Traumatic Brain Injury

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Overview of TBI in the Military/Veterans

Traumatic brain injuries (TBIs) within the military are considered one of the "signature injuries" of the recent US military conflicts in the Middle East including Operation Enduring Freedom/Operation Iraqi Freedom and Operation New Dawn (OEF/OIF/OND) [1]. Given the advancements in protective armor and battlefield medicine, many service members are surviving their injuries when compared to previous combat operations. These war heroes may return stateside with polytraumatic injuries. Polytrauma is defined by the Department of Veterans Affairs (VA) as TBI plus "two or more injuries, one of which may be life threatening, sustained in the same incident that affect multiple body parts or organ systems and result in physical, cognitive, psychological, or psychosocial impairments and functional disabilities [2]." TBI can co-occur in this unique population along with pain, amputations, spinal cord injury, burns, visual disturbances, and other psychological conditions such as anxiety, depression, and posttraumatic stress disorder (PTSD), thus making this complex polymorbid population a challenge to treat.

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Definition of TBI

The Veterans Affairs/Department of Defense (VA/DoD) defines TBI as a "traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force and is indicated by new onset or worsening of at least one of the following clinical signs immediately following event: any period of loss of or decreased level of consciousness; any loss of memory for events immediately before or after the injury; any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.); neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient; [an] intracranial lesion [3] Table 14.1."

It is important to note that while external forces include any object striking the head or vice versa, it also encompasses penetrating injury, blast forces, and acceleration/deceleration movement without direct external trauma. Furthermore, the event itself without manifestation of altered consciousness, altered mentation, memory loss, or the aforementioned clinical signs does not constitute a TBI [3].

There are significant challenges associated with diagnosing TBI retrospectively, as often is the case when service members return from deployment and screen positive as a veteran. The diagnosis is usually based solely on the veterans' recollection of events, sometimes occurring many years ago. Highlighting these difficulties is one 2012 study that demonstrated that service members who reported loss of consciousness with their mild TBI were significantly less likely to have abnormal neuroimaging than those who suffered a mild TBI and did not report loss of consciousness [4].

Another concern in correctly establishing a diagnosis is the difficulty in teasing out whether alteration of consciousness occurred as a result of the physical or psychological trauma. Furthermore, the high prevalence of PTSD in the military population, as well as the overlapping nature of symptomatology with TBI, also hinders the ability to establish a firm diagnosis.

Table 14.1 TBI severity grading

	Mild	Moderate	Severe
Loss of consciousness	0–30 min	30 min–24 h	>24 h
Alteration of consciousness	Up to 24 h	>24 h	>24 h
Posttraumatic amnesia	0–1 day	1–7 days	>1 week
Structural imaging	Normal	Normal or abnormal	Normal or abnormal

Adapted from the VA/DoD Clinical Practice Guidelines 2016

Epidemiology with Causes of TBI Including Blast Wave Physics

The Defense and Veterans Brain Injury Center (DVBIC) reports that since the year 2000, there have been 379,519 service members worldwide who have received a first-time diagnosis of traumatic brain injury, 82.3% of which were graded as mild (Fig. 14.1).

Explosions during OEF/OIF were responsible for 78% of the injuries suffered, accenting the importance of research into blast wave physics and the brain [5]. Blast waves are a unique phenomenon that can lead to brain injury through four distinct mechanisms. The primary mechanism is through direct effect of the blast wave itself on the vasculature and soft tissue components of the brain. The secondary aspect involves the debris that is launched through the air as a result of the blast and includes rocks, shrapnel, or any other projectile that may result in blunt or penetrating injury. The tertiary mechanism involves the force of the blast throwing the entire individual against a blunt object, the ground, or a wall, for example. Lastly, the quaternary effect of a blast relates to the inhalation injuries, burns, and/or potential toxic exposures that compound the traumatic nature of this event [6].

The primary mechanism of injury through blast wave exposure deserves special mention as debate exists as to the underlying physics of the event. Two leading hypotheses are as follows: (1) the blast wave itself is transmitted through intracranial structures resulting in direct deformation closely resembling acceleration-deceleration-type injurious motion [7]. (2) The blast wave impacts the torso, pressurizing the underlying vasculature and large cavities resulting in oscillations of the fluid within. These oscillations carry with them the kinetic energy of the blast wave to the intracranial structures, thus culminating in injury and initiation of the inflammatory cascade [8].

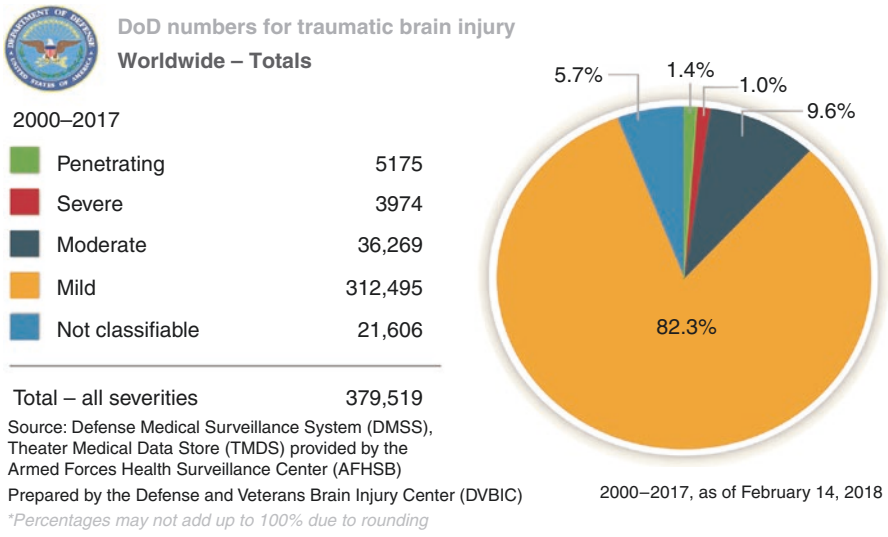

Fig. 14.1 Total number of Department of Defense traumatic brain injuries reported by the Defense and Veterans Brain Injury Centers (DVBIC). (Reprinted with permission from public domain: http://dvbic.dcoe.mil/)

The mechanisms for injury in blunt head trauma are more straightforward. Acceleration-deceleration motion within the skull affects the brain itself as its motion within the skull is independent from the more rigid structures. Beyond the direct distortion of the brain through translational forces, this motion can cause a coup-contrecoup injury, in which the brain impacts one side of the skull and bounces backward, impacting the opposite side as well. Ultimately, contusions and swelling may result at polar ends of the brain [9]. A second mechanism is that of rotational acceleration. Rotational acceleration can cause damage secondary to the shearing forces on tissues of different densities within the brain. These shearing forces cause what is known as diffuse axonal injury (DAI), or, in other words, widespread injury to the white matter tracts, and are hypothesized as the cause of persistent deficits in mild TBI [10, 11].

Initial In-Theater Evaluation and Management of Mild TBI

As mentioned previously, objective identification of mild traumatic brain injuries is difficult, as symptoms may resolve quickly, there may be entangling of psychological trauma, and there is yet to be a worldwide standard for diagnosis. Within the VA/DoD system, diagnosis is made by identifying loss of consciousness, alterations of consciousness, or posttraumatic amnesia due to disruption of brain function secondary to external forces.

To further aid in diagnosis, some federal agencies have opted to mandate predeployment testing utilizing the Automated Neuropsychological Assessment Metric (ANAM). The ANAM is a battery of neurocognitive tests that help establish a baseline predeployment and can identify decline in the postdeployment setting [12].

Once in theater, a screening for potential concussion after an inciting event is through the use of the Military Acute Concussion Evaluation (MACE). The MACE test is a measure developed by the Defense and Veterans Brain Injury Center (DVBIC) in 2006. The MACE is designed to help obtain a detailed history of the event and identify acute symptomatology through history and brief neurocognitive examinations. Independent research has shown that the MACE exam is a useful, reliable, and valid measure of cognitive dysfunction after mild TBI, although it cannot be used in isolation to diagnose concussion [13]. Through this method, first responders in theater can better triage those with suspected brain injuries to higher centers of care as appropriate.

After a service member obtains a diagnosis of concussion, their recovery process is dependent on symptom burden. The DVBIC and the Office of the Army Surgeon General have developed guidelines for return to activity in the military setting. A step-wise approach, similar to that seen in return-to-play guidelines in the sports world, is advocated.

Service members are progressed through six different stages of activity, the first of which is a 24-h mandatory rest period. Additional time for recovery may be warranted but is determined through clinical examination and symptomatology. Of

note, if this is a service member's first concussion, and symptoms resolve within 24 h, exertional testing may be trialed without having to undergo the six steps for full return to activity. Individuals could conceivably return to activity afterward if they successfully remain asymptomatic.

A second concussion obtained within a year of the first automatically mandates a rest period of 1 week after resolution of symptoms. A third concussion within 1 year necessitates a full neurological examination, including neuroimaging, a functional assessment, and neuropsychological testing.

Progression within the return-to-activity guidelines involves daily subjective scoring through the Neurobehavioral Symptom Inventory (NSI), which helps elicit severity of physical and cognitive symptom burden perceived after TBI, and Borg's Rate of Perceived Exertion (RPE), which quantifies the self-assessed perception of physical exertion exhibited by the service member. For objective measures, theoretical maximum heart rate (TMHR), calculated using 220 minus years of age, and blood pressure are tracked. A score of 2 or higher on the NSI for any symptom, resting heart rate of greater than 100, and resting blood pressure of greater than 140/90 mm Hg will warrant another 24 h at the service member's current stage [14]. Even with these activity guidelines, many service members return stateside with lingering effects of their TBI and other comorbid conditions.

Polytrauma System of Care

Assessment of all severities of brain injury is accomplished through the VA Polytrauma System of Care which is a tiered comprehensive network of rehabilitation care comprised of the Polytrauma Rehabilitation Centers (PRCs), Polytrauma Network Sites (PNSs), Polytrauma Support Clinic Teams (PSCTs), and Polytrauma Point of Contacts (PPOCs). There are five PRCs nationwide: San Antonio, Tampa, Palo Alto, Minneapolis, and Richmond [15]. The PRCs are regional hubs for clinical care, education, and research.

Colocated at each PRC are residential brain injury programs, robust outpatient programs, VA Amputee System of Care, VA Spinal Cord Injury Centers, and Assistive Technology Centers of Excellence. Each PRC is staffed with a full interdisciplinary team trained to handle these complex conditions, as well as a wide array of consultative services. Several of the inpatient beds are also dedicated for emerging consciousness programs, which are specifically designed to help service members with disorders of consciousness [16]. In addition, all of the PRCs are accredited by the Commission on Accreditation of Rehabilitation Facilities (CARF).

The Polytrauma Transitional Rehabilitation Programs are located at each of the PRCs and are designed as a residential rehabilitation program to monitor and optimize the ability of service members to live independently and successfully reintegrate into the community [17]. Residents typically continue physical, cognitive, and behavioral therapies in a subacute setting under 24-h supervision by licensed

practical nurses. Other aspects of the program involve focus on living skills, home maintenance, shopping, food preparation, return to drive, money management, community social skills, and vocational training among other aspects of independent living [15].

PNS's are postacute outpatient sites containing both Commission on Accreditation of Rehabilitation Facilities (CARF) accredited inpatient facilities and outpatient facilities for medically stabilized service members. They are 23 PNSs sites which assist in coordinating care across all of the Veterans Integrated Service Networks (VISNs), which consist of regional PSCTs and PPOCs. PNSs can additionally help as a first-line triage facility for service members with polytrauma to determine the need for referral into a PRC or PTRP [18].

PSCTs continue the interdisciplinary approach to management but through outpatient facilities that help manage and monitor veterans with any long-term, chronic needs. Referrals stem from PNSs and PRCs as veterans continue to functionally improve. These centers can also refer back if they identify any new or worsening conditions that may be related to polytrauma or TBI.

Finally, PPOCs typically consist of social workers or case managers knowledgeable about the Polytrauma System of Care. Their roles are to assist with the monitoring of long-term needs in this patient population and to refer to higher levels of care when necessary. Direct treatment at PPOCs is generally limited in scope [19–21] (Fig. 14.2).

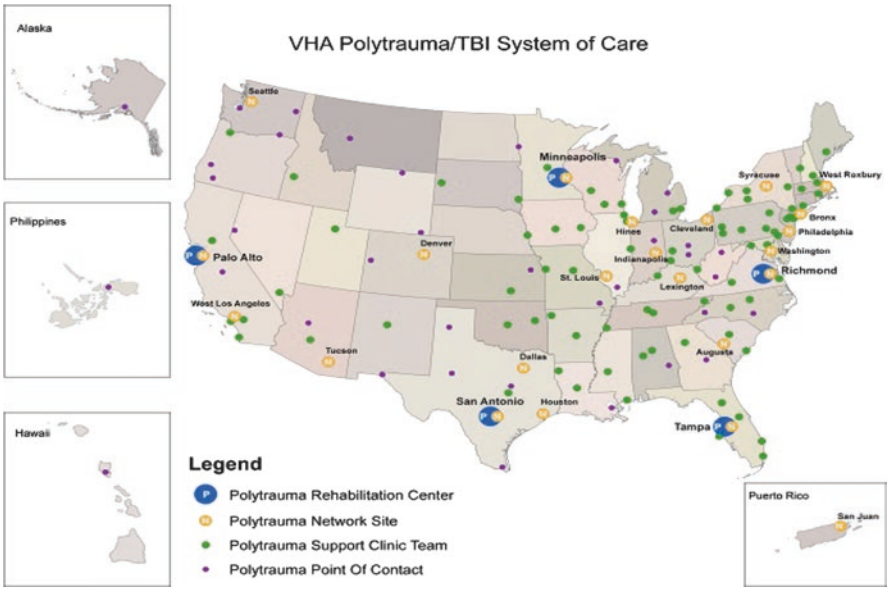

Fig. 14.2 Polytrauma System of Care locations. (Reprinted with permission from public domain: www.polytrauma.va.gov)

Assessment of TBI in the VA

In 2007, the VA has implemented a TBI screening measures for all veterans returning from the conflicts in Iraq and Afghanistan to identify and treat those with possible TBI, which may have gone unreported and untreated [22]. The initial screening consists of four questions assessing any exposure to an inciting event that could cause a TBI and the resultant symptoms that the veteran experienced and continues to experience [23] Table 14.2.

A positive screen results in the veteran undergoing a comprehensive VHA TBI evaluation (CTBIE) which includes full history and physical examination and history of TBI events with persistent sequelae, administration of the Neurobehavioral Symptom Inventory (NSI), and providing a diagnosis and treatment plan which is typically through the interdisciplinary polytrauma rehabilitation teams [24]. Since April 2007, over 1.1 million OEF/OIF/OND Veterans have been screened for possible mild traumatic brain injury (mTBI) with over 154,000 completed CTBIEs.

Table 14.2 VA/DoD TBI clinical reminder

Traumatic brain injury screening
The patient reports service in Operation Iraqi Freedom, Operation Enduring Freedom, Operation New Dawn, Operation Inherent Resolve or Operation Freedom's Sentinel.
Section 1: The veteran experienced the following events during OIF/OEF deployment:
Blast or explosion – IED (improvised explosive device), RPG (rocket-propelled grenade), land mine, grenade, etc.
Vehicular accident/crash (any vehicle, including aircraft)
Fragment wound or bullet wound above the shoulders
Fall
Section 2: The veteran had the following symptoms immediately afterwards:
Losing consciousness/"knocked out"
Being dazed, confused or "seeing stars"
Not remembering the event
Concussion
Head injury
Section 3: The veteran states the following problems began or got worse afterward:
Memory problems or lapses
Balance problems or dizziness
Sensitivity to bright light
Irritability
Headaches
Sleep problems
Section 4: The veteran relates he/she is currently having or has had the following symptoms within the past week:
Memory problems or lapses
Balance problems or dizziness
Sensitivity to bright light
Irritability
Headaches
Sleep problems

Table 14.3 Common symptoms of postconcussive syndrome

Potential symptomatology in postconcussive syndrome		
Physical	Cognitive	Behavioral
Headache	Impaired memory	Sleep disturbances
Sensory deficits	Attention/concentration deficits	Irritability and anger
Visual disturbances	Difficulty with executive functions	Anxiety
Nausea/vomiting	Impaired processing speeds	Depression
Balance problems	Impaired communication	Isolation
Phono/photophobia		
Tinnitus		

Postconcussive Symptoms

Postconcussive syndrome is an umbrella term used to describe any number of nonspecific symptoms occurring at a nonspecific time after a TBI and persisting beyond a nonspecific time frame for recovery [25]. Of note, the 5th international conference on concussion in sport held in Berlin recently proffered that normal recovery be defined as greater than 10–14 days in adults and greater than 4 weeks in children [26]. Regardless of timing, symptoms to be aware of include physical ailments such as headaches, sensory deficits, and balance problems; cognitive issues such as difficulty with attention and concentration, memory problems, and executive dysfunction; and emotional/behavioral difficulties such as sleep disturbances, depression, and anxiety.

Risk factors for persistent postconcussive syndrome include lower education, lower rank, female sex, secondary gain, and psychiatric comorbidities [27]. The single most effective strategy for treatment after mild traumatic brain injury has been found to be early education about concussion, potential symptoms and their management, and the natural expected course of recovery [28] Table 14.3.

Evaluation and Management of Common Symptoms After TBI

Posttraumatic Headache

With one of the highest incidences of any postconcussive symptom, and as the most common secondary headache disorder, posttraumatic headaches (PTH) should be screened for appropriately [29]. The International Classification of Headache Disorders version 3 criteria label PTH as a "headache attributed to trauma or injury to the head and/or neck." Although they admit the time frame is arbitrary, requirements for diagnosis remain a headache that develops within 1 week of the concussion, arousal from coma, or attainment of the ability to sense or report pain. PTH is termed "persistent PTH" when headaches continue for greater than 3 months [30]. In some individuals, PTH can continue for years, leading to a decrease in the quality of life and potential loss of work [31]. Risk factors for prolonged PTH include female gender, multiple TBIs, and premorbid migraine history [32].

There are no clinical characteristics that distinguish PTH from a primary headache, such as migraines. Treatment, therefore, follows the same principles as for the primary headache phenotype it most closely resembles in that individual. Some of the frequently encountered primary headache types are migraines, which present as unilateral and throbbing in nature, often time accompanied by an aura; cervicogenic headache, which stems from the cervical spine and is associated with neck pain and limited range of motion; tension-type headache, which is associated with stress and presents in a band-like fashion, described as tightness; and neuralgic headache, which occurs with irritation of the occipital nerves, producing pain distributed along the path of the nerves, and can often be reproduced through palpation [33].

Identifying triggers, optimizing sleep, limiting caffeine and alcohol intake, and reducing stress are all personal measures that a service member can focus on to help reduce the frequency of PTH [34, 35]. Consideration of ice, heat, physical therapy, acupuncture, and cognitive behavioral therapy is appropriate to lessen dependence on pharmaceuticals [36]. If headaches are unresponsive to environmental and behavioral modifications, the next consideration will be between medications and procedural interventions, depending on the headache type and frequency.

If medications are warranted, a decision between abortive and prophylactic treatment must be made. Prophylactic medications include beta-blockers, antidepressants, and antiepileptics and are used to reduce headache frequency to less than 10 per month [37]. Abortive therapies are used for breakthrough headache relief and include acetaminophen, nonsteroidal anti-inflammatory drugs, and triptans. A selection of a few common choices is listed in the table below.

Sleep Disturbances

Sleep disturbances are also highly prevalent after TBI and can disrupt or prolong natural recovery if not effectively addressed. Inadequate sleep quality has been implicated as an independent risk factor for persistent neurobehavioral conditions [38]. One study of veterans who had committed suicide highlighted that those with sleep disturbances were quicker to commit suicide than those veterans without sleep complaints, estimating a 57% loss of survival time [39].

Insomnia is one of the most common sleep disturbances encountered and has been reported to occur in 30–60% of individuals after a concussion [40]. It has been found to be associated with decreased quality of life, fatigue, pain, suicidal ideation, PTSD, and depression [41–43]. Other sleep disturbances encountered after TBI include hypersomnia, obstructive sleep apnea, periodic limb movement, and narcolepsy [44].

Ideally, this condition will respond to behavioral interventions, such that pharmacological treatments may not be needed. This entails that the provider obtains a good history that includes pre- and postinjury sleep habits, caffeine use, alcohol use, nicotine use, diet, exercise habits, current medications, comorbid conditions, mood, TV and cellphone habits, history of nightmares, and any other potential contributors to poor sleep in general.

The American College of Physicians (ACP) now recommend cognitive behavioral therapy for insomnia (CBT-I) as the first-line treatment [45]. In fact, a recent randomized controlled trial of 151 active duty army members found CBT-I to be effective in not only treating insomnia but also improving mental health, curbing caffeine and nicotine use, and reducing daytime fatigue [46]. Pharmaceutical options for when CBT-I is not available include melatonin and melatonin-receptor agonists, z-drugs (sedative/hypnotics), and medications within the antidepressant family.

Cognitive Dysfunction

Cognitive impairments can be seen in the immediate aftermath of concussion and may affect any cognitive domain, including processing speeds, attention, memory, and executive function [47]. Executive function is a term that describes the combined behavioral and cognitive functions, controlled through the prefrontal cortex, that is needed to accomplish higher order tasks by way of planning, adequate judgment, memory retrieval, and motivation [48]. When executive function is impaired, individuals are more likely to have disorganized memory encoding, such that they will conflate or misremember events [49, 50].

Generally, most individuals with cognitive complaints will report resolution within a 6-month period, although about 15% will describe persistent difficulties [51, 52]. In fact, this was further confirmed in one study comparing 902 service member's ANAM scores pre- and postdeployment for those reporting TBI vs no TBI. Seventy percent of those who suffered a TBI did not show a deviation from their predeployment baseline, and only those with active symptomatology and TBI were shown to be at highest risk for cognitive dysfunction [53].

Management should include a comprehensive history to assess other causes of cognitive clouding including alcohol and/or drug use, sleep disorders, mental health conditions, and medication side effects. After those conditions are addressed, referral for neuropsychological testing will assist in identifying the cognitive domains affected in service members with persistent impairments, thus helping guide efforts in cognitive rehabilitation.

Although research is divided at present in regard to the efficacy of cognitive rehabilitation, several small studies successfully demonstrated improvements in attention, processing speeds, memory, and executive dysfunction [48, 54–56]. Thus, it may be a worthwhile effort, as current pharmaceutical options carry with them a host of side effects. Methylphenidate, for instance, has been studied in the moderate to severe TBI population and has shown benefits in improving processing speed but has a side effect profile that includes emotional lability, aggression, headaches, insomnia, psychosis, arrhythmias, and a high potential for abuse and dependence [57–59].

Dizziness/Vestibular

Balance is achieved through coordination of the vestibular, visual, and proprioceptive systems chiefly through the brainstem. The vestibular system is composed of the semicircular canals, which recognize angular acceleration, and otolithic organs,

which recognize linear acceleration [60]. Insult to these systems, by way of blunt or blast trauma to the head, can result in vertigo, dizziness, and/or postural instability and cause prolonged issues if more systems are involved, as is the case in polytrauma patients [61].

Initial assessment should involve a detailed history, to include onset, frequency, duration, characterization, worsening and alleviating factors, and associations to be able to target better appropriate treatments. The differential should initially remain broad and include orthostasis, vertigo, ataxia, benign paroxysmal positional vertigo (BPPV), Meniere's disease, and other causes of impaired balance. Additionally, a thorough review of medications is warranted as dizziness as a side effect is quite common with many drugs [35].

Management and treatment differ among the etiologies of dizziness. For example, a diagnosis of BPPV can be treated by repositioning maneuvers; a diagnosis of orthostasis with hydration, medication review, and salt tablets; or a diagnosis of peripheral or central vertigo with physical therapy and consideration of short-term vestibular suppressant medications [62]. Of special mention is vestibular physical therapy, which has shown efficacy in the treatment of unilateral peripheral vertigo and chronic Meniere's disease and significant symptom reduction in central vertigo [61].

Depression

There is an increased risk of suicide in military members that have suffered multiple TBIs, with one study reporting a three- to fourfold increase in risk as compared to the normal population [63, 64]. Screening for depression is essential as prevalence after TBI is high, estimated at about 30% [65]. In addition, emotional distress may lead to a heavier symptom burden in postconcussive syndrome if not effectively treated [19758488]. However, screening should occur at variable times even though prevalence is highest in the first year post-TBI, as lifetime risk is increased in general after TBI, and some studies demonstrate development of depressive symptoms in the second year and beyond [66].

Risk factors for depression after TBI have been postulated to include premorbid history of alcohol or substance abuse, premorbid depression, location of brain injury, and older age, but there is an overall lack of consistent data in this population [67–70]. Assessment of these depressive disorders under the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition, may most appropriately be within the criteria for mood disorders due to another medical condition [American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.)]. Utilization of psychiatric scales including the Beck Depression Inventory, Hamilton Depression Scale, and the Neurobehavioral Functioning Inventory Depression Scale has been found as valid and reliable options for assessment [66].

Nonpharmaceutical options such as psychotherapy and psychoeducation are preferred treatment methods in this population in order to avoid side effects carried by medications that may interfere with cognition or recovery. Unfortunately, a 2015 systematic review of cognitive and behavioral rehabilitation interventions only found limited support for these methods, but more research is certainly warranted

and underway [48]. If treatment with medications is necessary, selective serotonin reuptake inhibitors (SSRIs) have been considered first-line treatment secondary to their generally favorable side effect profile [71]. However, many pharmaceutical options exist, and careful selection should be made to optimize benefits and limit side effects.

Posttraumatic Stress Disorder and TBI

Concurrent posttraumatic stress disorder (PTSD) with mild TBI is to be expected considering the context of military injuries [72]. Prevalence of PTSD among military service members and veterans with TBI spans anywhere from 12% to 89% [73]. Symptom burden is more severe in individuals with coexisting mild TBI and PTSD than those with PTSD alone, and unfortunately, there is significant overlap in experienced symptoms with both diagnoses, making it challenging to determine a best pathway for treatment [74]. Shared symptoms include depression, anxiety, sleep disturbances, emotional lability, and cognitive dysfunction [75].

Management for those suffering with PTSD and TBI is difficult, as research in this specialized population is limited and some treatments may be of benefit to one pathological entity while simultaneously a detriment to the other. For example, the use of benzodiazepines may help in the treatment of PTSD, but is relatively contraindicated in TBI, as studies have shown that benzodiazepines may hinder neuroplasticity [76]. Similarly, prescribing neurostimulants to help cognitive functioning in TBI patients may worsen anxiety and insomnia in PTSD.

Current strategies include the use of evidence-based psychotherapies to help not only treat PTSD but also to potentially disentangle which symptoms can be attributed to either diagnosis. Cognitive processing therapy and prolonged exposure therapy have shown promise in decreasing symptom burden in individuals with TBI and PTSD [77, 78]. The VA/DoD Clinical Practice Guidelines for PTSDs state if pharmaceutical management is needed, first-line medications for the treatment of PTSD include sertraline, paroxetine, fluoxetine, and venlafaxine, but close monitoring and judicious use are essential.

Lastly, and potentially most ideal, comprehensive treatment with an interdisciplinary team may help tackle the complexities of such patients, as was shown in a 2014 study of twenty-four veterans with PTSD and TBI. After an 8-week intervention, researchers found a reduction of overall symptom burden and improvements in quality of life and occupational performance [79].

Neurodegeneration/CTE in Veterans

Chronic traumatic encephalopathy (CTE) is an insidious, progressive neurodegenerative process that is hypothesized to occur secondary to sustaining repetitive traumatic brain injuries, as no evidence to date exists that a single TBI can lead to this diagnosis [80]. CTE is only diagnosed posthumously through autopsy [81]. At

autopsy, neuropathologists observe a characteristic distribution of hyperphosphorylated tau protein distinct from other neurodegenerative processes, with a propensity to accumulate in the depths of the cerebral sulci in an irregular pattern [82, 83]. Of note, CTE has been described in individuals without history of concussion. Therefore, CTE is deemed a product of repetitive head injuries and subconcussive blows, but not necessarily concussions [84].

Clinical presentation is similar to that of persistent postconcussion syndrome and can include nonspecific symptoms from a vast array of domains. Behavioral symptoms like explosivity, impulsivity, and paranoia, cognitive symptoms like memory loss and impaired attention, and physical symptoms like headaches and dysarthria have all been described in this setting [85].

Most studies to date are in large part focused on sports athletes. However, in a 2012 study by Goldstein et al., a postmortem comparison of the neuropathology of four military veterans with a history of blast exposure and/or blunt concussion and four sports athletes with a history of blunt concussion was made and found to be remarkably similar. CTE-linked tau neuropathology was indistinguishable among the brains and deposited in the characteristic distribution pattern as would be expected with development of CTE. This study was indeed intriguing, although limited by the small sample size, inherent selection bias, inability to account for confounding factors, and difficulty establishing causality through postmortem analysis [86].

Although research is blossoming quickly to better understand this unique disease entity, at present there lacks large, longitudinal prospective studies to guide prevention, education, and management strategies, especially in the military population. Additionally, as diagnosis is only made at autopsy, controversy still exists as to how to identify this process in the living. As we await further research, a holistic approach and symptom-focused treatment remain the mainstay of management.

Pharmacology in Mild TBI

If physical therapies, psychotherapies, environmental and behavioral modifications, and education are insufficient in controlling persistent symptoms following mild TBI, pharmaceuticals may be indicated to provide relief. As previously alluded to in the antecedent sections, pharmacotherapy in the TBI population necessitates careful consideration as to not hinder recovery or cause additional complications secondary to side effects. In fact, many medications carry with them a side effect profile that resembles the symptoms experienced after a TBI. Thus, a medication review is warranted first and foremost, and optimization is advised prior to enlisting any new drug.

It is important to remember that, as with all medications, the approach should be to start low and go slow. Educate the patient as to the medication, the intended use, and potential side effects they may experience so they can alert their providers if issues arise. Be wary of polypharmacy, especially in a population with a multitude of symptomatology, and attempt to define an appropriate but finite length of time for the medication. Finally, in the TBI population, try to avoid or use extreme caution with any medication that may lower the seizure threshold [35] Table 14.4.

Table 14.4 Selection of common pharmaceutical options in the treatment of postconcussive syndrome

Medication	Classification	Dosage	Side effects	Notes
Headaches (abortive medications)				
Naproxen	Nonsteroidal anti-inflammatory drug	Initial: 750 mg PO as needed; max dose: 1250 mg/day	Abdominal pain, constipation, dizziness, headache, nausea, GI bleed, cardiovascular risk	
Acetaminophen	Analgesic	Initial: 325–650 mg PO as needed q4hours; max dose: 3250 mg/day	Dizziness, disorientation, rash, Stevens-Johnson syndrome, agranulocytosis	
Sumatriptan	Serotonin 5-HT-receptor agonist	Initial: 25 mg PO as needed; max dose: 200 mg/day	Paresthesias, dizziness, warm/hot sensation, chest pressure, diaphoresis	
Headaches (prophylactic medications)				
Amitriptyline	Tricyclic antidepressant	Initial: 10–25 mg PO daily	Headache, sedation, constipation, confusion	Anticholinergic effects, may worsen cognition
Topiramate	Antiepileptic	Titrate over 4 weeks to a dose of 50 mg PO BID	Decrease in serum bicarbonate, dizziness, fatigue, nausea, nervousness	
Propranolol	Beta-blocker	Initial: 80 mg/day PO	Bradycardia, hypotension, depression, fatigue, insomnia, nausea	Also effective in treating aggression and agitation
Depression				
Sertraline	SSRI	Initial: 50 mg PO daily	Decreased sex drive, diarrhea, nausea	SSRIs are generally considered first-line treatment
Amitriptyline	Tricyclic antidepressant	Initial: 25–50 mg PO daily	Headache, sedation, constipation, confusion	Anticholinergic effects, may worsen cognition
Venlafaxine	SNRI	Initial: 75 mg PO daily	Insomnia, hypertension, contraindicated in narrow-angle glaucoma	

Bupropion	Aminoketone	Initial: (immediate-release) 100 mg PO q12h	Headache, dry mouth, nausea, insomnia, agitation, dizziness	Lowers seizure threshold
Insomnia				
Melatonin	Pineal hormone	Initial: 5 mg PO 3–4 h before sleep	Daytime fatigue, dizziness, drowsiness, headache, irritability	Found to improve daytime alertness
Trazodone	Antidepressant	Initial: 50 mg/PO qDay	Blurred vision, dizziness, dry mouth, headache, nausea, constipation, QT prolongation	Concern for QT prolongation exists, but in general, medication is well tolerated
Zolpidem	Sedative/hypnotic	Initial: (immediate-release) 5 mg PO qHS	Should be avoided for long-term use in TBI. Dizziness, headache, hallucinations, memory disorder, visual disturbances	May impair cognitive recovery with long-term use
Cognitive impairments				
Methylphenidate	Stimulant	Initial: (immediate-release) 20 mg/day PO divided q12h, 30 min before meals	Headache, seizures, arrhythmia, psychosis, angina, tachycardia, agitation	Found to improve cognitive complaints and posttraumatic stress symptoms in a study of patients with PTSD, TBI, or both
Donepezil	Acetylcholinesterase inhibitor	Initial: 5 mg PO qHS	Nausea, diarrhea, insomnia, headache, hallucinations, confusion	Studies are only in moderate to severe TBI patients but demonstrate improvement in short-term memory
Amphetamine/dextroamphetamine	Stimulant	Initial: 5 mg PO qDay	Anorexia, headache, insomnia, anxiety, tachycardia, nausea, emotional lability, dizziness	Risk for substance abuse

Adapted from Bhatnagar et al. [37]

Conclusion

Mild traumatic brain injuries continue to be a highly prevalent and hotly researched topic, but much work still needs to be done to adequately assess and manage the service members afflicted. Education remains the most important and effective treatment, especially in the early stages of injury. Reassurance and support are enough for most as symptoms are expected to resolve in a short time. However, for those suffering with persistent postconcussive syndrome, a holistic approach and symptomatic treatment, first with nonpharmaceuticals, are ideal. A judicious and finite use of medications may be warranted for the few who require them.

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