# Neuropsychiatric Disturbances Associated with Traumatic Brain Injury: A Practical Approach to Evaluation and Management

Vani Rao, MD[1] Vassilis Koliatsos, MD[1,2] Faizi Ahmed, MD[1] Constantine Lyketsos, MD, MHS[1] Kathleen Kortte, PhD[3]

[1] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland
[2] Departments of Pathology and Neurology, Division of Neuropathology, Johns Hopkins University School of Medicine, Baltimore, Maryland
[3] Department of Physical Medicine and Rehabilitation, Division of Rehabilitation Psychology and Neuropsychology, Johns Hopkins School of Medicine, Baltimore, Maryland

**Address for correspondence** Vani Rao, MD, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, 5300 Alpha Commons Drive, 4th floor; Suite 425;, Baltimore, MD 21224 (e-mail: vrao@jhmi.edu).

Semin Neurol 2015;35:64–82.

## Abstract

Traumatic brain injury (TBI) causes a wide variety of neuropsychiatric disturbances associated with great functional impairments and low quality of life. These disturbances include disorders of mood, behavior, and cognition, and changes in personality. The diagnosis of specific neuropsychiatric disturbances can be difficult because there is significant symptom overlap. Systematic clinical evaluations are necessary to make the diagnosis and formulate a treatment plan that often requires a multipronged approach. Management of TBI-associated neuropsychiatric disorders should always include nonpharmacological interventions, including education, family involvement, supportive and behavioral psychotherapies, and cognitive rehabilitation. Pharmacological treatments include antidepressants, anticonvulsants, antipsychotics, dopaminergic agents, and cholinesterase inhibitors. However, evidence-based treatments are extremely limited, and management relies on clinical empiricism and resemblance of TBI neuropsychiatric symptom profiles with those of idiopathic psychiatric disorders. Although the understanding of TBI-associated neuropsychiatric disorders has improved in the last decade, further research is needed including prospective, longitudinal studies to explore biomarkers that will assist with management and prognosis as well as randomized-controlled studies to validate pharmacological and nonpharmacological treatments. The current review summarizes the available literature in support of a structured, systematic evaluation approach and treatment options as well as recommendations for further research directions.

**Keywords**
- traumatic brain injury
- neuropsychiatry
- postconcussion
- depression
- posttraumatic stress disorder
- chronic traumatic encephalopathy
- anxiety
- mood
- mania
- behavior
- psychosis
- apathy
- sleep

Traumatic brain injury (TBI) is associated with various long-term morbidities. Among them, neuropsychiatric disturbances account for a significant portion of chronic disability and poor quality of life. Survivors of TBI have higher rates of psychiatric disorders compared with the general population.[1] Based on our own unpublished data (V. Rao) of 101 patients with TBI of all degrees of severity followed prospectively for 1 year, 80% had at least one Axis I diagnosis (See ►**Table 1**). A simplified biological explanation for the increased vulnerability of TBI patients to develop neuropsychiatric

**Issue Theme** Traumatic Brain Injury; Guest Editor, Geoffrey Ling, MD, PhD, FAAN, FANA



**DOI** http://dx.doi.org/10.1055/s-0035-1544241.
**ISSN** 0271-8235.

**Table 1** Example of rates of psychiatric diagnoses in the first year after traumatic brain injury

| Psychiatric diagnoses | Rates ($N = 103$) (%) |
|---|---|
| Any psychiatric diagnosis | 85.4 |
| 2 or more Axis 1 psychiatric diagnoses | 60.1 |
| Any depression | 52.4 |
| Any alcohol or substance abuse/ dependence | 36.9 |
| Pathological crying/laughter | 33.0 |
| Any anxiety disorder | 31.1 |
| New-onset mood disorder | 30.0 |
| Personality change | 15.5 |
| Posttraumatic stress disorder | 8.7 |
| Apathy | 8.7 |

**Table 2** Unique features of neuropsychiatric disturbances associated with traumatic brain injury

| |
|---|
| Clinical presentation |
| Possible direct relationship with cerebral injury |
| Bidirectional relationship between TBI and psychiatry |
| Phenomenology of TBI NPDs varies substantially among patients. |
| Diagnostic approach |
| No standard validated diagnostic system to capture TBI NPD |
| Need to use a stepwise, multipronged approach |
| Clinical management |
| Treatment must be multidisciplinary and multipronged |
| No FDA-approved pharmacological interventions |

Abbreviations: FDA, US. Food and Drug Administration; NPD, neuropsychiatric disturbances; TBI, traumatic brain injury.

disturbances (NPDs) is that brain regions involved in emotional regulation, behavioral control, and higher-order cognitive operations are the ones most frequently affected by TBI. The inferior frontal and temporopolar regions are classically involved in contrecoup contusions from violent impacts to the head, presumably because of their encasement in and friction with irregular osseous compartments in the anterior and middle cranial fossae. Callosal (commissural) and other long tracts are especially vulnerable to impulses associated with rotational acceleration as occurs in motor vehicle crashes and high-impact falls. All these regions and pathways are essential for higher CNS functions.[2]

Neuropsychiatric disturbances tend to occur irrespective of TBI severity and are often persistent.[3–5] These problems should be diagnosed and treated promptly because they can significantly interfere with recovery and rehabilitation in the acute post-TBI period as well as with long-term outcomes and quality of life.

Neuropsychiatric disorders associated with TBI have many unique features that contribute to the clinical presentation, differential diagnosis, and appropriate treatment regimen (see ►**Table 2**). Appreciation of these features will assist the practicing clinician in better assessing and formulating these disturbances as well as establishing the best intervention plan.

## Unique Features of the Clinical Presentation

One of the key clinical features of TBI is the heterogeneity of clinical presentation among individuals. Neither the presentation nor the treatment of TBI-associated neuropsychiatric disturbances is uniform. Comorbidities are common and symptoms and syndromes cross diagnostic boundaries. Apathy, for example, can present as a symptom of depression, but also constitutes an amotivation syndrome in the absence of positive dysphoric symptoms of depression. Depression after TBI can be associated with anxiety, agitation, and irritability, a presentation raising questions as to whether these are symptoms of depression or of other comorbid entities. Substance abuse is common in individuals with TBI; therefore, substance intoxication, withdrawal, and/or substance-induced psychiatric disorders should always be considered in the differential diagnosis of psychiatric symptoms after TBI. Given these complexities in clinical presentation, it is critical that individuals with TBI-associated neuropsychiatric disturbances are appropriately evaluated by clinicians who are experts in TBI.

Traumatic brain injury has a bidirectional correlation with psychiatric disturbances. It is not only that TBI is associated with higher rates of psychiatric disorders, but also psychiatric illness is a risk factor for TBI. Vassallo et al found that, after adjusting for demographic and other variables such as academic difficulties and remote psychiatric difficulties, individuals with mood, anxiety, and conduct disorders were 2.5, 1.6, and 1.7 times, respectively, more likely to sustain TBI.[6] Fann and colleagues found that individuals with known psychiatric illnesses had an adjusted TBI relative risk of 1.7 compared with people without psychiatric diagnosis.[7] Similarly, individuals without a formal psychiatric diagnosis, but who had filled a psychiatric medication prescription in the previous year had an adjusted relative risk for TBI of 1.6 compared with people with no history of psychiatric medication prescription. Finally, those who had utilized psychiatric services had an adjusted relative risk for TBI of 1.3 compared with those who had not.

## Unique Features in Approach to Diagnosis

The diagnosis of TBI-associated neuropsychiatric disorders is often challenging because there are no established diagnostic criteria by which to distinguish such disturbances from other primary psychiatric conditions. Fujii and Ahmed have postulated that better diagnosis of these disturbances may better guide management and inform prognosis.[8] Accurate diagnosis is also important from a medicolegal perspective, because compensation is often awarded to TBI

survivors only if TBI can be shown to have caused the psychiatric symptoms. From a research perspective, accurate diagnosis may shed light on the mechanisms of not only psychiatric symptoms associated with TBI, but also similar symptoms associated with other neurologic disorders and with primary psychiatric disorders. The *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) is the most commonly used diagnostic system for categorizing psychiatric disorders in the United States. This system, now in its fifth iteration (*DSM-5*), has a separate category for psychiatric disorders due to general medical conditions.[127] However, the key criterion for making the diagnosis is a definitive causative link between mental illness and injury, for example, depression and TBI, and such a temporal association cannot be readily substantiated. Jorge and Arciniegas posit that when a clear temporal association cannot be made, it is best to consider TBI as a treatment-informing comorbidity rather than an etiological factor, and we agree with this position.[9] Additionally, there are many symptoms of TBI per se that are also common in idiopathic psychiatric disorders, such as fatigue, sleep disturbance, changes in appetite, disinhibition, impulsivity, and difficulties with attention and concentration. This overlap can lead to overdiagnosis. On the other hand, some TBI symptoms such as anosognosia and apathy may lead to underdiagnosis. In summary, in the absence of well-validated criteria to diagnose TBI NPDs, we propose continuing to use the *DSM* criteria, but bearing in mind the challenges discussed above.

Given the complexities of the clinical presentation of TBI-associated neuropsychiatric disturbances and the challenges of accurate diagnosis, as suggested by Neikrug and Ancoli-Israel, for the treatment of sleep disturbances, a stepwise approach is also advised for the evaluation of TBI NPDs (see ►**Fig. 1**).[10] The evaluation process should begin with a comprehensive neuropsychiatric examination to screen for common mood, behavioral, and cognitive disturbances found in TBI patients. The neuropsychiatric evaluation process may include a very detailed history, informed use of screening instruments to better characterize the symptoms, a neurologic exam to screen for localizing or diffuse neurologic impairments as a diagnostic aid and consideration of important comorbidities, and a problem-focused medical workup to determine possible alternative explanations or contributing factors such as infections or endocrine abnormalities. The patient may then be referred for ancillary tests, such as brain magnetic resonance imaging (MRI) and neuropsychological testing, to help define the nature and severity of some impairments, especially cognitive deficits. Because medical comorbidities, use of medications, and substance misuse are common comorbidities, delirium and substance intoxication/withdrawal/induced symptoms should always be considered in the differential diagnosis. Formulation should always be multidimensional and include preinjury, injury, and postinjury factors. Reliance on a model that stresses biopsychosocial, cultural, and personality dimensions is important for the diagnostic formulation. One structured approach to this issue is of Drs. McHugh and Slavney's "Four Perspectives"— Disease, Dimensional, Behavioral, and Life Story—that has been described previously.[11]

## Unique Features in Clinical Management

Traumatic brain injury-associated psychiatric symptoms may cross many realms, and thus a multipronged approach is critical to manage and reduce the impact on daily life

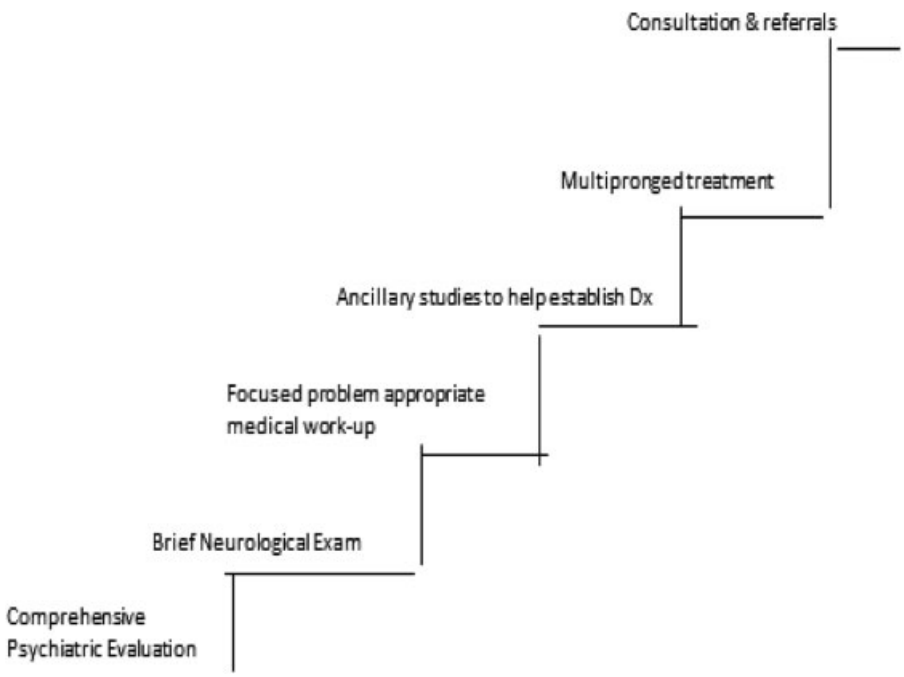


**Fig. 1** Stepwise approach for the evaluation of traumatic brain injury- (TBI-) associated neuropsychiatric disturbances. DX, diagnosis.

functioning and adjustment. Management should combine nonpharmacological and pharmacological interventions. The success of the intervention process relies, to a considerable extent, on the full engagement of the patient and his or her key supports in all aspects of management.[12] Interventions should be structured in such a fashion as to provide a framework for understanding the trauma and its neuropsychiatric consequences, discussing myths and facts, describing the recovery course, making appropriate referrals to brain injury support groups, providing support and reassurance, and structuring the treatment approach to accommodate cognitive impairments and difficulties with treatment adherence that are inherent in any psychiatric condition. Behavioral interventions for management of fatigue, sleep disturbances, and cognitive impairments rely on a strong therapeutic alliance and the expertise of the clinician in appropriately structuring the therapeutic environment such as to maximize patient engagement. If indicated, referrals should be made to substance abuse rehabilitation programs. Finally, inpatient psychiatric hospitalization should be considered whenever there are concerns about safety, such as acute suicidality or assaultiveness. Failure of outpatient psychiatric treatment and the need to establish a diagnosis may be additional indications for inpatient admission.

It is important to note that despite the high rates of TBI-associated psychiatric disorders, there are no pharmacological interventions approved by the U.S. Food and Drug Administration (FDA). Clinicians must extrapolate from the treatment of idiopathic psychiatric disturbances. Reports from pilot trials and small case series still form the basis for treatment recommendations. Sometimes, a single agent can be used to treat many neuropsychiatric conditions linked to TBI, thus familiarity with specific agents and related literature is key for informed interventions. For example, selective serotonin reuptake inhibitors (SSRIs) may be used for treatment of depression, impulsivity, and aggression. Because of some common comorbidities of TBI-associated neuropsychiatric disturbances such as seizures, medications should be carefully chosen, often starting at the lowest available dose and then gently titrating upwards; patients should be closely monitored for side effects and drug interactions.

## Review of Specific TBI Neuropsychiatric Disturbances

Neuropsychiatric disturbances associated with TBI can be broadly classified into disorders of mood, behavior, and cognition. To provide a practical clinical approach to evaluation, diagnosis, and management, we will now review common disorders based on the literature and our clinical experience. ►**Table 3** summarizes the core features, risk factors, differential diagnosis, and management of these disorders.

### Mood Disorders

TBI-associated mood disorders have been mentioned in the medical literature for more than a century. Adolf Meyer referred to these symptoms as "traumatic insanities," and proposed that there might be a general association between these symptoms and brain lesions.[13]

#### TBI-Associated Depression

Traumatic brain injury-associated depression is a collective term used to describe heterogeneous conditions ranging from relatively short periods of sadness in response to stressful situations, known as adjustment disorders with depressed mood, to prolonged, persistent sadness sometimes associated with anhedonia, and vegetative signs and symptoms (e.g., changes in sleep, appetite, energy, concentration) and cognitive problems, predominantly executive dysfunction. The latter can last for weeks to months (major depressive episode), or in a milder form, persist for 2 or more years (dysthymia). In this review, we will focus on major depression and dysthymia and briefly refer to them as TBI depression.

##### *Rates*

The prevalence of TBI depression is said to range widely from 13% at 1 year to 60% at 8 years after TBI.[1,3] In a more recent review, the one-year frequency of post-TBI depression was estimated to range from 25 to 50%, with a lifetime prevalence of 26 to 64%.[9] The unusually wide range in reported rates of TBI depression may be attributed to differences in sampling and methodology, but the exact impact of these factors on prevalence rates is unknown.[14]

##### *Risk Factors and Mechanisms*

A personal history of mood disorders and poor social functioning are well-established risk factors for TBI depression.[15,16] There are no consistent data on demographic risk factors.[9] Only a few studies have examined the association of genetic factors with TBI depression. In a study of 60 persons with TBI 30 years after injury, Koponen and colleagues noted that there were no difference in rates of psychiatric disorders between the ones with and those without the APOE4 allele.[17] In a study comparing 75 persons with TBI depression to 99 with a history of TBI but no depression, Chan and colleagues found no association between serotonin transporter gene polymorphisms and TBI depression.[18] An extension of this study examined the relationship between single nucleotide polymorphisms (SNPs) in serotonin transmission-related genes and response to citalopram. They noted that the methylene tetrahydrofolate reductase (MTHFR) C-(677)T and brain-derived neurotrophic factor (BDNF) val66met SNPs predicted greater response to treatment; the serotonin transporter (5HTTLPR including rs25531) SNP predicted a higher incidence of adverse events.

In addition, there is no consistent data on brain regions associated with TBI depression. Magnetic resonance structural imaging and volumetric studies have noted abnormalities in frontal regions, basal ganglia, and hippocampi. Left-sided or anterior frontal lesions were strongly correlated with TBI depression.[15,19–21] The few pilot studies using magnetic resonance spectroscopic imaging (MRSI) noted associations with biochemical abnormalities in the frontal, basal ganglionic, and thalamic regions.[22,23] Small cohort and pilot studies using MRI diffusion tensor imaging (DTI) have noted white

**Table 3** Neuropsychiatric disturbances associated with traumatic brain injury

| Neuropsychiatric diagnosis | Core features | Differential diagnosis | Risk factors | Management and commonly used medications & dosages |
|---|---|---|---|---|
| Major depression | Episodes of sadness, loss of pleasure, guilt, low self-esteem, hopelessness, suicidal thoughts, with or without psychosis ± anxiety, ± irritability, ± substance misuse | Grief<br>Pathological crying<br>Primary apathy syndrome | Lesions to frontal & basal ganglia, thalamus<br>Pre-TBI psychiatric history<br>Poor psychosocial support | Psychiatric admission if suicidal<br>CBT<br>SSRIs: Sertraline 25–150 mg/d; escitalopram 5–20 mg/d |
| Mania | Episodes of hyperenergized state with elated mood or irritability, decreased need for sleep, racing thoughts, rapid speech and impulsivity, with or without psychosis | Personality change secondary to TBI<br>ADHD | Subcortical lesions | Psychiatric admission if violent or acutely psychotic<br>Quetiapine 25–400 mg/d<br>Valproate 500–2000 mg/d<br>Carbamazepine 100–400 mg/d |
| Psychosis | Delusional disorders<br>Auditory hallucinations<br>Persecutory delusions | Schizophrenia<br>PTSD<br>Seizures | Left or bihemispheric lesions | Psychiatric admission if agitated, aggressive or acutely psychotic<br>Second-generation antipsychotics<br>Quetiapine 25–400 mg/d<br>Risperidone 0.5–3 mg/d |
| Anxiety | Persistent low-level anxiety and constant worry about everyday things<br>Or: Anxiety associated with re-experiencing trauma, avoidant behavior, emotional numbing, and hypervigilance | Generalized anxiety disorder<br>PTSD | Right hemispheric lesions | CBT<br>SSRIs as in depression |
| Apathy | Lack of motivation and initiative in the absence of positive symptoms of depression | Depression<br>Delirium | Frontal lobe lesions | Establish daytime structure and routine Psychostimulants: Methylphenidate 5–20 mg/d |
| Cognitive disturbances | Most common impairments are information processing speed, attention, and working memory with other domains being affected depending upon sites of damage in the brain (attention, learning, and memory; visuospatial processing; language; executive functioning; social cognition; awareness) | Other sequelae from TBI can affect cognitive efficiency, including sleep disturbance, mood disorders, pain, fatigue | Lesions in the cerebral cortex, subcortical structures, and/or disruption of widespread white matter pathways<br>Lower preinjury functioning<br>Preinjury history of:<br>Prior brain injury or neuropathology<br>Learning or attention problems<br>Mood disturbance<br>Substance abuse<br>Chronic pain<br>Sleep disorders | Environmental modification and stimulation balance<br>Cognitive rehabilitation<br>Psychostimulants: Methylphenidate 5–20 mg/d<br>Cholinesterase inhibitors: Donepezil 5–10 mg/d |

**Table 3** (*Continued*)

| Neuropsychiatric diagnosis | Core features | Differential diagnosis | Risk factors | Management and commonly used medications & dosages |
|---|---|---|---|---|
| Sleep disturbance | Insomnia: Difficulty in initiating & maintaining sleep<br>Hypersomnia: Excessive daytime sleepiness & fatigue<br>Circadian rhythm disorders: Timing of sleep disturbed—bedtime either early or late but able to get enough sleep | Medical & psychiatric comorbidities | Substance abuse<br>Poor sleep hygiene | Sleep hygiene<br>Pharmacological management depends on the type of sleep disturbance |

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBT, cognitive-behavioral therapy; FDA, US. Food and Drug Administration; NPD, neuropsychiatric disturbances; PTSD, posttraumatic stress disorder; SSRIs, selective serotonin reuptake inhibitors; TBI, traumatic brain injury.

matter disruption in several regions: forceps minor, right frontal aslant tract, right uncinate fasciculus, and left superior longitudinal fasciculus; left superior longitudinal fasciculus, superior and middle temporal gyrus, superior longitudinal fasciculus, inferior frontal and superior temporal white matter.[24–26] Such associations are interesting, but obviously quite diverse and call for more research in this area.

*Core Features*

The core features of TBI depression include persistent sadness, anhedonia, feelings of low self-worth, hopelessness, guilt, and suicidal thoughts, with intent and a plan in the most severe cases. TBI depression is often associated with other comorbidities such as anxiety, aggression, and alcohol misuse. In a study of 91 persons with TBI of all severities, Jorge et al noted that 76% of persons with depression had comorbid anxiety disorders and 57% had aggression.[19] This group of researchers also noted that a pre-TBI history of alcohol abuse is associated with a higher risk for developing depression after TBI and the presence of affective disturbance post-TBI increases the risk of relapse of alcohol abuse. See ►**Table 4** for the differential diagnosis of TBI depression.

*Behavioral Interventions*

Ongoing support, reassurance, and education regarding TBI are invaluable in all persons with TBI and neuropsychiatric symptoms. Most studies dealing with behavioral interventions have focused on NPD as a group, and only a few have dealt with specific disturbances, such as TBI depression. Bedard et al examined the effect of mindfulness-based cognitive therapy (MBCT) in 23 patients with TBI depression.[27] Following weekly sessions for 8 weeks, and using a combination of Kabat-Zinn's manualized mindfulness-based stress reduction program and Segal and colleagues' manual for MBCT, they noted a significantly reduction in depressive symptoms. Cognitive-behavioral therapy (CBT) techniques have also been shown to be beneficial in increasing patients' understanding of the emotional issues associated with TBI and their ability to use coping strategies.[28] Bell and colleagues studied 366 patients with mTBI through telephone counseling. Their intervention focused on education, symptom management, and encouragement to resume everyday activities. Fatigue and sleep problems were noted to be significantly reduced in the intervention group 6 months after injury compared with the control group that received the usual standard of care.[29] In a recent study, Fann et al showed that cognitive-behavioral therapy by telephone (CBT-T) is both acceptable and feasible in individuals with TBI of all degrees of severity.[30] In their study, no differences were noted on depressive symptoms based on the Hamilton Depression Rating Scale (HAMD) between intervention and control groups. However, those who received more than eight sessions of CBT reported significantly greater improvement in patient-reported depressive symptoms compared with those receiving usual care.

Web-based counseling has also been found to be effective in improving emotional well-being. Caregiver depression and family dysfunction is common after TBI and it is important to

**Table 4** Differential diagnosis of major depression

| Signs and symptoms | Major depression | Dysthymia | Adjustment disorder with depression | Apathy | Pathological crying |
|---|---|---|---|---|---|
| Sadness | Episodic, persistent for weeks | Chronic persistent for years | Transient; related to trauma | Absence of sadness | Absence or mild sadness |
| Tearfulness | Often proportionate to sadness | Occasional | Transient; related to trauma | Absent | Frequent & out of proportion to sadness |
| Neurovegetative symptoms—changes in sleep, appetite, energy, concentration | Usually present and severity depends on severity of depression | Can be present, but mild in severity | Transient | Absent | Usually absent |
| Suicidal thoughts | Usually present in moderate-severe depression | May be present | Usually not present | Absent | Absent |
| Decrease in self-worth | Often persistent with guilt | Mild in severity when present | Often absent | Absent | Often absent |
| Hopelessness | Often present | | Often absent | Absent | Often absent |
| Treatment | Psychotherapy + antidepressants | Psychotherapy + antidepressants | Psychotherapy | Stimulants | Antidepressants (SSRIs) or mood stabilizers |

Abbreviations: SSRIs, selective serotonin reuptake inhibitors.

address caregiver needs, provide support, and make the appropriate referrals for evaluation and treatment whenever necessary.[31,32]

*Pharmacological Interventions*

In 2006, experts in the Neurobehavioral Guidelines Working Group reviewed the current state of the literature on the pharmacological treatment of neurobehavioral sequelae of TBI and concluded that there is insufficient evidence to support the establishment of standards in the treatment of TBI related-depression, mania, anxiety, and psychosis.[33] Medications used in the treatment of primary depressive disorders are generally useful for the treatment of TBI depression,[9] and a syndromic approach to treatment with existing antidepressant medications is the mainstay of pharmacological management. Selective serotonin reuptake inhibitors are often considered first-line agents because of their benign side-effect profile. Sertraline, citalopram, and escitalopram are favored among the SSRIs because of their limited drug–drug interaction. A recent DBPCT study by Ashman et al found no statistically significant difference between sertraline and placebo in a group of 52 patients with TBI depression.[34] But a nonrandomized, single-blind, placebo run-in trial of sertraline in 15 patients with mild TBI by Fann et al found that 87% had a response and 67 achieved remission.[35] Ashman et al argue that the lack of effectiveness in their study may be secondary to the heterogeneity of their sample and the longer duration of time since TBI. Methylphenidate and other stimulants may also be used to augment the effect of antidepressants, especially when there is evidence of fatigue or executive function deficits. In a study of 30 mild-moderate TBI patients, Lee et al compared the effect of sertraline versus methylphenidate versus placebo and noted that both methylphenidate and sertraline significantly improved symptoms of depression, but only methylphenidate showed improved cognitive functions.[36] The authors note that those in the methylphenidate arm also had improvement in daytime sleepiness, which may be a factor in the lesser effect of sertraline in improving cognitive function. The tricyclic agent (TCA) desipramine was shown to reduce depressive symptoms in a small study of 10 participants.[37] However, TCAs are usually avoided because many are strongly anticholinergic and some carry a seizure risk. Similarly, monamine oxidase inhibitors are best avoided because of the need to comply with dietary restrictions and their drug interactions with other CNS-acting agents, such as other antidepressants. Serotonin-norepinephrine reuptake inhibitors are being used in clinical practice with evident success and no significant adverse effects, but they have not been systematically studied.

*Other Interventions*

Electroconvulsive therapy (ECT) was found to be safe and effective in a retrospective chart review of a small group of 11 TBI patients.[38] Jorge and Arciniegas have suggested some common-sense approaches to use ECT: Use low energy levels to generate a seizure of approximately 20 seconds, use pulsatile currents, increase between-treatment time intervals to 2 to 5 days, and keep the number of treatments to a minimum.[9] Nondominant unilateral ECT has a decreased risk of cognitive side effects. Other instrumental treatment modalities such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagal nerve stimulation, and deep brain stimulation are still very much in the research stage.

## TBI-Associated Mania

*Rates*

There are few studies on TBI mania, but reported rates range from 5 to 9%.[39,40] In a sample of more than 5,000 individuals living in the community, Silver et al noted an estimated lifetime relative risk for bipolar and related disorders to be 1.1, which is similar to the lifetime risk of bipolar disorders in the general population.[41]

*Risk Factors*

Risk factors appear to be a family history of affective disorder, subcortical atrophy prior to the traumatic event, right hemispheric limbic structure lesions, and posttraumatic epilepsy.[39,40,42] Some investigators noted that TBI rates are higher among unaffected members of families with bipolar disorder, an observation that might raise the question if genetic vulnerability to bipolar disorder increases risk for TBI.[9,43]

*Core Features*

Mania is generally characterized by a state of heightened energy that affects emotion, cognition, and behavior; it lasts usually not more than several days and impairs functioning. Common symptoms include increased energy and psychomotor activity, elevated or irritable mood, rapid thinking with shift from one idea to another, rapid pressured speech, decreased need for sleep, sometimes impulsive or reckless behavior, and possibly psychotic symptoms.

*Differential Diagnosis*

Personality change due to TBI is a diagnostic term used to describe stable changes in affective or behavioral disposition (traits) setting in the aftermath of TBI and falling into several discrete categories, usually featured by irritability/aggression, impulsivity/ disinhibited behavior, mood lability, or lack of motivation. In some individuals, these changes may represent exaggerations of previous personality traits and in others the development of new traits. The presence of these symptoms can pose a challenge in the diagnosis of mania. The key differentiating feature is that in mania these symptoms are intermittent and episodic, whereas in personality change the symptoms are persistent and define the individual's new personality profile. Collateral history from family members and longitudinal follow-up can best help establish this diagnosis. Diagnostic accuracy is important because it can impact treatment. If symptoms are due to mania, aggressive treatment with mood stabilizers (see below) is indicated and is usually effective. On the other hand, if mood lability is a new personality trait, nonpharmacological interventions such as behavioral modification

may be preferred as first-line treatment. Some antidepressants such as SSRIs can be used to treat impulsivity or irritability associated with personality change, but in individuals with mania or even history of mood cycling, such an intervention may worsen symptoms.

Another diagnosis to consider in the differential, especially in patients with acquired executive function deficits after TBI, is attention deficit hyperactivity disorder (ADHD). Even in the absence of TBI, differentiating ADHD and mania can be sometimes difficult. This is even more challenging in individuals with TBI because inattention and impulsivity can be seen in the absence of ADHD or bipolar disorder. To complicate issues further, ADHD and bipolar disorder can coexist. Certain features can help differentiate the two: Mania is an episodic condition alternating with periods of normal mood, with a symptom duration from days to weeks, and the symptoms are often not triggered, or when triggered continue to last far beyond the duration of the triggering event. Attention deficit hyperactivity disorder is chronic; mood symptoms are typically triggered and last between minutes to hours. When the two are present together, it is best to focus first on the treatment of bipolar disorder.

Pathological laughter is also in the differential diagnosis. Pathological laughter, which can occur independently or alternating with crying (pseudobulbar affect), is characterized by episodes of uncontrollable laughter that occur spontaneously or are triggered by a trivial stimulus; it is typically not associated with happiness or other manic symptoms, or if such symptoms are present, laughter is out of proportion to the mood state.

*Behavioral Interventions*

There is a paucity of empirical data on the treatment of TBI mania. Nonpharmacological measures include education on TBI and mood disorders, and supportive therapy for the patient and family. Clinicians should have a low threshold for hospitalization in patients with acute mania because they are often at considerable risk for harm to themselves or others.

*Pharmacological Interventions*

There are two very small open-label trials supporting the use of valproate and lithium,[44,45] and a case report showing improvement in mania with electroconvulsive therapy (ECT).[46] Treatment with anticonvulsants such as carbamazepine or valproate may be more appropriate compared with lithium because of concerns of lithium-associated cognitive and motor side effects.[47] Other agents used in the treatment of idiopathic bipolar disorder, such as lamotrigine and oxcarbazepine or second-generation antipsychotics such as risperidone, quetiapine, olanzapine, aripiprazole, and lurasidone, have also been used successfully in clinical practice. Although all these agents can be used for both induction and maintenance of treatment effect, a practical and effective approach might be to use quetiapine or risperidone as first-line agents for induction in acute mania, and valproate or carbamazepine for maintenance of effect.

## TBI-Associated Anxiety Disorders

*Rates*

A wide range of anxiety disorders may occur after TBI. Posttraumatic stress disorder and generalized anxiety disorder appear to be most prominent and occur at similar frequencies. Bryant and colleagues studied 1,084 patients with mild TBI at 12-month follow-up and found the following prevalence rates: generalized anxiety disorder 13.4%, posttraumatic stress disorder 13.0%, agoraphobia 12.8%, social phobia 9.0%, and obsessive-compulsive disorder 4.0%.[48] It is important to note that according to some studies, there is a much higher prevalence of PTSD (posttraumatic stress disorder) in Iraq and Afghanistan war veterans.[49] Among the 836 patients who had confirmed TBI, 63.9% also had PTSD and 35.6% were given a diagnosis of an anxiety disorder other than PTSD.

*Risk Factors and Mechanisms*

Injury sustained during war or with loss of consciousness (LOC) at the time of injury confers a significantly greater risk of development of PTSD.[49] Hoge and colleagues noted high rates of PTSD in veterans with mild TBI and LOC.[50] Those with altered mental status developed PTSD in 27% of cases, compared with 16% for any injury that did not involve altered mental status or LOC, and 9% with no injury. Right-hemisphere lesions are more often associated with anxiety disorder compared with left-sided lesions.[51] Older age has been associated with TBI anxiety in a few studies.[52,53] Bryant[54] has also noted that people with mild TBI may have "insufficient cognitive resources"; therefore, they may not be able to utilize appropriate cognitive compensatory strategies leading to increased risk for PTSD.

Neuroanatomical correlates of TBI anxiety include injury to the frontolimbic circuits. Post-TBI anxiety has been hypothesized to be secondary to focal and diffuse injury that can perturb the inhibitory functioning of the prefrontal cortex and lead to over-activation of the amygdala and other subcortical limbic structures.[52,53] Koenigs and colleagues in a study of 193 Vietnam war veterans found that lesions in either the ventromedial prefrontal cortex (vmPFC) or amygdala were actually associated with reduced rates of PTSD.[55] The authors concluded that the neurobiological basis of anxiety disorders may be the complex interaction between vmPFC and the amygdala that is impaired when TBI causes an imbalance in excitatory and inhibitory components of these circuits. Deficits in executive function (attention/working memory, information processing) have also been found to correlate with anxiety disorders.[52] Also, right hemisphere lesions are frequent in individuals with anxious depression.

*Core Features*

"Free floating" anxiety associated with persistent worry about everyday activities and tension, and fearfulness is one of the cardinal features of TBI anxiety disorders.[56] Core features of posttraumatic stress disorder include re-experiencing symptoms of trauma in the form of flashbacks or nightmares; avoidance of symptoms by staying away from

people, places, or objects associated with trauma; and hyperarousal symptoms such as being easily startled or waking up easily from sleep. Comorbidities associated with TBI anxiety disorders include major depression and substance abuse.

*Differential Diagnosis*

When making a diagnosis of generalized anxiety disorder, it is always important to determine if the condition is a state of episodic illness or the individual's personality trait featured by chronic feelings of anxiety and worries about little things. Acute stress disorder (ASD) and adjustment disorder with anxiety symptoms should be considered in the differential diagnosis of PTSD. Acute stress disorder is a brief stress-related condition where anxiety symptoms emerge within a month of exposure to the traumatic event and last for less than a month. Adjustment disorder with anxiety is also a stress-related condition. In general, anxiety symptoms decrease as the stressful situation subsides. Symptoms that follow mild TBI, known as postconcussive symptoms or syndrome (PCS) can also be confused with PTSD because there is a significant overlap between the two conditions and sometimes the two coexist. Stein and McAllister point out that mechanisms and locations of injury are not good predictors for the development of PTSD, PCS, or both.[57] Comprehensive evaluation, use of good clinical judgment, and refraining from oversimplification (e.g., if there is trauma, the person should have PTSD) are important aspects of management.

*Behavioral Interventions*

As with other neuropsychiatric disorders that emerge after TBI, there is limited research guiding treatment for TBI anxiety disorders. To date, there have been no randomized controlled trials for psychotherapeutic interventions. However, there is some evidence for the use of CBT in combination with neurorehabilitation for targeting general anxiety symptoms in patients with mild-to-moderate TBI.[58]

Bryant and colleagues conducted a randomized controlled trial of CBT on 24 civilian patients with mild TBI and acute stress disorder.[59] Their goal was to prevent PTSD; control participants received supportive counseling. Only 8% of patients receiving CBT developed PTSD compared with 58% in the supportive counseling arm; at 6-month follow up, these numbers were 17% and 58%, respectively. Uncontrolled studies using various other psychotherapeutic modalities (cognitive processing therapy, exposure therapy) have also shown improvement in PTSD symptoms.[60,61]

*Pharmacological Interventions*

There is very little data on the psychopharmacological treatment of TBI-associated anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, and social phobia. There is some support for the use of SSRIs for anxiety symptoms in TBI depression trials in which anxiety symptoms were measured as secondary outcomes. One such case is an 8-week trial of sertraline with a mean dose of 75 mg/d discussed in the TBI-Associated Depression section, where anxiety was measured with the Symptom Checklist-90-R.[35] In a 10-week trial of 25–200 mg/d of sertraline also discussed above, the Beck Anxiety Inventory showed a decrease in anxiety symptoms, although there was no significant difference compared with the control arm.[34]

Capehart and Bass reviewed the Department of Defense/Veteran's Affairs Clinical Practice Guideline (VA/DoD CPG) for the Management of PTSD in the context of treatment of comorbid TBI.[62] First-line recommendations were sertraline and citalopram. Second-line choices included fluoxetine, mirtazapine, or nefazodone. Caution was raised regarding mirtazapine's possible mild anticholinergic effects. Tricyclic antidepressants were recommended as third-line options. Prazosin was recommended as an adjunct for persistent nightmares. As we have previously suggested, TBI patients may have increased susceptibility to the adverse effects of benzodiazepines, including drowsiness, ataxia, slurred speech, memory impairment, psychomotor impairment, and possibly disinhibition.

## TBI-Associated Psychosis

*Rates*

Psychotic symptoms are not uncommon after TBI, with incidence ranging from 0.9 to 8.5.[8] Using Danish nationwide population-based data, Orlovska et al noted that the incidence rate ratio for schizophrenia-spectrum disorders was 1.6 in a population of 113,906 individuals with TBI history after controlling for several confounds (gender, age, calendar year, presence of a psychiatric family history, epilepsy, infections, autoimmune diseases, and fractures not involving the skull or spine).[63]

*Risk Factors*

Head injury between the ages of 11 to 15 and the presence of congenital neurological disorders have been found to be the strongest predictors for the development of psychosis.[63,64]

*Core Features*

Fuji and Ahmed report that there are predominantly two types of TBI-related psychosis: delusional disorders and schizophrenia-like psychosis.[8] Capgras syndrome and reduplicative paramnesia are the two most common forms of delusions encountered after TBI, though other types of delusions are also seen: delusions of jealousy, delusions of being dead, delusion of doubles, etc. Common symptoms of schizophrenia-like psychosis include persecutory delusions and auditory hallucinations with negative symptoms, whereas delusions of reference and bizarre delusions are less common. The average duration of post-TBI interval for the manifestation of psychotic symptoms is approximately 3 to 4 years, with symptoms of delusional disorder manifesting earlier and symptoms of schizophrenia-like psychosis later.

Electroencephalographic (EEG) abnormalities are seen in both types of psychosis, with slowing of waves more common than spiking, notably in the frontotemporal regions. Neuroimaging studies have noted abnormalities more commonly on the left or on both hemispheres, rather than on the right.[65] Similar to EEG findings, computed tomography (CT) has

revealed lesions predominantly in the frontotemporal region. single Photon emission computed tomography/ positron emission tomography (SPECT/PET) data in patients with schizophrenia-like psychosis often show abnormalities in the temporal lobes. TBI psychosis is seen in all degrees of severity of TBI. Neuropsychological deficits, specifically executive dysfunction and memory problems, are often seen in TBI-associated delusional and schizophrenia-like psychoses. Post-TBI seizures are present in approximately 20 to 30% of patients who develop post-TBI psychosis, compared with 7% in TBI patients without psychosis.[65]

*Differential Diagnosis*

Common differential diagnoses include schizophrenia, partial complex seizures, and PTSD. In the case of schizophrenia, Fujii and Ahmed note that even though there are many overlapping features between the two conditions, the clinical presentation of negative symptoms, structural imaging findings of cerebral atrophy, and widespread abnormalities in PET or SPECT studies (hypoperfusion in the frontal and temporal lobes, thalamus, and basal ganglia) are more suggestive of schizophrenia.[8] In the case of partial complex seizures, the problem is that these events may co-occur with TBI psychosis; however, these events are episodic, brief, and stereotypical, often accompanied by characteristic pre- and postictal symptoms. In PTSD, symptoms of dissociation, derealization, and depersonalization can be confused with psychosis. However, the context of such symptoms and thoughts associated with them are specifically related to trauma and co-occur with the core PTSD symptoms of hyperarousal, intrusive thoughts, and avoidance.

*Behavioral Interventions*

Nonpharmacological measures for the treatment of TBI psychosis is similar with that of schizophrenia, and include supportive work with the patient and family and attention to basic everyday needs related to self-care, living situation, social relationships, and vocation.

*Pharmacological Interventions*

Although no clinical pharmacological trials have been conducted to our knowledge, common sense and experience advocate the use of antipsychotics and anticonvulsants. Case reports suggest efficacy of second-generation antipsychotics, which we recommend over first-generation antipsychotics because neuroleptics may interfere with neural recovery.[66–68] When there are concerns about the presence of seizures, anticonvulsants may be preferable. Delusional-type symptoms that appear to be closely related to frontal lobe dysfunction may also benefit from antipsychotics.

## TBI-Associated Personality Disorders

### Apathy

*Rates*

Post-TBI apathy is common, with reported prevalence in the range of 10 to 71.1%.[69,70]

*Risk Factors*

Factors that predict the development of apathy post-TBI have not been well characterized. Severe disability, as measured with the Glasgow Outcome Scale, may increase the risk of apathetic behaviors by several-fold.[70] Rao and colleagues found associations with frontal lobe dysfunction within 3 months of TBI and with sleep disruption 1 year post-TBI.[71] Apathy has also been found to have associations with specific cognitive deficits related to frontal lobe dysfunction.[72] Takayanagi et al compared TBI patients with apathy to the deficit syndrome of schizophrenia using three-dimensional MRI, and noted volume reductions of the hippocampus, thalamus, and brainstem. Reductions of left hippocampal volume correlated strongly with apathy severity.[73] However, apathy severity was negatively correlated with performance on measures of verbal learning and memory. Starkstein and Pahissa have recently noted that neuroimaging studies have favored associations with abnormalities in anterior cingulate regions, the thalamus, and dorsal tegmentum of midbrain pons that is related to the arousal system.[74]

*Core Features*

Core features of apathy include disinterest/disengagement, inertia, lack of motivation, and absence of emotional responsivity. The diagnostic criteria proposed by Starkstein and Leentjens and the Apathy Evaluation Scale are commonly used for diagnosis.[75,76]

*Behavioral Interventions*

Treatment options include verbal cueing, task checklists, computer retraining, cognitive interventions, music therapy, structured activity kits, and multisensory stimulation.[77]

*Pharmacological Interventions*

Anecdotal reports, small case series, and reviews have reported improvement in apathy with methylphenidate,[78,79] dextroamphetamine, amantadine,[80] and acetylcholinesterase inhibitors.[81]

### TBI-Associated Suicide

*Rate*

Suicide after TBI is high, both in civilian and military populations, and individuals with TBI are 1.5 to 4 times more likely to die by suicide. A review by Simpson and Tate of 48 studies concluded that the risk of suicide, suicide attempts, and suicidal ideation is increased in TBI survivors when compared with the general population, even after adjusting for psychiatric comorbidities.[82] Suicidal ideation occurs in approximately 20% of persons with TBI across all degrees of severity, and the suicide attempt rate is approximately 18% in individuals with severe TBI. In a recent review of approximately 560 patients at all levels of TBI severity, Mackelprang et al noted that 25% of the sample reported suicidal ideation during the first year after TBI, a number much higher than the 3.7% reported for the general population.[83]

*Risk Factors*
Common risk factors include a history of mood disorder, substance abuse, prior suicide attempt, and severe TBI.[82]

*Core Features*
The presence of both passive and active suicidal thoughts, intent, and plan should be inquired of all patients presenting with TBI-associated neuropsychiatric disturbances. The majority of people with suicidal thoughts have a psychiatric illness, most commonly mood disorders, PTSD, and/or substance abuse.

*Interventions*
The first rule in taking care of persons with suicidal thoughts is to maintain safety. If suicidal thoughts are acute, active, intense with intent and/or plan to die, immediate hospitalization should be considered. Management of suicidal thoughts associated with psychiatric disturbances after TBI is similar to the management of psychiatric disturbances themselves, but with extra caution to maximize safety.

### TBI-Associated Sleep Disturbances

Sleep disturbances are common after TBI, alone or as part of other neuropsychiatric disorders, and disrupt recovery. Assessment of sleep patterns is essential because there are many different types of sleep disturbances each one of which requires specialized treatment. Sleep disturbances can be secondary to brain injury or caused by secondary factors related or unrelated to TBI (medical comorbidities, pain, medication side effects, etc.).

#### Rates

Sleep disturbances after TBI are more common than in the general population. About 50% of TBI patients, with TBI severity ranging anywhere from mild to severe, have been found to experience chronic insomnia.[84] Rao and colleagues studied a small cohort of patients with TBI in the acute postinjury period ($< 3$ months) and found significantly higher sleep scores post-TBI compared with pre-TBI in several sleep domains, including sleep amount, sleep adequacy, and daytime somnolence.[85] Mathias and Alvaro conducted a meta-analysis examining the prevalence of sleep disturbances after TBI, and found increased rates of insomnia, hypersomnia, sleep apnea, and sleepwalking.[86]

#### Risk Factors

Milder severity of injury, severe depressive symptoms, severe pain, and fatigue have been found to be predictors of insomnia.[84] Clinchot and colleagues found that injury severity inversely correlates with sleep disturbances.[87]

#### Core Features

Common sleep disturbances after TBI include insomnia (difficulty in initiating or maintaining sleep or early morning awakening with inability to go back to sleep), sleep apnea (especially its common form, obstructive sleep apnea), hypersomnia (excessive daytime sleepiness despite several hours of sleep at night), circadian rhythm sleep–wake cycle disorders (misalignment between the endogenous biological clock and the sleep–wake schedule that is forced by lifestyle), and parasomnias (nonrapid eye movement [NREM] sleep arousal disorders such as sleepwalking, sleep terror, and REM sleep behavior disorder).

#### Behavioral Interventions

Common types of behavioral interventions for sleep disturbances after TBI include education on sleep hygiene and healthy lifestyle, light therapy, and psychotherapy. Lifestyle changes include exercise and sleep hygiene, and should be recommended for all sleep disturbances. A recent randomized, placebo-controlled study of 30 patients found home-based light therapy effective in reducing daytime sleepiness and fatigue. Patients were exposed 45 min/d for 4 weeks.[88] Cognitive-behavioral therapy for insomnia (CBT-I) is commonly used to treat insomnia in patients with TBI. A single-case design study of 11 patients found significant reductions in total wake time and improvements in sleep efficiency. Improvement was maintained at 3 months.[89] The recently published guidelines of the Defense Centers of Excellence (DCoE) for sleep disturbances after concussion/mild TBI recommend reassurance and education as first-line treatments for short-term insomnia, and sleep hygiene and progressive muscle relaxation training for chronic insomnia. Second-line treatment for chronic insomnia includes referral for CBT-I.[90]

#### Pharmacological Interventions

There are very few studies on pharmacological interventions for sleep disturbances after TBI and we are far from having a satisfactory evidence-based picture. Whenever sleep disturbance is associated with another psychiatric disorder such as major depression, anxiety disorders, or psychotic disorders, it is important to treat the underlying psychiatric disorder. In patients with primary insomnia, a reasonable approach is to use medications that are effective in treating insomnia in individuals without TBI. For several of these compounds, such as melatonin, amitriptyline, lorazepam, and zopiclone, there is also some support from small clinical trials.[91,92] Non-benzodiazepine sedative hypnotics, such as zolpidem and zaleplon, can be safely used short-term, but they may cause anterograde amnesia, sensory distortion, sleepwalking, and nocturnal eating.[93] Special caution needs to be exercised in the use of benzodiazepines because of concerns of addiction, and motor and cognitive side effects, and paradoxical rage outbursts. For complex or unusual or persisting sleep disturbances, it is best to order sleep studies or refer patients to sleep specialists.

### TBI-Associated Behavioral Disturbances

A wide variety of TBI-associated neuropsychiatric disorders can be viewed and classified as disturbances of behavior or described as a behavior dyscontrol disorder. These problems often lead to disruption of daily life functioning and warrant clinical attention. We have not attempted to capture all these behavioral disturbances, in view of recent excellent topical reviews.[94] Instead, we shall focus here on behavioral dyscontrol disorder as a paradigmatic TBI-associated behavioral

change that very often requires neuropsychiatric interventions.

The term behavioral dyscontrol disorder is used to describe a common consequence of TBI characterized by emotional dysregulation, disruptive behavior, and executive dysfunction. Mood disturbances include irritability, anger, rage, and affective lability. Behavior disturbances include hyperactivity, impulsivity, aggression, and inappropriate crying or laughter. Cognitive dysfunction may include impaired attention and memory, distractibility, impaired judgment, and conceptual disorganization. The behavioral disturbances are often concerning to the individual, very stressful for the family and caregivers, and they are difficult to manage, often requiring multidisciplinary teams— neuropsychiatrists, behavioral therapists, case managers, caregivers, etc. In a small retrospective chart review, we conducted in 54 patients followed in our TBI clinic we noted that post-TBI behavior dyscontrol problems are associated with severe TBI, lower scores on the Mini Mental State Exam (MMSE), unemployment, and poor response to pharmacological treatment, patterns that underscore the challenges encountered in management.[95]

Management of post-TBI behavior problems should always be multipronged. This includes a combination of environmental modification strategies,[96] behavioral therapy with positive and negative reinforcement, vocational training,[97] and supportive and family therapy.[98] Pharmacotherapy should be based on the presence of comorbid neuropsychiatric disturbances. For example, if there are co-occurring depressive symptoms, one should consider an SSRI; if there are executive function deficits, one should consider stimulants or dopaminergic agents. Mood-stabilizing anticonvulsants are first-line agents if behavioral problems occur in the context of manic symptoms or if there is comorbid seizure disorder; second-generation antipsychotics top the list if there is psychosis. Other agents that have been found to be beneficial include high-dose β blockers and possibly also SNRIs and mirtazapine.[33,99–101]

Amantadine has recently been studied in a randomized controlled trial for the treatment of patients with irritability and aggression after TBI. Traumatic brain injury had to have occurred over 6 months prior to enrollment, and creatinine clearance had to be within the normal range. Amantadine (200 mg daily) resulted in improvement of irritability in 80% of patients compared with 44% of placebo participants. Aggression scores were also decreased, although this did not differ significantly from placebo. No differences in adverse effects were noted between groups. The authors theorized that amantadine may improve irritability and aggression by enhancing cognitive function leading to improved cognitive reappraisal and behavioral control.[102]

## Postconcussive Syndrome

### Rate

In the acute phase of TBI, approximately 70 to 80% of people experience a constellation of emotional, cognitive, and physical symptoms termed postconcussive symptoms. These symptoms, typically referred to as postconcussive syndrome, may also be encountered in various combinations in nonbrain injuries, general medical illnesses, or other neuropsychiatric disorders.[103] Studies indicate that in most people with concussion and normal structural brain imaging the prognosis is good, with spontaneous recovery and no long-term adverse outcomes.[104,105] Symptoms usually resolve within a few weeks of injury, and the vast majority of patients are symptom free within 3 to 6 months.[106] A recent study by Eisenberg and colleagues evaluated more than two-hundred 11-to-22-year-old patients for postconcussive symptoms.[107] These patients were evaluated within 3 days of head injury using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and followed for 3 months after the concussion or until all symptoms resolved. Most symptoms had resolved within 14 days. The mean duration of symptoms was longest for irritability (16 days), sleep disturbance (16 days), frustration (14 days), and poor concentration (14 days). Symptoms that resolved quickly included nausea, dizziness, double vision, and interestingly, low mood. One month after injury, reports of headache, fatigue, and subjective difficulties in thinking were encountered seen in 20 to 25% of patients. By day 90, only 15% of patients continued to report symptoms. Other studies have shown that only 10 to 15% of individuals with mild TBI continue to have symptoms 3 months after injury.[108,109]

### Core Features

Postconcussive symptomatology can present as three symptom clusters: mood, cognition, and physical symptoms.[110] Mood symptoms include depression, anxiety, and irritability. Cognitive dysfunction includes decreased attention/concentration and often impaired memory, various degrees of executive dysfunction, and varied levels of conceptual disorganization. Physical symptoms include headache, nausea, dizziness, vertigo, diplopia, insomnia, deafness, tinnitus, light and noise sensitivity, fatigue, and problems with coordination. The underlying pathogenesis of postconcussive symptoms is unknown, but is thought to involve diffuse axonal injury. Case reports and small case series have suggested abnormalities in the temporal and frontal lobes as well as the thalamus.[111–113]

### Risk Factors

Persistence of postconcussive symptoms beyond 3 months should alert clinicians to look for other causes such as major mental illness (e.g., major depression, PTSD), medical problems such as endocrine deficiencies, adverse effects of medications, use of illicit drugs, and embellishment of symptoms or malingering secondary to ongoing litigation.

### Interventions

Given that the etiology of postconcussive syndrome is not clear and that there are likely multiple factors associated with the persistent of the symptoms, interventions should be multifaceted. Both behavioral and pharmacological interventions may be considered. Cornerstone of management is psychoeducation on the nature of mild TBI, typical course

of recovery, factors that may be contributing to the persistence of in the specific patient, and an intervention plan.[114] Behavioral pain and fatigue management strategies are key for the patient to learn adaptive strategies for symptom management while reducing behaviors that exacerbate symptoms. These patients typically change life activities, schedules, and approaches and they need guidance on how to return to a healthy approach to life that maximizes the functioning of body and brain. Pharmacological treatment options should be symptom focused, and importantly, address comorbid psychiatric disorders.

## TBI-Associated Cognitive Disturbances

### Rates

Traumatic brain injury leads to disruption of brain functioning secondary to impact on the cerebral cortex, subcortical structures, and widespread white matter pathways, which all subserve cognitive functioning. Impairments in cognition are extremely common after moderate to severe TBI, but less common after mild traumatic brain injury (mTBI). Although mTBI leads to cognitive deficits early after the injury and most of these changes normalize in the long run.[115,116] Among those with favorable medical recoveries following TBI (any severity), cognitive measures are the best predictors of return to important life roles, such as returning to independent living and to working.[117–119]

### Risk Factors

The clinical presentation of any one individual following TBI is variable depending upon the intensity, severity, and location of the injury in the brain. It is true that more severe injuries are associated with worse cognitive outcomes.[120,121] However, clinicians must keep in mind that cognitive–behavioral functioning and life functioning are relatively poorly predicted by the severity of injury. There are individual differences in regards to preinjury functioning, intellect, and preexisting conditions that contribute to the nature and severity of cognitive-behavioral impairments postinjury. Pre-existing factors can include learning and attention disorders, substance abuse, prior neuropathology (e.g., prior brain injury, history of seizures), major depression, chronic pain, and sleep disorders.[122,123] A rule of thumb for any one patient is that it is more about the brain that was injured than the severity of brain injury itself. A patient with a severe TBI may return to working, parenting, and engagement in typical life activities, whereas another patient with a mild TBI may be challenged to return to working and balancing the responsibilities of all his or her life roles. Determining all the pre-injury risk factors for persistent impairments secondary to TBI as well as the constellation of postinjury cognitive–behavioral–emotional impairments is critical for designing an appropriate intervention plan.

### Core Features

The constellation of cognitive impairments following TBI is variable given that it depends upon the location of the injury in the brain. However, there is increasing recognition that there is a cluster of symptoms that tend to characterize traumatic brain injury, and progression of these impairments evolve along four stages based on the timing in relationship to the TBI event.[124,125] The first stage corresponds to the period of loss of consciousness, occurring soon after the injury and ranges from a brief alteration of consciousness to prolonged coma. In mTBI, the vast majority of patients do not have any loss of consciousness or very brief momentary alterations, whereas the vast majority of patients with moderate to severe injuries have more substantial periods of loss of consciousness lasting from hours to months. The second stage is associated with a wide range of symptoms of cognitive and behavioral dysfunction including agitation, confusion, disorientation, and changes of psychomotor activity.

The second stage represents a form of posttraumatic delirium, labeled posttraumatic confusional state.[126] For individuals with mTBI, this stage may only last hours to a couple of days, whereas for individuals who suffer moderate to severe injuries, stage 2 may persist for weeks to months. For up to 85% of individuals with mTBI, the cognitive symptoms resolve during this stage, and these individuals return to daily life roles without any persistent problems (see the Postconcussive Syndrome section for a discussion of the other 15%).[104,105] For individuals with moderate to severe TBI, the cognitive impairment progresses to stage 3.

Stage 3 involves relatively rapid recovery in the next several months of the ability of the brain to attend, process, and remember information. This third stage of recovery is rooted in the healing of brain tissue, reduction of edema, and reorganization of higher cortical functions. How long this process takes or will last is unknown, but it is well accepted that by 2 years postinjury, the vast majority of natural recovery processes have been completed. Functional recovery through the processes of remediation and compensation are not time limited, and thus improvements in life functioning and return to daily life roles is only limited by the extent of persistent cognitive–behavioral–emotional impairments and the engagement of the individual in the neurorehabilitative process.

The fourth stage is associated with moderate to severe injuries and is characterized by permanent cognitive sequelae in which the individual must learn to accept, adapt, and adjust. Cognitive deficits after the subacute period correspond to the *DSM-5* entry of major or minor neurocognitive disorder due to TBI.[127] The constellation of impairments that patients present with can involve every cognitive domain, including attention, memory, visuospatial processing, language, social cognition, and executive functioning. The most common impairments are in information processing speed, attention, and working-memory functioning.[2] Patients tend to report memory as the most common problem post-TBI, but the subjective experience of memory decline may be more related to the impairments in information processing speed, attention, and working memory. Additionally, other concomitant sequelae of TBI affect learning and memory efficiency, including sleep disturbance, headache pain, emotional adjustment, and stress. That is not to say that learning and memory impairments do not occur with TBI. Research

findings support that there are a wide range of learning and memory complaints, but there is no particular pattern that is associated with TBI in terms of frequency or extent of impairment following moderate to severe TBI.[128] When the damage involves the frontal systems of the brain, changes in executive functioning occur, which can include working memory, prospective memory, strategic planning, cognitive flexibility, reasoning, and self-monitoring. Individuals with moderate to severe TBI may have limited understanding of their impairments and thus have difficulty fully engaging in the rehabilitation process. Awareness syndromes after TBI are common, and the level of awareness problem is related to the location of lesions in the brain and the coping resources that the individual employs to adapt and adjust to the brain injury.[129,130]

### Interventions

In the early stages (stages 1 and 2) of recovery following moderate to severe TBI, clinicians should focus on modifying the environment to maintain safety for the individual. Given the cognitive impairments and lack of understanding of the constellation of motor and sensory impairments, the individual may attempt tasks that put him or her at risk for additional harm. Individuals with reduced arousal, confusion, and disorientation may attempt to pull out tubes and intravenous lines, may scratch themselves, may attempt to walk without assistance, or may attempt to elope. It is important that these individuals receive frequent reassurance and reorientation to their current situation. Clinicians should take a errorless learning approach[131] to both evaluate the patients current level of orientation to place and situation, but also to provide the needed reorientation to the accurate information. With the impairments in attention, memory, and awareness, it is critical that the patient not be allowed to make mistakes on which he or she may perseverate, thus reinforcing confabulated misinformation. With provision of a safe environment and feedback regarding the current situation, the individual will begin to incorporate new information about his or her situation and functioning as his or her level of arousal and attention improves. Once the individual is able to consistently lay down new memories, then intervention specifically aimed at addressing the cognitive impairments can be employed. The core interventions for cognitive impairments are founded in remediation techniques for the attentional problems and using external strategies and equipment to assist the individual in compensating for the other cognitive impairments. For a review of such strategies, see Haskins' and colleagues' *Cognitive Rehabilitation Manual*, which is based upon the comprehensive scientific reviews of the literature.[131] Cognitive rehabilitation is typically offered by speech-language pathologists, occupational therapists, and rehabilitation neuropsychologists with expertise in working with individuals with brain injuries within the context of a comprehensive neurorehabilitation program. In addition to cognitive rehabilitation, there are some pharmacological options for augmenting cognitive functioning, including classical and atypical psychostimulants and cholinomimetic agents such as methylphenidate, donepezil, and amantadine.[132,133]

### Chronic Traumatic Encephalopathy

It is hypothesized that repetitive mTBI in some cases causes a neurodegenerative disease known as chronic traumatic encephalopathy (CTE). Clinical problems associated with CTE include mood dysregulation (depression, irritability, dysphoria), behavioral disturbances (aggression, violence, apathy), cognitive deficits (immediate and delayed recall, executive functioning), and other neurological abnormalities (impaired balance, gaze, movement, olfaction).[134] Chronic traumatic encephalopathy is the same disease as the classical entity of punch-drunk or dementia pugilistica that has been established in boxers since the 1930s,[135–137] but has been recently extended to other collision and contact sports, especially football, through the work of Mckee[138] and Omalu.[139,140] The majority of examined cases still belong to boxers, and suggest a distinct neuropathology featured by a tauopathy that favors superficial cortical layers, deep sulcal cortices, and perivascular regions. The overall distribution of tau pathology is extensive and involves large cortical regions with frontal and temporal predominance and several subcortical sites in the basal ganglia, amygdala, thalamus, hypothalamus, and brainstem.[138]

Although these researchers have proposed clinical and neuropathological staging systems in the fashion that has been already established for Alzheimer disease (AD) and other neurodegenerative diseases, the lack of prospective data and in vivo biomarkers, the presumed long incubation period of illness, and competing clinical and neuropathological considerations make such staging premature.[141] Problems regarding specificity of clinical presentation and neuropathology and methodological and other challenges have been recently reviewed by us.[142]

A study of 2,552 retired professional football players found that those with three or more concussions, likely fitting the current Department of Veterans Affairs and Department of Defense criteria for mTBI, had a fivefold higher prevalence of mild cognitive impairment compared with retirees without a history of concussion. These retirees were also found to have an earlier onset of AD.[143] Another study of retired professional football players from the National Football League found that although overall mortality rates were reduced when compared with the general population, mortality from neurodegenerative disease was 3 times higher.[144] Mortality due to amyotrophic lateral sclerosis and AD was 4 times higher. A recent retrospective cohort study exploring the link between TBI and risk for dementia followed 188,764 veterans with or without past history of TBI, and at year 9 found that 16% of veterans with TBI had dementia, compared with 10% of those without TBI. All subtypes of dementia were increased, including AD, vascular, and Lewy body dementia. The main strengths of this study are the large size of the cohort of older veterans and great access to inpatient and outpatient medical records nationwide. Its weaknesses include lack of clarity as to how long ago the TBI occurred and how severe it was, and its restriction to men.[145]

### Future Directions

Neuropsychiatric complications of TBI are very common, cause significant impairments, and interfere with quality of

life and psychosocial rehabilitation of TBI survivors. Correctly diagnosing and formulating the symptoms is essential to formulating a treatment plan. Evidence-based treatment options for post-TBI neuropsychiatric syndromes are extremely limited. There is a great paucity of randomized controlled pharmacological trials, and no FDA-approved drugs are available specific for TBI. Management often relies on empirical information and resemblance of symptoms with those of idiopathic psychiatric disorders for which validated treatments exist. In general, it is best to take a multidisciplinary approach that involves the patient, family, other clinicians, and case managers or coaches.

Future efforts by researchers should include prospective cohort studies using blood, cerebrospinal fluid and neuroimaging methods with appropriate controls to better understand the development and prognostic markers of TBI-associated neuropsychiatric disturbances. The time is also ripe to conduct more randomized controlled trials of pharmacological and nonpharmacological treatments, although the lessons from pervious negative trials are not very informative and some authorities in the field blame the extreme variability of individuals, TBI mechanisms and severities, and neuropsychiatric and other medical comorbidities. New treatment strategies, such as the use of telephone or web-based counseling and other nonpharmacological strategies, should be explored further. For further discussion on the topic, refer to a recent review by Vasihnavi et al.[146]

Research and treatment initiatives by the DoD are dedicated to bridge the gaps in this field. Academic centers throughout the globe have amplified research efforts over the last decade and have significantly advanced our knowledge base, although funding for research in general and for TBI in particular is nowhere at the level necessary to accelerate discovery. In the field of neuroscience, we face the additional challenge of a major gap between basic science discoveries and clinical translation. Our greatest hope lies in the heightened sensitivity of the public on the problems and perils of TBI, including its profound and persistent neuropsychiatric consequences, caused by the spreading epidemic of repeat concussions in young athletes and the enduring effects of blast TBI in veterans of recent wars.

## References


1 Deb S, Lyons I, Koutzoukis C, Ali I, McCarthy G. Rate of psychiatric illness 1 year after traumatic brain injury. Am J Psychiatry 1999; 156(3):374–378

2 McAllister TW, Flashman LA, Sparling MB, Saykin AJ. Working memory deficits after traumatic brain injury: catecholaminergic mechanisms and prospects for treatment — a review. Brain Inj 2004;18(4):331–350

3 Hibbard MR, Uysal S, Kepler K, Bogdany J, Silver J. Axis I psychopathology in individuals with traumatic brain injury. J Head Trauma Rehabil 1998;13(4):24–39

4 Koponen S, Taiminen T, Portin R, et al. Axis I and II psychiatric disorders after traumatic brain injury: a 30-year follow-up study. Am J Psychiatry 2002;159(8):1315–1321

5 Whelan-Goodinson R, Ponsford JL, Schönberger M, Johnston L. Predictors of psychiatric disorders following traumatic brain injury. J Head Trauma Rehabil 2010;25(5):320–329

6 Vassallo JL, Proctor-Weber Z, Lebowitz BK, Curtiss G, Vanderploeg RD. Psychiatric risk factors for traumatic brain injury. Brain Inj 2007;21(6):567–573

7 Fann JR, Leonetti A, Jaffe K, Katon WJ, Cummings P, Thompson RS. Psychiatric illness and subsequent traumatic brain injury: a case control study. J Neurol Neurosurg Psychiatry 2002;72(5): 615–620

8 Fujii DE, Ahmed I. Psychotic disorder caused by traumatic brain injury. Psychiatr Clin North Am 2014;37(1):113–124

9 Jorge RE, Arciniegas DB. Mood disorders after TBI. Psychiatr Clin North Am 2014;37(1):13–29

10 Neikrug AB, Ancoli-Israel S. Sleep disorders in the older adult - a mini-review. Gerontology 2010;56(2):181–189

11 Rao V, Handel S, Vaishnavi S, et al. Psychiatric sequelae of traumatic brain injury: a case report. Am J Psychiatry 2007; 164(5):728–735

12 Lequerica AH, Kortte K. Therapeutic engagement: a proposed model of engagement in medical rehabilitation. Am J Phys Med Rehabil 2010;89(5):415–422

13 Meyer A. The anatomical facts and clinical varieties of traumatic insanity. J Neuropsychiatry Clin Neurosci 2000;12(3):407–410

14 Osborn AJ, Mathias JL, Fairweather-Schmidt AK. Depression following adult, non-penetrating traumatic brain injury: a meta-analysis examining methodological variables and sample characteristics. Neurosci Biobehav Rev 2014;47C:1–15

15 Jorge RE, Robinson RG, Arndt SV, Starkstein SE, Forrester AW, Geisler F. Depression following traumatic brain injury: a 1 year longitudinal study. J Affect Disord 1993;27(4):233–243

16 Fann JR, Burington B, Leonetti A, Jaffe K, Katon WJ, Thompson RS. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry 2004;61(1):53–61

17 Koponen S, Taiminen T, Kairisto V, et al. APOE-epsilon4 predicts dementia but not other psychiatric disorders after traumatic brain injury. Neurology 2004;63(4):749–750

18 Chan F, Lanctôt KL, Feinstein A, et al. The serotonin transporter polymorphisms and major depression following traumatic brain injury. Brain Inj 2008;22(6):471–479

19 Jorge RE, Robinson RG, Moser D, Tateno A, Crespo-Facorro B, Arndt S. Major depression following traumatic brain injury. Arch Gen Psychiatry 2004;61(1):42–50

20 Jorge RE, Acion L, Starkstein SE, Magnotta V. Hippocampal volume and mood disorders after traumatic brain injury. Biol Psychiatry 2007;62(4):332–338

21 Chen J-K, Johnston KM, Petrides M, Ptito A. Neural substrates of symptoms of depression following concussion in male athletes with persisting postconcussion symptoms. Arch Gen Psychiatry 2008;65(1):81–89

22 Rao V, Spiro J, Degoankar M, et al. Lesion location in depression post traumatic brain injury using magnetic resonance spectroscopy: preliminary results from a pilot study. Eur J Psychiatry 2006;20:65–73

23 Rao V, Munro CA, Rosenberg P, et al. Neuroanatomical correlates of depression in post traumatic brain injury: preliminary results of a pilot study. J Neuropsychiatry Clin Neurosci 2010;22(2): 231–235

24 Strain J, Didehbani N, Cullum CM, et al. Depressive symptoms and white matter dysfunction in retired NFL players with concussion history. Neurology 2013;81(1):25–32

25 Matthews SC, Strigo IA, Simmons AN, O'Connell RM, Reinhardt LE, Moseley SA. A multimodal imaging study in U.S. veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. Neuroimage 2011;54 (Suppl 1):S69–S75

26 Rao V, Mielke M, Xu X, et al. Diffusion tensor imaging atlas-based analyses in major depression after mild traumatic brain injury. J Neuropsychiatry Clin Neurosci 2012;24(3):309–315
27 Bédard M, Felteau M, Marshall S, et al. Mindfulness-based cognitive therapy: benefits in reducing depression following a traumatic brain injury. Adv Mind Body Med 2012;26(1):14–20
28 Anson K, Ponsford J. Evaluation of a coping skills group following traumatic brain injury. Brain Inj 2006;20(2):167–178
29 Bell KR, Hoffman JM, Temkin NR, et al. The effect of telephone counselling on reducing post-traumatic symptoms after mild traumatic brain injury: a randomised trial. J Neurol Neurosurg Psychiatry 2008;79(11):1275–1281
30 Fann JR, Bombardier CH, Vannoy S, et al. Telephone and in-person cognitive behavioral therapy for major depression after traumatic brain injury: a randomized controlled trial. J Neurotrauma 2014
31 Harris JK, Godfrey HP, Partridge FM, Knight RG. Caregiver depression following traumatic brain injury (TBI): a consequence of adverse effects on family members? Brain Inj 2001;15(3): 223–238
32 Leach LR, Frank RG, Bouman DE, Farmer J. Family functioning, social support and depression after traumatic brain injury. Brain Inj 1994;8(7):599–606
33 Warden DL, Gordon B, McAllister TW, et al; Neurobehavioral Guidelines Working Group. Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma 2006;23(10):1468–1501
34 Ashman TA, Cantor JB, Gordon WA, et al. A randomized controlled trial of sertraline for the treatment of depression in persons with traumatic brain injury. Arch Phys Med Rehabil 2009;90(5): 733–740
35 Fann JR, Uomoto JM, Katon WJ. Sertraline in the treatment of major depression following mild traumatic brain injury. J Neuropsychiatry Clin Neurosci 2000;12(2):226–232
36 Lee H, Kim SW, Kim JM, Shin IS, Yang SJ, Yoon JS. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Hum Psychopharmacol 2005;20(2):97–104
37 Wroblewski BA, Joseph AB, Cornblatt RR. Antidepressant pharmacotherapy and the treatment of depression in patients with severe traumatic brain injury: a controlled, prospective study. J Clin Psychiatry 1996;57(12):582–587
38 Kant R, Coffey CE, Bogyi AM. Safety and efficacy of ECT in patients with head injury: a case series. J Neuropsychiatry Clin Neurosci 1999;11(1):32–37
39 Koponen S, Taiminen T, Hiekkanen H, Tenovuo O. Axis I and II psychiatric disorders in patients with traumatic brain injury: a 12-month follow-up study. Brain Inj 2011;25(11):1029–1034
40 Jorge RE, Robinson RG, Starkstein SE, et al. Secondary mania following traumatic brain injury. Am J Psychiatry 1993;150(6): 916–921
41 Silver JM, Kramer R, Greenwald S, Weissman M. The association between head injuries and psychiatric disorders: findings from the New Haven NIMH Epidemiologic Catchment Area Study. Brain Inj 2001;15(11):935–945
42 Shukla S, Cook BLS, Mukherjee S, Godwin C, Miller MG. Mania following head trauma. Am J Psychiatry 1987;144(1):93–96
43 Malaspina D, Goetz RRJH, Friedman JH, et al. Traumatic brain injury and schizophrenia in members of schizophrenia and bipolar disorder pedigrees. Am J Psychiatry 2001;158(3): 440–446
44 Hale MS, Donaldson JO. Lithium carbonate in the treatment of organic brain syndrome. J Nerv Ment Dis 1982;170(6):362–365
45 Pope HG Jr, McElroy SL, Satlin A, Hudson JI, Keck PE Jr, Kalish R. Head injury, bipolar disorder, and response to valproate. Compr Psychiatry 1988;29(1):34–38
46 Clark AF, Davison K. Mania following head injury. A report of two cases and a review of the literature. Br J Psychiatry 1987; 150:841–844
47 Dikmen SS, Machamer JE, Winn HR, Anderson GD, Temkin NR. Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. Neurology 2000;54(4):895–902
48 Bryant RA, O'Donnell ML, Creamer M, McFarlane AC, Clark CR, Silove D. The psychiatric sequelae of traumatic injury. Am J Psychiatry 2010;167(3):312–320
49 Carlson KF, Nelson D, Orazem RJ, Nugent S, Cifu DX, Sayer NA. Psychiatric diagnoses among Iraq and Afghanistan war veterans screened for deployment-related traumatic brain injury. J Trauma Stress 2010;23(1):17–24
50 Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. N Engl J Med 2008;358(5):453–463
51 Jorge RE, Robinson RG, Starkstein SE, Arndt SV. Depression and anxiety following traumatic brain injury. J Neuropsychiatry Clin Neurosci 1993;5(4):369–374
52 Gould KR, Ponsford JL, Spitz G. Association between cognitive impairments and anxiety disorders following traumatic brain injury. J Clin Exp Neuropsychol 2014;36(1):1–14
53 Kinsella G, Moran C, Ford B, Ponsford J. Emotional disorder and its assessment within the severe head injured population. Psychol Med 1988;18(1):57–63
54 Bryant RA. Disentangling mild traumatic brain injury and stress reactions. N Engl J Med 2008;358(5):525–527
55 Koenigs M, Huey ED, Raymont V, et al. Focal brain damage protects against post-traumatic stress disorder in combat veterans. Nat Neurosci 2008;11(2):232–237
56 Lewis L, Rosenberg SJ. Psychoanalytic psychotherapy with brain-injured adult psychiatric patients. J Nerv Ment Dis 1990;178(2): 69–77
57 Stein MB, McAllister TW. Exploring the convergence of posttraumatic stress disorder and mild traumatic brain injury. Am J Psychiatry 2009;166(7):768–776
58 Soo C, Tate R. Psychological treatment for anxiety in people with traumatic brain injury. Cochrane Database Syst Rev 2007;(3): CD005239
59 Bryant RA, Moulds M, Guthrie R, Nixon RD. Treating acute stress disorder following mild traumatic brain injury. Am J Psychiatry 2003;160(3):585–587
60 Chard KM, Schumm JA, McIlvain SM, Bailey GW, Parkinson RB. Exploring the efficacy of a residential treatment program incorporating cognitive processing therapy-cognitive for veterans with PTSD and traumatic brain injury. J Trauma Stress 2011; 24(3):347–351
61 Wolf GK, Strom TQ, Kehle SM, Eftekhari A. A preliminary examination of prolonged exposure therapy with Iraq and Afghanistan veterans with a diagnosis of posttraumatic stress disorder and mild to moderate traumatic brain injury. J Head Trauma Rehabil 2012;27(1):26–32
62 Capehart B, Bass D. Review: managing posttraumatic stress disorder in combat veterans with comorbid traumatic brain injury. J Rehabil Res Dev 2012;49(5):789–812
63 Orlovska S, Pedersen MS, Benros ME, Mortensen PB, Agerbo E, Nordentoft M. Head injury as risk factor for psychiatric disorders: a nationwide register-based follow-up study of 113,906 persons with head injury. Am J Psychiatry 2014;171(4):463–469
64 Fujii DE, Ahmed I. Risk factors in psychosis secondary to traumatic brain injury. J Neuropsychiatry Clin Neurosci 2001;13(1):61–69
65 Fujii DE, Fujii DC. Psychotic disorder due to traumatic brain injury: analysis of case studies in the literature. J Neuropsychiatry Clin Neurosci 2012;24(3):278–289
66 Butler PV. Diurnal variation in Cotard's syndrome (copresent with Capgras delusion) following traumatic brain injury. Aust N Z J Psychiatry 2000;34(4):684–687
67 Schreiber S, Klag E, Gross Y, Segman RH, Pick CG. Beneficial effect of risperidone on sleep disturbance and psychosis following traumatic brain injury. Int Clin Psychopharmacol 1998;13(6): 273–275

68 Michals ML, Crismon ML, Roberts S, Childs A. Clozapine response and adverse effects in nine brain-injured patients. J Clin Psychopharmacol 1993;13(3):198–203
69 Kant R, Duffy JD, Pivovarnik A. Prevalence of apathy following head injury. Brain Inj 1998;12(1):87–92
70 van Reekum R, Stuss DT, Ostrander L. Apathy: why care? J Neuropsychiatry Clin Neurosci 2005;17(1):7–19
71 Rao V, McCann U, Bergey A, Han D, Brandt J, Schretlen DJ. Correlates of apathy during the first year after traumatic brain injury. Psychosomatics 2013;54(4):403–404
72 Andersson S, Bergedalen AM. Cognitive correlates of apathy in traumatic brain injury. Neuropsychiatry Neuropsychol Behav Neurol 2002;15(3):184–191
73 Takayanagi Y, Gerner G, Takayanagi M, et al. Hippocampal volume reduction correlates with apathy in traumatic brain injury, but not schizophrenia. J Neuropsychiatry Clin Neurosci 2013;25(4): 292–301
74 Starkstein SE, Pahissa J. Apathy following traumatic brain injury. Psychiatr Clin North Am 2014;37(1):103–112
75 Starkstein SE, Leentjens AF. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry 2008;79(10): 1088–1092
76 Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the apathy evaluation scale. Psychiatry Res 1991;38(2):143–162
77 van Reekum R, van Reekum E. Apathy. In: Arciniegas DB, Zasler ND, Vanderploeg RD, Jaffee MS, eds. Management of Adults with Traumatic Brain Injury. Arlington, VA: American Psychiatric Publishing; 2013:283–302
78 Gualtieri CT, Evans RW. Stimulant treatment for the neurobehavioural sequelae of traumatic brain injury. Brain Inj 1988;2(4): 273–290
79 Lane-Brown A, Tate R. Interventions for apathy after traumatic brain injury. Cochrane Database Syst Rev 2009;(2):CD006341
80 Kant R, Smith-Seemiller L. Assessment and treatment of apathy syndrome following head injury. NeuroRehabilitation 2002; 17(4):325–331
81 Tenovuo O. Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury-clinical experience in 111 patients. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29(1):61–67
82 Simpson G, Tate R. Suicidality in people surviving a traumatic brain injury: prevalence, risk factors and implications for clinical management. Brain Inj 2007;21(13-14):1335–1351
83 Mackelprang JL, Bombardier CH, Fann JR, Temkin NR, Barber JK, Dikmen SS. Rates and predictors of suicidal ideation during the first year after traumatic brain injury. Am J Public Health 2014; 104(7):e100–e107
84 Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. J Head Trauma Rehabil 2006;21(3):199–212
85 Rao V, Spiro J, Vaishnavi S, et al. Prevalence and types of sleep disturbances acutely after traumatic brain injury. Brain Inj 2008; 22(5):381–386
86 Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. Sleep Med 2012;13(7):898–905
87 Clinchot DM, Bogner J, Mysiw WJ, Fugate L, Corrigan J. Defining sleep disturbance after brain injury. Am J Phys Med Rehabil 1998; 77(4):291–295
88 Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SM. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. Neurorehabil Neural Repair 2014;28(4): 303–313
89 Ouellet MC, Morin CM. Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design. Arch Phys Med Rehabil 2007;88(12): 1581–1592
90 DCoE Clinical Recommendation. Management of sleep disturbances following concussion/mild traumatic brain injury: guidance for primary care management in deployed and nondeployed settings. Defense Centers of Excellence website. Available at: https://dvbic.dcoe.mil/material/management-sleep-disturbances/clinical-recommendation. Accessed July 24, 2014
91 Li Pi Shan RS, Ashworth NL. Comparison of lorazepam and zopiclone for insomnia in patients with stroke and brain injury: a randomized, crossover, double-blinded trial. Am J Phys Med Rehabil 2004;83(6):421–427
92 Kemp S, Biswas R, Neumann V, Coughlan A. The value of melatonin for sleep disorders occurring post-head injury: a pilot RCT. Brain Inj 2004;18(9):911–919
93 Inagaki T, Miyaoka T, Tsuji S, Inami Y, Nishida A, Horiguchi J. Adverse reactions to zolpidem: case reports and a review of the literature. Prim Care Companion J Clin Psychiatry 2010;12(6):
94 Arciniegas DB, Wortzel HS. Emotional and behavioral dyscontrol after traumatic brain injury. Psychiatr Clin North Am 2014;37(1): 31–53
95 Rao V, Spiro JR, Handel S, Onyike CU. Clinical correlates of personality changes associated with traumatic brain injury. J Neuropsychiatry Clin Neurosci 2008;20(1):118–119
96 Campbell JJ III, Duffy JD, Salloway SP. Treatment strategies for patients with dysexecutive syndromes. J Neuropsychiatry Clin Neurosci 1994;6(4):411–418
97 Sohlberg MM, Mateer CA. Training use of compensatory memory books: a three stage behavioral approach. J Clin Exp Neuropsychol 1989;11(6):871–891
98 Epstein NB, Bishop DS. Problem-centered systems therapy of the family. In: Gurman A, Kniskern D, eds. Handbook of Family Therapy. New York, NY: Brunner/Mazel; 1981:444–482
99 Greendyke RM, Kanter DR, Schuster DB, Verstreate S, Wootton J. Propranolol treatment of assaultive patients with organic brain disease. A double-blind crossover, placebo-controlled study. J Nerv Ment Dis 1986;174(5):290–294
100 Yudofsky SC, Williams DT, Gorman J. Propranolol in the treatment of rage and violent behavior in patients with chronic brain syndromes. Am J Psychiatry 1981;138(2):218–220
101 Wortzel HS, Oster TJ, Anderson CA, Arciniegas DB. Pathological laughing and crying: epidemiology, pathophysiology and treatment. CNS Drugs 2008;22(7):531–545
102 Hammond FM, Bickett AK, Norton JH, Pershad R. Effectiveness of amantadine hydrochloride in the reduction of chronic traumatic brain injury irritability and aggression. J Head Trauma Rehabil 2014;29(5):391–399J
103 Makdissi M, Cantu RC, Johnston KM, McCrory P, Meeuwisse WH. The difficult concussion patient: what is the best approach to investigation and management of persistent (>10 days) postconcussive symptoms? Br J Sports Med 2013;47(5):308–313
104 Belanger HG, Vanderploeg RD. The neuropsychological impact of sports-related concussion: a meta-analysis. J Int Neuropsychol Soc 2005;11(4):345–357
105 Larrabee GJ, Rohling ML. Neuropsychological differential diagnosis of mild traumatic brain injury. Behav Sci Law 2013;31(6): 686–701
106 Levin HS, Mattis S, Ruff RM, et al. Neurobehavioral outcome following minor head injury: a three-center study. J Neurosurg 1987;66(2):234–243
107 Eisenberg MA, Meehan WP III, Mannix R. Duration and course of post-concussive symptoms. Pediatrics 2014;133(6):999–1006
108 Rutherford WH, Merrett JD, McDonald JR. Symptoms at one year following concussion from minor head injuries. Injury 1979; 10(3):225–230
109 McLean A Jr, Temkin NR, Dikmen S, Wyler AR. The behavioral sequelae of head injury. J Clin Neuropsychol 1983;5(4):361–376
110 McAllister TW, Arciniegas D. Evaluation and treatment of postconcussive symptoms. NeuroRehabilitation 2002;17(4):265–283

111 Gray BG, Ichise M, Chung DG, et al. Technetium-99m-HMPAO SPECT in the evaluation of patients with a remote history of traumatic brain injury: a comparison with x-ray computed tomography. J Nucl Med 1992;33:52–58
112 Langfitt TW, Obrist WD, Alavi A, et al. Computerized tomography, magnetic resonance imaging, and positron emission tomography in the study of brain trauma. Preliminary observations. J Neurosurg 1986;64(5):760–767
113 Messé A, Caplain S, Pélégrini-Issac M, et al. Specific and evolving resting-state network alterations in post-concussion syndrome following mild traumatic brain injury. PLoS ONE 2013;8(6):e65470
114 Nygren-de Boussard C, Holm LW, Cancelliere C, et al. Nonsurgical interventions after mild traumatic brain injury: a systematic review. Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014;95(3, Suppl)S257–S264
115 Røe C, Sveen U, Alvsåker K, Bautz-Holter E. Post-concussion symptoms after mild traumatic brain injury: influence of demographic factors and injury severity in a 1-year cohort study. Disabil Rehabil 2009;31(15):1235–1243
116 Dikmen SS, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG. Cognitive outcome following traumatic brain injury. J Head Trauma Rehabil 2009;24(6):430–438
117 Drake AI, Gray N, Yoder S, Pramuka M, Llewellyn M. Factors predicting return to work following mild traumatic brain injury: a discriminant analysis. J Head Trauma Rehabil 2000;15(5): 1103–1112
118 Ponsford J, Draper K, Schönberger M. Functional outcome 10 years after traumatic brain injury: its relationship with demographic, injury severity, and cognitive and emotional status. J Int Neuropsychol Soc 2008;14(2):233–242
119 Willemse-van Son AH, Ribbers GM, Hop WC, Stam HJ. Community integration following moderate to severe traumatic brain injury: a longitudinal investigation. J Rehabil Med 2009;41(7):521–527
120 Sigurdardottir S, Andelic N, Wehling E, et al. Neuropsychological functioning in a national cohort of severe traumatic brain injury: demographic and acute injury-related predictors. J Head Trauma Rehabil 2014
121 Draper K, Ponsford J. Cognitive functioning ten years following traumatic brain injury and rehabilitation. Neuropsychology 2008;22(5):618–625
122 Levin H, Hanten G, Max J, et al. Symptoms of attention-deficit/hyperactivity disorder following traumatic brain injury in children. J Dev Behav Pediatr 2007;28(2):108–118
123 Rapoport MJ, McCullagh S, Shammi P, Feinstein A. Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci 2005;17(1):61–65
124 Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. Psychiatr Clin North Am 2014;37(1):1–11
125 Cripe LI. The neuropsychological assessment and management of closed head injury: general guidelines. Cogn Rehabil 1987; 5:18–22
126 Sherer M, Nakase-Thompson R, Yablon SA, Gontkovsky ST. Multidimensional assessment of acute confusion after traumatic brain injury. Arch Phys Med Rehabil 2005;86(5):896–904
127 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013
128 Curtiss G, Vanderploeg RD, Spencer J, Salazar AM. Patterns of verbal learning and memory in traumatic brain injury. J Int Neuropsychol Soc 2001;7(5):574–585
129 Kortte KB, Wegener ST. Denial of illness in medical rehabilitation populations: theory, research, and definition. Rehabil Psychol 2004;49:187–199
130 Prigatano GP, Klonoff PS. A clinician's rating scale for evaluating impaired self-awareness and denial of disability after brain injury. Clin Neuropsychol 1998;12:56–67
131 Haskins EC, Cicerone K, Dams-O'Connor K, Eberle R, Langenbahn D, Shapiro-Rosenbaum A, eds. Cognitive rehabilitation manual: translating evidence-based recommendations into practice. Reston, VA: American Congress of Rehabilitation Medicine Publishing; 2012
132 Wheaton P, Mathias JL, Vink R. Impact of pharmacological treatments on cognitive and behavioral outcome in the postacute stages of adult traumatic brain injury: a meta-analysis. J Clin Psychopharmacol 2011;31(6):745–757
133 Silver JM, Koumaras B, Chen M, et al. Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology 2006;67(5):748–755
134 Gavett BE, Cantu RC, Shenton M, et al. Clinical appraisal of chronic traumatic encephalopathy: current perspectives and future directions. Curr Opin Neurol 2011;24(6):525–531
135 Corsellis JAN, Bruton CJ, Freeman-Browne D. The aftermath of boxing. Psychol Med 1973;3(3):270–303
136 Martland HS. Punch drunk. JAMA 1928;91(15):1103–1107
137 Millspaugh JA. Dementia pugilistica. U S Nav Med Bull 1937; 35:297–303
138 McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol 2009;68(7):709–735
139 Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. Neurosurgery 2005;57(1):128–134, discussion 128–134
140 Omalu BI, DeKosky ST, Hamilton RL, et al. Chronic traumatic encephalopathy in a national football league player: part II. Neurosurgery 2006;59(5):1086–1092, discussion 1092–1093
141 Wortzel HS, Brenner LA, Arciniegas DB. Traumatic brain injury and chronic traumatic encephalopathy: a forensic neuropsychiatric perspective. Behav Sci Law 2013;31(6):721–738
142 Koliatsos VE, Xu L. Neurodegeneration in cumulative sports concussions: emphasis on neurofibrillary tangles. In: Kobeissy F, ed. Brain Neurotrauma: Molecular, Neuropsychological, and Rehabilitation Aspects. Boca Raton, FL: CRC Press; 2015
143 Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. Neurosurgery 2005;57(4): 719–726, discussion 719–726
144 Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology 2012;79(19):1970–1974
145 Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. Neurology 2014;83(4):312–319
146 Vaishnavi S, Rao V, Fann JR. Neuropsychiatric problems after traumatic brain injury: unraveling the silent epidemic. Psychosomatics 2009;50(3):198–205