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Pages 789 — 812**Review: Managing posttraumatic stress disorder in combat veterans with comorbid traumatic brain injury****Bruce Capehart, MD, MBA;<sup>1\*</sup> Dale Bass, PhD<sup>2</sup>**<sup>1</sup>*Durham Department of Veterans Affairs Medical Center, OEF/OIF Program and Mental Health Service Line, Durham, NC; and Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, NC;* <sup>2</sup>*Department of Biomedical Engineering, Pratt School of Engineering, Duke University, Durham, NC*

**Abstract**—Military deployments to Afghanistan and Iraq have been associated with elevated prevalence of both posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) among combat veterans. The diagnosis and management of PTSD when a comorbid TBI may also exist presents a challenge to interdisciplinary care teams at Department of Veterans Affairs (VA) and civilian medical facilities, particularly when the patient reports a history of blast exposure. Treatment recommendations from VA and Department of Defense's (DOD) recently updated *VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress* are considered from the perspective of simultaneously managing comorbid TBI.

**Key words:** chronic pain, cognitive rehabilitation, comorbidity, posttraumatic stress disorder, psychopharmacology, psychotherapy, substance use disorders, traumatic brain injury, VA/DOD clinical practice guidelines, veterans.

**Abbreviations:** CBT = cognitive-behavior psychotherapy, CPG = clinical practice guideline, CPT = cognitive processing therapy, DOD = Department of Defense, FDA = Food and Drug Administration, ICU = intensive care unit, IED = improvised explosive device, MACE = Military Acute Concussion Evaluation, MOS = military occupational specialty, MRI = magnetic resonance imaging, mTBI = mild TBI, OIF/OEF = Operation Iraqi Freedom/Operation Enduring Freedom, PCL = PTSD Checklist, PE = prolonged exposure, PLMS = periodic limb movements of sleep, PTSD = posttraumatic stress disorder, RCT = randomized controlled trial, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = serotonin-specific reuptake inhibitor, STAR\*D = Sequenced Treatment Alternatives for Relief of Depression, T3 = tri-iodothyronine, TBI = traumatic brain injury, TCA = tricyclic antidepressant, VA = Department of Veterans Affairs, VBIED = vehicle-borne IED.

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**INTRODUCTION**

The improvised explosive device (IED) is one of the most commonly encountered weapons in Operations Iraqi Freedom and Enduring Freedom (OIF/OEF), and its battlefield use creates serious risk for physical injury or death [1–3]. The IED threat, together with blunt trauma head injury mechanisms, has altered recent approaches to combat veteran<sup>1</sup> mental health care by highlighting the topic of traumatic brain injury (TBI), and in particular mild TBI (mTBI). For the mental health clinician, the IED threat is another wartime event that can lead to posttraumatic stress disorder (PTSD), and proper management of the veteran population exposed to IEDs requires the clinician to consider both psychiatric disorders and the possibility of a comorbid mTBI.

Casualties from explosions are a significant cause of morbidity among OIF/OEF veterans. IEDs and explosions from other ordnance accounted for nearly 80 percent of all casualties reported to a military trauma registry from October 2001 through January 2005 [4], and relative to previous military actions, casualties from Afghanistan and Iraq received proportionally more face, head, and neck injuries [2]. There are no direct comparisons of TBI prevalence across military conflicts in the 20th century. As a proxy for relative risk for TBI across different military conflicts, Owens et al. studied the anatomic location of combat wounds in World War II, the conflicts in Korea and Vietnam, and OIF/OEF [4]. They found a statistically significant difference, because 30 percent of OIF/OEF combat wounds involved the head and neck compared with 16 percent in the Vietnam war and 21 percent in both the Korean war and World War II.

As in prior military conflicts, improved combat medical care leads to an increased need for postwar rehabilitation of injuries. Among veterans of the present conflicts, the incidence of TBI is higher than it was in prior conflicts, perhaps because of blast injuries. The Department of Defense (DOD) and Department of Veterans Affairs (VA) mental health communities face a difficult clinical challenge in the diagnosis and management of psychiatric sequelae of war when the veteran was exposed to explosions: determining whether the presenting symptoms are best explained by PTSD or another psychiatric diagnosis, residual symptoms of mTBI, or both a psychiatric diagnosis and mTBI. This article addresses the diagnosis and treatment of PTSD among combat veterans with a particular focus on comorbid mTBI and the most recent version of the [VA/DOD Clinical Practice Guideline for Management of Post-Traumatic Stress](#) [5].

The military and VA healthcare systems are familiar with the high prevalence rate of PTSD among combat veterans. Among OIF/OEF veterans who sought treatment at a VA healthcare facility, the PTSD prevalence is 13 to 21 percent

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[6–7]. The range of wartime traumatic events that can lead to PTSD must now include the dangers posed by exploding IEDs. To the practicing mental health clinician, it should be clear how an exploding IED could cause PTSD, but the patient's symptoms could also be caused by mTBI. Cognitive complaints can accompany the clinical presentation of PTSD, typically a subjective decline in short-term memory that can result from diminished concentration. However, if a comorbid TBI is present, memory could be affected directly. Two reports suggest blast-related TBI as a risk factor for memory impairments [8–9], although another study of combat veterans with blast-related mTBI found no memory changes compared with a control group [10]. However, mTBI from blunt trauma is not known to adversely affect memory, but moderate to severe TBI from blunt trauma can cause memory impairments [11–12].

The possible presence of mTBI in the combat veteran causes additional diagnostic and management complications. TBI is associated with neuropsychiatric sequelae such as depression, mania, or psychosis [13]; substance use disorders [14]; and medical problems including sleep disorders [15–16], chronic pain [17], and endocrine deficiencies [18–19]. These associated neuropsychiatric conditions could occur as a direct result of the traumatic injury or present after the injury as an emotional reaction to the effect of TBI on daily life [20]. There may not be a clear underlying etiology for a mood or anxiety disorder occurring after TBI, and the informed clinician will employ the biopsychosocial formulation (or a similar multidimensional approach) to enhance the diagnosis and understanding of these symptoms [20–21]. The psychiatric symptoms associated with TBI often respond to treatment based on the symptoms that correspond to the related Axis I condition [22], although the presence of TBI may affect diagnostic considerations and treatment options.

This review seeks to address four primary objectives related to managing comorbid PTSD and TBI: cognitive problems among combat veterans, blast as an injury source for TBI, diagnosis and management of PTSD in the setting of mTBI, and management of additional neuropsychiatric comorbidity in the combat veteran with PTSD and mTBI. These considerations will be placed in context with the 2010 update to the VA/DOD clinical practice guideline (CPG) for PTSD [5].<sup>2</sup>

## METHODS

We searched the MEDLINE database for published articles on psychiatric conditions associated with TBI and including blast trauma. The authors' clinical and laboratory experience supplemented these articles, particularly in the relationship of basic science studies of blast injury to clinical situations.

## RESULTS

### Cognitive Problems Among Combat Veterans

Cognitive problems remain a major focus of attention for the treatment-seeking OIF/OEF veteran population diagnosed with PTSD, a relatively large group given the prevalence of PTSD noted previously. Cognitive problems can have many different etiologies, including psychiatric diagnoses (e.g., major depression, substance use disorders), medication effects (e.g., tricyclic medications prescribed for neuropathic pain), medical or neurologic disorders (e.g., sleep apnea), or TBI. Despite the possibility of a brain injury causing dysfunction among any of the major functions in the central nervous system, including cognition, no clear consensus exists in the medical literature regarding the underlying cause of cognitive complaints in the OIF/OEF veteran population with both PTSD and TBI. When faced with clinical symptoms but no clear etiology, clinicians should manage the patient's symptoms. This symptom-management approach is advocated by the VA/DOD CPG for concussion/mTBI [23].

The medical literature does not clearly indicate whether cognitive changes after a combat deployment are best explained by psychiatric diagnoses or by TBI. Several studies support psychiatric conditions as the primary reason for persisting cognitive complaints or postconcussive symptoms [24–28]. Two studies report results that are most likely due to blast injury and not PTSD [29–30], and other results cannot rule out TBI as a contributor or cause of cognitive changes in combat veterans [10,31–32] or point toward TBI as a cause of cognitive complaints [33]. More likely, as suggested in some of the studies listed, when PTSD and TBI are both present, there may be a synergistic worsening of cognition.

Further complicating this issue is a lack of interdisciplinary research teams [34] and the need for careful diagnostic methods when the presence or absence of PTSD and TBI are determined from clinical symptoms, some of which overlap the two disorders. Some of the largest studies reporting TBI prevalence among OIF/OEF combat veterans rely on telephonic or mailed self-report measures for both PTSD and TBI [35]. A study of PTSD self-report measures compared with clinician-administered instruments for PTSD diagnosis found a nearly 20-fold higher prevalence of PTSD with the self-report measure [36], a finding that was not explained by subsyndromal PTSD [37]. More recently, further evidence for collinearity of PTSD and TBI self-report measures comes from Levin et al., who found higher PTSD Checklist (PCL) scores among blast-exposed veterans with TBI than among veterans without TBI [8]. However, the difference in PCL scores normalized after adjusting for the difference in postconcussive symptoms between the two groups. These findings suggest that the prevalence of PTSD may be inappropriately high when only self-report measures are used. The presence of PTSD is suggested as an explanation for a range of symptoms attributed to mTBI/concussion [28], yet that proposal relies on the assumption that an injury caused by explosion is fundamentally the same as an injury caused by blunt trauma. Recent experiments established that blast trauma can cause lethal injury when only the head is exposed to blast [38], thus lending support to case reports of blast TBI cited previously. There is not yet enough known about blast brain trauma to rely on self-report instruments for the diagnosis of either PTSD or TBI in the combat veteran.

### Blast Injury as Novel Injury Cause in Combat Veterans

Although current media and scientific attention is focused on TBI from wartime incidents, the causes of TBI among U.S. military servicemembers and veterans include combat, training accidents, and nonmilitary accidents. Blunt trauma remains an important cause of head injury among veterans, even during combat deployments. According to DOD casualty statistics on fatal injuries during OIF/OEF not attributable to enemy action, 541 fatalities (42% of the total 1,299 fatalities not caused by hostile fire) from October 2001 through July 2011 were caused by accidental crashes of military aircraft or motor vehicles [39]. Blunt trauma can cause TBI, and the clinical course and sequelae associated with blunt head trauma are well-characterized based on civilian experience. Penetrating head trauma does occur among combat veterans but is far less frequent than either injury from blunt injury or blast exposure. From September 2001 through September 2007, penetrating head trauma accounted for 11 percent of the 2,898 military hospital admissions for U.S. Army soldiers deployed to Afghanistan or Iraq [40], and a similar evaluation of Joint Theater Trauma Registry patients with TBI from 2003 through 2007 showed penetrating trauma in 18.5 percent [41]. These percentages represent upper bounds for penetrating trauma cases because they are based on military medical facility admissions, and therefore do not include many mTBI cases that were not evaluated by a military physician. The

association of blast with TBI is a novel environmental hazard with current military operations, and given the unique physics of blast exposure, blast TBI is inconsistently characterized in the clinical literature.

Combat experience in Afghanistan or Iraq is associated with a greatly increased risk of blast exposure, particularly for selected military occupational specialties (MOSs) such as Infantry, Military Police, Transportation, or Explosive Ordnance Disposal (military bomb disposal experts). Some of these veterans have experienced repeated blast exposure during overseas deployment, most commonly from an IED, typically a small charge up to 50 pounds placed on the side of a road, and the usually larger vehicle-borne IED (VBIED), a device with up to several thousand pounds of explosive.

An exploding IED can injure nearby persons by several injury mechanisms: blast, blunt impact, and fragment penetration [42]. Of these three mechanisms, penetrating injury is uncommon compared with blunt impact and blast injury [43], and when it does occur, the available medical history readily informs the question of possible TBI.

The perceptions of blasts among veterans and healthcare professionals have been informed by years of television and cinematic portrayals, and unfortunately, the entertainment industry fails to portray blast effects accurately. For example, a common cinematic scene involves actors being tossed across rooms or open spaces by an explosion, and this result is rather uncommon except for in those blasts that are large enough to be severely injurious or lethal. An injury from a blast wave typically results from a very fast wave that cannot be observed without high-speed cameras. For a detailed explanation, several excellent sources may be helpful to readers [44–46].

Injury risk from blast exposure has been studied intensely since World War I, with a primary focus on the observations of lung injury among exposed victims [47]. Multiple studies show the pulmonary vulnerability to fatal injury from a blast wave [48–49], but recent results show primary brain blast trauma can occur at about twice the levels needed to cause fatalities from pulmonary sequelae, yet these levels are within the blast intensity from a typical roadside IED at 1 to 2 m distance [38].

Damage to neurons, glia, or the blood-brain barrier may occur at levels of blast that are near or below the level of pulmonary threshold injury [38]. This finding suggests that even civilians who survive a blast injury may be at risk for TBI, in addition to the risk of PTSD. This risk for PTSD will include surviving an explosion, witnessing wounds or fatalities among other survivors, or being hospitalized with a serious medical problem caused by the explosion (e.g., severe burns, adult respiratory distress syndrome). Approximately 1 year after an accidental traumatic event not caused by terrorism, 6 percent of hospitalized trauma patients developed new-onset PTSD [50]. The comparable figure among hospitalized victims of terrorist suicide bomb attack is approximately 50 percent [51]. One possible cause of the higher rate of PTSD among terrorist bomb victims is the higher likelihood of greater injury from an explosion. Terrorist bomb attacks in the civilian setting can result in blast-related lung damage with the need for subsequent mechanical ventilation [52] or surgical repair of traumatic injuries [53]. Compared with civilian trauma from nonterrorist causes, victims of terrorist explosive attacks were more likely to experience injury to more than one body region, to have a longer hospital or intensive care unit (ICU) length of stay, to have a greater injury severity score, and to require posthospital rehabilitation [54]. Admission to the ICU after physical injury was associated with a threefold greater risk of developing PTSD [55].

However, the typical civilian injuries to the thorax, abdomen, and pulmonary system are far less common in the combat environment because of the nearly universal use of ballistic protective body armor. These armor systems increase the pulmonary system blast tolerance. Literature reports in the 1980s claimed an increase in lung injury risk from wearing body armor, and if true, this greater risk could create elevated intrathoracic pressure. However, body armor materials and design have evolved since the 1980s, and current U.S. military and civilian armor substantially decreases the blast transmitted to the thorax, as shown in unpublished research by our group.<sup>3</sup> This protection substantially decreases the risk of pulmonary injuries at a given distance from the explosion. The implication from this armor protection is fewer fatalities from blast lung trauma but exposure of the brain to blast waves that were lethal in prior conflicts.

#### Diagnosis of TBI in Setting of PTSD or Other Psychiatric Conditions

The VA/DOD CPG for concussion/mTBI (version 1.0, April 2009) defines TBI as “a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of *at least one* of the following clinical signs, immediately following the event” (emphasis added) [23]. The clinical signs are any period of decreased or loss of consciousness, any period of posttraumatic amnesia, any alteration of cognition (confusion, disorientation, slowed thinking), neurologic deficits that may be transient, or intracranial lesions. TBI severity is based on the extent or duration of these clinical signs.

Returning combat veterans are screened for TBI at all VA medical facilities. This screen includes a four-part screening tool intended to detect an injury event, immediate postinjury signs or symptoms of TBI, ongoing TBI sequelae, and current TBI sequelae. A positive screen leads to a thorough evaluation using a template-driven history, physical examination, and neurologic examination from a VA clinician with additional training in TBI diagnosis and management.

Despite the VA’s universal TBI screening for returning combat veterans, cases of mTBI are almost certainly being missed. It is highly likely that cases of moderate to severe TBI resulted in medical treatment at a military facility, and the missed TBI cases are probably mTBI. Other potential contributors to possible underdiagnosis of mTBI include an incomplete appreciation of mTBI sequelae (including not fully considering TBI as a cause of psychiatric symptoms) and misperceptions of blast injury biomechanics, topics reviewed by the authors in 2012 that were addressed in a recent review article [56]. There are numerous complexities associated with both blast biomechanics and the challenges with accurately representing military or terrorist blast injury in the laboratory, and a full discussion of these topics is not within the scope of this article; interested readers may refer to our recent review cited previously [56]. The misperceptions of blast biomechanics are an important clinical factor in missed TBI diagnoses: blast injuries evaluated in a busy civilian trauma center resulted in a missed diagnosis rate of 36 percent of primary blast TBI cases [57]. An additional factor in missed TBI diagnosis could be the presence of multiple life-threatening injuries to the pulmonary, orthopedic, abdominal, or vascular systems or the incorrect belief that TBI does not occur without loss of consciousness [58].

The combat veteran with persistent or unusual neuropsychiatric problems should undergo further evaluation for TBI if there is any history of head trauma. TBI can present with a wide variety of neuropsychiatric signs and symptoms [13], and no single clinical picture or unifying pathophysiologic model exists for blunt, blast, and penetrating trauma [59]. It may be useful to inform the veteran that a clinically meaningful TBI can result from an injury that involved only an altered level of consciousness and did not include loss of consciousness. This information may help the veteran provide additional history about head trauma that involved an alteration of consciousness (e.g., report of “feeling dazed” or “having my bell rung”), posttraumatic amnesia, or a transient neurologic deficit. These reports may result

from injuries associated with blast trauma or blunt trauma such as from contact sports, military parachute drops, and hand-to-hand combat training. It is important to emphasize that while a TBI can result from an injury that did not cause loss of consciousness, the usual clinical course for blunt head trauma without loss of consciousness is a very good to complete recovery with few to no clinically meaningful sequelae.

In addition to the MOSs mentioned previously associated with a greater risk of blast exposure, selected other MOSs are associated with elevated head injury risk, including Armor (i.e., tank crew), Infantry in a mechanized unit (i.e., tracked infantry fighting vehicle), any service in an Airborne unit, and any service in a Special Operations unit. Any reported blunt head injury event should lead to TBI evaluation, even if the veteran does not believe the injury led to a concussion or TBI. Further evaluation for possible TBI is recommended after blast exposure from any non-VBIED blasts that occurred closer than 30 feet; VBIED blasts within 100 yards should lead to a TBI evaluation.

Although the VA's screening program for TBI includes all returning combat veterans, there are occasions when a positive screen does not lead to a TBI evaluation. The TBI diagnostic criteria do not require loss of consciousness for the diagnosis, but the veteran may view an injury event without loss of consciousness as insignificant and decline further evaluation. Scheduled appointments for a TBI evaluation may not be kept because of the veteran's work schedule, transportation difficulties, or financial constraints. A mild head injury may be viewed as "normal" in some military occupations and not deserving of medical evaluation. These responses should be addressed so individual patients and their healthcare team will have more information with which to make decisions about treatment options, and for those patients still serving in an Active or Reserve military component, decisions about neuropsychological testing should be considered when the clinician holds moderate to high suspicion for TBI or for persisting cognitive complaints after other psychiatric symptoms and comorbid medical conditions have been addressed [23]. Neuropsychological evaluation can assist with difficult diagnostic situations. These situations can include impaired attention in a veteran with PTSD, suspected TBI, and a possible prior history of attention deficit hyperactivity disorder; determination of any regional specificity to neuropsychological testing results; and measures of the neuropsychological test validity. Neuropsychological testing may also be helpful prior to referral for psychotherapy for PTSD. Psychotherapists may wish to adjust their therapeutic approach based on the cognitive testing results (e.g., provide written handouts to compensate for relatively weak verbal learning). At our institution, we adopted an approach with a selected number of tests for screening, and if the scores reflect poor performance, a neuropsychologist reviews the screening test results and determines whether a full neuropsychological evaluation is warranted. The variety of neuropsychological tests may lead to different, equally valid screening batteries, but as a general guideline, each screening battery should assess attention, verbal memory, visual memory, visuospatial function, executive function, and expressive or receptive aphasia.

Bedside tests of cognition have very limited utility in the diagnosis of TBI. The Mini Mental State Examination is not recommended for TBI evaluation [60], and there are no published trials of the Montreal Cognitive Assessment in patients with TBI. The Military Acute Concussion Evaluation (MACE) was developed by the Defense and Veterans Brain Injury Center and can be obtained from their Web site (<http://www.dvbic.org>). The MACE appears to be a reliable instrument for TBI assessment, but according to a recent military medical study, the MACE is only effective if administered within 12 hours of a head injury [61].

In general, conventional computed tomography and magnetic resonance imaging (MRI) scans are not useful for diagnosis of mTBI [62]. More advanced MRI techniques such as diffusion tensor imaging, which may not be readily available to clinicians outside TBI research protocols, have shown more promise to detect structural changes associated with mTBI [62–63], but these results are not consistent across studies [8,64], perhaps because of imaging protocol differences [65]. Laboratory testing is not yet helpful in TBI diagnosis, although tests of oculomotor function may be useful [63].

Testing of oculomotor function may be a useful adjunct tool for TBI diagnosis. The advantages to oculomotor testing in the evaluation of suspected TBI include noninvasive test procedure, established normative values, and difficulty with creating feigned abnormal results. Other investigators have established oculomotor function as a sensitive test for detecting abnormalities among patients with moderate to severe TBI from blunt head trauma [66–68]. Oculomotor testing may have unique value in TBI evaluation after blast exposure because psychiatric comorbidity is not known to alter test results. Vestibular changes, which can also affect oculomotor function, have been reported in OIF/OEF veterans exposed to blast [69–70]. More recently, it was shown that 30 percent of blast-exposed veterans have at least one abnormal finding on oculomotor testing, and for two of these cases, this testing was used to localize the anatomic lesion to the brainstem.<sup>4</sup> These oculomotor and vestibular changes may be related to cerebellar dysfunction reported among blast-exposed OIF/OEF veterans [29]. Oculomotor and vestibular testing can be especially useful because feigned or exaggerated results can be detected and addressed during the testing. False positive reading of abnormal oculomotor function can occur after recent benzodiazepine use, but after approximately 1 week, the oculomotor system adapts to the benzodiazepine [71]. Intravenous administration of fentanyl 100 µg adversely affected oculomotor function, but the effect does not last more than 15 to 30 min [72]. Oculomotor function is not known to be affected by serotonin-specific reuptake inhibitor (SSRI) antidepressants, indicating that these medications should not produce a false positive reading of abnormal function [73]. The lack of oculomotor effect from SSRI antidepressants is important because these medications are first-line pharmacotherapy agents in PTSD and major depression. Overall, the published data on psychiatric conditions or TBI and oculomotor function support oculomotor movement testing as a sensitive indicator of brain pathology.

#### General Principles for Managing PTSD in Combat Veteran with TBI

Managing comorbid PTSD and TBI remains a challenge for DOD and VA clinicians in mental health, TBI/polytrauma, and primary care because no clear guidance exists on the simultaneous management of these two conditions [74]. While recognizing that there is no single right algorithm for every clinical situation, our usual approach to outpatient care for PTSD with comorbid TBI follows four general principles: (1) treat PTSD with appropriate psychopharmacologic and psychotherapeutic modalities, (2) identify and treat any comorbid neuropsychiatric conditions or substance use disorders, (3) identify and treat any associated medical comorbidities, and (4) directly address cognitive sequelae of TBI. Based on the presenting clinical symptoms, the severity of those symptoms, and patient preferences, treating clinicians should consider varying this recommended approach. For example, a clinic patient with recurrent seizures each week would be better served by immediate consultation with neurology prior to a discussion about psychotherapy for PTSD.

The risk for suicide is a concern with both PTSD and TBI. Three studies examining suicide rates among persons with TBI found an increased risk with standard mortality ratios of 2.7 to 4.1, depending on the study; comorbid substance use disorders increased the suicide risk [75]. PTSD similarly confers an increased risk for suicidal thoughts and perhaps also behaviors, although the association between PTSD and suicide attempts may be mediated by psychiatric comorbidity [76]. Screening for suicide and treating psychiatric comorbidity are therefore recommended for veterans with PTSD and comorbid TBI.



As a general rule, neuropsychiatric conditions that appear after TBI are managed similarly to the corresponding idiopathic Axis I condition. Cognitive sequelae could be classified as neuropsychiatric conditions, but for the purposes of this treatment approach, the cognitive difficulties are considered separately. Management of comorbid PTSD and TBI generally should follow the VA/DOD CPG for each condition, and following the steps mentioned earlier in order from 1 to 4 is recommended for most clinical situations. Additional recommended resources are companion articles in this issue by Gibson (PTSD and chronic pain) [77] and Schoenfeld et al. (PTSD and insomnia) [78].

After a diagnosis is made and supported by a biopsychosocial formulation, the initial step in psychiatric treatment is forming an effective therapeutic alliance. The quality of this alliance is known to exert a positive effect on psychotherapy outcome across multiple types of psychotherapy, including both cognitive therapy and behavioral therapy [79]. In a large study of PTSD treatment with sertraline or prolonged exposure (PE), a strong therapeutic alliance was positively associated with adherence to PE but not with adherence to sertraline [80]. Separately, a study of cognitive-behavior psychotherapy (CBT) for PTSD among persons diagnosed with severe mental illness found psychotherapy superior to treatment as usual. CBT reduced PTSD symptoms and improved the patient's rating of the therapeutic alliance [81]. Further, a trial of CBT for schizophrenia failed to show a relationship between the subject's rating of therapeutic alliance and the therapist's questioning the rational basis for psychotic symptoms, a result that supports the conclusion that therapists can challenge a patient's false belief if a solid therapeutic relationship exists [82]. Similar research results from other chronic conditions may inform the need for therapeutic alliance in TBI care. The strength of the therapeutic alliance was found to predict outcomes in a trial of CBT for depression among persons with multiple sclerosis [83], a condition that commonly presents with comorbid cognitive difficulties. Finally, there is a known relationship between the health outcomes and the symmetry of patient and physician beliefs regarding the influence of patient behavior on health outcomes. A study of VA primary care providers and their patients demonstrated greater medication adherence to antihypertensive medication when the patient and physician shared similar beliefs about the relationship between patient behavior and health outcome [84]. Although the study outcomes did not extend to all medications studied, the results suggest improved outcomes that are in part supported by a harmonious patient-physician relationship.

Similarly, research results support the need for developing a therapeutic alliance in TBI care. The value of a strong therapeutic alliance has been reported in a treatment case series of neuropsychiatric sequelae of TBI [85]. TBI can be associated with poor awareness of cognitive deficits or emotional difficulty. Results from the CBT in schizophrenia trial suggest that a solid therapeutic alliance may allow therapists to challenge poor awareness of cognitive deficits. Additional results cited previously may support the value of a therapeutic alliance from a comparison of TBI to other conditions. However, a study evaluating the relationship between alliance and outcomes found that therapeutic alliance strength was associated with remaining in postacute brain injury rehabilitation but not with functional status at discharge [86]. A survey of psychologists working on psychological sequelae of TBI endorsed the need to build the therapeutic alliance, and this group frequently employed a variety of techniques to strengthen it, including education about TBI and its emotional consequences, memory aids, shorter or more focused therapy sessions, involvement of family members, and behavioral techniques to help the patient better understand post-TBI functional limits [87]. Building a strong therapeutic alliance is also recommended for vocational rehabilitation after TBI [88]. The value of a strong therapeutic alliance is most likely similarly high when treating veterans with comorbid PTSD and TBI.

#### **Psychotherapy for PTSD: Considerations with Comorbid TBI**

The VA/DOD CPG for PTSD is a comprehensive summary of PTSD treatment and should be readily available for any VA or military clinician who regularly evaluates or manages patients with PTSD. The CPG highly recommends that persons diagnosed with PTSD receive one of the evidence-based psychotherapies: cognitive processing therapy (CPT), PE, or eye movement desensitization response. Within the VA system, both CPT and PE are widely available. Certain antidepressants are also highly recommended. According to the VA/DOD CPG for PTSD, antidepressant medication is believed to be less effective than one of the evidence-based psychotherapies, but antidepressants are preferred over no treatment.

The current VA/DOD CPG for PTSD recommends both CPT and PE, but there are few data to guide psychotherapy selection for the veteran with PTSD and comorbid TBI. Recent psychotherapy trials offer encouraging findings for treatment response. A 2007 Cochrane Review of psychotherapy for anxiety in persons with TBI found only two trials with acceptable methods [89]. One trial reported a reduction in anxiety after CBT for acute stress disorder. The second trial demonstrated that a combination of CBT plus cognitive rehabilitation led to a reduction in anxiety. The Cochrane Review noted the presence of 20 studies that did not follow a randomized controlled trial (RCT) design, most of which were case studies or small case series.

More specific to psychotherapy for PTSD, a trial of CPT combined with cognitive rehabilitation plus psycho-education groups reported significant reductions in PTSD symptom scores after a 7-week inpatient program [90]. The CPT offered in this study included both group and individual treatment. The reduction in PTSD severity occurred for veterans with mild, moderate, and severe TBI.

A recent trial of PE suggests efficacy in combat veterans with comorbid TBI and cognitive deficits [91]. Separately, another outpatient study compared PE alone with PE plus cognitive restructuring, a therapy intended to address the patient's negative cognitive assumption. Results did not reveal any differences in outcomes between the two interventions [92]. This result suggests that successful outcomes from PE do not rely on the same cognitive mechanisms used by CPT, raising the possibility that PE would be an effective intervention for veterans with significant cognitive problems. A published trial on virtual reality exposure therapy for PTSD reported 16 of 20 subjects demonstrated a clinically meaningful and statistically significant reduction in PTSD symptoms; the authors noted without further detail that two treatment responders were diagnosed with mild or moderate TBI [93]. An interim report from an ongoing trial comparing PE with virtual reality exposure therapy stated that both therapies resulted in clinical improvement in PTSD symptom; however, this report did not include details that could have allowed a comparison of treatment response with respect to TBI diagnosis [94].

Although these results with both CPT and PE are encouraging for veterans with PTSD and comorbid TBI, each of these studies have important limits. The CPT trial was conducted in the controlled environment of an inpatient unit. The virtual reality PE trials offered early but encouraging results, but replication with a larger group is required. Additionally, the interim report from the ongoing virtual reality trial used the veterans' self-report of blast exposure as a proxy for mTBI, raising a question about the severity or perhaps existence of TBI among those participants. Military and VA clinicians would greatly benefit from additional research on treating combat-related PTSD with comorbid mild to moderate TBI, particularly with respect to modified psychotherapy approaches that could accommodate cognitive deficits.

#### **Pharmacotherapy for PTSD: Considerations for Comorbid TBI**

The 2010 VA/DOD CPG for PTSD recommends first-line medication choices for treating PTSD: the SSRI antidepressants sertraline and paroxetine and the serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant

venlafaxine [5]. The CPG supports these choices by citing high quality RCTs for each of these three medications. Lesser degrees of support are offered for other SSRI antidepressants (fluoxetine, citalopram) and for the antidepressants mirtazapine and nefazodone. These antidepressant medications create the pharmacologic foundation for PTSD care. Details about specific antidepressants and their use in PTSD can be found in the PTSD CPG or in Jeffreys et al. in this issue [95].

Antidepressant medication is known to be useful for treating mood and anxiety disorders that are diagnosed after TBI. Two recent reviews of pharmacologic options for managing depressive symptoms after TBI recommended sertraline as first-line therapy based on clinical trial data, a favorable side-effect profile, and few drug-drug interactions, with citalopram also a recommended option [21,96]. Two double-blind RCTs in 2009 showed conflicting results with sertraline for depression after TBI. In the first trial of 51 subjects with TBI and depression, the results failed to show any difference in depressive symptoms for sertraline compared to placebo [97]. In the second trial, 99 subjects were randomized to sertraline or placebo, and a statistically significant difference occurred for fewer depressive symptoms with sertraline at 12 weeks than with placebo [98]. One unique double-blind RCT compared sertraline, methylphenidate, and placebo [81]. Results from this trial showed a statistically significant decline in depressive symptoms with either sertraline or methylphenidate compared with placebo, but only when results were measured on the Hamilton Depression Rating Scale; no statistically significant improvement on Beck Depression Inventory scores occurred. Methylphenidate improved several measures of cognition, but neither sertraline nor placebo helped cognitive function [99]. Unsurprisingly, the CPG for mTBI recommends antidepressants for depression, and stimulants are recommended for fatigue or concentration difficulties. However, the 2010 CPG for PTSD does not recommend stimulants for treatment of PTSD.

Other antidepressants are not associated with strong data for use in TBI. Paroxetine is recommended only with caution since its cholinergic side effects may worsen cognition, and fluoxetine should be avoided because of multiple effects on the cytochrome P450 system and the possibility for drug-drug interactions [21]. No published studies or cases exist on TBI and the antidepressants escitalopram, mirtazapine, or nefazodone. A single case report is available on bupropion treatment of post-TBI restlessness [100], but because bupropion is not effective for PTSD, it will not be considered further. Data are available that support the use of tricyclic antidepressants (TCAs) for PTSD, but given the adverse effects of anticholinergic activity upon cognition, TCAs are not recommended as first-line choices in treating comorbid PTSD and TBI.

The sum of these studies points strongly toward sertraline as the most reasonable first-line option in treating comorbid PTSD and TBI. Citalopram is a second choice after sertraline, but caution is recommended after the recent Food and Drug Administration (FDA) warning about possible cardiac side effects of citalopram above 40 mg per day, although a recent review of 1.3 million person-years of antidepressant exposure did not find any elevated risk for sudden cardiac death or ventricular rhythm problems among patients who took SSRIs, SNRIs, TCAs, nefazodone, or bupropion, all compared with a reference group of paroxetine users [101]. After sertraline or citalopram, with the possible inclusion of escitalopram instead of citalopram, there are few published data to guide choices. Reasonable second-line antidepressant choices include fluoxetine, mirtazapine, or nefazodone. Mirtazapine can cause mild anticholinergic effects [102] and sedation [103], effects that could aggravate memory problems. Nefazodone can cause serious hepatotoxicity [104], probably via inhibition of hepatocyte mitochondria [105], and alternatives should be carefully considered before it is used. The TCAs are third-line choices for similar reasons and a lower therapeutic index.

The 2010 VA/DOD CPG for PTSD recommends prazosin as an augmenting agent for persisting nightmares. No published clinical studies exist on prazosin in TBI. Given its recommended use for nightmares in PTSD, prazosin should be considered in the veteran with both PTSD and TBI, but with a low starting dose and a slow upward titration to avoid hypotension. The 2010 VA/DOD CPG for PTSD does not recommend the use of anticonvulsants for PTSD. No evidence exists to support antipsychotic medication as monotherapy for PTSD, and there is insufficient evidence for or against atypical antipsychotics as augmenting agents, with the exception that risperidone is not recommended as an augmenting agent based on a recent trial [106]. Benzodiazepines are problematic in PTSD and TBI. In PTSD, benzodiazepines may aggravate the fear response, interfere with PE psychotherapy treatment, and present a risk for iatrogenic substance dependence [5]. In TBI, benzodiazepines can worsen confusion and dizziness [23]. These medications should be avoided when treating anxiety related to PTSD and especially so in the presence of a comorbid TBI.

#### Treatment of Other Psychiatric Conditions in Comorbid PTSD-TBI

In general, treating psychiatric symptoms in persons with TBI should follow the same guidance as for geriatric patients: use lower initial doses and titrate upward slowly [107–109]. Medication adherence problems may arise from cognitive difficulty but could be mitigated by caregiver assistance [110]. A personal digital assistant and family member involvement in the patient's care may improve medication adherence and consistent attendance at outpatient clinic appointments.

The overlapping symptoms of PTSD and TBI can lead to confusion over what symptom to treat when and with what intervention. If a strategy of "PTSD First" is followed and the re-experiencing symptoms abate but there are persisting symptoms of increased arousal (e.g., insomnia, irritability, impaired concentration) or symptoms suggesting depression (e.g., lack of interest in usual activities, fatigue or low energy), then the patient may have untreated TBI sequelae or a second psychiatric disorder. The presence of impaired motivation caused by TBI-related subcortical damage can create a significant diagnostic challenge [111]. The clinical picture can include apathy, cognitive slowing, motor slowing, and a blunted emotional response, creating a clinical presentation that can resemble major depression. If a subcortical motivation problem is present, cautious use of low-dose stimulant medications (as outlined later) may be appropriate.

As part of the differential diagnosis in this clinical situation, it is also appropriate to consider the possibility of a mood disorder such as major depression. The patient with impaired motivation caused by TBI may not feel distressed by the impaired motivation. Depressed mood and true anhedonia suggest a mood disorder instead of a motivation deficit. An additional consideration for the irritable patient is a manic mixed state that may result from an adverse reaction to SSRI or SNRI antidepressants prescribed for PTSD [112].

As discussed previously, the CPG for mTBI recommends treating depression even if the depression has no clear etiologic relationship to the mTBI, and the recommended medications are the SSRIs. There is a single case report documenting the combination of risperidone and galantamine decreasing the combination of apathy with psychosis after TBI [113]. The MAO (monoamine oxidase) inhibitor selegiline is associated with one open label trial reporting less apathy after nonresponse to methylphenidate [114]. Bupropion was established in the Sequenced Treatment Alternatives for Relief of Depression (STAR\*D) study as a useful augmenting agent for SSRI medications in the pharmacology of depression, but it should be used cautiously in the setting of TBI because of the elevated seizure risk. When bupropion is not a reasonable choice, alternatives such as buspirone or tri-iodothyronine (T3) are suggested.

Both buspirone and T3 were effective in the STAR\*D study for depression, but neither augmentation strategy has been systematically evaluated in patients with TBI.

### Substance Use Disorders in Comorbid PTSD-TBI

The CPGs for PTSD and mTBI recommend screening for substance use disorders. Substance use disorders should be treated to minimize the possible effects on anxiety, cognition, and sleep. Substance use can aggravate mood, anxiety, or cognition either as a direct substance effect (e.g., alcohol use) or indirectly by interfering with sleep.

Graham and Cardon conducted a comprehensive review of substance use disorders associated with TBI [14]. Their review examined alcohol, cannabis, and stimulants (cocaine and other stimulants together). Results indicated a general decrease in alcohol use after TBI. However, problematic alcohol use after TBI represents a subgroup of patients who need special attention and are likely to have a more difficult clinical course. Similar results showing a decline in problematic alcohol use after TBI were reported in a prospective study [115]. These results could be explained by hospitalization (i.e., no access to alcohol) or recommendations to abstain [115], or alternatively, represent binge use of alcohol that led to the TBI accompanied by a postinjury desire to avoid further head injuries. Data on cannabis were limited to a single case study and no data were reported for stimulants. These data are generally supported by a 2009 study of psychiatric comorbidity after TBI. In this study, the substance use disorder prevalence rate declined from 41 percent preinjury to only 21 percent postinjury [116]. However, Carlson et al. evaluated administrative data from more than 13,000 OIF/OEF veterans and compared the presence of any substance use disorder diagnosis to results of TBI screening. Results showed the prevalence of substance use disorders as 9.7 percent, 20.2 percent, and 26.2 percent, respectively, for veterans who screened negative for TBI, screened positive but were not found to have TBI, and screened positive and were later diagnosed with TBI [117]. These results may be different from other published reports with the use of administrative data. A study examining 10-year outcomes after TBI found 32 percent of the study subjects endorsed hazardous levels of alcohol use [118]. When PTSD and TBI are simultaneously present in a patient, the cognitive sequelae or emotional dysregulation associated with TBI may require novel approaches or adjustments to existing treatment protocols [119].

Unlike the reduction in substance use associated with TBI, PTSD is associated with increased prevalence of substance use disorders. Data from the National Comorbidity Survey demonstrated a higher rate of cannabis use among persons with either current or lifetime diagnosis of PTSD [120]. The diagnosis of an alcohol use disorder and/or a drug use disorder was associated with PTSD in OIF/OEF veterans; 63 percent of these veterans with either alcohol or drug use disorders were diagnosed with PTSD, and 76 percent of veterans with both alcohol and drug use disorder diagnoses were found to have PTSD [121]. A community survey of nearly 10,000 veterans from the 1991 Gulf war revealed that problem alcohol use patterns were 2.7 times more likely to occur among veterans with PTSD than among veterans not diagnosed with PTSD [122]. Various studies have found alcohol or drug use disorder prevalence rates of 39 to 84 percent among Vietnam veterans [123].

Both psychological and physical trauma can combine with substance use to adversely affect neuroanatomy. PTSD is known to adversely affect hippocampus volume, and among persons diagnosed with PTSD, a lifetime history of alcoholism was an independent contributor to reduced hippocampal volume [124]. TBI can adversely affect the hippocampus. Imipramine administered after TBI in an animal model improved cognitive outcomes compared with the placebo group, and this outcome was correlated with increased hippocampal neurogenesis [125]. Other antidepressant medications are associated with neurogenesis, but its role in treating depression or anxiety is not yet clear [126]. The potential interactions among TBI, alcohol, and PTSD are yet to be explored in preclinical or clinical studies, and this research has the potential to enhance combat veteran healthcare.

Even with poorly understood interactions among TBI, alcohol, and other substance use disorders and PTSD, clinicians can offer effective interventions. Seeking Safety is a recommended psychotherapeutic intervention for comorbid PTSD and substance use disorders. This therapy has demonstrated effectiveness in both male [127] and female [128] veterans. Anecdotal cases at our institution show efficacy for Seeking Safety in veterans with TBI, but this therapeutic intervention requires systematic evaluation in this patient population. A review of substance use disorders treatment for persons with TBI recommended skills-based interventions that provide community care. Peer support and motivation to attend outpatient treatment sessions were also recommended interventions. Until a systematic evaluation is available, treatment of the veteran with a "triple-diagnosis" (i.e., PTSD, TBI, and substance use disorder) will require an individual approach and interdisciplinary cooperation among the mental health, substance use, and TBI treatment teams.

### Managing Medical Complications of TBI in the Veteran with PTSD

Although psychiatrists collaborate with primary and specialty care physicians for the optimal management of many medical problems, these collaborations are particularly important for three particular medical diagnoses: chronic pain, endocrine deficiencies, and sleep disorders. All three of these conditions may occur in the combat veteran with both PTSD and TBI.

The comorbid medical and neurologic conditions associated with TBI can adversely affect clinical outcome. Patients with TBI reported high prevalence of chronic pain (43% [17]), sleep disorder (approximately 50% [15–16]), and endocrine disorders (approximately 25% [129]). Mitigating each of these associated conditions will improve patient outcome.

Chronic pain can adversely affect emotions and cognition. It remains an underrecognized clinical problem associated with TBI. PTSD is believed to mediate the relationship between chronic pain and TBI among persons diagnosed with all three conditions [130], a relationship that has been reported for OIF/OEF veterans diagnosed with PTSD, physical injuries, and chronic pain [20,131]. One recent meta-analysis of pain after TBI found the prevalence of chronic pain ranged from 43 percent in veterans to 51 percent in civilians [17]. These results remained significant after controlling for Axis I conditions, suggesting that pain is either a consequence of TBI or that the same injury that caused the TBI created comorbid injuries in other organ systems. Combat wounds in the present war are primarily blast injuries, and these injuries can simultaneously affect multiple functions within the brain while injuring multiple anatomic locations in the body. A multidimensional clinical approach from an interdisciplinary treatment team is recommended for optimal pain management [20,131].

A 2009 literature review found discouragingly little evidence to guide treatment of combat veterans with polytrauma and chronic pain, noting that the available treatment studies were either case reports or small case series [132]. Treatment for chronic pain and comorbid PTSD is complex because the two conditions can be mutually reinforcing, and unfortunately, there are no medication trials to evaluate treatment modalities for these comorbid conditions [133]. Opiates show mixed results in chronic pain and are not associated with better physical or psychosocial function, thus suggesting the need for careful consideration before their use in comorbid chronic pain and PTSD [133]. Just as in the comorbidity of substance use, PTSD, and TBI, there is a compelling need for research into the neuroscience and treatment modalities for this second type of triple diagnosis veteran with chronic pain, PTSD, and TBI.

PTSD is associated with sleep complaints, primarily initial insomnia from anxiety and middle insomnia from nightmares. Complicating this clinical picture is the common association of PTSD with use of substances known to interfere with sleep and behaviors that interfere with sleep. Persons with PTSD have high rates of excessive alcohol [121,134] and tobacco use [135], and for patients whose trauma occurred at night, the idea of going to sleep at night can be an intimidating experience.

The presence of comorbid TBI can add complexity to treating sleep complaints in a patient with PTSD. TBI has been associated with sleep disorders. Two prospective studies identified a nearly 50 percent prevalence of sleep disorders among persons with TBI [15–16]. Patients in these two studies typically reported fatigue or excessive sleepiness, and the polysomnographic data revealed various causes, including obstructive sleep apnea, periodic limb movements of sleep (PLMS), narcolepsy, and idiopathic hypersomnia.

Sleep disorders should be approached as a problem of initiating sleep, maintaining sleep, or failing to achieve restorative sleep. This organization of sleep disorders not only is the consensus of various professional groups in the sleep medicine field [136] but also is useful for treating PTSD and comorbid TBI. Conditions that interfere with initiating sleep include anxiety, caffeine or nicotine use in the evenings, and restless legs. Sleep can be broken up at night by sleep apnea, periodic limb movements, or REM (rapid eye movement) behavior disorder. PTSD can interfere with initiating sleep through hyperarousal and with maintaining sleep through nightmares [137]. The male veteran with PTSD and benign prostatic enlargement who awakens to urinate may face significant difficulty returning to sleep. In most situations, the proper intervention for sleep problems begins with a polysomnogram. An abnormal polysomnogram may indicate a need for referral to a sleep medicine specialist. If the polysomnogram does not find evidence of a sleep disorder, then the CPGs for both PTSD and mTBI recommend similar interventions: encourage good sleep hygiene, offer CBT for insomnia, and consider prazosin for nightmares [5]. When these interventions are not effective, medication for insomnia should be considered.

If a veteran with both PTSD and TBI reports sleep difficulty that may be due to depressive or anxiety symptoms, it is important to ensure that target symptoms do not represent anxiety for which a PTSD-specific intervention would be more appropriate. Prior to starting medication for sleep, determine whether a change in the SSRI or SNRI antidepressant could reduce anxiety and promote better sleep, and if nightmares are problematic, add prazosin. If a hypnotic medication is required, the CPG for PTSD recommends trazodone as a first-line medication. Chronic benzodiazepine use should be avoided with PTSD. However, the beneficial effect of improved sleep may outweigh the adverse effects of limited hypnotic medication use. The CPG for PTSD recommends nonbenzodiazepine hypnotics (e.g., zolpidem, eszopiclone, ramelteon) instead of benzodiazepines, and atypical antipsychotics are discouraged unless agitation is a severe problem. The atypical antipsychotics carry a significant risk for weight gain and related metabolic problems [138], and their use has been linked to an increased risk for obstructive sleep apnea [139].

Many medications to treat sleep difficulties can be problematic in comorbid TBI. Benzodiazepines are generally discouraged in persons with TBI because of concerns over adverse effects on cognition, coordination, alertness, and the risk for substance use disorders [110]. A recent review of hypnotic medications in patients with TBI recommended against benzodiazepines because of adverse effects on cognition [140]. The newer benzodiazepine-like medications (zolpidem, eszopiclone, and zaleplon) have not been systematically evaluated for insomnia associated with TBI [140]. The 2010 VA/DOD CPG for mTBI discourages benzodiazepines overall but suggests zolpidem when a hypnotic medication is required [23]. A recent literature review suggests trazodone or melatonin [140].

The alpha-1 adrenergic antagonist prazosin is well supported for mitigating PTSD-related nightmares [141], and improved sleep may help cognition. No data exist to support the alpha-1 antagonists solely for TBI in the absence of nightmares. A single trial reported the alpha-2 agonist guanfacine improved working memory in persons with mTBI but not in nondisabled controls [142], a finding that may relate to guanfacine's known FDA indication for attention-deficit hyperactivity disorder.

Endocrine disorders are surprisingly common after TBI, with one literature review reporting the prevalence at 27.5 percent [129]. The incidence of hypopituitarism in 104 patients hospitalized after TBI was 16 percent with risk factors determined as severe TBI, elevated intracranial pressure, and mechanical ventilation for more than 24 hour [143]. The largest study of hypopituitarism after TBI included more than 1,200 subjects and found an overall prevalence of 35 percent based on clinical suspicion or laboratory testing and an overall prevalence of 70 percent based on endocrine stimulation tests [144]. However, this study showed a relationship between TBI severity and prevalence of hypopituitarism, with mean Glasgow Coma Scale scores for none, single, or multiple endocrine deficiency at 12.3, 7.5, and 4.6, respectively. This finding most likely explains prior results that showed less than 1 percent of persons diagnosed with TBI also experienced a demonstrated endocrine abnormality [145]. Endocrine tests and/or subspecialty referral should be considered when presenting symptoms are consistent with an endocrine deficiency, especially in the setting of moderate to severe TBI. Neuropsychiatric symptoms that might suggest a need for endocrine testing include persistent depressive symptoms (because of possible hypothyroidism) and erectile dysfunction (because of possible gonadotropin dysfunction). After side effects from psychiatric medications and substance use have been eliminated as possible causes for these complaints, it would be reasonable to evaluate serum levels of free thyroxine, free T3, thyroid stimulating hormone, luteinizing hormone, follicle stimulating hormone, prolactin, and either testosterone or estrogen depending on sex [146]. Growth hormone and cortisol levels should be evaluated with a provocative test; this procedure likely will require referral to an endocrinologist. The CPG for mTBI makes no recommendations on endocrine testing, and the available medical literature suggests mTBI is not likely to be associated with an endocrine dysfunction.

### Managing Cognitive Complaints

Many veterans with TBI complain of cognitive difficulties. The underlying cause of these difficulties remains disputed in the medical literature, but the existence of veteran subjective complaints about cognition is a daily occurrence in many VA and DOD facilities. If recommended interventions for improving comorbid medical and psychiatric conditions do not adequately address cognitive complaints, then specific treatment for the cognitive problems is indicated. Like most psychiatric conditions, cognitive difficulty in a veteran with both PTSD and TBI is best treated with medication and therapy.

Cognitive rehabilitation is the term for therapy intended to improve functioning in one or more of the following areas: attention, vision and visuospatial functioning, language and communication skills, memory, or executive function [147]. These rehabilitative efforts are effective for moderate TBI [148]. The cognitive rehabilitation task force of the American Congress of Rehabilitation Medicine reviewed the relevant literature from 2003 to 2008 and concluded substantial evidence supports evidence-based rehabilitation for attention, memory, executive function, communication, and comprehensive interpersonal functioning [147]. The overall rehabilitation plan should address psychiatric conditions, psychosocial issues, chronic pain, employment or school, family or caregiver role in the veteran's recovery, and managing comorbid medical diagnoses.



The physician can make substantial medical contributions to cognitive rehabilitation. The initial step should be medication reconciliation to review prescription, over-the-counter, and herbal medications for any products or interactions that might adversely affect cognition. The mTBI CPG recommends careful attention to medications that will aggravate cognitive problems or lead to sedation, including alcohol, excessive caffeine, illicit drug use, benzodiazepines, sedating antihistamines, and anticholinergic medications. In some situations, continuing one of these medications may be a reasonable choice, but that possibility should include a discussion with the patient about the relative harms and benefits for that particular medication.

Medication trials for TBI-related cognitive effects should be interpreted in light of many trials occurring in acutely ill and/or severely injured patients, often in an inpatient setting. End points in this population may not translate to patients with mild to moderate injuries seen years after returning from combat (e.g., transition from a minimally conscious state to intermittent agitation may not predict a beneficial response in a patient with lesser deficits). The FDA has not approved any medications for TBI-related cognitive deficits; therefore, prescribing medications to improve cognition after TBI is considered "off-label" medication use. Off-label medication use should be reviewed with the patient and/or family members, particularly in the setting of comorbid PTSD. Clinicians should consider carefully the risks and benefits when treating conditions or prescribing medications outside the scope of usual clinical practice.

When addressing cognitive dysfunction after TBI, three important medication groups should be considered: dopaminergic agonists, acetylcholinesterase inhibitors, and stimulants. This topic was addressed in a 2009 review by Chew and Zafonte [149]. Their review concluded that some evidence existed to support dopaminergic agents for improving the level of arousal after moderate to severe TBI, and additional evidence supported stimulants for impaired attention.

Amantadine was found to improve the level of arousal following moderate to severe TBI, but not in all studies. Modafinil was effective in an open-label trial for enhancing wakefulness after TBI but did not separate from placebo in a subsequent RCT [149]. No controlled trial data exist to support the use of pramipexole or ropinirole in TBI, but these medications may be useful for comorbid restless legs or PLMS. Overall, further study is needed to evaluate the role of dopaminergic agonists in comorbid TBI. There are no published data on amantadine or modafinil in PTSD. Memantine, a medication similar to amantadine, was reported effective for PTSD symptoms in a single open-label trial [150]. With the uncertain benefit of dopaminergic agents in TBI and PTSD, their use should not be considered first-line interventions for these comorbid conditions.

Chew and Zafonte discuss medications for memory impairment associated with TBI and concluded that no clear recommendations can be made from the available evidence, although there are some encouraging RCT results [149]. One double-blind RCT showed improvements in attention and memory but not functional outcome among subjects randomized to donepezil [151]. A similar trial with rivastigmine did not show a difference over placebo, but a more severely injured subgroup did demonstrate some memory improvements with rivastigmine [152]. Stimulants have not been shown to clearly improve memory function after TBI, but their role in improving attention is better established [149].

There is a single case report of a Vietnam veteran developing PTSD symptoms after acetylcholinesterase inhibitor treatment. Four years after a right parietal stroke, the veteran did not report PTSD symptoms until treated with donepezil for declining cognitive function. The increased anxiety resolved when the donepezil was stopped but again recurred when galantamine was started [153].

These data on acetylcholinesterase inhibitors support their use for memory difficulty after TBI. The evidence of potential harm in PTSD is thus far limited to a single case report. The CPG for mTBI does not recommend medication for cognitive difficulties but does suggest the possibility of stimulant medication to relieve excessive fatigue. The acetylcholinesterase inhibitors could be a useful and safe consideration for addressing cognitive deficits among veterans with both TBI and PTSD, but the available data are not strongly encouraging of a large clinical benefit.

There are no controlled trials of atypical antipsychotics in treating cognitive problems after TBI. These medications may be useful in treating post-TBI psychotic symptoms. The 2010 VA/DOD CPG for PTSD does not recommend any antipsychotic medication as monotherapy for PTSD, and the CPG for mTBI does not address treatment of psychosis. Further, the CPG for mTBI discourages typical antipsychotic medication that may lower the seizure threshold. The atypical antipsychotics, except for risperidone, may be useful as adjunctive treatment for PTSD when the patient does not have a robust response to an SSRI or SNRI antidepressant medication if the antipsychotic medication will not cause side effects that are detrimental to the mTBI. In general, antipsychotic medication should be avoided for either PTSD or mTBI because of adverse side effects from these medications. As described previously, these medications can cause sedation, weight gain, and other metabolic changes, thus raising the risk of obstructive sleep apnea and medical complications such as hyperlipidemia or diabetes.

Stimulant medication shows strong evidence of improved attention after TBI. Methylphenidate has been shown in several RCTs to improve attention after TBI [149]. These trials include a double-blind crossover trial in chronic TBI [154] and several additional RCTs of mild and moderate to severe TBI [155–158]. Case report and chart review data also support dextroamphetamine for improved attention after TBI [149].

Even though stimulant medication has been shown effective in multiple RCTs for attention problems related to TBI, it should be used cautiously in veterans diagnosed with PTSD or any other anxiety disorder. The FDA-approved package insert for stimulant medications reports possible side effects as increased anxiety and risk of medication abuse or dependence. The VA/DOD CPG for PTSD does not report any efficacy data for stimulants in treating PTSD and does not recommend stimulants. The CPG for mTBI does recommend stimulant medication for persisting fatigue.

Substance abuse risk is a second important consideration with stimulant medications in PTSD. Given the known relationship between stimulant abuse and anxiety disorders, including PTSD [159–161], stimulant medication should be used cautiously in veterans with comorbid PTSD and TBI. It is not clear if the stimulant use represents attempts at self-medication or an increased susceptibility to substance use disorders [159].

Either worsening anxiety or an iatrogenic substance use disorder could result from prescribing stimulants to a veteran with PTSD and TBI. Therefore, a careful assessment of the risks and benefits is absolutely necessary prior to prescribing stimulants. The most reasonable approach when considering stimulant medication for veterans with TBI is an interdisciplinary care team that includes psychiatry, either neurology or psychiatry, neuropsychology, and psychology.

## DISCUSSION

The diagnosis and management of a veteran with PTSD and TBI is a particularly difficult clinical challenge. The interaction of these two conditions and their associated comorbidities, such as chronic pain or substance use, is yet to

be fully explored, and clinicians will be faced with situations where few published studies can guide decision-making. The clinical evaluation of veterans with PTSD and mTBI should include a biopsychosocial formulation or similar model. Some treatment options for TBI-related cognitive problems such as stimulant medication may be harmful in the setting of comorbid PTSD. Until better RCT data are available, the lack of high-quality trials and clear scientific consensus on the underlying pathologic mechanisms suggest that “N of one” trials are a reasonable clinical approach for creating individualized treatment options. The need for an individual approach to patients with comorbid PTSD and TBI may persist for some time given the varied clinical presentation of TBI. An individual treatment approach can increase the complexity of care because patients are less likely to receive a standardized approach to care. Therefore, veterans diagnosed with both PTSD and TBI are far more likely to require clinical collaboration within an interdisciplinary treatment approach that includes clinicians addressing TBI, PTSD, substance use, general medical conditions, and the outpatient case manager. For example, adding a low-dose TCA to prevent headaches may adversely affect cognition, or starting a SSRI or SNRI antidepressant can increase the risk of serotonin syndrome in a patient taking tramadol for pain. Interdisciplinary treatment teams and systems that facilitate clinician communication will optimize care. Within the VA system, the electronic medical record system provides a valuable tool for communication among clinicians, and similar civilian systems can fulfill a similar role. The case manager can further improve communication among clinicians and improve adherence to recommended care.

## CONCLUSIONS

Despite these areas where the clinician has little firm guidance, there is much that can and should be done for combat veterans who present with both PTSD and TBI. The 2010 VA/DOD CPG for PTSD cites evidence-based therapy as the most powerful treatment available for PTSD. Psychotherapy options that have been introduced recently for PTSD may require adaptations for optimal success in the setting of comorbid TBI, but these therapies appear successful among veterans with both PTSD and TBI. First-line psychopharmacologic options for PTSD are the SSRI and SNRI antidepressants, and these are not known to cause harm in the setting of TBI. Reducing the symptom burden of PTSD should increase the veteran's ability to engage in and benefit from rehabilitation efforts focused on pain, cognition, and daily function. The RCT results on enhanced functional status may be pending, but it is difficult to anticipate anything but beneficial effects upon TBI rehabilitation from fewer PTSD symptoms. VA and DOD clinicians are advised to follow the 2010 CPGs for PTSD and mTBI, to coordinate care with colleagues in other specialty or subspecialty disciplines, and to supplement the CPGs with published studies when further guidance is necessary.

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**Disclaimer:** This manuscript discusses off-label medication use. There are no medications with FDA-approved indications for neuropsychiatric conditions related to TBI. Opinions offered in this article belong solely to the authors and do not necessarily represent any official position of VA or any component of the U.S. Government.

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<sup>1</sup> “Veteran” refers to any member of the military who served in a combat zone, regardless of present military status (Active Duty, Reserve Component, or discharged).

<sup>2</sup> CPGs for PTSD and mTBI can be downloaded at no cost from <http://www.healthquality.va.gov>.



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