# Traumatic Brain Injury and Posttraumatic Stress Disorder: Conceptual, Diagnostic, and Therapeutic Considerations in the Context of Co-Occurrence

Jennifer J. Vasterling, Ph.D., Shawna N. Jacob, Ph.D., Ann Rasmusson, M.D.

The events leading to traumatic brain injury (TBI) are often psychologically traumatic (e.g., motor vehicle accidents) or occur within a broader context of psychological trauma, such as military combat or recurrent interpersonal violence. In such cases, posttraumatic stress disorder (PTSD) may develop and serve to complicate TBI recovery. Likewise, brain trauma may impede emotional resolution following psychological trauma exposure. This article addresses comorbid PTSD and TBI, including the epidemiology of PTSD following TBI; the clinical presentation of the comorbidity; potential mechanisms that complicate recovery from psychological trauma and TBI when they co-occur; and considerations for the clinical management of PTSD in the context of TBI, including implications for both psychosocial and psychopharmacological PTSD treatments. Although the authors address the full spectrum of TBI severity, because PTSD more commonly co-occurs with mild TBI, compared with moderate and severe TBI, the authors focus in particular on mild TBI.

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Emotional symptoms, when associated with traumatic brain injury (TBI), are often viewed through the lens of neural or neurobiological alterations associated with brain impact, or as reactions to the injury and associated functional impairment. Some TBI events (e.g., interpersonal assaults, motor vehicle accidents), however, involve the additional neuropsychiatric dimension of psychological trauma. TBI may also occur within contexts of severe ongoing stress (e.g., domestic violence, military combat). When TBI is associated with psychological trauma, posttraumatic stress disorder (PTSD) may also develop.

PTSD encompasses emotional, behavioral, and cognitive symptoms that arise following exposure to significant threat to life, serious physical injury, or sexual violence. PTSD was originally conceptualized as a purely fear-based disorder, but some psychobiological models emphasize PTSD development as reflecting an initially adaptive survival response ("flight or fight") that becomes maladaptive when sustained after the threat is removed. Recent taxonomy recognizes that nonanxiety-based symptoms (e.g., dysphoria) may also predominate clinical presentations and specifies intrusion symptoms (e.g., nightmares, intrusive thoughts), behavioral and cognitive avoidance of trauma reminders, negative cognition or mood (e.g., anhedonia, negative expectations), and heightened arousal (e.g., sleep disturbance, impaired concentration).[1] PTSD symptoms extend beyond the acute period following trauma exposure, differentiating PTSD from acute stress reactions, and lead to significant distress or functional impairment.

This article addresses comorbid PTSD and TBI, including the clinical presentation, potential mechanisms that complicate recovery from psychological trauma and TBI when they co-occur, and clinical management of PTSD in the context of TBI. It is important to note that we distinguish TBI and psychological trauma as historical events from their consequences (TBI-related symptoms and PTSD, respectively). Although we consider the full spectrum of TBI severity, we emphasize mild TBI throughout because, as discussed in the following section, PTSD occurs more commonly following mild (vs. moderate to severe) TBI.

## PREVALENCE OF PTSD FOLLOWING TBI

The scientific community once believed that alterations of consciousness associated with TBI precluded formation of a trauma memory, making it improbable for PTSD to develop following TBI. Experts, however, now recognize that PTSD may develop following TBI due to several factors: implicit (unconscious) encoding of affective and sensory experiences (e.g., sights and smells) associated with the traumatic event, conscious encoding of some aspects of the event, reconstruction of the trauma memory from secondary sources (e.g., family, other observers), and memory of circumstances surrounding the event that also may be psychologically

traumatic (e.g., sights at the scene of an accident after consciousness was regained). When psychological trauma is ongoing (e.g., military combat, domestic violence), PTSD may develop in response to the broader series of events, even if the specific event leading to TBI is not remembered.

Epidemiological data confirm that PTSD indeed develops following TBI, and, within the general population, in particular following mild TBI. For example, in a prospective study of 1,084 patients presenting with physical injury to a civilian trauma center, relative to patients whose injury did not involve TBI, those with mild TBI were approximately twice as likely to have developed PTSD one year later.[2] Similarly, the medical records of over 500,000 U.S. Air Force service members revealed increased risk of PTSD shortly following mild TBI and months later.[3] Consistent with earlier contentions that the complete failure to encode the trauma in some instances may be protective, a recent meta-analysis of predictors of psychiatric status following civilian TBI suggests that PTSD is associated with a shorter period of posttraumatic amnesia and memory of the event.[4] In military populations, however, both within the restricted range of mild TBI[5] and across a broader range of TBI severities, including greater than mild TBI,[6] risk of PTSD increases with the severity of the TBI.

Some military studies also document higher rates of PTSD associated with TBI than rates generally reported in civilian populations,[6] although the prevalence of TBI across civilian settings varies greatly. More generally elevated rates of the PTSD-TBI comorbidity in military populations may reflect disparate levels of exposure to psychological trauma, as compared with some civilian settings. For example, deployment TBI typically occurs within the context of more intensive combat (and associated psychological trauma exposure). Similarly, a national survey of 411 women military veterans highlighted the high prevalence of intimate partner violence among women veterans, which was associated with high rates of both TBI and PTSD, especially among those veterans with TBI and current symptoms.[7] In contrast, sports concussions, while stressful, are often not associated with *traumatic* stress. Whether civilian or military, risk of PTSD would be expected to vary according to the psychological characteristics of the TBI event and the context in which the TBI occurred, as well as with prior psychological trauma exposures and preexisting PTSD symptoms (e.g., service members with multiple war-zone deployments).

## CLINICAL PRESENTATION OF COMORBID PTSD AND TBI

Differential diagnosis and etiological attribution of symptoms, including both self-reported complaints and performance-based neurocognitive deficits, represent perhaps the most salient challenges related to the clinical presentation of patients exposed to both TBI and psychological trauma. Although symptoms of more severe TBI, especially when acute, can be relatively straightforward to differentiate from PTSD, etiological determination of nonspecific symptoms can be more difficult following relatively milder TBI. Some nonspecific symptoms (e.g., concentration difficulties and other cognitive problems, anger dyscontrol) may be treated successfully without regard for etiology. Differential diagnosis, however, becomes important in clinically managing PTSD, as some of the most effective interventions used to treat PTSD (e.g., exposure-based therapies) require clinician awareness of the disorder.

Different stages of recovery present distinct challenges to etiological attribution. At the time of the injury, psychobiological stress responses invoked by psychological trauma (e.g., disorientation, confusion, attentional and somatosensory disturbances) can mimic acute symptoms of mild TBI. Without clear loss of consciousness, it can be especially difficult to determine the extent to which symptoms of confusion and disorientation are due to neurophysiologic disruptions inherent to the TBI versus emotional and psychophysiological responses to psychological trauma. Similarly, it can be difficult to assess whether impaired recall of the TBI event reflects impaired encoding of the event due to psychological stress or whether the event was not adequately encoded due to a mechanically induced neural event.

Differentiation of acute TBI symptoms from emotional reactions to psychological trauma is less difficult as the TBI becomes more severe and expresses itself as prolonged loss of consciousness or is associated with skull fracture, seizure, and other indications of neural trauma.

When symptoms persist, it is likewise not always possible to confidently ascribe these enduring symptoms to TBI versus PTSD. Postacute, nonspecific symptoms following both mild and relatively more severe TBI overlap partially with those frequently associated with PTSD (e.g., dysphoric mood, anxiety, sleep disturbance, irritability, anger, poor concentration, fatigue, dysregulated arousal, memory deficits).[8] Even in the absence of TBI and PTSD, symptoms associated with TBI are commonly reported by individuals with idiopathic psychiatric disorders (e.g., depression, anxiety)[9] and by healthy individuals,[10] making "post-concussive" symptoms inherently difficult to attribute specifically to TBI. In addition, chronic pain may emerge directly from the TBI as headaches or in response to orthopedic and other somatic injuries associated with the TBI event.[11] Pain disorders, which may be intensified by PTSD independently of TBI,[12] can be associated with concentration problems and other symptoms typically thought of as TBI-related or exacerbated by TBI,[13] further complicating the clinical presentation.

Because neurocognitive performance deficits may manifest even following mild TBI in the acute stages of recovery and may persist in moderate and severe TBI and a smaller subset of mild TBIs, it can be tempting to invoke neuropsychological testing as an objective measure of brain dysfunction more readily linked to neural injury associated with the TBI than to psychiatric comorbidities. PTSD and associated psychological reactions, however, are also associated with neurocognitive performance deficits, including impairments

in domains commonly affected by TBI, such as learning, memory, executive functioning, and working memory.[14]

A growing literature suggests that chronic or late-occurring neurocognitive performance deficits expressed in patients with mild TBI and PTSD are often accounted for by PTSD or related symptoms, such as depression and sleep disturbance. For example, Storzbach et al.[15] found that, although war zone veterans exposed to blasts performed more poorly than non-blast-exposed veterans on select tests of learning and memory, spatial skills, and executive function, adjustment for PTSD symptom severity eliminated statistically significant group differences. Similarly, Verfaellie, Lee, Lafleche, and Spiro[16] found that among 160 war-zone veterans with history of blast exposure, mild TBI was associated only with lower manual dexterity, whereas PTSD symptoms were associated with less proficient cognitive performance across a number of domains. Of note, Verfaellie and colleagues[16] also found that self-reported sleep disturbance, a core symptom of PTSD, partially mediated associations between overall PTSD symptom severity and neurocognitive performance.

Adding to the cross-sectional literature, a prospective study of neuropsychological outcomes of war-zone deployment that adjusted for baseline neuropsychological performance found that unfavorable neuropsychological outcomes assessed on average within three months of return from deployment were associated with PTSD and depression but not with mild TBI.[17] The study likewise found that PTSD symptom increases from postdeployment assessment to a long-term follow-up assessment conducted over five years later were associated with poorer learning and memory performance, whereas mild TBI occurring during the same period was not.[18] Emerging evidence, however, suggests that an exception may be found in patients with white matter abnormalities, for whom neurocognitive impairment is associated with mTBI independently of PTSD.[19]

In contrast to the quality of symptoms expressed, the course of symptoms may help distinguish potential etiologies. Whereas PTSD symptoms may be delayed in their onset and worsen over time,[20] except in rare instances (e.g., slowly developing subdural hematoma or other complications), TBI symptoms and neurocognitive deficits in both children and adults typically manifest most prominently acutely and lessen over time.[21] However, as TBI increases in severity, neural recovery may proceed more slowly and be incomplete well after the injury, even in the absence of PTSD and other forms of overt psychopathology.[22] Thus, the failure of symptoms to recede cannot always be taken as indication of a non-TBI etiology, particularly as the severity of the TBI increases, but also in a subset of milder injuries.[23]

## MECHANISMS OF IMPEDED RECOVERY

Several factors likely account for prolonged expression of symptoms in patients exposed to psychological and brain trauma. In this section, we describe how PTSD and TBI may exert bidirectional influences on course and recovery.

### Influence of PTSD on TBI Recovery

Recent longitudinal studies suggest that PTSD and other psychological variables impede recovery of TBI, especially when the TBI is mild. For example, one longitudinal study of civilians with mild TBI and civilians with minor non-TBI physical injuries found that, whereas mild TBI predicted cognitive, emotional, behavioral, and physical (i.e., neuropsychiatric) symptoms in the acute period following the injury (one week postinjury), it did not do so three months later.[24] In contrast, premorbid psychiatric history and postinjury anxiety were the strongest predictors of neuropsychiatric symptoms three months after TBI, and concurrent PTSD symptoms at three-month follow-up were significantly associated with such symptoms. Similarly, Mac Donald et al.[25] found in a military sample that, in addition to mild TBI and older age, symptoms of PTSD in the acute stages following the injury (up to seven days) strongly predicted adverse outcomes six to twelve months later.

One potential mechanism underlying the association of PTSD with poorer TBI outcomes involves a negative feedback loop of anxiety and sensitivity to threat. Specifically, the hypervigilance to perceived threat associated with PTSD may extend to somatic symptoms as an index of a person's concern about their own physical integrity.[26] When somatic symptoms are perceived as threatening, they may receive disproportionate attention and manifest as an attentional bias,[27] thereby further enhancing both the salience of, and distress associated with, the symptoms. Such distress often then further strengthens the sensitivity to threat.

A second potential mechanism of impeded recovery associated with PTSD can be characterized as an attenuation of overall resilience, defined as a dynamic process encompassing positive adaptation within the context of significant adversity.[28] Psychiatric status is known to affect resilience,[29] which may in part explain the positive association between prior psychiatric diagnosis and reporting of neuropsychiatric symptoms following mild TBI.[24] Given that resilience has been shown to predict better functional outcomes, including fewer symptoms in individuals with mild TBI,[30] it is possible that the increased psychosocial burden of PTSD symptoms impedes the ability to cope with the sequelae of TBI, especially in individuals with a history of trauma exposure or PTSD prior to the TBI event.

### Influence of TBI on Recovery From Psychological Trauma

Neural disruption associated with TBI may affect both the onset and subsequent course of PTSD.[18,31] At the time of mild TBI and in the absence of prolonged loss of consciousness, disruptions in mental status may adversely affect the encoding of the trauma memory, leading to subsequent difficulties in the controlled retrieval of the memory. Although controversy exists regarding whether trauma memories differ qualitatively (i.e., are more fragmented) in persons with PTSD, degraded encoding of trauma memories has been purported to contribute to involuntary, re-experiencing symptoms as well as to

suboptimal processing of the trauma and associated affective disturbances.[32,33] TBI, even when mild, can also lead to at least transient disruption of the frontal subcortical neural circuitry involved in emotion regulation,[34] which can in turn increase susceptibility to heightened emotional responsivity following trauma and lower the threshold for PTSD.[35]

Although neurocognitive dysfunction resolves over time in the majority of mild TBI cases as neural functioning normalizes,[36] neural alterations and associated cognitive dysfunction are more likely to endure as the severity of the TBI increases. Of particular relevance to PTSD, TBI may result in axonal damage in the medial prefrontal cortex,[37] the dysregulation of which is also thought to be a prominent neural feature of PTSD.[38] Enduring medial prefrontal dysfunction may result in deficits in cognitive control that, in addition to altering emotion regulation, adversely affect volitional control and gating of trauma-related memories. For example, in nonclinical samples, better cognitive control was associated with fewer intrusive memories following exposure to analog trauma.[39] Likewise, diminished inhibitory capacity has been associated with more severe re-experiencing symptoms in PTSD samples.[40]

Related to the concept of resilience, enduring executive dysfunction may also influence the development and maintenance of PTSD via erosion of coping mechanisms. Empirical studies demonstrate an association between poorer executive functioning and implementation of maladaptive coping strategies in patients with history of TBI ranging in severity,[41] and maladaptive coping has been linked to poor psychosocial outcomes following TBI.[42] Thus, in the context of reduced cognitive resources, individuals may have difficulty implementing coping strategies, such as reappraising maladaptive thoughts (i.e., cognitive restructuring), that often help resolve psychological trauma.

## PTSD TREATMENT

In this section, we review the literature on psychosocial and pharmacological PTSD treatments delivered in the context of TBI.

### Psychosocial Interventions for PTSD

Prior to reviewing the literature on cognitive-behavioral therapy (CBT) for PTSD in patients with TBI, it is important to first understand what CBT encompasses. CBT interventions, by definition, have a cognitive emphasis. They differ, however, from cognitive rehabilitation, which targets enhancement or restoration of specific cognitive skills (e.g., attention, executive functioning, memory) and/or compensatory strategies. CBT, in contrast, targets a change in the content of thoughts and in the emotions associated with those thoughts and/or memories of the trauma. Interventions involving exposure to the trauma memory and/or cognitive restructuring have a particularly strong evidence base for treatment of PTSD.

Psychosocial treatments for PTSD, however, were not originally designed with TBI or comorbid chronic cognitive deficits in mind. Exposure-based interventions involve repeated exposure to trauma memories and their reminders with the goal of habituation and modifying memories to form new emotional associations, a process that may be affected by the presence of posttraumatic amnesia in moderate to severe TBI. Cognitive restructuring involves reappraisal of maladaptive thoughts related to the trauma with the goal of considering alternative appraisals of the trauma and its consequences. As such, the patient must have the capacity to inhibit unconstructive automatic responses and the mental flexibility to consider alternatives, both aspects of cognition that can be compromised in the early stages of mild TBI[43] and persist in more severe TBIs.[44] Further, it is possible that persisting memory, attentional, and executive difficulties associated with TBI could interfere with the patient's ability to engage in, or adhere to, treatment (e.g., attending to session content and remembering to complete homework assignments).[45] Thus, in considering PTSD interventions in the context of TBI, we take into account a growing literature that addresses the effectiveness of the interventions and whether modification or augmentative strategies may be beneficial.

CBT has been implemented in patients with PTSD and history of mild, moderate, and severe TBI, with positive treatment responses similar to those exhibited by patients with PTSD and no history of TBI and with no documented adverse events.[46–48] In a sample of PTSD patients who were undergoing CBT for PTSD-related insomnia and in which the majority (>75%) reported TBI history, less-proficient verbal memory was associated with mildly attenuated treatment response.[46] It is at least as likely that less-proficient verbal memory was associated with PTSD (and associated sleep problems) as opposed to TBI,[16] and similar relationships between verbal memory and CBT treatment response have been documented in PTSD patients without TBI.[49]

Among patients with TBI, CBT interventions targeting psychological trauma symptoms have also been effective in reducing symptoms of acute stress disorder,[50] depression,[48] and nonspecific postconcussive symptoms.[51] CBT treatment adherence among patients with PTSD and TBI, ranging from 22% to 53.7% in outpatient settings,[47,48] and up to 17% in inpatient/residential settings,[51,52] is comparable to that of patients with PTSD alone. Thus, although the research is still in its early stages, the available evidence suggests that CBT interventions commonly used to treat PTSD are both effective and safe in treating individuals with PTSD and TBI across a range of severities.

Little is known about the effects of modifying or augmenting PTSD interventions to accommodate co-occurring cognitive deficits or noncognitive neuropsychiatric symptoms. Regarding modification, there is currently no evidence that modifying either the delivery platform or core aspects of CBT interventions for PTSD results in superior outcomes in patients with TBI. In a small sample of veterans with comorbid

PTSD and TBI, Wolf, Strom, Kehle, and Eftekhari[53] modified the delivery platform of prolonged exposure therapy to include external memory aides, increase the structure of session content, and extend the session time, and found that PTSD symptoms were successfully reduced. Because the modified version was not compared with unmodified delivery of the treatment, however, the effects of the modification could not be examined. In the context of a residential treatment program for comorbid TBI and PTSD, Walter, Dickstein, Barnes, and Chard[52] found that a version of cognitive processing therapy that omitted the writing of a trauma narrative to allow for more focus on cognitive interventions was successful in reducing symptoms of PTSD, depression, and other neuropsychiatric symptoms but did not demonstrate better outcomes when compared with standard implementation of cognitive processing therapy.

Regarding augmentation (i.e., adjunct interventions delivered in addition to PTSD interventions), results from a randomized controlled trial suggest that an intervention focused on psychoeducation and cognitive compensatory strategies (cognitive symptom management and rehabilitation therapy [CogSMART]) successfully reduced nonspecific affective symptoms in military veterans with TBI and PTSD.[54] However, empirical evaluation of the added value of augmentative strategies in patients with PTSD and TBI is still needed.

### Pharmacological Treatment of PTSD and Implications for Comorbid TBI

At the time of this writing, there is limited empirical evidence with which to guide the pharmacological treatment of comorbid TBI and PTSD. In fact, treatment studies relevant to each condition generally exclude for the other condition. Here we overview psychopharmacological approaches to managing PTSD, taking into consideration potential implications arising from comorbid TBI. We also briefly review medications that are commonly used in the treatment of TBI and associated symptoms, but that may be contraindicated in PTSD.

Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line medications for the treatment of PTSD[55] based on the success of sertraline and paroxetine in large FDA registration trials. SSRIs may have the added benefit of targeting symptoms of common PTSD psychiatric comorbidities (e.g., depression, panic) and are recommended as first-line choice in treating depression associated with TBI.[56] Venlafaxine, which inhibits the reuptake of serotonin at lower doses, as well as norepinephrine at higher doses, also is a first-line pharmacological approach for treating PTSD, although venlafaxine has not been FDA-approved for this indication.[57–59] It is important, however, to consider that meta-analysis demonstrates only small to medium effect sizes for the difference in performance between SSRIs or SNRIs and placebo.[60] Thus, it may be difficult to discern whether symptom improvement in an individual patient is attributable to active drug, placebo effect, or other factors related to engagement in PTSD treatment.

The substantial rate of resistance to the potential therapeutic effect of SSRIs initially appeared to be related to male sex or veteran status; more recent overviews of SSRI treatment studies in PTSD suggest that resistance may be related to age, illness chronicity,[59] or possibly to ethnicity. Both SSRIs and venlafaxine are generally safe, although each may be associated with particular side effects. For example, agitation, insomnia, headache, sexual dysfunction, and increased bleeding risk may result from SSRI treatment (Table 1); similar side effects may result from SNRIs due to their serotonin reuptake blocking properties.[61] Additionally, visual changes due to increased intraocular pressure, anxiety, dizziness, and increased heart rate or blood pressure may result from the norepinephrine reuptake blocking properties of SNRIs. Some of these side effects may be confused with symptoms of PTSD or TBI, especially when the TBI is relatively more severe.

As recently reviewed by Rasmusson et al.,[62] SSRIs at doses substantially below those that block serotonin reuptake increase the production of metabolites of progesterone (e.g., allopregnanolone) with anxiolytic, antidepressant, antiaggression, and anti-PTSD-like effects. Allopregnanolone potently facilitates the effects of gamma-amino-butyric acid (GABA) at brain $GABA_A$ receptors and potently decreases the negative sequelae of brain ischemia and head trauma in rodent models.[63,64] Also as reviewed by Rasmusson et al.,[62] exposure to severe stress can reduce allopregnanolone levels in brain (e.g., prefrontal cortex) and the blood. Further, sex-specific deficits in the function of enzymes involved in allopregnanolone synthesis, and a negative relationship between severity of PTSD symptoms and levels of allopregnanolone and pregnanolone (a stereoisomer of allopregnanolone with equipotent effects at $GABA_A$ receptors) have been demonstrated in women and men with PTSD. Thus, it is possible that deficits in allopregnanolone may be reversed by SSRIs in some individuals, but that some enzymatic blocks in allopregnanolone synthesis may not be reversible and contribute to the substantial rates of SSRI treatment resistance in PTSD and depression. These observations may be of particular relevance to individuals exposed to neurotrauma and chronic or traumatic stress simultaneously, such as survivors of physical assault or military personnel exposed to blasts from improvised explosive devices during the recent conflicts in Iraq and Afghanistan.

A number of medications other than SSRIs are used as second-line or augmentation approaches for the treatment of PTSD (see Table 1). When symptoms of PTSD do not respond to treatment with an SSRI or SNRI, a tricyclic antidepressant or monoamine oxidase inhibitor may be considered. Research supporting the efficacy of these agents, however, is limited, and their administration can be accompanied by more significant side effects.[55]

A trial of bupropion, another antidepressant with dopamine and norepinephrine reuptake blocking properties, may be indicated if sexual dysfunction limits use of SSRIs or SNRIs. Bupropion may also be considered in the context of

**TABLE 1. Medications With Evidence From Controlled Trials and Support by Clinical Treatment Guidelines for Treatment of PTSD[a]**

| Class | Medication | Indication in PTSD | Considerations for Treating PTSD and TBI |
|---|---|---|---|
| SSRI | Fluoxetine; paroxetine[b,c,d]; sertraline[b,c] | Global symptoms of PTSD; comorbid conditions (e.g., depression, anxiety, panic); suicidal, aggressive, and impulsive behaviors | Also considered first line for treating depression TBI; may increase agitation and sleep disturbance or cause sexual dysfunction, especially at higher doses; some have anticholinergic effects; all can increase bleeding risk at doses that block serotonin reuptake, particularly in the elderly or individuals with tissue damage or alcohol use disorders associated with gastrointestinal inflammation or if combined with nonsteroidal anti-inflammatory drugs or platelet inhibitors |
| SNRI | Venlafaxine[c,d] | Global symptoms of PTSD; comorbid depression | May be associated with the same side effects as SSRIs, as well as dizziness; fatigue; headache; visual disturbance due to increased intraocular pressure; and signs of increased sympathetic system activity, such as palpitations or increased blood pressure |
| SARI | Trazodone[c] | Sleep disturbance | Risk of sedation; a small proportion of patients may experience anxiety, panic, agitation, or psychotic symptoms due to increased conversion of trazodone to m-CPP, particularly if combined with CYP2D6 inhibitors such as SSRIs, which slow metabolism of m-CPP |
| | Mirtazapine[d,e] | Depression symptoms; lower doses selectively block serotonin Type-2A receptors and can promote sleep; higher doses block norepinephrine reuptake and may inadvertently contribute to insomnia but help with depression | May increase somnolence, risk of dizziness |
| TCA | Amitriptyline; imipramine[b,c] | Global symptoms of PTSD; intrusive recollections | Can be associated with cognitive slowing; anticholinergic effects |
| MAOI | Phenelzine[b,c,d] | Global symptoms of PTSD; traumatic nightmares | Contraindicated for use with alcohol, illicit substances, certain prescription drugs; risk for hypertensive crisis, hepatic toxicity |
| Alpha-1 adrenergic receptor antagonist | Prazosin[b,c,d,f] | Traumatic nightmares; daytime dosing (lower than nighttime doses for sleep disturbance) may help with PTSD symptoms more generally | May cause orthostatic hypotension, dizziness, lightheadedness, and sedation, especially with first dose (so-called "first dose response"); dizziness, headache, drowsiness, anergia, weakness, palpitations, and nausea are relatively common adverse effects, and women are susceptible to these side effects at lower doses than men |

[a] Abbreviations: MAOI=monoamine oxidase inhibitor; m-CPP=meta-chlorophenylpiperazine; PTSD=posttraumatic stress disorder; SARI=serotonin agonist and reuptake inhibitor; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.
[b] For further details, see reference citation[55].
[c] For further details, see reference citation[57].
[d] For further details, see reference citation[58].
[e] For further details, see reference citation[66].
[f] For further details, see reference citation[70].

increased markers of inflammation (e.g., C-reactive protein) in association with anhedonia or psychomotor slowing. Inflammation effects on the synthesis, packaging, and release of dopamine, however, may limit the positive effects of bupropion and require novel approaches in the context of PTSD and TBI.[65]

Mirtazapine, an antidepressant that blocks serotonin type 2A ($5HT_{2A}$) receptors at low doses and norepinephrine reuptake at higher doses, may be especially advantageous in treating PTSD-comorbid depressive symptoms when used in conjunction with an SSRI.[66] Mirtazapine is associated with minimal side effects; drowsiness sometimes induced at lower doses of mirtazapine can be exploited in the treatment of PTSD-related insomnia.

Trazodone, another antidepressant with $5HT_{2A}$ blocking properties, also may be helpful in treating sleep disturbance associated with PTSD or possibly that induced by SSRI administration. Care must be taken, however, as a small but not insubstantial proportion of individuals demonstrate increased rates of CYP3A4 metabolism of trazodone to *meta*-chlorophenylpiperazine (m-CPP),[67] a compound that releases serotonin and directly activates or antagonizes a broad range of serotonin receptors. In turn, m-CPP can induce intense anxiety, agitation, perceptual disturbances, hallucinations, headache, and anorexia.[68] Coadministration of SSRIs, which block the normal metabolism of m-CPP by the enzyme CYP2D6,[69] may further potentiate these side effects, which can easily be misconstrued as a worsening of PTSD, onset of a comorbid anxiety or psychotic disorder, or complications of TBI.

Finally, emerging evidence supports the efficacy of prazosin, a noradrenergic $\alpha_1$ receptor inhibitor, as a treatment for insomnia due to trauma-related nightmares.[55] Meta-analytic review of six randomized controlled trials demonstrated that prazosin is efficacious in improving overall PTSD symptoms in addition to PTSD-related nightmares.[70] Relative to trazodone, prazosin is not sedating, although its use may be associated with headaches.[70]

Stimulants—sometimes prescribed for TBI—have been little studied in PTSD. A randomized, placebo-controlled pilot study found that patients with PTSD, history of TBI, or both responded positively to methylphenidate, a central nervous system stimulant commonly used to treat attention-deficit hyperactivity disorder (ADHD).[71] Patients tolerated methylphenidate well, reported fewer cognitive deficits as well as other postconcussive and PTSD symptoms, and showed improved performance on objective measures of attention and processing speed. This preliminary evidence suggests the need for further investigation of cognitive enhancing agents, which are not currently included in clinical practice guidelines, in the treatment of comorbid PTSD and TBI.

Several medication classes formerly considered as potential treatments for PTSD are not currently recommended, are contraindicated, or are used for only a narrow set of clinical presentations. These include benzodiazepines, antipsychotics, and anticonvulsants.

Benzodiazepines are not recommended in PTSD and, in general, are best avoided among persons with TBI given their sedating and amnestic effects as well as their adverse effects on motor function. Notably, benzodiazepines selectively target *synaptic* $GABA_A$ receptors, which have been shown to be downregulated in the amygdala after exposure to extreme stress. In contrast, low doses of alcohol and GABAergic neuroactive steroids such as allopregnanolone and ganaxolone also target *extrasynaptic* $GABA_A$ receptors, as does topiramate, perhaps accounting for the impact of allopregnanolone and ganaxolone on PTSD-like behaviors in rodent models[62] and topiramate on PTSD symptoms in humans.[72]

Conventional antipsychotics with primary antagonistic effects at dopamine type 2 receptors are also contraindicated in PTSD treatment. Atypical antipsychotics that antagonize $5HT_{2A}$ receptors, and often noradrenergic $\alpha_1$ receptors as well, are generally not recommended unless the patient is presenting with psychotic or dissociative symptoms not attributable to another disorder (e.g., delirium, dementia); atypical antipsychotics may also be considered in patients presenting with extreme hypervigilance/paranoia, aggression, and social isolation that have not responded to treatment with other medications.[55]

Anticonvulsants, a medication class potentially prescribed to prevent or treat seizures in patients with moderate to severe TBI, are typically not recommended for use in PTSD outside the context of TBI due to insufficient demonstration of their efficacy versus side effect profile[55]; anticonvulsants, however, are not contraindicated in PTSD if necessary for treatment of seizures associated with comorbid TBI.

In summary, the available evidence suggests that the pharmacological treatment of PTSD in patients with comorbid TBI is best approached similarly to that of PTSD alone. Many of the medication side effects relevant to TBI are also relevant to PTSD, although the risk of certain side effects may be especially concerning in patients with comorbid PTSD and TBI, as they may be even more vulnerable to medication-induced exacerbation of symptoms or side effects (e.g., agitation/insomnia/ impulsivity and risk of self-/other harm). The general consensus in prescribing to patients with PTSD and TBI history is to start with low doses and titrate slowly; be cognizant of possible drug interactions; and use caution when potential medication side effects might increase risk of TBI-associated problems, such as cognitive deficits, sensory and balance issues, and seizures.[73] In the meantime, research is evolving to focus on development of new treatments and the precision medicine targeting of such treatments to pathological processes that contribute to PTSD and TBI risk, severity, and chronicity at the individual patient level.

## SUMMARY AND CONCLUSIONS

Many TBI events have the potential to be psychologically traumatic (e.g., motor vehicle accidents) or occur within a context of ongoing psychological trauma (e.g., military combat, domestic violence). In instances when TBI and psychological trauma co-occur, PTSD may develop or worsen if present prior to the TBI. Clinical outcomes may be

less positive in patients with TBI history and PTSD, as TBI may impede recovery from psychological trauma, and PTSD may impede recovery from TBI. Although the mechanisms are not fully understood, the cumulative burden of each condition on neural and associated neurocognitive function may contribute to impediments in recovery. Similarly, added disease burden may adversely affect coping mechanisms dependent on cognitive processes, as well as more generally degrade psychosocial resilience. Finally, heightened sensitivity to threat associated with PTSD may sensitize patients to TBI-related symptoms, which may in turn increase anxiety, resulting in a negative feedback loop that serves to sustain both PTSD symptoms and others that may be TBI-related.

Perhaps because of partial overlap of underlying neural substrates and commonalities in psychological responses to brain injury and psychological trauma, there is significant overlap between TBI and PTSD symptoms. Such overlap can make etiological attributions challenging, but it is nonetheless important to recognize PTSD when present following TBI because PTSD symptoms are often amenable to treatment. Thus, recognition of PTSD both allows for positive expectations by patients and ensures that patients receive an evidence-based PTSD intervention that will maximize their potential for recovery. It is likewise important to identify history of TBI in patients presenting with PTSD symptoms, especially when the TBI is recent, so that psychoeducation regarding TBI, including positive expectations for recovery, can be provided. Finally, because PTSD and TBI may both be associated with risk taking behaviors via decreased inhibition, it may be beneficial to anticipate behaviors (e.g., anger dyscontrol, recklessness) that could put the patient at risk for another TBI.

There is currently no evidence to suggest that core features of evidence-based PTSD treatments, including those with cognitive components, should be modified. CBT interventions, including those with exposure components, have been successfully implemented within a broad range of TBI severities. Modifications to CBT delivery platforms, although not examined against unmodified delivery platforms in patients with PTSD and TBI, have proven to be effective, suggesting that they do not degrade mechanisms of action central to the interventions.

Psychosocial augmentative interventions, such as those targeting cognitive skills and other nonspecific symptoms (e.g., insomnia, anger dyscontrol), although effective in addressing nonspecific symptoms, have not been examined in relation to their added value when implemented in the context of evidence-based PTSD interventions. Likewise, little is known regarding the effectiveness of psychopharmacologic agents in the treatment of PTSD in patients with history of TBI, but central nervous system effects potentially affecting cognition and sensorimotor function should be taken into consideration.

In summary, although patients with PTSD and TBI may initially present with a somewhat more complicated clinical presentation, with appropriate treatment, there is reason to believe that symptoms can be successfully managed. Further research is needed regarding the added value of modified delivery platforms for psychosocial interventions, augmentative strategies, and psychopharmacological interventions.

## AUTHOR AND ARTICLE INFORMATION

From the Psychology Service, VA Boston Healthcare System, Boston (JJV, SNJ); the National Center for PTSD at VA Boston Healthcare System, Boston (JJV, AR); the Department of Psychiatry, Boston University School of Medicine, Boston (JJV, SNJ, AR); and the Psychiatry Service, VA Boston Healthcare System, Boston (AR).

Send correspondence to Dr. Vasterling; email: jennifer.vasterling@va.gov

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