PTSD symptoms. Similar overlapping patterns of reduced resting-state functional connectivity have also been reported in regions involved in working memory in those with mild TBI and PTSD.[231] One study examining a group of military veterans and civilians found that older participants with comorbid mild TBI and PTSD showed greater variability in functional connectivity across several brain networks than older controls, which may have contributed to hypervigilance observed in the comorbid group.[232] Furthermore, PET scans suggest altered metabolic function in brain regions involved in emotional processing in mild TBI patients with persistent and significant comorbid PTSD. PET scans indicate that changes in other brain regions involved in similar functions are associated with hyperarousal and post-concussive symptoms.[233] Changes in brain structure and function detected with comorbid mild TBI and PTSD have also been associated with other symptoms, including sleep disturbances,[105,234] fatigue,[235] cognitive impairment,[236] and autonomic nervous system symptoms.[237]

TREATMENT IMPLICATIONS

Clinical Practice Guidelines

Several military-relevant guidelines on the treatment of mild TBI and PTSD are available (Table 3). The *VA/DOD CPG for the Management and Rehabilitation of Post-Acute Mild TBI* focuses on symptom management, education, and evidence-based diagnosis and treatment of possible comorbid conditions.[8] The *VA/DOD CPG for the Management of PTSD and Acute Stress Disorder* emphasizes a collaborative treatment approach, manualized trauma-focused psychotherapy, and recognition of possible comorbid conditions.[137] Prescribing

medication for patients with comorbid TBI and PTSD is challenging as some medications can exacerbate the symptoms of one condition while effectively treating the other.[238] Thus, special attention is required during integrated mild TBI and PTSD care. It is also critical to consider the specific PTSD subtype and symptom presentation to develop a treatment plan that is tailored to the needs of the individual patient.[239]

Difficulties with patient retention can challenge effective treatment.[240] One of the most common barriers to treatment compliance is the deficit in executive function that may exist in patients with comorbid mild TBI and PTSD.[241] Therefore, greater executive functioning at baseline has been associated with improvements in quality of life following participation in cognitive processing therapy, or CPT.[242] For individuals with impairments in executive functioning, calendars, worksheets, and session modifications may help promote adherence.[243] In addition, problems with emotional regulation, impulse control, and symptom severity from PTSD as well as the stigma related to seeking treatment can limit the patient's ability to engage in treatment or lead to dropping out.[244] These cognitive and psychological barriers can result in poor treatment outcomes. Therefore, the efficacy of PTSD and mild TBI treatments should also be evaluated with consideration given to the likelihood of compliance with treatment recommendations.

Both nonpharmacological and pharmacological approaches can be useful for treating PTSD and TBI. In one systematic review of 26 studies on treatments for comorbid mild TBI and PTSD, CPT and other kinds of cognitive behavioral therapy reduced PTSD symptoms in patients when combined with other treatments.[245] Pharmacological agents showed some promise in treating chronic PTSD. Novel treatments like vestibular rehabilitation and eye movement desensitization and reprocessing or EMDR are promising for comorbid TBI and PTSD but require further study.[246] The efficacy of many of these treatments has not been adequately evaluated with comorbid PTSD and mild TBI, and most studies focus on one of the two conditions. Given the unique circumstances resulting from comorbid occurrence, these approaches may not adequately address the overall symptom burden.

Nonpharmacological Interventions

One systematic review on psychotherapy for military-related PTSD found that the treatments supported by the most evidence were CPT, trauma-focused exposure therapies, and EMDR.[247] While other PTSD treatments are well-supported by evidence, fewer studies have been performed with comorbid PTSD and mild TBI patients. Studies of prolonged exposure or PE therapy,[164] CPT,[248] and mindfulness intervention[249] have had positive results. Several studies show that cognitive rehabilitation interventions can reduce psychiatric symptoms.[250] Combined strategies for administering therapies to better address comorbid TBI and PTSD are currently being explored. One such therapy is the SMART-CPT approach, which integrates the compensatory cognitive training aspects of Cognitive Symptom Management and Rehabilitation Therapy with CPT. A randomized, controlled trial found that while both CPT and SMART-CPT produced nearly equivalent reductions in PTSD and post-concussive symptoms, SMART-CPT was better able to improve learning and memory, attention, and problem solving.[251] Additionally, SMART-CPT resulted in improvements in life satisfaction,

family and health outcomes, and daily activities similar to those resulting from CPT. SMART-CPT can also be administered in less time than both treatments separately.[251]

Another strategy involves intensive care programs that utilize an interdisciplinary approach to treat PTSD symptoms in service members with TBI. Qualitative analyses revealed that service members and veterans with chronic TBI prefer multidisciplinary care models that integrate mental health treatment; thus, using these models may reduce stigma that can be associated with PTSD or mental health care.[252] One example is a two-week intervention known as the Home Base Intensive Clinical Program. Home Base is a national nonprofit organization that provides mental health services to military service members, veterans, and their families. The ICP utilizes what is known as a massed care approach, combining PE, CPT, or cognitive rehabilitation for trauma-focused treatment. Individuals complete both core programming and individualized therapy.[253] At discharge from the program, service members and veterans with TBI reported decreased PTSD and post-concussive symptoms in one study.[253]

Similar programs for service members with comorbid TBI and PTSD are available through the National Intrepid Center of Excellence and Intrepid Spirit Center.[254,255] The four-week NICoE intensive outpatient program has been shown to significantly reduce neuropsychological and behavioral symptoms in service members with mild TBI history and comorbid mental health conditions, including PTSD symptoms. One study that evaluated the effectiveness of the four-week NICoE intensive outpatient program measured symptoms at program discharge in 1,271 participants, though approximately less than 15% of participants responded to follow-up inquiries at 1-, 2-, and 3-months post-treatment.[256] While these programs aim to be comprehensive, they are time-intensive, lack standardized administration, have not been evaluated against a control intervention, and have a limited amount of data on long-term outcomes. These gaps highlight opportunities for future research to improve treatment programs.

A form of cognitive behavioral therapy known as stress inoculation training, or SIT, has also shown efficacy in treating comorbid mild TBI and PTSD symptoms. A study that implemented SIT in a group of veterans with comorbid mild TBI and PTSD found that it effectively reduced PTSD symptoms and improved self-reported concentration and engagement in valued or functional activities in daily life.[257] SIT is recommended not as a replacement for primary treatments, but to support and enhance CPT and PE therapy.[257] Improvement in cognition and emotional disturbance has also been seen in the goal-oriented attentional self-regulation, or GOALS, cognitive rehabilitation training program.[258] One randomized controlled trial in veterans compared GOALS training to brain-health education training. Participants who completed GOALS showed a decrease in PTSD symptoms and significant improvements in attention, executive functioning, mood disturbances, and complex functional task performance.[258] The primary target of GOALS training is to focus on improving self-regulation and cognitive control to achieve personalized goals. Thus, applying the skills learned in this training can have a considerable positive impact on quality of life.[258]

Repetitive transcranial magnetic stimulation, a non-invasive brain stimulation technique, is also being explored as a potential treatment for comorbid mild TBI and PTSD.[259] Some have

proposed rTMS may promote cognitive restoration after TBI, particularly when used in combination with behavioral interventions.[260] A review of all rTMS studies completed between 2002 and 2018 showed that, when combined with psychotherapy, high-frequency rTMS over the dorsolateral prefrontal cortex or other frontal regions effectively alleviated depressive symptoms associated with PTSD or core PTSD symptoms, respectively.[261] However, optimal dosing and session protocols remain unclear.[261] In one study, when rTMS was applied at low frequency to the dorsolateral prefrontal cortex, it alleviated hyperarousal resulting from comorbid anxiety. Subsequent studies have shown it can alleviate symptoms in service members and veterans with comorbid TBI and PTSD.[262] These studies have also observed benefits by targeting regions that may be more directly involved in PTSD symptoms, including the amygdala.[263]

As other studies report wide variability in responses to rTMS,[264] some researchers have proposed using personalized rTMS strategies to improve efficacy. These include alpha-guided rTMS, or α-rTMS, and rTMS guided by neuroimaging. For example, α-rTMS involves tailoring the frequency of the treatment to that of an individual's alpha band, which is a frequency of brain activity observed on EEG that supports cognitive processes like working memory.[265] One 2025 preliminary study showed that α-rTMS significantly decreased both self-reported TBI and PTSD symptoms in a cohort of 33 special operations forces personnel.[266] Another study also showed a significant reduction in PTSD and depression symptoms in a group of 18 SOF personnel with TBI history.[267] Additionally, some have observed that certain neuroimaging features can predict response to rTMS and can be used to tailor treatment.[259] However, studies on these approaches often lack control groups, making it difficult to come to definite conclusions on efficacy.

Researchers have also examined the efficacy of a variety of other nonpharmacological interventions, including music therapy,[268] yoga,[269] and others, for managing symptoms associated with PTSD. While these studies have shown benefits, these studies have methodological concerns, such as small sample sizes and lack of control conditions for comparison. Thus, current evidence is insufficient to determine whether these benefits would generalize to the broader population of service members with PTSD or comorbid PTSD and TBI. More testing is required to determine whether various nonpharmacological interventions will be efficacious treatment options leading to lasting clinically relevant outcomes.

Pharmacological Interventions

Though psychotherapy is the first-line treatment for PTSD, a study of 207,354 adults with TBI observed low psychotherapy participation, and psychotropic medication was more commonly used for individuals diagnosed with anxiety or PTSD post-TBI.[270] Antidepressants have been widely studied as a potential treatment for PTSD. SSRIs and SNRIs, such as sertraline and venlafaxine, respectively, are the first line of prescribed medications for PTSD. They have been shown to effectively reduce symptoms in multiple clinical trials.[271] Tricyclic antidepressants and MAOIs have also been tested for alleviating PTSD symptoms and have

shown some efficacy, although adverse effects make these medications less desirable candidates for therapeutic interventions.[272]

Beta blockers such as prazosin have yielded both negative and positive results in clinical trials. While some studies have shown that prazosin can effectively reduce post-traumatic nightmares, avoidance, and hypervigilance, others have found no difference between prazosin and placebo-treated groups in symptom severity.[273] Propranolol is also a potential treatment for PTSD symptoms, but the data generally do not support its efficacy as a stand-alone treatment.[274] One randomized controlled trial found that mifepristone also did not significantly reduce symptoms relative to placebo.[275] A different randomized control trial suggested methylphenidate (a central nervous system stimulant) can reduce PTSD, depression, cognitive, and post-concussive symptoms in a mixed military and civilian population with mild TBI, PTSD, or both,[276] but larger randomized control trials at multiple sites are needed to confirm these findings. Other classes of drugs, such as anticonvulsants or mood stabilizers, antipsychotics, benzodiazepines, and psychedelics have also been considered as potential therapies. However, these drugs have either not been effectively evaluated in large randomized clinical trials, or have shown serious adverse effects, minimal efficacy, or both, making them undesirable candidates for the treatment of comorbid mild TBI and PTSD.[272]

Factors Protective Against PTSD Symptoms

One study of factors that are protective against self-harm found patients who reported having personal protective factors (such as social competency and positive temperament), social protective factors (such as social support in the form of family, colleagues, and community connection),[277] and other factors (including pets and hobbies) were less likely to be diagnosed with PTSD.[278] A study of veterans showed that higher dispositional optimism and higher levels of community integration also protected against PTSD.[279] Resilience is another important factor associated with outcomes after TBI and reduced PTSD symptoms after injury.[238,280] As mentioned above, longer durations of post-traumatic amnesia are associated with a reduction in the development of PTSD.[189] This finding explains why those with moderate or severe TBI associated with prolonged loss of consciousness are less likely to develop PTSD than those with mild TBI.

CONCLUSION

Substantial evidence demonstrates that comorbid TBI and PTSD can considerably impact the function and psychological well-being of service members and veterans. Military providers treating service members and veterans with PTSD and comorbid mild TBI are often faced with complex decision-making as these patients present with more severe or persistent symptoms that are resistant to treatment than individuals diagnosed with only one of these conditions. Research shows that standard PTSD treatments can help with the main PTSD symptoms. However, treatments that address the challenges of both conditions together are needed. Promising research with imaging, blood, and other fluid biomarkers is ongoing and has potential to guide management and clinical decision-making in the future.

Further research is needed to identify more effective diagnostic and assessment tools, treatment options, and prognostic tools to benefit patients with PTSD who have a history of mild TBI.

TABLES

Table 1: Mild TBI Clinical Tools

Tool	Assessment Type	Domain Assessed	VA/DOD Specific (Y/N)
Veterans' Health Administration TBI Clinical Reminder	Screening	Symptoms	Y
Automated Neuropsychological Assessment Metric 4 TBI-MIL	NCAT	Cognitive function	Y
Cognigram	NCAT	Cognitive function	N
Immediate Post-Concussion Assessment	NCAT	Cognitive function	N
Canadian CT Head Rule	Screening	Multiple domains	N
Military Acute Concussion Evaluation 2	Screening	Multiple domains	Y
New Orleans Criteria	Screening	Multiple domains	N
Neurobehavioral Symptom Inventory	Self-report	Symptoms	N

Table 2: PTSD Clinical Tools

Tool	Assessment Type	Domain Assessed	VA/DOD Specific (Y/N)
Minnesota Multiphasic Personality Inventory	Self-report	Personality	N
Post-Deployment Health Assessment	Assessment	Self-reported symptoms	Y
Post-Deployment Health Reassessment	Assessment	Self-reported symptoms	Y
Clinician-Administered PTSD Scale	Assessment	Symptoms	N
Deployed Mental Health Assessment	Assessment	Symptoms	Y
Primary Care PTSD Screen	Screening	Symptoms	N
PTSD Checklist — Military Version	Self-report	Symptoms	Y
PTSD Checklist — Civilian Version	Self-report	Symptoms	N
Rivermead Post-Concussion Symptoms Questionnaire	Self-report	Symptoms	N

Table 3: Military Relevant Clinical Recommendations/Clinical Practice Guidelines

CR/CPG	Website Address	Last Revised
Military Acute Concussion Evaluation 2	health.mil/MACE2	2021
VA/DOD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury	healthquality.va.gov/guidelines/rehab/mtbi/index.asp	2021
VA/DoD Clinical Practice Guideline for Posttraumatic Stress Disorder	healthquality.va.gov/guidelines/MH/ptsd/	2023
Traumatic Brain Injury Center of Excellence Clinical Recommendation on Neuroimaging Following Concussion/Mild Traumatic Brain Injury: Guidance for the Primary Care Manager	health.mil/Neuroimaging-mTBI-CR	2024

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