RESEARCH REVIEW ON PAIN AND TRAUMATIC BRAIN INJURY

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PURPOSE

The purpose of this research review is to summarize peer-reviewed scientific literature on pain associated with traumatic brain injury (TBI) in the military, including its characteristics, risk factors, comorbidities, effects on recovery, pathophysiology, evaluation, and treatment.

Information in this research review is current as of July 2024 and is subject to change given emerging research and evidence.

BACKGROUND

TBI is a signature injury of modern war, and in the military population, blast exposure has become a more common cause of TBI than penetrating head impacts and injuries due to rotational acceleration of the head.[1-6] In the military, most TBIs are classified as mild, with a Glasgow Coma Scale score of 13–15, confused or disoriented state lasting less than 24 hours, loss of consciousness for up to 30 minutes, and/or memory loss lasting less than 24 hours. Despite the often subtle nature of mild TBI (mTBI), a considerable proportion of individuals with mTBI experience long-term postconcussive symptoms, such as disturbed cognitive function, mood, and sleep, as well as somatic symptoms, which include pain.[7-9] Research on quality of life after TBI suggests that pain associated with the injury may have a central role in disability, recovery, and return to productivity and work after TBI.[10-13]

Generally, pain is defined as an unpleasant sensory and emotional experience associated with—or resembling that associated with—actual or potential tissue damage.[14] Based on this definition, pain is a subjective and multidimensional phenomenon that differs considerably across individuals. An estimated 52% of all civilians with TBI and 43–81% of individuals with TBI in the military experience pain symptoms,[15,16] which includes neuropathic, nociceptive, inflammatory, centralized, or psychogenic pain (Table 1).[17-19] Acute pain occurs within the first seven days of the injury and resolves within three months,[20,21] and research suggests pain during this period is primarily due to physical, nociceptive processes rather than psychological factors.[22] In contrast, pain that persists or recurs for longer than three months is considered chronic,[21,23] and many studies indicate that chronic pain following TBI involves a combination of molecular and neuropsychological mechanisms, leading to complex interactions between pain and other TBI outcomes.[24] These interactions complicate the evaluation and treatment of pain after TBI and have distinct implications for recovery in active duty military personnel and veterans.[20,25,26]

PAIN AFTER TBI AND ASSOCIATED RISK FACTORS

Types of Pain after TBI

Research on pain associated with TBI has largely focused on chronic pain, leading to an improved understanding of its manifestations and potential risk factors. Chronic pain can be categorized as nociceptive, neuropathic, or mixed. Nociceptive pain involves mechanical disruption to the skin or muscle tissue and is the result of an inflammatory response to an injury.[20,27] Neuropathic pain is somatic referred pain caused by a lesion or disease of the central somatosensory nervous system.[19,28] Mixed chronic pain can involve both nociceptive and neuropathic components.[27] Notably, chronic pain associated with TBI can result not only from

the head trauma itself, but also from bodily trauma sustained during the incident that resulted in a head impact, such as a vehicle collision, fall, or exposure to an injurious level of blast overpressure.[20]

Persistent posttraumatic headache is the most common postconcussive symptom and the most frequently reported form of chronic pain among military service members.[29-31] One study of over 5,000 service members returning from Iraq or Afghanistan found that almost 98% of those who sustained a mTBI reported having headaches during the last three months of deployment; posttraumatic headache that developed within the first four weeks after trauma limited service members' ability to perform their usual duties in 37% of these cases and also resulted in more frequent sick call visits than nontraumatic headache.[32] Due to its high prevalence and complexity, persistent posttraumatic headache after TBI is now classified by the International Classification of Headache Disorders (ICHD) as a unique form of secondary headache lasting for more than three months after head trauma.[33] The ICHD also specifies that the headache must have developed within seven days of the injury to be considered secondary to TBI.[33] The *2023 Department of Veteran Affairs (VA) and Department of Defense (DOD) Clinical Practice Guideline (CPG) for the Management of Headache* utilizes the ICHD definition of persistent posttraumatic headache and characterizes this condition as a headache attributed to traumatic injury of the head, neck, body, or any combination of these areas.[21]

While headache is the most common form of chronic pain associated with TBI, cases of chronic neck, shoulder, back, and limb pain have also been reported in both military and civilian TBI patients.[16,24,34-39] One retrospective study of individuals who sustained a moderate-to-severe TBI 15 or more years prior to the study and were between ages 16 and 28 at the time of injury found that 79% reported experiencing musculoskeletal pain, defined as pain, stiffness, or aching around a joint.[40] Back pain persisting 10 years after moderate-to-severe TBI was reported in 7.5% of patients in a study of over 400 participants.[41] A recent study using data from over 1,700 individuals enrolled in the civilian arm of the TBI Model Systems (TBIMS) longitudinal study on moderate-to-severe TBI reported that pain was most prevalent in the back (65%), legs or feet (61%), shoulder (48%), head (47%), and neck (45%); additionally, 44% experienced pain daily, 24% experienced pain several times a week, and 32% reported constant pain.[42] Photosensitivity and ocular pain have also been reported to occur along with other chronic pain symptoms after TBIs of all severities.[43,44] However, more studies are needed to obtain more accurate estimates of the proportion of individuals who develop extracranial forms of chronic pain after TBI.

Injury Characteristics Associated with Post-TBI Pain Symptoms

Although the development of persisting pain after TBI is difficult to predict, associations between the incidence of chronic pain after TBI and features of the initial injury have been reported.[45] Two recent studies investigating mTBI symptoms in U.S. Marines revealed that blast-related mTBI was significantly associated with more frequent reports of neurological and musculoskeletal symptoms, including pain, than impact-related mTBI;[46,47] similarly, another study of U.S. Marines showed that individuals who sustained blast-related TBIs were significantly more likely to report headache within 30 days of returning from deployment than those who sustained impact-related TBIs.[46-48] However, a separate study of service members who were treated at polytrauma rehabilitation centers did not observe a significant difference in the incidence of pain between service members who sustained TBIs of any severity from injurious

levels of blast exposure and those with TBIs from other causes,[49] suggesting that factors other than the mechanism of injury may contribute to pain symptoms after TBI.

Other characteristics that may be associated with chronic pain after TBI include features of the initial injury, deployment-related TBI, and a history of multiple TBIs. Those who experience more severe pain at the time of the initial injury have been found to be significantly more likely to develop chronic pain after mTBI in a recent meta-analysis[37] and in another study of over 100 individuals with non-severe TBI.[50] Additionally, loss of consciousness at the time of the injury has been associated with an increased risk for chronic pain following TBI of any severity,[5,51,52] but presence and duration of retrograde amnesia after mTBI have not been found to be associated with pain symptoms.[53,54] Members of Special Operations Forces (SOF), who exhibit an elevated risk of TBI due to inherent occupational risks, were also found to more frequently report chronic pain after moderate-to-severe TBI than those in conventional forces in a recent TBIMS study.[55] Mild TBIs and moderate-to-severe TBIs sustained during deployment were also found to be significantly associated with back pain in veterans.[39] Additionally, studies of repetitive head impacts in civilian athletes and military service members have revealed that individuals with a history of multiple mTBIs are more likely to report pain symptoms and to report more severe pain than those who sustain one TBI.[56-59]

The majority of studies investigating the relationship between TBI severity and incidence of chronic pain have shown that mTBI is associated with a greater incidence of chronic pain than moderate-to-severe TBI.[15,60,61] For example, one meta-analysis including over 4,200 individuals reported that the prevalence of chronic pain was 75% in those with mTBI, while that in individuals with moderate-to-severe TBI was 32%,[15] and these rates are consistent among different studies.[15,60,61] It is unclear why mTBI is associated with a higher prevalence of chronic pain, but some investigators speculate that those with more severe TBIs may have difficulty reporting or processing their symptoms due to memory or language deficits or executive dysfunction.[15,62] They also may be more likely to use potent analgesics, thus reducing self-reported pain.[63,64]

However, some studies have reported a higher prevalence of chronic pain during the first year after injury in those who sustained more severe TBIs[65,66]; one study of over 100,000 veterans observed that 59% of those with mTBI experienced chronic pain, while the prevalence of chronic pain was 64% in those with moderate-to-severe TBI, but whether this difference was statistically significant was not reported.[65] The authors of this study speculate that this discrepant finding may be related to their reliance on pain diagnoses rather than self-report, and the study population, which included young veterans who predominantly incurred blast-related TBIs and exhibited comorbid depression and posttraumatic stress disorder (PTSD). Additional studies are needed to reach consensus on the relationship between TBI severity and chronic pain, particularly in the military population.

Individual Characteristics Associated with Post-TBI Pain Symptoms

Many studies have investigated the demographic risk factors associated with chronic pain after TBI. Most studies have reported a higher incidence of pain in females after mTBI[67-69] and sex differences in pain localization after TBI of any severity.[38] However, some studies dispute this finding, showing no differences in pain intensity between males and females after mTBI[38,70] or

that initial sex differences in pain symptoms disappeared at 6–12 months after mild-to-moderate TBI.[71] Most studies on racial differences in post-TBI pain symptoms report higher pain intensity among nonwhite individuals with TBIs of all severities.[67,69,72-74] Racial differences in pain intensity were also found to increase with age in a civilian TBIMS study of 621 participants with moderate-to-severe TBI.[74] Another study reported older age and probable mTBI as correlates of chronic pain in military personnel who sustained blast exposure.[75] However, another study reported no differences in back pain 10 years after moderate-to-severe TBI between civilians older than 50 and those younger than 50,[41] suggesting chronic pain after TBI in older individuals may be related to blast exposure.

To date, studies on the lifestyle and genetic factors that may confer an increased risk of chronic pain after TBI have been limited. In one study on the influence of self-reported physical activity and pain symptoms one month after mTBI, moderate physical activity, walking, and total physical activity one to two weeks post-injury predicted greater pain inhibitory capacity.[76] Sedentary behavior during recovery was also associated with worse pain inhibition after TBI and greater pain catastrophizing,[76] which is a coping style involving exaggerated negative appraisal of actual or anticipated pain and feelings of helplessness in the context of pain.[77] Regarding genetic factors, one study reported a greater incidence and severity of pain in concussed athletes with the ε4 allele of the apolipoprotein E gene,[78] which is involved in neuronal repair and synaptogenesis after injury.[79] Since the ε4 allele has a disadvantageous effect on neuronal repair,[80] this finding suggests a potential mechanism through which tissue damage sustained during injury mediates pain symptoms in individuals with this allele. Another study identified two haplotypes of the gene encoding brain-derived neurotrophic factor (BDNF), an important mediator of neuroplasticity, that were associated with the development of chronic pain one year after mTBI.[12] The identification of other lifestyle and genetic factors associated with the development of chronic pain after TBI could improve the prediction of long-term pain symptoms during the clinical evaluation of those with TBI and lead to novel avenues for preventing chronic pain in these individuals.

Collectively, research to date demonstrates heterogeneity in the types of pain experienced after TBI, which is not limited to posttraumatic headache. These studies also suggest the development of chronic pain after TBI may be influenced by both the mechanism and characteristics of the initial injury, as well as specific demographic, lifestyle, and genetic factors. While this work has enabled an improved understanding of potential predictors of chronic pain after TBI, several limitations of these studies should be considered. First, only a few studies have investigated each of the relationships discussed above, and some used relatively small sample sizes, limiting the generalizability of the findings. Additionally, the study population may affect the identified associations between individual or injury characteristics and chronic pain after TBI; for example, the limited amount of data from females and racial minorities in the military may challenge the study of the demographic factors associated with chronic pain after blast-related TBI.[74] Future research should aim to address these limitations to reach a more precise understanding of the factors that confer an increased risk of developing chronic pain after TBI.

CHRONIC PAIN, OTHER TBI OUTCOMES, AND RECOVERY

Many researchers have advocated for the conceptualization of TBI as a dynamic, chronic disease rather than an isolated event,[81-83] since TBIs can initiate a decline in function lasting years after

the initial insult.[83,84] Pain contributes to this functional impairment and is particularly challenging for those undergoing rehabilitation after TBI as it can cause them to resist mobilization efforts due to activity-related increases in pain.[85] Chronic pain after TBI thus impacts an individual's ability to return to work and productivity.[10,11,42,86,87] Pain may also affect service member return to duty and on the job performance by mediating other TBI symptoms. For example, in a study using data from 322 participants enrolled in the Long-term Impact of Military-relevant Brain Injury Consortium Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) prospective longitudinal study, researchers developed various models to investigate how pain influenced postural stability and balance.[88] In one model, sustaining three or more mTBIs resulted in a significant increase in pain interference, which measures the extent to which pain restricts engagement with physical, cognitive, emotional, and recreational activities.[89] In this study, each point increase in pain interference also decreased the composite equilibrium score, reflecting increasingly impaired balance.[88] Several other studies have similarly demonstrated significant associations between pain interference or the incidence of pain and reduced life satisfaction,[90,91] as well as lower health-related quality of life after TBI.[92,93]

Additionally, studies have revealed that the impact of chronic pain on recovery and quality of life after TBI is variable across individuals and can change over time. A recent TBIMS study utilized extreme phenotyping, a method of classifying those at the extreme ends of a specific characteristic, to identify the factors associated with low versus high pain interference after moderate-to-severe TBI; the results showed significant differences in all measures of concurrent function between the groups, with those in the low-interference group experiencing better function.[94] Another study observed five distinct longitudinal patterns phenotypes of pain in a cohort of over 40,000 post-9/11 veterans who sustained TBIs of any severity.[95] The pain symptoms associated with these five phenotypes impacted patient life activities to different degrees, were associated with different treatments, and either remained stable in intensity or worsened over five years. Other smaller studies have revealed that moderate-to-severe TBI patients show significant improvements in the bodily pain component of quality-of-life scores in the years after TBI, indicating that pain symptoms in some individuals can resolve after TBI and may have less of an impact on quality of life over time.[84,96]

The complexity of pain in TBI patients likely contributes to the differences in findings across studies on how pain affects quality of life after TBI. Pain in those with TBI is often accompanied by prolonged neurocognitive, psychiatric, or somatic symptoms, and the interactions among these symptoms may contribute to how pain affects recovery. For example, in one study of over 1,000 elderly adults, investigators found that the association between TBI and functional and physical impairment was no longer significant after adjusting for neuropsychological disorders,[82] emphasizing the important role of mental health in patient recovery. The interaction of pain, TBI, and psychiatric symptoms—also known as the polytrauma clinical triad—is particularly pronounced in military service members and veterans and has been studied extensively in these populations.[3,20,97,98] Additionally, sleep disturbances, which are also prevalent in military personnel, can affect the influence of pain on recovery from TBI.[99]

The Relationship between Neuropsychiatric Disorders and Pain after TBI

In the military population, the most common neuropsychiatric disorders shown to interact with pain during TBI recovery include PTSD and depression. PTSD is particularly common among

military personnel, and some researchers have proposed "consequence of war syndrome" as a model for describing how the inherent stresses of deployment, difficulties reintegrating into life after deployment, PTSD, and other postconcussive symptoms interact to affect service member quality of life.[100-104] One study of over two million active duty service members reported that the prevalence of comorbid PTSD and chronic pain in individuals who sustained TBIs of any severity was 5.99 per 1,000 individuals.[105] In another study focusing specifically on Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) veterans, the cooccurrence of these three conditions over a three-year period was 6.0%.[106] These findings suggest the polytrauma clinical triad is relatively common, but its incidence may depend on the specific experiences or duties of the service member.

Regarding the interaction between pain and PTSD, one study of over 300 OEF/OIF/OND veterans who sustained mTBIs revealed that those who had PTSD also reported significantly higher pain intensity than those without PTSD.[107] Consistent with this finding, in a sample of 1,500 service members enrolled in the LIMBIC-CENC study, those who had both mTBI history and PTSD had the highest pain interference scores and the most individuals reporting severe pain.[36] Recent TBIMS studies have similarly reported significant interactions between pain incidence and interference and PTSD among other psychosocial outcomes.[108,109]

Several other large studies (N>100) have also found that PTSD severity in service members and veterans who have sustained TBIs is significantly associated with pain interference.[110-113] However, in one study of OEF/OIF/OND veterans, individuals with PTSD with or without mTBI reported significantly worse psychosocial functioning than those with mTBI alone and those with neither mTBI nor PTSD; importantly, this finding was still significant after adjusting for the severity of chronic pain, suggesting that chronic pain is not always a major contributor to the psychosocial impairment associated with PTSD.[114] Distress tolerance, or an individual's perceived ability to endure negative emotional states, has been proposed as one possible contributor to these variable outcomes and has been found to significantly affect PTSD severity, quality of life, and other functional outcomes in combat veterans.[115] Specifically, as distress tolerance improved, posttraumatic stress symptom severity and sleep quality improved.[115]

Depression is also an important contributor to quality of life after TBI and has been associated with pain symptoms in both civilians and service members who sustain head injuries.[91,116] One study of 83 veterans with TBI of any severity found that while pain was significantly associated with employment status, this relationship was mediated by depressive symptoms.[117] Consistent with this finding, in 146 individuals with moderate-to-severe TBI undergoing inpatient rehabilitation one year after injury, depressive symptoms were significantly associated with pain one year after TBI, even after adjusting for demographic and injury characteristics.[67] However, evidence suggests that the relationship between pain and depression may be bidirectional, as pain has been found to independently contribute to and predict depressive symptoms after TBI of any severity.[118,119] Studies have also found connections among pain, PTSD, and depression in individuals who have sustained a TBI.[120] For example, the risk of chronic pain among veterans was found to be higher in individuals who had sustained a TBI and had both depression and PTSD than in those with no TBI, PTSD, or depression in one study.[65]

Pain symptoms have also been shown to interact with other mood and cognitive symptoms of TBI. For example, some studies have observed that pain symptoms after TBI of any severity are

significantly associated with feelings of anger and violent impulses.[121-123] A small study of combat veterans reported that worse executive function and slowed processing speed were associated with pain catastrophizing in individuals who sustained mTBIs.[124] Pain was also shown to be associated with worse semantic fluency and impaired attention and memory in individuals with TBI of any severity.[125] Importantly, these studies all emphasize that the pain symptoms occurring in the TBI patients often cooccurred with PTSD or depression, making it difficult to determine the precise relationship between pain and these mood and cognitive symptoms of TBI. Together, these studies demonstrate a bidirectional relationship between chronic pain and neuropsychiatric symptoms of TBI.

The Relationship between Sleep-Wake Disturbances and Pain after TBI

In addition to neuropsychiatric symptoms, sleep-wake disturbances, such as insomnia, excessive daytime sleepiness, and fatigue, are frequently reported in individuals with TBI,[126] and research indicates that these symptoms are closely related to pain after TBI.[60,99,127-129] Human studies have shown that a loss of rapid eye movement (REM) sleep can be hyperalgesic[130] and that sleep disturbances after mTBI are more common in those with pain symptoms.[131] In one study, mTBI was associated with altered electroencephalogram (EEG) activity during different stages of sleep and decreased sleep quality, and these disruptions were exacerbated in individuals with mTBI who reported pain symptoms.[132] A TBIMS Pain Collaborative Study found that those with moderate-to-severe TBI who developed chronic pain symptoms were more likely to have sleep-related breathing disorders during acute rehabilitation,[133] and pain has also been reported to disrupt sleep in veterans with TBIs of any severity.[134] Additionally, individuals with mTBI who exhibit pain symptoms have been found to require more sleep than those who did not experience pain symptoms one month after injury,[135] emphasizing the important role that sleep has in recovery. The benefits of sleep in those who experience pain symptoms after TBI may be mediated by melatonin; this endogenous hormone is a key regulator of the circadian rhythm and has been shown to suppress pain and inflammation.[136] Together, these studies suggest that the relationship between sleep-wake disturbances and pain symptoms is bidirectional and may involve changes in brain activity or circadian regulation.

Other studies indicate that sleep, neuropsychiatric symptoms, and pain in TBI patients all interact. In one study of 137 veterans who sustained TBIs of any severity, 52% were reported to experience co-occurring PTSD, insomnia, and pain.[137] Another study of veterans found that those with a history of both TBI (any severity) and PTSD reported worse pain, greater pain intensity, and more frequent sleep disturbances than individuals who did not sustain a TBI or did not have PTSD.[138] Additionally, more severe insomnia in veterans with TBI (any severity) was found to be significantly associated with greater depression and PTSD symptoms and slower processing speed.[139] In a study of individuals with TBIs of any severity enrolled in the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study, the severity of insomnia was correlated with pain symptoms and quality of life at multiple timepoints after injury, including 2 weeks and 3, 6, and 12 months post-TBI.[129] More severe insomnia, depression, anxiety, and pain have also been reported in individuals with mTBI who reported greater disability after the injury.[140]

Collectively, published literature suggests that chronic pain, psychiatric symptoms, and sleep impairments exhibit complex interactions, which may contribute synergistically to disability

after TBI. These interactions also pose challenges to the evaluation and treatment of pain in individuals with TBI. Consistent with this complexity, some studies have demonstrated that a multidisciplinary approach to pain management that targets both neuropsychiatric and pain symptoms of TBI may be more effective at promoting recovery than reliance on a single treatment modality.[141] Thus, studies in this area emphasize the importance of considering chronic pain within the context of the overall health of the individual, rather than as an isolated symptom, when managing TBI symptoms.

PATHOPHYSIOLOGY OF PAIN ASSOCIATED WITH TBI

Pain after TBI arises from the interactions of biochemical, physiologic, and psychologic mechanisms that involve both the peripheral and central nervous systems.[85] During the acute period after TBI, somatic pain pathways are triggered when the mechanical injury causes cellular breakdown and the release of biochemical factors that stimulate nociceptors.[7,85] These specialized, high-threshold pain receptors are located on sensory neurons, which synapse with neurons in the dorsal horn of the spinal cord, allowing transmission of nociceptive signals to the central nervous system where they can be processed.[85] This pathway works in concert with what is known as the descending pain pathway, which transmits pain signals from the brain stem to the spinal cord and periphery.[142]

There is growing consensus that chronic pain after TBI involves nociceptive sensitization, which refers to the hyperresponsiveness of the peripheral or central components of the pain system, as well as reduced inhibition of these pain-promoting pathways.[85,143] Preclinical studies have revealed several important processes that contribute to nociceptive sensitization and the development of chronic pain in animal models of TBI. Collectively, these studies suggest that the imbalance of pain inhibitory and facilitatory processes associated with pain after TBI may be mediated by disrupted serotonergic,[144-148] adrenergic,[144,148] opioid,[146,149] glutamatergic,[150] and transient receptor potential vanilloid 1 (TRPV1) signaling;[151] epigenetic changes;[152-154] neuroinflammatory factors;[147,153,155-157] and growth factors, such as BDNF.[158] While these findings have potential for advancing our knowledge of the signaling processes that promote chronic pain, the precise role of these processes in humans requires further study.

Several case-control and cross-sectional studies have revealed that TBI patients with more intense pain exhibit reduced endogenous pain modulatory function and evidence of mechanical allodynia.[23,159-164] Magnetic resonance imaging (MRI) studies have demonstrated that central pain after TBI also involves changes in fractional anisotropy in the spinothalamocortical tract[165] and the periaqueductal gray,[166] which is a structure near the top of the brain stem that is involved in the descending pain pathway. Additionally, studies have shown changes in the default mode network and functional connectivity associated with persistent pain after TBI.[167-171] Other studies conducted using proton magnetic resonance spectroscopic imaging have reported that the levels of N-acetylaspartate, a marker of neuronal density and viability, are reduced in brain regions involved in nociception and pain modulation in TBI patients with chronic pain symptoms.[172,173] Together, these clinical findings indicate that neuronal loss and maladaptive processes of neuroplasticity may play important roles in the development of pain after TBI.

EVALUATION OF PAIN

Since pain is a subjective phenomenon, self-report assessments are often used to characterize the experience of pain after TBI, including the location, duration, intensity, and exacerbating factors of pain sensations.[174] Verbal descriptors, numeric ratings, and visual analog scales are the most frequently used tools to evaluate pain intensity.[175] In both civilian and military hospital settings, numeric rating scales are the most preferred by patients and the most commonly used of these tools; however, visual analog scales are more sensitive assessments of pain.[176] The verbal descriptor scale uses words to describe pain intensity and is considered a reliable measure of pain levels.[177] The Sports Concussion Assessment Tool (SCAT) is used to evaluate sports-related mTBI and has a section for documenting pain symptoms.[178] The Neurobehavioral Symptom Inventory (NSI)[179] is another nonspecific assessment of neurologic symptoms that can be used to record pain among other symptoms after deployment or TBI. In the military, the Defense and Veterans Pain Rating Scale (DVPRS 2.0) has been validated as a tool for assessing pain in active duty service members and veterans.[180] Additionally, the Post-Deployment Health Assessment (PDHA)[181] is a mandatory self-report questionnaire completed within 30 days of return from deployment; using the PDHA, service members record potentially concussive exposures, complete an mTBI screen if exposed, and report symptoms, including pain symptoms, for which they sought care during deployment.[182] The Post-Deployment Health Re-Assessment (PDHRA) is then completed six months later.[183] (**Table 2**)

Pain interference has emerged as an important indicator of how pain impacts daily activities and functioning and can be measured using many different tools, such as the Brief Pain Inventory[184] and the Pain Disability Index[185] among others. While these tools have been applied across a variety of chronic conditions, the Patient-Reported Outcomes Measurement Information System (PROMIS)[186] and Quality of Life in Neurological Disorders measurement system[187] provide more comprehensive assessments of pain interference and evaluate items that are more relevant to the level of pain interference in an individual. The Traumatic Brain Injury Quality of Life (TBI-QOL) measurement system was designed to complement these assessments and includes a Pain Interference bank with measures that are specific to individuals with TBI.[87,174,188,189] In a recent study of over 500 individuals with TBI, the TBI-QOL Pain Interference bank demonstrated good comparability and reliability across different administration formats (i.e., as a 10-item short form or computerized test).[174] This scale has also been used to detect differences in pain interference in military personnel with mTBI.[88,190]

Although self-report tools are the most commonly used methods of evaluating pain in TBI patients, certain conditions—such as altered mental state, intubation, unconsciousness, and sedation—may challenge communication and the ability to use these tools with nonverbal individuals with more severe TBI.[191,192] Pain in these critically ill TBI patients can be evaluated using behavioral pain tools, such as the Behavioral Pain Scale,[193] and may manifest as flushing, sudden eye opening, eye weeping, and flexion of limbs, even in individuals who are unconscious.[194-196] The Analgesia Nociception Index has been proposed as a tool for assessing pain in critically ill TBI patients who are mechanically ventilated and relies on the noninvasive detection of heart rate variability.[197] Additionally, changes in EEG patterns reflected in the bispectral index system were shown to correlate with pain behaviors in these patients in one study, but only in individuals with left-sided TBI.[198] The authors speculated that the lateralization of bispectral index system results could relate to hemispheric differences in pain

processing, as the right hemisphere may have a more prominent role.[199] Although these studies suggest that alternatives to behavioral pain scales show promise for detecting pain in nonverbal patients, fluctuations in vital signs and EEG patterns in these individuals may not be specific to pain.[200]

To address the limitations of self-report tools and behavioral pain scales and develop more objective measures of pain in TBI patients, some investigators have aimed to identify blood-based or imaging biomarkers of pain. One study of over 200 military service members measured the plasma levels of calcitonin gene-related peptide (CGRP) and nerve growth factor (NGF), two proteins thought to be involved in pain pathology and nociceptive sensitization.[201] The investigators found significantly lower levels of both CGRP and NGF in those who experienced pain symptoms after TBI than in those who did not.[202] While there are some guidelines on the use of imaging techniques during the evaluation of TBI patients,[203] most individuals with mTBIs do not exhibit findings of trauma on computed tomography scans or MRI that could help explain pain symptoms in those who develop chronic pain.[204] To address this challenge, some investigators have aimed to develop imaging methods that could be used to identify the underlying causes of pain symptoms such as excessive neuroinflammation[205] and alterations in cerebral perfusion[206] that cannot be detected using conventional imaging. However, additional research is needed to validate these strategies and develop more robust standards for the use of these tools before they can be implemented in the routine evaluation of pain in individuals with TBI. With further study, these tools could enable advances in the individualized treatment of pain symptoms following TBI.

TREATMENT AND MANAGEMENT OF PAIN AFTER TBI

The medical complexity of pain after TBI, which may co-occur with other TBI symptoms, as well as the heterogeneous and dynamic nature of pain symptoms,[95] lead to vast individual differences in how pain is treated after TBI. The treatment of chronic pain symptoms after TBI may begin with a modest medication protocol that is refined over time and individualized based on the needs of the patient. Pain that is refractory to first-line medications may be treated with narcotic analgesics, physical therapy, nerve blocking procedures, and spinal cord stimulation in more severe cases.[141] Treating pain in civilians and military personnel who have sustained TBIs often involves both pharmaceutical and nonpharmaceutical approaches, including behavioral and psychological strategies, such as cognitive behavioral therapy (CBT), stress management, and lifestyle changes, and alternative techniques have also been studied.[207-211]

Clinical guidelines exist for treating pain in active duty military personnel and veterans who sustain TBIs (**Table 3**). The *2021 VA/DOD CPG for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury* describes evidence-based practices for treating postconcussive symptoms, including headache and persistent pain.[212] The Traumatic Brain Injury Center of Excellence (TBICoE) also developed various clinical recommendations (CRs) for treating pain after TBI that describe the risk factors associated with pain in individuals with TBI (e.g., TBI history, previous neuropsychological symptoms, presence of life stressors during the time of the TBI).[213,214] While these guidelines state that the treatment of chronic pain in those with mTBI should be similar to that in those without mTBI, they also acknowledge the

complexity of pain symptoms after mTBI that is related to co-occurring neuropsychiatric disorders and sleep disturbance. For example, the *2020 TBICoE CR for the Management of Sleep Disturbances Following Mild TBI* recommends that pain symptoms be investigated in those with persisting sleep disturbances.[215] Overall, a battery of clinical tools are available to support clinicians in treating service members with symptoms of pain after TBI.

Pharmaceutical Management of Pain Associated with TBI

The *2023 VA/DOD CPG for the Management of Headache* provides recommendations for pharmacological treatment of post-traumatic headache pain.[21] The CPG strongly recommends the use of the monoclonal antibodies erenumab, fremanezumab, or galcanezumab for preventing episodic or chronic migraine. The CPG also emphasizes that the use of opioids for chronic pain management should be avoided until all other avenues of pain control have been attempted. Many individuals who experience pain symptoms after TBI self-treat with over-the-counter medications, such as acetaminophen or nonsteroidal anti-inflammatory medications, which often provide limited long-term pain relief.[216] To address the limitations of these medications, several alternatives have been investigated. Amitriptyline, a tricyclic antidepressant, has been investigated as a treatment for pain in TBI patients in small studies,[217] but there is currently insufficient evidence of its efficacy in these individuals. S-adenosylmethionine, which is a non-prescription supplement, was shown to have good safety and tolerability in the treatment of multiple postconcussive symptoms and to improve or have no effect on pain symptoms in a recent meta-analysis.[218] Other emerging potential therapeutic targets for treating pain after TBI that have been investigated primarily in preclinical studies include the apelin/APJ system,[219] N-acetylaspartylglutamate,[220] BDNF,[221] and cathepsin B;[222] oral cannabidiol,[223] and intranasal oxytocin[224] have also been investigated as potential treatments in animal models.

CPGs generally discourage prescribing opioids for individuals with chronic pain after TBI due to an increased risk of adverse outcomes;[225] however, there is evidence that individuals with greater TBI severity and comorbid mental health burden are more likely to be prescribed opioids for chronic pain.[63,64,226] One study of over 35,000 veterans who sustained TBIs of any severity reported that approximately 25% used opioids chronically, while most ceased opioid therapy after two months.[227] Initiation of opioid use was significantly associated with female sex, back pain, arthritis or joint pain, and neuropathic pain, while headache pain was associated with lower odds of chronic opioid use.[227] Increasing pain severity has also been found to increase the odds of chronic opioid use.[63] In another study of over 50,000 veterans with TBI of any severity, the presence of emotional symptoms was the strongest predictor of the initiation of opioid therapy, although vestibular, cognitive, and somatic/sensory symptoms evaluated on the NSI were also significantly associated with opioid use.[228] Additionally, in a study of individuals with TBI of any severity, the ones at highest risk for opioid use were those with recent TBIs (sustained within the last 10 years), a first TBI sustained after age 40, and a history of more than two TBIs.[229]

Importantly, pain can increase the likelihood of opioid misuse after TBI, which may be particularly challenging in individuals with comorbid psychiatric disorders[230]; opioid misuse after TBI likely involves mechanisms related to microglial priming, neuroinflammation, modified synaptic plasticity, and changes in opioid receptor expression.[231] In one study of over 49,000 veterans, individuals who sustained a TBI of any severity were found to have three times higher risk of nonfatal opioid overdose than those who did not sustain a TBI.[232] This association

was not found after adjustment for co-occurring psychiatric and individual conditions (e.g., mood disorders, anxiety, substance abuse, and PTSD), indicating the important role that comorbid conditions have in the potential outcomes of long-term opioid use by individuals with TBI. The *2022 VA/DOD CPG for Opioid Therapy for Chronic Pain* prioritizes safe opioid prescribing practices for military service members and veterans and lists TBI, as well as certain sleep and psychiatric disorders, as significant risk factors for adverse effects from opioid therapy.[233]

Nonpharmaceutical Management of Pain Associated with TBI

Nonpharmaceutical therapies are recommended as a first-line treatment method of pain symptoms after TBI, and rehabilitation therapies are also endorsed as potentially beneficial.[21,212] Implementing a healthy lifestyle is particularly important to reduce the long-term risk of TBI-associated secondary pathologies, including chronic pain. In this context, health is not just the absence of disease but the interaction of physical health, mental health, and social wellbeing.[234,235] Lifestyle-related interventions that may help to alleviate chronic pain after TBI include promoting healthy sleeping habits and treating sleep disturbances.[236-238] CBT is also commonly used for the treatment of chronic pain in the general population and includes strategies that aim to reduce pain intensity and pain-related disability.[210,239] CBT has been shown to be effective in the treatment of pain and sleep disturbances after TBI.[240-242] A few studies have investigated the use of dietary interventions, such as a ketogenic diet, for the treatment of TBI symptoms.[243] Such interventions are safe, but the effects on pain symptoms are unclear. Regular exercise has also been reported to promote improvements in perceived pain in preclinical[244] and clinical[245] studies, while intensive mobility training has limited effects on pain.[246]

Several alternatives have been studied for treating pain after TBI and include yoga, mindfulness meditation, and osteopathic manipulative treatment. Yoga is a mindfulness-based intervention shown to be more effective for improving headache and lower back pain than pain in other areas of the body[247,248] and to improve fatigue, depression, physical health, cognitive performance, and quality of life.[249] Additionally, a recent TBIMS extreme phenotypes study revealed that yoga was associated with a higher odds of extreme perceived improvement in pain symptoms after moderate-to-severe TBI than no change in pain symptoms.[250] Collectively, studies suggest that yoga and mindfulness meditation may have beneficial effects in TBI patients based on self-report measures.[251-257] Osteopathic manipulative treatment utilizes hands-on methods to promote muscle fluidity and reduce chronic pain,[258-260] but its efficacy in TBI patients has been understudied. However, in the TBIMS study on perceived improvements from pain treatments after moderate-to-severe TBI, massage and physical therapy were associated with a higher odds of extreme improvements.[250] Notably, some studies on these potential treatments for chronic pain after TBI exhibit several concerns, such as heterogeneous study designs, potential placebo effects, and difficulties in determining appropriate controls.[261]

Other alternative treatments for pain symptoms after TBI have been studied in recent years, though findings on these methods are limited. Several small studies (N<30) have reported that repetitive transcranial magnetic stimulation treatment of pain in individuals with TBI decreased pain intensity and incidence within one week after treatment[262-273] and was associated with changes in functional connectivity[262] or diffusion tensor imaging metrics[263] in brain regions involved in pain inhibition. A TBIMS study reported that acupuncture treatment of pain

symptoms is common and is used more in males and those reporting a higher number of pain sites.[274] Other investigators studying acupuncture treatment of TBI patients have shown promising or no effects on pain symptoms, but many of these studies have been small and exhibit poor methodological quality.[274-278] However, battlefield acupuncture, which is a form of auricular acupuncture, has been proposed as a safe, simple, and effective treatment for pain in military service members and veterans that could provide an efficient alternative to opioid therapy for use on the battlefield.[279,280] One study reported that this treatment reduced self-reported pain in 88%, 80%, 52%, and 51% of veterans with chronic pain at 0, 1, 7, and 30 days posttreatment, respectively.[281] Studies on hyperbaric oxygen therapy[282] and photobiomodulation[283,284] for the treatment of chronic pain after TBI have methodological flaws, preventing robust conclusions on their efficacy. Additional well-designed studies in larger samples that are conducted across longer time periods are needed to confirm the utility of these alternative strategies for the treatment of chronic pain after TBI.

Clinical Considerations Regarding the Management of Pain in Individuals with TBI

Despite the wide variety of options available for pain management, symptoms may persist or recur in some individuals. Many researchers have aimed to better identify those at risk for poor treatment outcomes and methods of facilitating precision treatment of pain after TBI.[94] To this end, studies have identified barriers to treating pain in individuals with TBI that medical personnel should consider when developing treatment plans. Individuals with pain after TBI report considerable challenges related to healthcare access and utilization, and these barriers are associated with reports of greater unmet rehabilitation needs in the years after TBI.[285]

Through provider interviews, a recent TBIMS study investigated factors preventing individuals with chronic pain after TBI from utilizing treatment, and four key themes emerged.[286] These included cognitive deficits of patients (reported by 67% of interviewed providers); patient comorbidities (63%); mental health and/or substance abuse issues (59%); and patient participation or noncompliance (62%).[286] Another recent TBIMS study with provider interviews identified nine barriers that reached saturation, defined as a theme mentioned by over 20% of interviewees.[287] Cognitive disability was again identified as a key theme, as well as issues related to the coordination and continuity of treatment, such as lack of or pause in services due to the COVID-19 pandemic.[287] In other studies, health care providers treating military service members have also reported a need for patient and family educational material on options for managing pain after TBI and trainings tailored to provider specialty.[104,288,289] Scheduling, high out-of-pocket costs, and lack of support have also been reported as important issues.[290]

Studies on the facilitators of effective treatment have found several factors associated with high-quality treatment of pain after TBI. Adequate treatment coordination and continuity have been consistently reported as facilitators of chronic pain health care utilization.[287] In one study, treatment tailored to the specific patient needs (endorsed by 100% of interviewed providers), interdisciplinary team engagement (97%), and community resource availability (48%) were key themes providers identified as related to improved health care utilization in chronic pain treatment after TBI.[287] However, to apply this information to patient care, implementation science is needed to develop strategies of translating these findings into actionable changes. In

fact, the National Academies of Sciences, Engineering, and Medicine (NASEM) report on accelerating progress in TBI specifically describes the need to promote research translation using implementation science.[291] To this end, one TBIMS study identified four primary objectives and implementation strategies for improving the treatment of pain after TBI, such as developing dissemination guidelines and best practices, as well as increasing workforce readiness to treat pain in these individuals.[286]

While the barriers to and facilitators of effective treatment of pain after TBI have begun to emerge, questions remain regarding the factors that may confer better treatment outcomes and the optimal approach for designing an effective treatment plan. One TBIMS study applying the extreme phenotypes approach identified an extreme no-change phenotype, which involved either no change in pain or worse pain (*N*=290), and an extreme improvement phenotype, characterized by pain that was reported as moderately to a great deal better (*N*=512).[292] Those who were female and married and those with better motor function, lower pain intensity, and less frequent pain had higher odds of exhibiting the extreme improvement phenotype. However, to advance precision medicine for chronic pain after TBI, it is important to consider how phenotypes related to different treatment outcomes are defined. For example, one study found that even individuals who report similar levels of pain on self-report assessments after TBI exhibit considerable differences in treatment;[95] thus, some strategies for evaluating pain, such as pain intensity scales, may not be the most effective tools for developing interventions tailored to the patient's needs. Additional studies are needed to reach conclusions on the indicators that should be used to establish patient phenotypes and enable personalized treatment of pain after TBI.

CONCLUSION

Clinical and research programs in the military aim to develop more objective measures of TBI that can be used to predict patient outcome.[293] These efforts may improve our ability to prevent and treat pain symptoms. The identification of injury-related, demographic, and genetic risk factors may provide novel opportunities to advance the personalized long-term treatment of TBI patients by allowing the early identification of those who are most likely to develop chronic pain. However, these efforts are challenged by the complexity of pain symptoms in individuals who sustain TBIs, which often co-occur with neuropsychiatric disorders and sleep disturbances. Therefore, treatment should utilize an interdisciplinary approach that emphasizes non-pharmacologic strategies and aims to resolve the underlying causes of pain, as well as exacerbating factors. Treatment should also focus on promoting functional recovery and return to duty, while minimizing the effects of pain on quality of life. With further study, emerging therapies may be identified to resolve the limitations of current strategies for treating chronic pain in TBI patients.

KEY POINTS

- Chronic pain in TBI patients can involve nociceptive, neuropathic, and mixed mechanisms, and although headache is the most common form of chronic pain in these individuals, pain in the neck, back, and other areas is not uncommon.
- Emerging evidence suggests that severe pain at the time of the TBI, loss of consciousness, female sex, a history of multiple TBIs, and other characteristics may be associated with an increased risk of chronic pain after TBI.

- Pain in TBI patients is often accompanied by neuropsychiatric symptoms, such as PTSD and depression, as well as sleep disturbances, complicating effective patient management and compromising quality of life after TBI.
- Evaluating pain in TBI patients is challenging due to the subjective nature of pain and the limitations of self-report tools. The development of more objective measures, such as biomarkers, may enable more comprehensive pain assessment in the TBI population with further study.
- While alternative therapies such as acupuncture have been proposed for the treatment of chronic pain after TBI, their long-term efficacy is yet to be confirmed.

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APPENDIX A

Table 1: Types of Pain after TBI

PAIN STATE	DEFINITION
Neuropathic[19]	• Results from sensory nerve damage • **Symptoms:** burning, tingling, or shock-like, spontaneous pain
Nociceptive[19]	• Reflects activation of nociceptors by intense mechanical stimuli; also referred to as mechanical pain • **Symptoms:** pain is localized to the area of the mechanical stimulus
Inflammatory[17,19]	• Results from tissue damage and inflammatory process • **Symptoms:** redness, warmth, swelling of the affected area
Centralized[19]	• Pain in the absence of an identifiable noxious stimulus, inflammation, or neural damage; may involve increased pain facilitation or decreased pain inhibition
Psychogenic[18]	• Pain that mostly involves emotional conflict or psychosocial problems, rather than damage to somatosensory structures

Table 2: Tools Used to Evaluate Pain in TBI Patients

TOOL	DESCRIPTION	VA/DOD SPECIFIC (Y/N)
Sport Concussion Assessment Tool-6 (SCAT-6)[178]	• Used to assess sports-related concussion • Includes questions related to pain symptoms at the time of injury	N
Defense and Veterans Pain Rating Scale (DVPRS) 2.0[180]	• A pain assessment tool that uses a numerical rating scale, functional word descriptors, color coding, and pictorial facial expressions matched to pain levels	Y
Post-Deployment Health Assessment (PDHA)[182]	• Mandatory self-report questionnaire completed within 30 days of return from deployment • Can be used to record pain symptoms experienced during deployment	Y
Post-Deployment Health Reassessment (PDHRA)[183]	• Mandatory self-report questionnaire completed six months after return from deployment • Can be used to record pain symptoms experienced during and after deployment	Y
Neurobehavioral Symptom Inventory (NSI)[179]	• A 22-item self-report questionnaire of neurobehavioral symptoms, including pain	N

Table 3: Clinical Tools for Managing Pain in TBI Patients

TOOL	SUMMARY AND RECOMMENDATIONS
VA/DOD CPG for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury (2021)[212]	• Provides an overview of the assessment and treatment of TBI patients with persistent pain • Recommends nonpharmacologic therapies as a first-line treatment method, while avoiding opioid treatments until other strategies have been tested
VA/DOD CPG for the Management of Headache (2023)[21]	• Provides recommendations for pharmacological and non-pharmacological treatment of post-traumatic headache pain
VA/DOD CPG for Opioid Therapy for Chronic Pain (2022)[233]	• Highlights that TBI is a risk factor for adverse outcome of opioid therapy • States the potential harms and benefits should be weighed before recommending opioid treatment for pain treatment
TBICoE Clinical Recommendation: Management of Headache Following mTBI: Guidance for Primary Care Management in Deployed and Non-deployed Setting[213]	• Describes the characteristics of headache and other types of pain associated with posttraumatic headache, different headache types, and the differential assessment, diagnosis, and treatment recommendations for headache types
TBICoE Clinical Recommendation: Cognitive Rehabilitation for Service Members and Veterans Following Mild to Moderate Traumatic Brain Injury[214]	• Recommends that treating pain during post-acute (7–12 weeks post injury) should be a primary focus • Emphasizes that referral for pain management may be warranted before or during cognitive rehabilitation
TBICoE Clinical Recommendation: Management of Sleep Disturbances Following mTBI: Guidance for Primary Care Management in Deployed and Non-Deployed Settings[215]	• Highlights comorbidities implicated in sleep disturbances including chronic pain • Recommends investigating pain symptoms if excessive daytime sleepiness persists beyond 2–4 weeks following mTBI

REFERENCES

1. French LM. Military traumatic brain injury: An examination of important differences. *Ann N Y Acad Sci*. 2010;1208:38-45.
2. Rosenfeld JV, McFarlane AC, Bragge P, Armonda RA, Grimes JB, Ling GS. Blast-related traumatic brain injury. *Lancet Neurol*. 2013;12(9):882-893.
3. Reid MW, Velez CS. Discriminating military and civilian traumatic brain injuries. *Mol Cell Neurosci*. 2015;66(Pt B):123-8.
4. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med*. 2008;358(5):453-63.
5. Wilk JE, Thomas JL, McGurk DM, Riviere LA, Castro CA, Hoge CW. Mild traumatic brain injury (concussion) during combat: Lack of association of blast mechanism with persistent postconcussive symptoms. *J Head Trauma Rehabil*. 2010;25(1):9-14.
6. Patil VK, St Andre JR, Crisan E, et al. Prevalence and treatment of headaches in veterans with mild traumatic brain injury. *Headache*. 2011;51(7):1112-21.
7. Choe MC. The pathophysiology of concussion. *Curr Pain Headache Rep*. 2016;20(6):42.
8. Hasoon J. Blast-associated traumatic brain injury in the military as a potential trigger for dementia and chronic traumatic encephalopathy. *US Army Med Dep J*. 2017;(1-17):102-105.
9. Polinder S, Cnossen MC, Real R, et al. A multidimensional approach to post-concussion symptoms in mild traumatic brain injury. *Front Neurol*. 2018;9:1113.
10. Xiong C, Martin T, Sravanapudi A, Colantonio A, Mollayeva T. Factors associated with return to work in men and women with work-related traumatic brain injury. *Disabil Health J*. 2016;9(3):439-48.
11. Dawson DR, Schwartz ML, Winocur G, Stuss DT. Return to productivity following traumatic brain injury: Cognitive, psychological, physical, spiritual, and environmental correlates. *Disabil Rehabil*. 2007;29(4):301-13.
12. Khoury S, Segal J, Parisien M, et al. Post-concussion symptoms and chronic pain after mild traumatic brain injury are modulated by multiple locus effect in the BDNF gene through the expression of antisense: A pilot prospective control study. *Can J Pain*. 2017;1(1):112-126.
13. Young JA. Pain and traumatic brain injury. *Phys Med Rehabil Clin N Am*. 2007;18(1):145-63, vii-viii.
14. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain*. 2020;161(9):1976-1982.
15. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: A systematic review. *JAMA*. 2008;300(6):711-9.
16. 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.
17. Vardeh D, Mannion RJ, Woolf CJ. Toward a mechanism-based approach to pain diagnosis. *J Pain*. 2016;17(9 Suppl):T50-69.
18. Isagulyan ED, Makashova ES, Myasnikova LK, et al. Psychogenic (nociplastic) pain: Current state of diagnosis, treatment options, and potentials of neurosurgical management. *Prog Brain Res*. 2022;272(1):105-123.
19. International Association for the Study of Pain. IASP Terminology. Updated 2021. Available from: https://www.iasp-pain.org/resources/terminology/?ItemNumber=1698#Neuropathicpain
20. Mehalick ML, Glueck AC. Examining the relationship and clinical management between traumatic brain injury and pain in military and civilian populations. *Brain Inj*. 2018;32(11):1307-1314.
21. Department of Veteran Affairs & Department of Defense. VA/DoD CPG for the Management of Headache (2023). Updated 2023. https://www.healthquality.va.gov/guidelines/pain/headache/VA-DoD-CPG-Headache-Full-CPG.pdf
22. Kuperman P, Granovsky Y, Granot M, et al. Psychophysic-psychological dichotomy in very early acute mTBI pain: A prospective study. *Neurology*. 2018;91(10):e931-e938.

23. Ofek H, Defrin R. The characteristics of chronic central pain after traumatic brain injury. *Pain*. 2007;131(3):330-340.
24. Khoury S, Benavides R. Pain with traumatic brain injury and psychological disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;87(Pt B):224-233.
25. Bosco MA, Murphy JL, Clark ME. Chronic pain and traumatic brain injury in OEF/OIF service members and Veterans. *Headache*. 2013;53(9):1518-22.
26. Gauntlett-Gilbert J, Wilson S. Veterans and chronic pain. *Br J Pain*. 2013;7(2):79-84.
27. Morlion B. Pharmacotherapy of low back pain: Targeting nociceptive and neuropathic pain components. *Curr Med Res Opin*. 2011;27(1):11-33.
28. Baron R, Binder A, Wasner G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol*. 2010;9(8):807-19.
29. Linder SL. Post-traumatic headache. *Curr Pain Headache Rep*. 2007;11(5):396-400.
30. Holtkamp MD, Grimes J, Ling G. Concussion in the Military: An evidence-base review of mTBI in US military personnel focused on posttraumatic headache. *Curr Pain Headache Rep*. 2016;20(6):37.
31. Kumar RG, Ketchum JM, Hammond FM, et al. Health and cognition among adults with and without Traumatic Brain Injury: A matched case-control study. *Brain Inj*. 23 2022;36(3):415-423.
32. Theeler BJ, Flynn FG, Erickson JC. Headaches after concussion in US soldiers returning from Iraq or Afghanistan. *Headache*. 2010;50(8):1262-72.
33. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
34. Taylor BC, Hagel EM, Carlson KF, et al. Prevalence and costs of co-occurring traumatic brain injury with and without psychiatric disturbance and pain among Afghanistan and Iraq War veteran V.A. users. *Med Care*. 2012;50(4):342-6.
35. Kwan V, Vo M, Noel M, Yeates K. A scoping review of pain in children after traumatic brain injury: Is there more than headache? *J Neurotrauma*. 2018;35(7):877-888.
36. O'Neil ME, Agyemang A, Walker WC, et al. Demographic, military, and health comorbidity variables by mild TBI and PTSD status in the LIMBIC-CENC cohort. *Brain Inj*. 2022;36(5):598-606.
37. Cheever K, McDevitt J, Phillips J, Kawata K. The role of cervical symptoms in post-concussion management: A systematic review. *Sports Med*. 2021;51(9):1875-1891.
38. Pugh MJ, Finley EP, Wang CP, et al. A retrospective cohort study of comorbidity trajectories associated with traumatic brain injury in veterans of the Iraq and Afghanistan wars. *Brain Inj*. 2016;30(12):1481-1490.
39. Suri P, Stolzmann K, Williams R, Pogoda TK. Deployment-related traumatic brain injury and risk of new episodes of care for back pain in veterans. *J Pain*. 2019;20(1):97-107.
40. Brown S, Hawker G, Beaton D, Colantonio A. Long-term musculoskeletal complaints after traumatic brain injury. *Brain Inj*. 2011;25(5):453-61.
41. Hammond FM, Corrigan JD, Ketchum JM, et al. Prevalence of medical and psychiatric comorbidities following traumatic brain injury. *J Head Trauma Rehabil*. 2019;34(4):E1-e10.
42. Harrison-Felix C, Sevigny M, Beaulieu CL, et al. Characterization and treatment of chronic pain after traumatic brain injury-comparison of characteristics between individuals with current pain, past pain, and no pain: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):5-17.
43. Balba NM, McBride AA, Callahan ML, et al. Photosensitivity is associated with chronic pain following traumatic brain injury. *J Neurotrauma*. 2022;39(17-18):1183-1194.
44. Lee CJ, Felix ER, Levitt RC, et al. Traumatic brain injury, dry eye and comorbid pain diagnoses in US veterans. *Br J Ophthalmol*. 2018;102(5):667-673.
45. Radresa O, Chauny JM, Lavigne G, Piette E, Paquet J, Daoust R. Current views on acute to chronic pain transition in post-traumatic patients: Risk factors and potential for pre-emptive treatments. *J Trauma Acute Care Surg*. 2014;76(4):1142-50.

46. Belding JN, Fitzmaurice S, Englert RM, Koenig HG, Thomsen CJ, Olaghere da Silva U. Self-reported concussion symptomology during deployment: Differences as a function of injury mechanism and low-level blast exposure. *J Neurotrauma*. 2020;37(20):2219-2226.
47. Belding JN, Khokhar B, Englert RM, Fitzmaurice S, Thomsen CJ. The persistence of blast- versus impact-induced concussion symptomology following deployment. *J Head Trauma Rehabil*. 2021;36(6):E397-e405.
48. Englert RM, Belding JN, Thomsen CJ. Self-reported symptoms in U.S. Marines following blast- and impact-related concussion. *Mil Med*. 2023;188(7-8):e2118-e2125.
49. Sayer NA, Chiros CE, Sigford B, et al. Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the Global War on Terror. *Arch Phys Med Rehabil*. 2008;89(1):163-70.
50. Browne AL, Appleton S, Fong K, et al. A pilot randomized controlled trial of an early multidisciplinary model to prevent disability following traumatic injury. *Disabil Rehabil*. 2013;35(14):1149-63.
51. Hendrikx LJ, Murphy D. Understanding the link between traumatic brain injury accompanied by loss of consciousness and well-being: A sample of UK military veterans. *J Head Trauma Rehabil*. 2021;36(1):34-43.
52. Kanefsky R, Motamedi V, Mithani S, Mysliwiec V, Gill JM, Pattinson CL. Mild traumatic brain injuries with loss of consciousness are associated with increased inflammation and pain in military personnel. *Psychiatry Res*. 2019;279:34-39.
53. Luoto TM, Iverson GL, Losoi H, et al. Clinical correlates of retrograde amnesia in mild traumatic brain injury. *Brain Inj*. 2015;29(5):565-72.
54. Ponsford J, Willmott C, Rothwell A, et al. Factors influencing outcome following mild traumatic brain injury in adults. *J Int Neuropsychol Soc*. 2000;6(5):568-79.
55. Garcia A, Kretzmer TS, Dams-O'Connor K, et al. Health conditions among Special Operations Forces versus conventional military service members: A VA TBI Model Systems Study. *J Head Trauma Rehabil*. 2022;37(4):E292-e298.
56. Hänni S, Vedung F, Tegner Y, Marklund N, Johansson J. Soccer-related concussions among swedish elite soccer players: A descriptive study of 1,030 players. *Front Neurol*. 2020;11:510800.
57. Covassin T, Moran R, Wilhelm K. Concussion symptoms and neurocognitive performance of high school and college athletes who incur multiple concussions. *Am J Sports Med*. 2013;41(12):2885-9.
58. Wilk JE, Herrell RK, Wynn GH, Riviere LA, Hoge CW. Mild traumatic brain injury (concussion), posttraumatic stress disorder, and depression in U.S. soldiers involved in combat deployments: Association with postdeployment symptoms. *Psychosom Med*. 2012;74(3):249-57.
59. Coffman C, Reyes D, Hess MC, et al. Relationship between headache characteristics and a remote history of TBI in veterans: A 10-Year retrospective chart review. *Neurology*. 2022;99(2):e187-e198.
60. Beetar JT, Guilmette TJ, Sparadeo FR. Sleep and pain complaints in symptomatic traumatic brain injury and neurologic populations. *Arch Phys Med Rehabil*. 1996;77(12):1298-302.
61. Flynn S, Moore B, van der Merwe AJ, et al. Headaches in traumatic brain injury: Improvement over time, associations with quality of life, and impact of migraine-type headaches. *J Head Trauma Rehabil*. 2023;38(2):E109-e117.
62. Sherman KB, Goldberg M, Bell KR. Traumatic brain injury and pain. *Phys Med Rehabil Clin N Am*. 2006;17(2):473-90, viii.
63. Hudson TJ, Painter JT, Martin BC, et al. Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans. *Pain*. 2017;158(6):1039-1045.
64. Seal KH, Bertenthal D, Barnes DE, et al. Traumatic brain injury and receipt of prescription opioid therapy for chronic pain in Iraq and Afghanistan veterans: Do clinical practice guidelines matter? *J Pain*. 2018;19(8):931-941.
65. Seal KH, Bertenthal D, Barnes DE, Byers AL, Strigo I, Yaffe K. Association of traumatic brain injury with chronic pain in Iraq and Afghanistan veterans: Effect of comorbid mental health conditions. *Arch Phys Med Rehabil*. 2017;98(8):1636-1645.

66. Gironda RJ, Clark ME, Ruff RL, et al. Traumatic brain injury, polytrauma, and pain: Challenges and treatment strategies for the polytrauma rehabilitation. *Rehabil Psychol*. 2009;54(3):247-58.
67. Hoffman JM, Pagulayan KF, Zawaideh N, Dikmen S, Temkin N, Bell KR. Understanding pain after traumatic brain injury: Impact on community participation. *Am J Phys Med Rehabil*. 2007;86(12):962-9.
68. Meltzer KJ, Juengst SB. Associations between frequent pain or headaches and neurobehavioral symptoms by gender and TBI severity. *Brain Inj*. 2021;35(1):41-47.
69. Higgins DM, Kerns RD, Brandt CA, et al. Persistent pain and comorbidity among Operation Enduring Freedom/Operation Iraqi Freedom/operation New Dawn veterans. *Pain Med*. 2014;15(5):782-90.
70. Mollayeva T, Cassidy JD, Shapiro CM, Mollayeva S, Colantonio A. Concussion/mild traumatic brain injury-related chronic pain in males and females: A diagnostic modelling study. *Medicine (Baltimore)*. Feb 2017;96(7):e5917.
71. Bay E, Sikorskii A, Saint-Arnault D. Sex differences in depressive symptoms and their correlates after mild-to-moderate traumatic brain injury. *J Neurosci Nurs*. 2009;41(6):298-309; quiz 310-1.
72. Naugle KM, Nguyen T, Smith JA, Saxe J, White FA. Racial differences in head pain and other pain-related outcomes after mild traumatic brain injury. *J Neurotrauma*. 2023;40(15-16):1671-1683.
73. Sander AM, Christensen K, Loyo K, et al. Coping with chronic pain after traumatic brain injury: Role of race/ethnicity and effect on participation outcomes in a TBI Model Systems sample. *Arch Phys Med Rehabil*. 2023;104(7):1099-1106.
74. Sander AM, Williams M, Loyo K, et al. Disparities in chronic pain experience and treatment history among persons with traumatic brain injury: A Traumatic Brain Injury Model Systems Study. *J Head Trauma Rehabil*. 2023;38(2):125-136.
75. Stratton KJ, Hawn SE, Amstadter AB, Cifu DX, Walker WC. Correlates of pain symptoms among Iraq and Afghanistan military personnel following combat-related blast exposure. *J Rehabil Res Dev*. 2014;51(8):1189-1202.
76. Naugle KM, Corrona S, Smith JA, Nguyen T, Saxe J, White FA. Physical activity behavior in the first month after mild traumatic brain injury is associated with physiological and psychological risk factors for chronic pain. *Pain Rep*. 2021;6(4):e969.
77. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: A critical review. *Expert Rev Neurother*. 2009;9(5):745-58.
78. Merritt VC, Ukueberuwa DM, Arnett PA. Relationship between the apolipoprotein E gene and headache following sports-related concussion. *J Clin Exp Neuropsychol*. 2016;38(9):941-9.
79. Finnoff JT, Jelsing EJ, Smith J. Biomarkers, genetics, and risk factors for concussion. *Pm r*. 2011;3(10 Suppl 2):S452-9.
80. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: A causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci USA*. 2006;103(15):5644-51.
81. Masel BE, DeWitt DS. Traumatic brain injury: A disease process, not an event. *J Neurotrauma*. 2010;27(8):1529-40.
82. Kornblith ES, Langa KM, Yaffe K, Gardner RC. Physical and functional impairment among older adults with a history of traumatic brain injury. *J Head Trauma Rehabil*. 2020;35(4):E320-e329.
83. Dams-O'Connor K, Juengst SB, Bogner J, et al. Traumatic brain injury as a chronic disease: Insights from the United States Traumatic Brain Injury Model Systems Research Program. *Lancet Neurol*. 2023;22(6):517-528.
84. Andelic N, Howe EI, Hellstrøm T, et al. Disability and quality of life 20 years after traumatic brain injury. *Brain Behav*. 2018;8(7):e01018.
85. Walker WC. Pain pathoetiology after TBI: Neural and nonneural mechanisms. *J Head Trauma Rehabil*. 2004;19(1):72-81.
86. Cook AJ, Meyer EC, Evans LD, et al. Chronic pain acceptance incrementally predicts disability in polytrauma-exposed veterans at baseline and 1-year follow-up. *Behav Res Ther*. 2015;73:25-32.
87. Amtmann D, Bamer AM, McMullen K, et al. Pain across traumatic injury groups: A National Institute on Disability, Independent Living, and Rehabilitation Research model systems study. *J Trauma Acute Care Surg*. 2020;89(4):829-833.

88. Walker WC, Nowak KJ, Kenney K, et al. Is balance performance reduced after mild traumatic brain injury?: Interim analysis from Chronic Effects of Neurotrauma Consortium (CENC) multi-centre study. *Brain Inj*. 2018;32(10):1156-1168.
89. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. *Pain*. 2010;150(1):173-182.
90. Agtarap SD, Campbell-Sills L, Jain S, et al. Satisfaction with life after mild traumatic brain injury: A TRACK-TBI study. *J Neurotrauma*. 2021;38(5):546-554.
91. Noyes ET, Tang X, Sander AM, et al. Relationship of medical comorbidities to psychological health at 2 and 5 years following traumatic brain injury (TBI). *Rehabil Psychol*. 2021;66(2):107-117.
92. Williamson ML, Elliott TR, Berry JW, Underhill AT, Stavrinos D, Fine PR. Predictors of health-related quality-of-life following traumatic brain injury. *Brain Inj*. 2013;27(9):992-9.
93. Sherer M, Poritz JMP, Tulsky D, Kisala P, Leon-Novelo L, Ngan E. Conceptual structure of health-related quality of life for persons with traumatic brain injury: Confirmatory factor analysis of the TBI-QOL. *Arch Phys Med Rehabil*. 2020;101(1):62-71.
94. Hoffman JM, Ketchum JM, Agtarap S, et al. Characterizing extreme phenotypes for pain interference in persons with chronic pain following traumatic brain injury: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):31-42.
95. Song K, Wang CP, McGeary DD, et al. Five-year pain intensity and treatment trajectories of post-9/11 veterans with mild traumatic brain injury. *J Pain*. 2020;21(9-10):1005-1017.
96. Grauwmeijer E, Heijenbrok-Kal MH, Ribbers GM. Health-related quality of life 3 years after moderate to severe traumatic brain injury: A prospective cohort study. *Arch Phys Med Rehabil*. 2014;95(7):1268-76.
97. Sayer NA. Traumatic brain injury and its neuropsychiatric sequelae in war veterans. *Annu Rev Med*. 2012;63:405-19.
98. Halbauer JD, Ashford JW, Zeitzer JM, Adamson MM, Lew HL, Yesavage JA. Neuropsychiatric diagnosis and management of chronic sequelae of war-related mild to moderate traumatic brain injury. *J Rehabil Res Dev*. 2009;46(6):757-96.
99. Powell MA, Corbo V, Fonda JR, Otis JD, Milberg WP, McGlinchey RE. Sleep quality and reexperiencing symptoms of PTSD are associated with current pain in U.S. OEF/OIF/OND veterans with and without mTBIs. *J Trauma Stress*. 2015;28(4):322-9.
100. Dieter JN, Engel SD. Traumatic brain injury and posttraumatic stress disorder: Comorbid consequences of war. *Neurosci Insights*. 2019;14:1179069519892933.
101. Grandhi R, Tavakoli S, Ortega C, Simmonds MJ. A review of chronic pain and cognitive, mood, and motor dysfunction following mild traumatic brain injury: Complex, comorbid, and/or overlapping conditions? *Brain Sci*. 2017;7(12).
102. Lusk J, Brenner LA, Betthauser LM, et al. A qualitative study of potential suicide risk factors among Operation Iraqi Freedom/Operation Enduring Freedom soldiers returning to the Continental United States (CONUS). *J Clin Psychol*. 2015;71(9):843-55.
103. Otis JD, McGlinchey R, Vasterling JJ, Kerns RD. Complicating factors associated with mild traumatic brain injury: Impact on pain and posttraumatic stress disorder treatment. *J Clin Psychol Med Settings*. 2011;18(2):145-54.
104. Sayer NA, Rettmann NA, Carlson KF, et al. Veterans with history of mild traumatic brain injury and posttraumatic stress disorder: Challenges from provider perspective. *J Rehabil Res Dev*. 2009;46(6):703-16.
105. Laughter S, Khan M, Banaag A, Madsen C, Koehlmoos TP. Prevalence of polytrauma clinical triad among active duty service members. *Mil Med*. 2022;187(7-8):e856-e861.
106. Cifu DX, Taylor BC, Carne WF, et al. Traumatic brain injury, posttraumatic stress disorder, and pain diagnoses in OIF/OEF/OND veterans. *J Rehabil Res Dev*. 2013;50(9):1169-76.
107. Stojanovic MP, Fonda J, Fortier CB, et al. Influence of mild traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) on pain intensity levels in OEF/OIF/OND veterans. *Pain Med*. 2016;17(11):2017-2025.

108. Ketchum JM, Hoffman JM, Agtarap S, et al. Relationship between extreme pain phenotypes and psychosocial outcomes in persons with chronic pain following traumatic brain injury: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):56-67.
109. Hanks R, Ketchum JM, Peckham M, et al. Associations of chronic pain with psychosocial outcomes after traumatic brain injury: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):18-30.
110. Ord AS, Epstein EL, Shull ER, Taber KH, Martindale SL, Rowland JA. Factors associated with recovery from posttraumatic stress disorder in combat veterans: The role of deployment mild traumatic brain injury (mTBI). *Rehabil Psychol*. 2022;67(3):356-368.
111. Khokhar BR, Lindberg MA, Walker WC. Post-mTBI pain interference in a U.S. military population: A Chronic Effects of Neurotrauma Consortium study. *Mil Med*. 2021;186(3-4):e293-e299.
112. Avallone KM, Smith ER, Ma S, et al. PTSD as a Mediator in the relationship between post-concussive symptoms and pain among OEF/OIF/OND veterans. *Mil Med*. 2019;184(1-2):e118-e123.
113. Hoot MR, Levin HS, Smith AN, et al. Pain and chronic mild traumatic brain injury in the US military population: A Chronic Effects of Neurotrauma Consortium study. *Brain Inj*. 2018;32(10):1169-1177.
114. Jackson CE, Green JD, Bovin MJ, et al. Mild traumatic brain injury, PTSD, and psychosocial functioning among male and female U.S. OEF/OIF veterans. *J Trauma Stress*. 2016;29(4):309-16.
115. Martindale SL, Vujanovic AA, Ord AS, Cary A, Rowland JA. Distress tolerance mitigates effects of posttraumatic stress, traumatic brain injury, and blast exposure on psychiatric and health outcomes. *Rehabil Psychol*. 2023;68(4):385-395.
116. Sullivan-Singh SJ, Sawyer K, Ehde DM, et al. Comorbidity of pain and depression among persons with traumatic brain injury. *Arch Phys Med Rehabil*. 2014;95(6):1100-5.
117. Winter L, Moriarty H, Robinson K. Employment status among U.S. military veterans with traumatic brain injury: Mediation analyses and the goal of tertiary prevention. *Front Neurol*. 2019;10:190.
118. Bay E, Donders J. Risk factors for depressive symptoms after mild-to-moderate traumatic brain injury. *Brain Inj*. 2008;22(3):233-41.
119. Sigurdardottir S, Andelic N, Roe C, Schanke AK. Depressive symptoms and psychological distress during the first five years after traumatic brain injury: Relationship with psychosocial stressors, fatigue and pain. *J Rehabil Med*. 2013;45(8):808-14.
120. Jaramillo CA, Cooper DB, Wang CP, et al. Subgroups of US IRAQ and Afghanistan veterans: Associations with traumatic brain injury and mental health conditions. *Brain Imaging Behav*. 2015;9(3):445-55.
121. Blakey SM, Wagner HR, Naylor J, et al. Chronic pain, TBI, and PTSD in military veterans: A link to suicidal ideation and violent impulses? *J Pain*. 2018;19(7):797-806.
122. Miles SR, Martindale SL, Flanagan JC, et al. Putting the pieces together to understand anger in combat veterans and service members: Psychological and physical contributors. *J Psychiatr Res*. 2023;159:57-65.
123. Weyer Jamora C, Schroeder SC, Ruff RM. Pain and mild traumatic brain injury: The implications of pain severity on emotional and cognitive functioning. *Brain Inj*. 2013;27(10):1134-40.
124. Hoffman SN, Herbert MS, Crocker LD, et al. The role of pain catastrophizing in cognitive functioning among veterans with a history of mild traumatic brain injury. *J Head Trauma Rehabil*. 2019;34(4):E61-e66.
125. Cherup NP, Robayo LE, Vastano R, Fleming L, Levin BE, Widerström-Noga E. Neuropsychological function in traumatic brain injury and the influence of chronic pain. *Percept Mot Skills*. 2023;130(4):1495-1523.
126. Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: Frequency, characteristics, and risk factors. *J Head Trauma Rehabil*. 2006;21(3):199-212.
127. Lavigne G, Khoury S, Chauny JM, Desautels A. Pain and sleep in post-concussion/mild traumatic brain injury. *Pain*. 2015;156 Suppl 1:S75-s85.

128. Ouellet MC, Beaulieu-Bonneau S, Morin CM. Sleep-wake disturbances after traumatic brain injury. *Lancet Neurol*. 2015;14(7):746-57.
129. Wickwire EM, Albrecht JS, Capaldi VF, 2nd, et al. Association between insomnia and mental health and neurocognitive outcomes following traumatic brain injury. *J Neurotrauma*. 2023;40(21-22): 2376-2385.
130. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. *Sleep*. 2006;29(2):145-51.
131. Chaput G, Giguère JF, Chauny JM, Denis R, Lavigne G. Relationship among subjective sleep complaints, headaches, and mood alterations following a mild traumatic brain injury. *Sleep Med*. 2009;10(7):713-6.
132. Khoury S, Chouchou F, Amzica F, et al. Rapid EEG activity during sleep dominates in mild traumatic brain injury patients with acute pain. *J Neurotrauma*. 2013;30(8):633-41.
133. Martin AM, Pinto SM, Tang X, et al. Associations between early sleep-disordered breathing following moderate-to-severe traumatic brain injury and long-term chronic pain status: A Traumatic Brain Injury Model Systems study. *J Clin Sleep Med*. 2023;19(1):135-143.
134. Lew HL, Pogoda TK, Hsu PT, et al. Impact of the "polytrauma clinical triad" on sleep disturbance in a department of veterans affairs outpatient rehabilitation setting. *Am J Phys Med Rehabil*. 2010;89(6):437-45.
135. Suzuki Y, Khoury S, El-Khatib H, et al. Individuals with pain need more sleep in the early stage of mild traumatic brain injury. *Sleep Med*. 2017;33:36-42.
136. Chaudhry SR, Stadlbauer A, Buchfelder M, Kinfe TM. Melatonin moderates the triangle of chronic pain, sleep architecture and immunometabolic traffic. *Biomedicines*. 2021;9(8):984.
137. Lang KP, Veazey-Morris K, Andrasik F. Exploring the role of insomnia in the relation between PTSD and pain in veterans with polytrauma injuries. *J Head Trauma Rehabil*. 2014;29(1):44-53.
138. Balba NM, Elliott JE, Weymann KB, et al. Increased sleep disturbances and pain in veterans with comorbid traumatic brain injury and posttraumatic stress disorder. *J Clin Sleep Med*. 2018;14(11):1865-1878.
139. Miller M, Williams R, Pagulayan K, Barber J, Ehde DM, Hoffman J. Correlates of sleep disturbance in veterans with traumatic brain injury and chronic pain: A cross-sectional study. *Disabil Health J*. 2022;15(1):101203.
140. Mollayeva T, Pratt B, Mollayeva S, Shapiro CM, Cassidy JD, Colantonio A. The relationship between insomnia and disability in workers with mild traumatic brain injury/concussion: Insomnia and disability in chronic mild traumatic brain injury. *Sleep Med*. 2016;20:157-66.
141. Branca B, Lake AE. Psychological and neuropsychological integration in multidisciplinary pain management after TBI. *J Head Trauma Rehabil*. 2004;19(1):40-57.
142. Chen Q, Bharadwaj V, Irvine KA, Clark JD. Mechanisms and treatments of chronic pain after traumatic brain injury. *Neurochem Int*. 2023:105630.
143. Latremoliere A, Woolf CJ. Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *J Pain*. 2009;10(9):895-926.
144. Irvine KA, Sahbaie P, Ferguson AR, Clark JD. Loss of diffuse noxious inhibitory control after traumatic brain injury in rats: A chronic issue. *Exp Neurol*. 2020;333:113428.
145. Irvine KA, Sahbaie P, Ferguson AR, Clark JD. Enhanced descending pain facilitation in acute traumatic brain injury. *Exp Neurol*. 2019;320:112976.
146. Chen Q, Sahbaie P, Irvine KA, Clark JD. Mild traumatic brain injury-induced augmented postsurgical pain is driven by central serotonergic pain-facilitatory signaling. *Anesth Analg*. 2023; 138(4):866-877.
147. Sahbaie P, Irvine KA, Liang DY, Shi X, Clark JD. Mild traumatic brain injury causes nociceptive sensitization through spinal chemokine upregulation. *Sci Rep*. 2019;9(1):19500.
148. Sahbaie P, Irvine KA, Shi XY, Clark JD. Monoamine control of descending pain modulation after mild traumatic brain injury. *Sci Rep*. 2022;12(1):16359.

149. Best KM, Mojena MM, Barr GA, Schmidt HD, Cohen AS. Endogenous opioid dynorphin is a potential link between traumatic brain injury, chronic pain, and substance use disorder. *J Neurotrauma*. 2022;39(1-2):1-19.
150. Neale JH, Olszewski RT, Gehl LM, Wroblewska B, Bzdega T. The neurotransmitter N-acetylaspartylglutamate in models of pain, ALS, diabetic neuropathy, CNS injury and schizophrenia. *Trends Pharmacol Sci*. 2005;26(9):477-84.
151. da Silva Fiorin F, do Espírito Santo CC, do Nascimento RS, et al. Capsaicin-sensitive fibers mediate periorbital allodynia and activation of inflammatory cells after traumatic brain injury in rats: Involvement of TRPV1 channels in post-traumatic headache. *Neuropharmacology*. 2020;176:108215.
152. Liang DY, Sahbaie P, Sun Y, et al. TBI-induced nociceptive sensitization is regulated by histone acetylation. *IBRO Rep*. 2017;2:14-23.
153. Liang DY, Shi X, Liu P, et al. The chemokine receptor CXCR2 supports nociceptive sensitization after traumatic brain injury. *Mol Pain*. 2017;13:1744806917730212.
154. Irvine KA, Clark JD. Chronic pain after traumatic brain injury: Pathophysiology and pain mechanisms. *Pain Med*. 2018;19(7):1315-1333.
155. Nguyen T, Nguyen N, Cochran AG, et al. Repeated closed-head mild traumatic brain injury-induced inflammation is associated with nociceptive sensitization. *J Neuroinflammation*. 2023;20(1):196.
156. Balog BM, Sonti A, Zigmond RE. Neutrophil biology in injuries and diseases of the central and peripheral nervous systems. *Prog Neurobiol*. 2023;228:102488.
157. Sharif NA. Neuroaxonal and cellular damage/protection by prostanoid receptor ligands, fatty acid derivatives and associated enzyme inhibitors. *Neural Regn Res*. 2023;18(1):5-17.
158. Feliciano DP, Sahbaie P, Shi X, Klukinov M, Clark JD, Yeomans DC. Nociceptive sensitization and BDNF up-regulation in a rat model of traumatic brain injury. *Neurosci Lett*. 2014;583:55-9.
159. Carey C, Saxe J, White FA, Naugle KM. An Exploratory study of endogenous pain modulatory function in patients following mild traumatic brain injury. *Pain Med*. 2019;20(11):2198-2207.
160. Defrin R. Chronic post-traumatic headache: Clinical findings and possible mechanisms. *J Man Manip Ther*. 2014;22(1):36-44.
161. Defrin R, Riabinin M, Feingold Y, Schreiber S, Pick CG. Deficient pain modulatory systems in patients with mild traumatic brain and chronic post-traumatic headache: Implications for its mechanism. *J Neurotrauma*. 2015;32(1):28-37.
162. Naugle KM, Carey C, Evans E, Saxe J, Overman R, White FA. The role of deficient pain modulatory systems in the development of persistent post-traumatic headaches following mild traumatic brain injury: An exploratory longitudinal study. *J Headache Pain*. 2020;21(1):138.
163. Flowers M, Leung A, Schiehser DM, et al. Severities in persistent mild traumatic brain injury related headache is associated with changes in supraspinal pain modulatory functions. *Mol Pain*. 2021;17:17448069211037881.
164. Leung A, Shukla S, Yang E, et al. Diminished supraspinal pain modulation in patients with mild traumatic brain injury. *Mol Pain*. 2016;12:1744806916662661.
165. Kim JH, Ahn SH, Cho YW, Kim SH, Jang SH. The Relation between injury of the spinothalamocortical tract and central pain in chronic patients with mild traumatic brain injury. *J Head Trauma Rehabil*. 2015;30(6):E40-6.
166. Jang SH, Park SM, Kwon HG. Relation between injury of the periaqueductal gray and central pain in patients with mild traumatic brain injury: Observational study. *Medicine (Baltimore)*. 2016;95(26):e4017.
167. Niu X, Bai L, Sun Y, et al. Disruption of periaqueductal grey-default mode network functional connectivity predicts persistent post-traumatic headache in mild traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2019;90(3):326-332.
168. Niu X, Bai L, Sun Y, et al. Mild traumatic brain injury is associated with effect of inflammation on structural changes of default mode network in those developing chronic pain. *J Headache Pain*. 2020;21(1):135.
169. Bosak N, Branco P, Kuperman P, et al. Brain connectivity predicts chronic pain in acute mild traumatic brain injury. *Ann Neurol*. 2022;92(5):819-833.

170. Ofoghi Z, Dewey D, Barlow KM. A systematic review of structural and functional imaging correlates of headache or pain after mild traumatic brain injury. *J Neurotrauma*. 2020;37(7):907-923.
171. Newsome MR, Wilde EA, Bigler ED, et al. Functional brain connectivity and cortical thickness in relation to chronic pain in post-911 veterans and service members with mTBI. *Brain Inj*. 2018;32(10):1236-1244.
172. Robayo LE, Govind V, Salan T, et al. Neurometabolite alterations in traumatic brain injury and associations with chronic pain. *Front Neurosci*. 2023;17:1125128.
173. Widerström-Noga E, Govind V, Adcock JP, Levin BE, Maudsley AA. Subacute pain after traumatic brain injury is associated with lower insular n-acetylaspartate concentrations. *J Neurotrauma*. 2016;33(14):1380-9.
174. Carlozzi NE, Kisala PA, Boulton AJ, et al. Measuring pain in TBI: Development of the TBI-QOL Pain Interference Item Bank and Short Form. *Arch Phys Med Rehabil*. 2020;101(1):11-19.
175. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: A systematic literature review. *J Pain Symptom Manage*. 2011;41(6):1073-93.
176. Hoot MR, Khokhar B, Walker WC. Self-report pain scale reliability in veterans and service members with traumatic brain injuries undergoing inpatient rehabilitation. *Mil Med*. 2020;185(3-4):370-376.
177. Gracely RH, McGrath P, Dubner R. Ratio scales of sensory and affective verbal pain descriptors. *Pain*. 1978;5(1):5-18.
178. Patricios JS, Schneider KJ, Dvorak J, et al. Consensus statement on concussion in sport: The 6th International Conference on Concussion in Sport-Amsterdam. 2022. *Br J Sports Med*. 2023;57(11):695-711.
179. Silva MA. Review of the Neurobehavioral Symptom Inventory. *Rehabil Psychol*. 2021;66(2):170-182.
180. Polomano RC, Galloway KT, Kent ML, et al. Psychometric testing of the Defense and Veterans Pain Rating Scale (DVPRS): A new pain scale for military population. *Pain Med*. 2016;17(8):1505-19.
181. Health Readiness and Combat Support. Post-Deployment Health Reassessment. Updated 2023. Available from: https://health.mil/Military-Health-Topics/Health-Readiness/Reserve-Health-Readiness-Program/Our-Services/PDHRA
182. Post Deployment Health Assessment. Available from: https://www.esd.whs.mil/Portals/54/Documents/DD/forms/dd/dd2796.pdf
183. Post Deployment Health Re-Assessment. Available from: https://www.esd.whs.mil/Portals/54/Documents/DD/forms/dd/dd2900.pdf
184. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singap*.1994;23(2):129-38.
185. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills*. 1984;59(3):974.
186. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 Suppl 1):S3-s11.
187. Cella D, Lai JS, Nowinski CJ, et al. Neuro-QOL: Brief measures of health-related quality of life for clinical research in neurology. *Neurology*. 2012;78(23):1860-7.
188. Tulsky DS, Kisala PA, Victorson D, et al. TBI-QOL: Development and calibration of item banks to measure patient reported outcomes following traumatic brain injury. *J Head Trauma Rehabil*. 2016;31(1):40-51.
189. Tulsky DS, Tyner CE, Boulton AJ, et al. Development of the TBI-QOL Headache Pain Item Bank and Short Form. *J Head Trauma Rehabil*. 2019;34(5):298-307.
190. Lange RT, Brickell TA, Bailie JM, Tulsky DS, French LM. Clinical utility and psychometric properties of the Traumatic Brain Injury Quality of Life Scale (TBI-QOL) in US military service members. *J Head Trauma Rehabil*. 2016;31(1):62-78.

191. Ribeiro CJN, Lima A, de Araújo RAS, et al. Psychometric properties of the Behavioral Pain Scale in traumatic brain injury. *Pain Manag Nurs*. 2019;20(2):152-157.
192. Martelli MF, Zasler ND, Bender MC, Nicholson K. Psychological, neuropsychological, and medical considerations in assessment and management of pain. *J Head Trauma Rehabil*. 2004;19(1):10-28.
193. Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med*. 2001;29(12):2258-63.
194. Arbour C, Choinière M, Topolovec-Vranic J, Loiselle CG, Puntillo K, Gélinas C. Detecting pain in traumatic brain-injured patients with different levels of consciousness during common procedures in the ICU: Typical or atypical behaviors? *Clin J Pain*. 2014;30(11):960-9.
195. Arbour C, Gélinas C. Behavioral and physiologic indicators of pain in nonverbal patients with a traumatic brain injury: An integrative review. *Pain Manag Nurs*. 2014;15(2):506-18.
196. López-López C, Arranz-Esteban A, Arias-Rivera S, Solís-Muñoz M, Pérez-Pérez T, Latorre-Marco I. Application of the Behavioural Indicators of Pain Scale in patients with traumatic brain injury. *J Adv Nurs*. 2020;76(7):1862-1870.
197. Jendoubi A, Abbes A, Ghedira S, Houissa M. Pain measurement in mechanically ventilated patients with traumatic brain injury: Behavioral pain tools versus Analgesia Nociception Index. *Indian J Crit Care Med*. 2017;21(9):585-588.
198. Arbour C, Gélinas C, Loiselle CG, Bourgault P. An exploratory study of the bilateral bispectral index for pain detection in traumatic-brain-injured patients with altered level of consciousness. *J Neurosci Nurs*. 2015;47(3):166-77.
199. Ji G, Neugebauer V. Hemispheric lateralization of pain processing by amygdala neurons. *J Neurophysiol*. 2009;102(4):2253-64.
200. Arbour C, Choinière M, Topolovec-Vranic J, Loiselle CG, Gélinas C. Can fluctuations in vital signs be used for pain assessment in critically ill patients with a traumatic brain injury? *Pain Res Treat*. 2014;2014:175794.
201. Park KA, Fehrenbacher JC, Thompson EL, Duarte DB, Hingtgen CM, Vasko MR. Signaling pathways that mediate nerve growth factor-induced increase in expression and release of calcitonin gene-related peptide from sensory neurons. *Neuroscience*. 2010;171(3):910-23.
202. Scher AI, McGinley JS, VanDam LR, et al. Plasma calcitonin gene-related peptide and nerve growth factor as headache and pain biomarkers in recently deployed soldiers with and without a recent concussion. *Headache*. 2023;63(9):1240-1250.
203. Rau JC, Dumkrieger GM, Chong CD, Schwedt TJ. Imaging post-traumatic headache. *Curr Pain Headache Rep*. 2018;22(10):64.
204. Bruce ED, Konda S, Dean DD, Wang EW, Huang JH, Little DM. Neuroimaging and traumatic brain injury: State of the field and voids in translational knowledge. *Mol Cell Neurosci*. 2015;66(Pt B):103-13.
205. Albrecht DS, Granziera C, Hooker JM, Loggia ML. In vivo imaging of human neuroinflammation. *ACS Chem Neurosci*. 2016;7(4):470-483.
206. Gosset A, Wagman H, Pavel D, et al. Using single-photon emission computerized tomography on patients with positive quantitative electroencephalogram to evaluate chronic mild traumatic brain injury with persistent symptoms. *Front Neurol*. 2022;13:704844.
207. Spelman JF, Hunt SC, Seal KH, Burgo-Black AL. Post deployment care for returning combat veterans. *J Gen Intern Med*. 2012;27(9):1200-9.
208. Yedlinsky NT, Neff LA, Jordan KM. Care of the military veteran: selected health issues. *Am Fam Physician*. 2019;100(9):544-551.
209. Johnson SS, Levesque DA, Broderick LE, Bailey DG, Kerns RD. Pain self-management for veterans: Development and pilot test of a stage-based mobile-optimized intervention. *JMIR Med Inform*. 2017;5(4):e40.
210. Hoffman JM, Ehde DM, Dikmen S, et al. Telephone-delivered cognitive behavioral therapy for veterans with chronic pain following traumatic brain injury: Rationale and study protocol for a randomized controlled trial study. *Contemp Clin Trials*. 2019;76:112-119.

211. Ducic I, Sinkin JC, Crutchfield KE. Interdisciplinary treatment of post-concussion and post-traumatic headaches. *Microsurgery*. 2015;35(8):603-7.
212. Department of Veterans Affairs & Department of Defense. VA/DoD Clinical Practice Guideline for Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury. Updated 2021. Available from: https://www.healthquality.va.gov/guidelines/rehab/mtbi/
213. Traumatic Brain Injury Center of Excellence. TBICoE Clinical Recommendation: Management of Headache Following mTBI: Guidance for Primary Care Management in Deployed and Non-deployed Setting. Updated 2016. Available from: https://health.mil/Reference-Center/Publications/2020/07/31/Management-of-Headache-Following-ConcussionmTBI-Clinical-Recommendation
214. Traumatic Brain Injury Center of Excellence. TBICoE Clinical Recommendation: Cognitive Rehabilitation for Service Members and Veterans Following Mild to Moderate Traumatic Brain Injury. Updated 2019. Available from: https://www.health.mil/Reference-Center/Publications/2020/07/30/Cognitive-Rehabilitation-for-Following-Mild-to-Moderate-TBI-Clinical-Recommendation-Full
215. Traumatic Brain Injury Center of Excellence. TBICoE Clinical Recommendation: Management of Sleep Disturbances Following mTBI: Guidance for Primary Care Management in Deployed and Non-Deployed Settings. Updated 2020. Available from: https://health.mil/Reference-Center/Publications/2020/07/31/Management-of-Sleep-Disturbances-Following-ConcussionmTBI-Clinical-Recommendation
216. DiTommaso C, Hoffman JM, Lucas S, Dikmen S, Temkin N, Bell KR. Medication usage patterns for headache treatment after mild traumatic brain injury. *Headache*. 2014;54(3):511-9.
217. Hurwitz M, Lucas S, Bell KR, Temkin N, Dikmen S, Hoffman J. Use of amitriptyline in the treatment of headache after traumatic brain injury: Lessons learned from a clinical trial. *Headache*. 2020;60(4):713-723.
218. Schieffler DA, Matta SE. Evidence to support the use of s-adenosylmethionine for treatment of post-concussive sequelae in the military. *Mil Med*. 2022;187(9-10):e1182-e1192.
219. Li A, Zhao Q, Chen L, Li Z. Apelin/APJ system: An emerging therapeutic target for neurological diseases. *Mol Biol Rep*. 2023;50(2):1639-1653.
220. Neale JH, Yamamoto T. N-acetylaspartylglutamate (NAAG) and glutamate carboxypeptidase II: An abundant peptide neurotransmitter-enzyme system with multiple clinical applications. *Prog Neurobiol*. 2020;184:101722.
221. Kaplan GB, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. *Behav Pharmacol*. 2010;21(5-6):427-37.
222. Hook G, Jacobsen JS, Grabstein K, Kindy M, Hook V. Cathepsin B is a new drug target for traumatic brain injury therapeutics: Evidence for E64d as a promising lead drug candidate. *Front Neurol*. 2015;6:178.
223. Belardo C, Iannotta M, Boccella S, et al. Oral cannabidiol prevents allodynia and neurological dysfunctions in a mouse model of mild traumatic brain injury. *Front Pharmacol*. 2019;10:352.
224. Meidahl AC, Eisenried A, Klukinov M, Cao L, Tzabazis AZ, Yeomans DC. Intranasal oxytocin attenuates reactive and ongoing, chronic pain in a model of mild traumatic brain injury. *Headache*. 2018;58(4):545-558.
225. Trexler LE, Corrigan JD, Davé S, Hammond FM. Recommendations for prescribing opioids for people with traumatic brain injury. *Arch Phys Med Rehabil*. 2020;101(11):2033-2040.
226. Al Alyani O, Al-Farsi F, Al-Saadi T. Review of the prevalence of opioid use disorder following traumatic brain injury. *World Neurosurg*. 2023;177:127-136.
227. Hudson TJ, Painter JT, Gressler LE, et al. Factors Associated with opioid initiation in OEF/OIF/OND veterans with traumatic brain injury. *Pain Med*. 2018;19(4):774-787.

228. Bertenthal D, Yaffe K, Barnes DE, Byers AL, Gibson CJ, Seal KH. Do postconcussive symptoms from traumatic brain injury in combat veterans predict risk for receiving opioid therapy for chronic pain? *Brain Inj*. 2018;32(10):1188-1196.
229. Kumar RG, Ornstein KA, Corrigan JD, Sayko Adams R, Dams-O'Connor K. Association between lifetime history of traumatic brain injury, prescription opioid use, and persistent pain: A nationally representative study. *J Neurotrauma*. 2021;38(16):2284-2290.
230. Graham DP, Cardon AL. An update on substance use and treatment following traumatic brain injury. *Ann N Y Acad Sci*. 2008;1141:148-62.
231. Jammoul M, Jammoul D, Wang KK, Kobeissy F, Depalma RG. Traumatic brain injury and opioids: Twin plagues of the twenty-first century. *Biol Psychiatry*. 2023;95(1):6-14.
232. Fonda JR, Gradus JL, Brogly SB, McGlinchey RE, Milberg WP, Fredman L. Traumatic brain injury and opioid overdose among post-9/11 veterans with long-term opioid treatment of chronic pain. *J Head Trauma Rehabil*. 2020;35(3):209-217.
233. Department of Veteran Affairs & Department of Defense. VA/DOD CPG for Opioid Therapy for Chronic Pain. Updated 2022. Available from: https://www.healthquality.va.gov/Guidelines/Pain/Cot/Vadodotcpg022717.Pdf
234. Driver S, Juengst S, Reynolds M, et al. Healthy lifestyle after traumatic brain injury: A brief narrative. *Brain Inj*. 2019;33(10):1299-1307.
235. Pieczynski J, Cosio D, Pierce W, Serpa JG. Mind-body interventions for rehabilitation medicine: Promoting wellness, healing, and coping with adversity. *Phys Med Rehabil Clin N Am*. 2020;31(4):563-575.
236. Wickwire EM, Schnyer DM, Germain A, et al. Sleep, sleep disorders, and circadian health following mild traumatic brain injury in adults: Review and research agenda. *J Neurotrauma*. 2018;35(22):2615-2631.
237. Lowe A, Neligan A, Greenwood R. Sleep disturbance and recovery during rehabilitation after traumatic brain injury: A systematic review. *Disabil Rehabil*. 2020;42(8):1041-1054.
238. Stewart K, Shakarishvili N, Michalak A, Maschauer EL, Jenkins N, Riha RL. Treating sleep disorders following traumatic brain injury in adults: Time for renewed effort? *Sleep Med Rev*. 2022;63:101631.
239. National Guideline A. NICE Evidence Reviews Collection. *Cognitive interventions for people with complex rehabilitation needs after traumatic injury: Rehabilitation after traumatic injury: Evidence review B2*. National Institute for Health and Care Excellence (NICE) Copyright © NICE 2022.; 2022.
240. Li X, Feng Y, Xia J, et al. Effects of cognitive behavioral therapy on pain and sleep in adults with traumatic brain injury: A systematic review and meta-analysis. *Neural Plast*. 2021;2021:6552246.
241. Fraser F, Matsuzawa Y, Lee YSC, Minen M. Behavioral treatments for post-traumatic headache. *Curr Pain Headache Rep*. 2017;21(5):22.
242. Mayer G, Happe S, Evers S, et al. Insomnia in neurological diseases. *Neurol Res Pract*. 2021;3(1):15.
243. Yarar-Fisher C, Li J, Womack ED, et al. Ketogenic regimens for acute neurotraumatic events. *Curr Opin Biotechnol*. 2021;70:68-74.
244. Bharadwaj VN, Sahbaie P, Shi X, Irvine KA, Yeomans DC, Clark JD. Effect of voluntary exercise on endogenous pain control systems and post-traumatic headache in mice. *J Pain*. 2023;24(10):1859-1874.
245. King PR, Beehler GP, Wade MJ. Self-reported pain and pain management strategies among veterans with traumatic brain injury: A pilot study. *Mil Med*. 2015;180(8):863-8.
246. Peters DM, Jain S, Liuzzo DM, et al. Individuals with chronic traumatic brain injury improve walking speed and mobility with intensive mobility training. *Arch Phys Med Rehabil*. 2014;95(8):1454-60.
247. Schmid AA, Van Puymbroeck M, Fruhauf CA, Bair MJ, Portz JD. Yoga improves occupational performance, depression, and daily activities for people with chronic pain. *Work*. 2019;63(2):181-189.

248. Groessl EJ, Liu L, Chang DG, et al. Yoga for Military veterans with chronic low back pain: A randomized clinical trial. *Am J Prev Med*. 2017;53(5):599-608.
249. Acabchuk RL, Brisson JM, Park CL, Babbott-Bryan N, Parmelee OA, Johnson BT. Therapeutic effects of meditation, yoga, and mindfulness-based interventions for chronic symptoms of mild traumatic brain injury: A systematic review and meta-analysis. *Appl Psychol Health Well Being*. 2021;13(1):34-62.
250. Hoffman JM, Ketchum JM, Agtarap S, et al. Characterizing extreme phenotypes for perceived improvement from treatment in persons with chronic pain following traumatic brain injury: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):43-55.
251. Saper RB, Lemaster CM, Elwy AR, et al. Yoga versus education for veterans with chronic low back pain: Study protocol for a randomized controlled trial. *Trials*. 2016;17(1):224.
252. Schmid AA, Miller KK, Van Puymbroeck M, Schalk N. Feasibility and results of a case study of yoga to improve physical functioning in people with chronic traumatic brain injury. *Disabil Rehabil*. 2016;38(9):914-20.
253. Hilton L, Hempel S, Ewing BA, et al. Mindfulness meditation for chronic pain: Systematic review and meta-analysis. *Ann Behav Med*. 2017;51(2):199-213.
254. Lovette BC, Kanaya MR, Bannon SM, Vranceanu AM, Greenberg J. "Hidden gains"? Measuring the impact of mindfulness-based interventions for people with mild traumatic brain injury: A scoping review. *Brain Inj*. 2022;36(9):1059-1070.
255. Wen PS, Herrin I, Pittman A. Feasibility of yoga to improve symptoms in individuals with severe, chronic traumatic brain injury: A mixed-methods case series. *Altern Ther Health Med*. 2022;28(1):32-37.
256. Khusid MA, Vythilingam M. The emerging role of mindfulness meditation as effective self-management strategy, Part 2: Clinical implications for chronic pain, substance misuse, and insomnia. *Mil Med*. 2016;181(9):969-75.
257. Krese KA, Donnelly KZ, Etingen B, et al. Feasibility of a combined neuromodulation and yoga intervention for mild traumatic brain injury and chronic pain: Protocol for an open-label pilot trial. *JMIR Res Protoc*. 2022;11(6):e37836.
258. Bonanno M, Calabrò RS. Back to the future: An appraisal of the role of osteopathic manipulative treatment in patients with neurological diseases. *Innov Clin Neurosci*. 2023;20(7-9):8-10.
259. Davis L, Hanson B, Gilliam S. Pilot study of the effects of mixed light touch manual therapies on active duty soldiers with chronic post-traumatic stress disorder and injury to the head. *J Bodyw Mov Ther*. 2016;20(1):42-51.
260. Wetzler G, Roland M, Fryer-Dietz S, Dettmann-Ahern D. CranioSacral therapy and visceral manipulation: A new treatment intervention for concussion recovery. *Med Acupunct*. 2017;29(4):239-248.
261. Minen M, Jinich S, Vallespir Ellett G. Behavioral therapies and mind-body interventions for posttraumatic headache and post-concussive symptoms: A systematic review. *Headache*. 2019;59(2):151-163.
262. Vaninetti M, Lim M, Khalaf A, et al. fMRI findings in MTBI patients with headaches following rTMS. *Sci Rep*. 2021;11(1):9573.
263. Kang DH, Kim GW. Changes in diffuse tensor imaging and therapeutic effect of repetitive transcranial magnetic stimulation in traumatic brain injury with central pain. *Brain Sci*. 2020;10(12).
264. Leung A, Shukla S, Fallah A, et al. Repetitive transcranial magnetic stimulation in managing mild traumatic brain injury-related headaches. *Neuromodulation*. 2016;19(2):133-41.
265. Leung A, Shirvalkar P, Chen R, et al. Transcranial magnetic stimulation for pain, headache, and comorbid depression: INS-NANS Expert consensus panel review and recommendation. *Neuromodulation*. 2020;23(3):267-290.
266. Leung A, Metzger-Smith V, He Y, et al. Left dorsolateral prefrontal cortex rTMS in alleviating mTBI related headaches and depressive symptoms. *Neuromodulation*. 2018;21(4):390-401.
267. Choi GS, Kwak SG, Lee HD, Chang MC. Effect of high-frequency repetitive transcranial magnetic stimulation on chronic central pain after mild traumatic brain injury: A pilot study. *J Rehabil Med*. 2018;50(3):246-252.

268. Li X, Lu T, Yu H, et al. Repetitive Transcranial magnetic stimulation for neuropathic pain and neuropsychiatric symptoms in traumatic brain injury: A systematic review and meta-analysis. *Neural Plast*. 2022;2022:2036736.
269. Meek BP, Hill S, Modirrousta M. Accelerated repetitive transcranial magnetic stimulation in the treatment of post-concussion symptoms due to mild traumatic brain injury: A pilot study. *Brain Inj*. 2021;35(1):48-58.
270. Mollica A, Greben R, Oriuwa C, Siddiqi SH, Burke MJ. Neuromodulation treatments for mild traumatic brain injury and post-concussive symptoms. *Curr Neurol Neurosci Rep*. 2022;22(3):171-181.
271. Mollica A, Safavifar F, Fralick M, Giacobbe P, Lipsman N, Burke MJ. Transcranial magnetic stimulation for the treatment of concussion: A systematic review. *Neuromodulation*. 2021;24(5):803-812.
272. Nardone R, Sebastianelli L, Versace V, et al. Repetitive transcranial magnetic stimulation in traumatic brain injury: Evidence from animal and human studies. *Brain Res Bull*. 2020;159:44-52.
273. Pink AE, Williams C, Alderman N, Stoffels M. The use of repetitive transcranial magnetic stimulation (rTMS) following traumatic brain injury (TBI): A scoping review. *Neuropsychol Rehabil*. 2021;31(3):479-505.
274. Sodders MD, Martin AM, Coker J, Hammond FM, Hoffman JM. Acupuncture use for pain after traumatic brain injury: A NIDILRR Traumatic Brain Injury Model Systems cohort study. *Brain Inj*. 2023;37(6):494-502.
275. Bell AE, Falconi A. Acupuncture for the treatment of sports injuries in an austere environment. *Curr Sports Med Rep*. 2016;15(2):111-5.
276. Jonas WB, Bellanti DM, Paat CF, 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):113-130.
277. Wen X, Yang Y, Li Y, et al. Effects of acupuncture treatment on posttraumatic headache after traumatic brain injury in patients: A protocol for systematic review. *Medicine (Baltimore)*. 2022;101(18):e29158.
278. Manni L, Albanesi M, Guaragna M, Barbaro Paparo S, Aloe L. Neurotrophins and acupuncture. *Auton Neurosci*. 2010;157(1-2):9-17.
279. King HC, Hickey AH, Connelly C. Auricular acupuncture: A brief introduction for military providers. *Mil Med*. 2013;178(8):867-74.
280. Kwak HY, Leem J, Seung HB, Kwon CY, Jeong HS, Kim SH. Acupuncture therapy for military veterans suffering from posttraumatic stress disorder and related symptoms: A scoping review of clinical studies. *Healthcare (Basel)*. 2023;11(22).
281. Federman DG, Radhakrishnan K, Gabriel L, Poulin LM, Kravetz JD. Group battlefield acupuncture in primary care for veterans with pain. *South Med J*. 2018;111(10):619-624.
282. Ablin JN, Lang E, Catalogna M, et al. Hyperbaric oxygen therapy compared to pharmacological intervention in fibromyalgia patients following traumatic brain injury: A randomized, controlled trial. *PLoS One*. 2023;18(3):e0282406.
283. Yang M, Yang Z, Wang P, Sun Z. Current application and future directions of photobiomodulation in central nervous diseases. *Neural regeneration research*. 2021;16(6):1177-1185.
284. Naeser MA, Martin PI, Ho MD, et al. Transcranial Photobiomodulation treatment: Significant improvements in four ex-football players with possible chronic traumatic encephalopathy. *J Alzheimers Dis Rep*. 2023;7(1):77-105.
285. Mahoney EJ, Silva MA, Reljic T, et al. Rehabilitation needs at 5 years post-traumatic brain injury: A VA TBI Model Systems Study. *J Head Trauma Rehabil*. 2021;36(3):175-185.
286. Haun JN, Nakase-Richardson R, Cotner BA, et al. Stakeholder engagement to identify implementation strategies to overcome barriers to delivering chronic pain treatments: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):E29-e40.
287. Nakase-Richardson R, Cotner BA, Martin AM, et al. Provider perspectives of facilitators and barriers to reaching and utilizing chronic pain healthcare for persons with traumatic brain injury: A

qualitative NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2024;39(1):E15-e28.
288. Merritt BP, Kretzmer T, McKenzie-Hartman TL, Gootam P. Neurobehavioral management of the polytrauma veteran. *Phys Med Rehabil Clin N Am*. 2019;30(1):133-154.
289. Johnson JM, Capehart BP. Psychiatric care of the post-september 11 combat veteran: A review. *Psychosomatics*. 2019;60(2):121-128.
290. Simmonds MJ, Finley EP, Vale S, Pugh MJ, Turner BJ. A qualitative study of veterans on long-term opioid analgesics: Barriers and facilitators to multimodality pain management. *Pain Med*. 2015;16(4):726-32.
291. National Academies of Sciences E, Medicine, Health, et al. Traumatic Brain Injury: A Roadmap for Accelerating Progress. In: Matney C, Bowman K, Berwick D, eds. National Academies Press (US) Copyright 2022 by the National Academy of Sciences. All rights reserved.; 2022.
292. Hoffman JM, Ketchum JM, Agtarap S, et al. Characterizing extreme phenotypes for perceived improvement from treatment in persons with chronic pain following traumatic brain injury: A NIDILRR and VA TBI Model Systems Collaborative Project. *J Head Trauma Rehabil*. 2023; 39(1):43-55.
293. Helmick KM, Spells CA, Malik SZ, Davies CA, Marion DW, Hinds SR. Traumatic brain injury in the US military: Epidemiology and key clinical and research programs. *Brain Imaging Behav*. 2015;9(3):358-66.