Psychiatric Disease and Post-Acute Traumatic Brain Injury

Dennis J. Zgaljardic,1,2 Gary S. Seale,1 Lynn A. Schaefer,3 Richard O. Temple,4 Jack Foreman,1 and Timothy R. Elliott5

Abstract
Psychiatric disorders are common following traumatic brain injury (TBI) and can include depression, anxiety, and psychosis, as well as other maladaptive behaviors and personality changes. The epidemiologic data of psychiatric disorders post-TBI vary widely, although the incidence and prevalence rates typically are higher than in the general population. Although the experience of psychiatric symptoms may be temporary and may resolve in the acute period, many patients with TBI can experience psychopathology that is persistent or that develops in the post-acute period. Long-term psychiatric disorder, along with cognitive and physical sequelae and greater risk for substance use disorders, can pose a number of life-long challenges for patients and their caregivers, as they can interfere with participation in rehabilitation as well as limit functional independence in the community. The current review of the literature considers the common psychiatric problems affecting individuals with TBI in the post-acute period, including personality changes, psychosis, executive dysfunction, depression, anxiety, and substance misuse. Although treatment considerations (pharmacological and nonpharmacological) are referred to, an extensive description of such protocols is beyond the scope of the current review. The impact of persistent psychiatric symptoms on perceived caregiver burden and distress is also discussed.

Key words: caregiver distress; maladaptive behaviors; mood disorder; TBI

Introduction
Psychiatric symptoms occur with great frequency and variability in patients with traumatic brain injury (TBI), regardless of injury severity, and can involve personality changes (e.g., poor anger/impulse control and irritability), maladaptive social behaviors, psychosis (e.g., delusions and/or hallucinations), depressed mood, poor disability adjustment, reduced coping skills, anxiety, and cognitive impairment (e.g., executive dysfunction).1–5 In their sample of patients with TBI admitted to a rehabilitation hospital, Fann and coworkers reported that 26% of their sample had major depression, 14% had dysthymia, 24% had generalized anxiety, and 8% were abusing substances.6 Hibbard and coworkers reported that the most common psychiatric diagnoses in their sample of patients with TBI included major depression, substance abuse, and post-traumatic stress disorder (PTSD).7 Deb and coworkers reported that 27.1% of their TBI cohort experienced psychiatric complications within 1 year post-injury compared with 16.4% in the general population.5 Of note were significantly higher rates of depression (13.9% vs. 2.1%) and anxiety disorder (9% vs. <1%). Silver and coworkers discovered that 43% of TBI patients in their sample had at least one psychiatric diagnosis compared with 20% of non-TBI participants.8 Table 1 provides a summary of incidence rates for common psychiatric disorders following TBI.

Psychiatric symptoms and maladaptive behaviors experienced by patients with TBI in the post-acute period can be a significant limiting factor for rehabilitation participation and positive functional outcomes.3,9,10 Further, such psychiatric disturbances are typically perceived by caregivers as a greater source of distress and burden than the physical or cognitive deficits experienced by their injured loved ones.11 The aim of the current review of the literature is to identify and discuss the persistent psychiatric symptoms and other maladaptive behaviors (e.g., substance misuse) that are commonly experienced by individuals with TBI (across injury severity) and addressed in post-acute treatment and rehabilitation. Further, a review of the literature discussing the psychological impact of TBI on caregivers in the post-acute period will be provided.

1Transitional Learning Center, Galveston, Texas.
2University of Texas Medical Branch, Galveston, Texas.
3Nassau University Medical Center, East Meadow, New York.
4Private Practice, Austin, Texas.
5Texas A&M University, College Station, Texas.
Personality Changes, Psychosis, and Cognitive Impairment After TBI

Disorientation, amnesia, aggression, and emotional lability

Brain injury severity (typically assessed by duration of loss of consciousness [LOC], Glasgow Coma Scale [GCS], and/or post-traumatic amnesia [PTA]) is associated with the development of cognitive deficits and personality and behavioral changes in the acute period (Table 2). PTA is the period of time from injury onset to the return of continuous day-to-day memories, and is typically viewed as a strong predictor of length of hospitalization, recovery rates, and functional outcome.9,13 The GCS and Galveston Orientation and Amnesia Test (GOAT) are two measures that are commonly used to assess levels of consciousness and PTA, respectively.9,14

Impairment of consciousness and amnesia are considered the prominent psychiatric and cognitive sequelae in the acute period following TBI. Patients experiencing PTA can display heightened levels of aggression and agitation including disorientation, impulsive behaviors, irritability, confabulatory responding, amnesia (retrograde and anterograde), and impaired attentional skills that may be initiated or prolonged by overstimulating environmental factors.36 However, Deb and coworkers reported that ~35% of TBI patients (with varying degrees of injury severity) had aggressive feelings such as irritability and frustration in the 1st year post-injury.1 Impulsivity and anger appear to be the predominant characteristics of aggression in the post-acute period.17 Aggressive behaviors are often associated with frontal lobe damage and prior history of TBI, with an incidence rate of ~34%.18-21 The presentation of aggressive behaviors across patients with TBI can vary, and such episodes are typically reactive, explosive, periodic, brief in duration, and with patients showing little remorse.4,16,22 Whereas cognitive behavioral therapy (CBT) and behavior modification techniques have been reported to be efficacious in curbing aggressive behaviors in patients with TBI, the use of β-blockers has been suggested for medication management.6,23 However, because the effective doses for β-blockers may be too high, antipsychotic and anticonvulsant mood stabilizers are more readily used.29 Using logistic regression models for single-case designs of community-dwelling patients with TBI, Brossart and coworkers reported that the use of a β-blocker was not associated with decreased agitation for the majority of their patients.24 More recently, using a randomized, double-blind, placebo-controlled trial, Hammond and coworkers discovered a significantly greater decrease in irritability and aggression in patients given amantadine (dopaminergic agent) than in those given placebo.25

Pathological laughter or crying (i.e., emotional lability) associated with pseudobulbar affect typically involves bilateral lesions of the corticobulbar pathways or unilateral lesions involving the prefrontal cortex.26 Individuals presenting with pseudobulbar affect can experience frequent episodes of uncontrollable emotional expression that appears to be exaggerated and/or incongruent with the intensity of the stimulus presented, or with their current mood state.26-28 In their sample of 92 patients with mild, moderate, and severe TBI, Tateno and coworkers reported that 10.9% of patients exhibited pathological laughter or crying within their 1st year post-injury.26 Of those patients, excessive emotional expression was reported to be associated with premorbid history of drug abuse, aggressive behaviors and anxiety (but not depression) post-injury, and high occurrence of frontal lesions, particularly involving the lateral aspect of the left frontal lobe. Ahmed and Simmons in their review indicated that treatment considerations for the management of pseudobulbar affect have typically included tricyclic antidepressants, selective serotonin reuptake inhibitors, and more recently, the compound dextromethorphan and quinidine.27

TBI-related psychosis

The incidence of psychosis post-TBI has been estimated to fall between <1% and 9%, whereas latencies between injury onset

---

**Table 1. Incidence Rates of Common Psychiatric Disorders after TBI**

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Reference</th>
<th>Incidence after TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggression</td>
<td>Tateno et al.21</td>
<td>3.7% (6 month period)</td>
</tr>
<tr>
<td>Depression</td>
<td>Rapoport et al.69</td>
<td>15.3% (average 48 days post-injury)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Koponen et al.164</td>
<td>20% (up to 15 years)</td>
</tr>
<tr>
<td>PTSD</td>
<td>Bryant and Harvey129</td>
<td>24% (6 month period)</td>
</tr>
<tr>
<td>Panic disorder, specific phobia,</td>
<td>Bombardier et al.130</td>
<td>11% (6 month period)</td>
</tr>
<tr>
<td>social phobia, and generalized anxiety</td>
<td>Koponen et al.164</td>
<td>18.3% (30 year period)</td>
</tr>
<tr>
<td>disorder (combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>Whelan-Goodinson et al.163 (alcohol)</td>
<td>11.7% (30 year period)</td>
</tr>
<tr>
<td></td>
<td>Whelan-Goodinson et al.163 (non-alcohol)</td>
<td>17.6% (up to 5 years)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33% (up to 5 years)</td>
</tr>
</tbody>
</table>

TBI, traumatic brain injury; PTSD, post-traumatic stress disorder.

---

**Table 2. Traumatic Brain Injury Severity Criteria**

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>13–15</td>
<td>9–12</td>
<td>3–8</td>
</tr>
<tr>
<td>LoC</td>
<td>&lt; 20 min</td>
<td>20 min - 36 h</td>
<td>&gt; 36 h</td>
</tr>
<tr>
<td>PTA</td>
<td>&lt; 1 day</td>
<td>1–7 days</td>
<td>&gt; 7 days</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; LoC, loss of consciousness; PTA, post-traumatic amnesia.

Adapted from Stein.12
and psychotic symptom presentation have been reported to occur between 2 weeks and 17 years with a mean latency of 4 years. However, Thomsen and coworkers reported that in their sample of 40 patients with severe TBI, 20% experienced psychosis 10–15 years post-injury. Fujii and Ahmed suggested that the variability in the criteria used to diagnose psychotic disorder caused by TBI may explain the wide range of incidence rates reported. The development of psychotic symptoms following TBI has been associated with pre-injury substance use, family history of schizophrenia, duration of loss of consciousness, and aphasia syndrome, as well as cortical damage within the frontal and temporal lobes. Despite varied reports in the literature, psychotic symptoms post-TBI appear to occur at similar rates across levels of injury severity.

The most common psychotic symptoms experienced by patients post-TBI include persecutory delusions and auditory hallucinations, whereas negative symptoms (e.g., alogia and flat affect) occur with less frequency than in individuals with schizophrenia without TBI. According to findings from a large epidemiological study of 5034 participants, 361 of whom were individuals with TBI, Silver and coworkers reported that all psychiatric diagnoses considered in their study were significantly more prevalent in the TBI group than in control participants, with the exception of bipolar disorder and schizophrenia. Based on these findings, Kim and coworkers posited in their review of the literature that TBI may be a significant influential factor in the expression of psychosis in those individuals with a genetic predisposition to schizophrenia. Differential diagnosis is further complicated by the fact that seizures, for example, which are common following TBI, are strongly associated in uninjured patients with psychosis. Fujii and Fujii indicated high comorbidity among psychotic symptoms, TBI, and seizure disorder. For medical management of psychosis, neuroleptic medications appear to be most effective for both patients with schizophrenia (without TBI) and psychotic disorder post-TBI, although treatment response can vary.

Executive dysfunction

Regions of the brain that are particularly vulnerable to TBI include the frontal lobe, anterior temporal lobe, corpus callosum, brainstem, and limbic structures such as the basal ganglia and hypothalamus. Subsequently, cognitive and behavioral processes commonly disrupted by TBI include arousal, attention, speed of information processing, new learning, memory retrieval, fluency, and executive functions (including organization and planning, sequencing, multitasking, judgment, and abstraction). More specifically, executive functions is a term used to describe higher order mental processes, mediated by the frontal lobes of the cerebral cortex, which are involved in the regulation of cognitive and...
behavioral responses to environmental contingencies. Further, executive dysfunction can occur following non-frontal damage (e.g., posterior association cortex and dorsomedial thalamic nucleus), because of the high interconnectivity the frontal lobes maintain with various cortical regions.

Because of the considerable negative influence that disorders of executive functions can have on a patient’s participation in activities of daily living, rehabilitation therapies, and other life activities (e.g., social, functional, and vocational), this condition is typically a strong predictor of poor psychosocial and functional outcomes, as well as poor disability adjustment. The classic case report of Phineas Gage chronicles the injury, persistent psychiatric symptoms, personality changes, and functional outcome of an individual who experienced a TBI involving the prefrontal region of the cortex. Behavioral changes in this patient were noted in the postacute period, despite relatively preserved memory and intellect. Damasio attributed Mr. Gage’s inability to make “moral decisions” to bilateral damage of the prefrontal cortex, more specifically the ventromedial region.

Individuals with prefrontal cortical damage, such as in the case of Mr. Gage, can present with a myriad cognitive deficits and personality changes that may fall into one of three executive dysfunction subtypes. First, an apathetic-akinetic syndrome can result from anterior cingulate (medial) prefrontal cortical damage. This area of the brain is believed to be involved in attentional processes such as response initiation, intention, inhibition, and conflict monitoring. This syndrome is typically characterized by diminished responsiveness to environmental stimuli (i.e., reduced processing speed) with reduced initiation and maintenance of desired behaviors (i.e., amotivation). Orbitofrontal damage (including the ventromedial cortex) can result in a disinhibited syndrome. The ventromedial cortex is typically associated with frontal monitoring of the limbic system such as disinhibition, circumstances in which decisions are made based upon a reinforcement/reward schedule required to maintain a behavioral set, impulse control, perseveration, and mood and personality. This syndrome is characterized by personality changes involving poor regulation of inhibitory and emotional mechanisms that can result in inappropriate, socially maladaptive behaviors. Lastly, a dysexecutive syndrome can result following damage to the dorsolateral aspect of the prefrontal cortex. This cortical region is reported to mediate executive cognitive functions, such as set-shifting, complex problem solving, activation of remote memories, organizational strategies, and working memory. This syndrome is typically characterized by “cognitive” deficits including problems with working memory, set-shifting, conditioned associate learning, maintenance of cognitive set, and memory retrieval (Figure 1).

McDonald and coworkers indicated that focused treatment (i.e., cognitive remediation and/or compensation), particularly with patients experiencing executive dysfunction, may include cognitive or behavioral strategies, either separately or in combination with a goal to “promote skill acquisition, internal initiation, and self-monitoring of performance of these skills.” For example, patients with TBI can show improvements in coping and self-management abilities following structured group training in social problem-solving skills. Use of such metacognitive skills (i.e., self-monitoring and self-regulation) to help increase awareness is supported by evidence-based practice guidelines in the treatment of executive functions following acquired brain injury. Affective awareness-training protocols have been designed to provide feedback to patients to increase injury awareness of neuropsychological sequelae, and emphasize the need for the patient to attempt to predict, monitor, and evaluate task performances. From a pharmacological standpoint, mood stabilizers have been suggested to provide the most benefit in reducing maladaptive behaviors and personality changes associated with executive dysfunction; however, the potential for negative side effects (e.g., reduced processing speed and/or memory) does exist.

Depression

In their review of the literature spanning over three decades, Kim and coworkers cited large variability with regard to incidence and prevalence of depression post-TBI. They reported incidence rates ranging from 11% to 33%, whereas prevalence rates varied widely, with up to 61% of patients meeting criteria for major depressive disorder. Their rationale for the inconsistency in the incidence and prevalence rates reported included limitations in the diagnostic methods utilized, variability in sampling methods, and differences in operational definitions used in describing both major depression and TBI severity. A more realistic estimate of the prevalence rates of depression and TBI was provided by Seel and Kreutzer as 30–38%, following >170 TBI patients for 4 years. Given that lifetime prevalence of depression in the United States has been reported to be 16.2%, there appears to be an increased risk of developing depression after TBI, over and above one’s lifetime risk. However, in a cross-sectional analysis, Ashman and colleagues found that rates of depression (and other Axis I disorders) following TBI can decline with time since injury.

Although depression is quite common in patients with TBI, it is not necessarily more common in patients with TBI than in patients with other types of traumatic or orthopedic injuries without TBI, or in those with persistent chronic pain. Complicating diagnosis further is the fact that many symptoms of depression and postconcussive syndrome (PCS) (i.e., mild TBI) overlap. These can include emotional symptoms such as irritability and excessive worry, cognitive symptoms such as decreased concentration and indecisiveness, and physical complaints such as fatigue, headache, and disrupted sleeping patterns. Ettenhofer and Barry discovered similar depressive symptom clusters in orthopedic injury patients and those with mild TBI, even though mild TBI patients presented with greater symptom frequency. Another study looked at only depressed patients without TBI, and found that post-concussion-like symptoms were extremely common.

Comorbid factors of depression post-TBI

Many factors can coincide with TBI, such as pain, fatigue, sleep disturbance, cognitive dysfunction, apathy, decreased mobility, and emotional processing deficits. For example, clinical attention to presence and source of persistent, chronic pain is particularly warranted, given the frequent occurrence of pain post-TBI (>50%) and its documented relationship to depression and impaired quality of life among patients with TBI. There is also a need to consider preexisting factors such as personal and family history of mood disorder, history of pre-injury psychological trauma, and individual coping styles when examining risk of developing depression following TBI. Any of these comorbid factors may result in the experience of depression by themselves, or may have a cumulative effect with a resulting increase in depression risk post-TBI. Consequently, patients with post-TBI depression may experience a worsening of such comorbid factors. For example, Ou et al. and colleagues, studying insomnia in patients with TBI, indicated that 50.2% of their sample reported experiencing insomnia, whereas 29.4% of the sample satisfied diagnostic criteria for an insomnia syndrome. Risk factors associated
with insomnia in their sample included mild TBI, and higher levels of fatigue, depression, and pain. Others have also reported increased prevalence of both insomnia and other sleep disturbances post-TBI. Given, then, that studies have shown increased risk of depression associated with insomnia, it would not be surprising for TBI patients with insomnia to have an increased risk of depression.

Symptoms related to apathy (i.e., reduced motivation or loss of interest) can coexist with depression in individuals with or without TBI. Further examination would help determine whether a patient was apathetic following TBI because of depression, or whether they were exhibiting poor awareness or denial of their deficits, anosognosia, or lack of concern about the deficit (i.e., anosodiaphoria). The latter conditions are thought to be the result of organic brain damage, particularly involving the right hemisphere (especially frontal or parietal regions); however, apathy in any form can greatly impact participation in rehabilitation.

Fatigue, not to be confused with apathy or depression, is typically viewed as a subjective phenomenon that can be expressed, for example, as experiencing a lack of energy or motivation, weakness, and/or sleepiness and has been reported to greatly impact patients' lifestyles by limiting participation in therapeutic, social, and/or leisure activities. The association between depressed mood and fatigue post-TBI is not entirely clear. The consensus from prior work indicates a consistent, but not necessarily causative association between subjective fatigue and psychiatric disorder in this patient population. In their study assessing potential correlates of fatigue in patients with TBI, Ponsford and coworkers discovered that patients with symptoms related to anxiety and depression were more likely to report significant levels of fatigue; however, so were patients who also experienced heightened levels of pain and cognitive dysfunction.

Disability adjustment and depression

Psychiatric symptoms post-TBI may present as a reaction to the injury itself and/or as a result of the experience of hospitalization, including loss of independence or separation from loved ones. Social isolation can be experienced immediately following TBI and has been reported in upwards of 60% of patients. In most cases, the limitations placed on a given patient’s ability to re-enter pre-injury environments (e.g., home, workplace, or recreational and/or academic settings) can result in an immediate reduction of routine social interactions including with friends, colleagues, and loved ones, as well as the ability to form new social and meaningful relationships.

Patients with TBI must cope with cognitive and physical limitations, as well as the very real possibility that their lives may not return to pre-injury levels. Folkman and coworkers defined coping as a “person’s cognitive and behavioral efforts to manage (reduce, minimize, master, or tolerate) the internal and external demands of the person–environment transaction that is appraised in taxing or exceeding the resources of the person.” Dysfunctional coping strategies following brain injury can limit or disrupt a given patient’s emotional interpretation and reaction to a given environment or situation. Cognitive impairment (e.g., executive dysfunction) and psychiatric changes post-TBI can limit an individual’s ability to cope, as well as restrict insight and judgment within a given social context or environment, although some patients can experience isolated changes in social behaviors or personality with relatively preserved intellectual functioning or performance on neuropsychological evaluation. Hence, psychological, cognitive, and behavioral sequelae secondary to TBI can very well lead to difficulty in gauging, monitoring, and self-regulating one’s ability to cope with or interpret everyday life situations and/or stressors, which can, in turn, lead to emotional dysregulation and maladaptive behaviors.

Krupa and coworkers discovered that TBI patients usually present with an avoidant rather than planning coping style. In their study, those patients who were deemed better “planners” were found to have better executive functioning skills, higher estimated premorbid intelligence, and appropriate emotional reactivity than patients with an avoidant coping style.

Pagulayan and colleagues reported, in their longitudinal study, that functional limitations caused by TBI in the post-acute period did precede depression. Specifically, depressive symptomatology among TBI patients at 1 year was greater than that reported at 6 months, and was preceded by perceived injury-related difficulties. The reverse was not found to be true. Malec and coworkers assessed self-appraisal in patients with TBI and self-reported depression; they found an association between perceived post-injury ability (including mobility, speech, cognition) and depression. Following >1500 TBI patients 1 year post-injury, Hart and colleagues found that almost half of their participants had either mild or major depression, and discovered that both were associated with decreased satisfaction with life and reduced participation in the community. Hibbard and coworkers examined the prevalence of depression within 5 years post-TBI and reported on the emergence of four patterns of depression: no depression, resolved depression, late-onset depression, and chronic depression, all of which were related to self-reported levels of psychosocial functioning in the post-acute period. They also discovered that depression commonly occurred with anxiety disorders. In a study of patients with chronic TBI (10–20 years post-injury), vocational, family, and social functioning were found to be most related to psychiatric and behavioral symptomatology (i.e., depression, anxiety, and hostility) rather than cognitive dysfunction. Therefore, even a decade or more post-injury, poor adjustment to disability from TBI and depression appear to negatively impact functional ability.

Although supportive psychotherapy and CBT have been reported to be underutilized among TBI patients who meet criteria for depressive disorder, these practices appear to be effective in this patient population. CBT has been suggested for use in patients with TBI as a means to alleviate symptoms related to depression, especially in the post-acute period. CBT can help patients become more aware of maladaptive thinking and cognitive “distortions,” which may be contributing factors to their depressive symptoms; however, reports on the effectiveness of CBT in reducing depressive symptoms post-TBI vary. Using a randomized control trial, Ashman and coworkers discovered that CBT was no more efficacious than supportive psychotherapy when treating depressive symptoms in community-dwelling patients with TBI and depression. Fann and coworkers reported on the effectiveness in alleviating depression in patients with TBI using CBT (either in person or over the telephone) when compared with those patients not receiving CBT as part of treatment. They did not discover an overall significant benefit of CBT (regardless of presentation format) over time compared with not receiving CBT. However, those patients receiving CBT via telephone intervention alone did show a significant decrease in depressive symptoms compared with those patients not receiving CBT. Bedard and coworkers reported that mindfulness-based cognitive therapy (using a randomized controlled trial) resulted in a greater decline in scores on the Beck Depression Inventory-II in patients with TBI compared with a control group. The decrease in symptoms for the intervention group was maintained for 3 months. From CBT another
more behavioral approach emerged, that of behavioral activation, or having the patient engage in activities to reduce depression.\textsuperscript{107} The idea behind this method is to increase positive environmental reinforcement while reducing inertia, avoidance, and rumination.

**Neuroanatomical and neurotransmitter correlates of depression post-TBI**

As has been discussed, depression in individuals with TBI may be the result of the reaction to the injury itself and/or result from psychosocial changes; however, emotional and behavioral sequelae can also be the direct result of specific underlying neurological impairment.\textsuperscript{108,109} For example, patients with left lateral prefrontal lesions or those localized to subcortical or limbic areas of the brain may be said to experience an “organic depression.”\textsuperscript{110,111} Structural imaging studies have reported volume loss in prefrontal, hippocampal, and orbitofrontal areas in patients with major depression without TBI.\textsuperscript{112–114} Similarly, functional imaging studies have reported hypometabolism involving dorsolateral, ventral, and orbital frontal cortices, anterior cingulate, as well as paralimbic areas in depressed individuals.\textsuperscript{115,116} Hemispheric lesion laterality may also play a role in the experience of depression post-TBI. Studies from the stroke literature report that left hemisphere damage may be specifically related to depressive symptoms, particularly left frontal regions, whereas damage to the right hemisphere, in contrast, may result in greater frequency of symptoms related to apathy, as opposed to depression.\textsuperscript{117}

The monoamine deficiency hypothesis purporting that decreased levels of serotonin, norepinephrine, and \(\gamma\)-aminobutyric acid (GABA) result in depression, is one theory applied to the experience of depression post-TBI.\textsuperscript{118} Disruptions in serotonin, glutamate, and dopamine levels have been described in TBI patients.\textsuperscript{109} Another, more recent, theory is that of dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis) by physical or emotional stress. Both overactivation and underactivation of the HPA axis have been reported in TBI.\textsuperscript{119} This theory posits that the amygdala and hippocampus, structures that regulate emotions and memory and have connections to the hypothalamus, are ultimately affected by neuroendocrine imbalance post-injury. Stress-induced cortisol release by the adrenal cortex appears to play a role in depression, and is characterized by a more chronic course of depression, hippocampal atrophy, and reduced levels of brain-derived neurotrophic factor (BDNF).\textsuperscript{113} Finally, there is the role of glutamate in the pathophysiology of major depressive disorder, and BDNF also appears to play a role in glutamate transmission.\textsuperscript{120} Pharmacological interventions that have been demonstrated as the most efficacious for depression in TBI patients are the selective serotonin reuptake inhibitor (SSRI) antidepressive medications, sertraline and citalopram in particular, as opposed to monoamine oxidase (MAO) inhibitors or the tricyclic antidepressants.\textsuperscript{121} Unfortunately, Bombardier and coworkers discovered that among patients meeting criteria for depression post-TBI, less than half received any form of antidepressant therapy.\textsuperscript{77}

**Anxiety Disorders**

Anxiety disorders have the highest collective prevalence in the general population, with lifetime prevalence estimated at \(\sim 29\%\).\textsuperscript{72} Anxiety disorders are a common comorbidity with TBI. For example, Hibbard and coworkers found a high prevalence of anxiety disorders (PTSD, obsessive compulsive disorder [OCD], and panic disorder).\textsuperscript{7} Ashman and coworkers used a cross-sequential design to examine psychiatric disorders following TBI.\textsuperscript{73} They discovered an increase in anxiety and other disorders in the first post-injury assessment period. Given the prevalence of various anxiety disorders in the general population, the relationship between brain injury and anxiety is complex and multifaceted. Of particular interest is the relationship between premorbid anxiety disorders and the development of anxiety following TBI. Gould and coworkers examined these relationships in brain injury survivors 1 year post-injury.\textsuperscript{122} In their cohort, 21.6\% of patients carried a premorbid anxiety disorder diagnosis. Following injury, 44.1\% of participants met diagnostic criteria for an anxiety disorder. The presence of a premorbid disorder was statistically predictive of the development of post-injury anxiety. However, the number of individuals with anxiety diagnoses more than doubled post-injury, suggesting that disorders can develop post-injury in an individual without premorbid anxiety problems.

The relationship between functional status following injury and the presence of an anxiety disorder has also drawn interest in the literature. It is unclear whether functional limitations imposed by a brain injury cause anxiety, or whether the individual’s anxiety creates functional difficulties. Schonberger and coworkers utilized a cross-lagged analysis to address this question.\textsuperscript{123} Observing 122 individuals across all levels of injury severity, they found that functional changes at 6 months post-injury predicted depression and anxiety one year post-injury onset. However, anxiety and depression were not in turn predictive of later functional status. The authors interpreted these findings as indicative of the importance of supporting patients psychologically as they cope with the functional consequences of their injuries.

One might ask whether there is something specific to brain injury that leads to anxiety or other mood disorders, or whether anyone with a medical illness would demonstrate increased incidence of psychiatric distress. Ponsford and coworkers compared individuals presenting in the emergency department with mild TBI with patients presenting with other trauma.\textsuperscript{124} Compared with trauma controls, mild TBI patients did not report greater symptoms of any particular class of disorders, including anxiety disorders. However, a trend was observed showing a higher prevalence of symptoms, across all psychiatric categories, in mild TBI patients when compared with trauma controls.

**Etiology of anxiety post-TBI**

The relationship between TBI and anxiety is likely multifactorial, reflecting multiple etiologies. Brain injuries often occur in a traumatic or otherwise emotionally arousing situations (e.g., motor vehicle collisions, assaults), and, therefore, the context in which the injury occurs could reasonably lead to anxiety reactions. However, neuroanatomical and neurometabolic disruption could also occur, leading directly to the experience of anxiety. In a fear-conditioning paradigm with rats, Reger and coworkers found that brain injured rats exhibited an overall increase in fear conditioning, and that they appeared to overgeneralize learned fear to both conditioned and novel stimuli.\textsuperscript{125} Injury resulted in upregulation of excitatory N-methyl-D-aspartate (NMDA) receptors in the basolateral amygdala complex. The authors concluded from these findings that mild TBI predisposed the brain toward heightened fear learning during stressful post-injury events via a molecular mechanism. Gray and McNaughton hypothesized disruption in a behavioral inhibition system as being responsible for the development of anxiety following TBI.\textsuperscript{126} This system, comprised mainly of the septo-hippocampal system, can malfunction in the presence of TBI and become overly
sensitive to stimuli, reacting too frequently to ambiguous or non-threatening stimuli. Although brain injuries of all severities have demonstrated susceptibility to anxiety reactions, mild TBI has drawn particular interest in the literature, both in civilian and military populations in the post-acute period. If neuronal mechanisms were primarily responsible for the relationship between TBI and anxiety, one would expect to see a positive relationship between TBI severity and anxiety. However, not only have these data been inconsistent, studies have reported inverse relationships whereby mild TBI patients report greater psychiatric symptoms than those with moderate or severe injuries over time.127,128

PTSD and other anxiety disorders

Given the traumatic nature of many circumstances that cause brain injuries, the relationship between TBI and PTSD is of particular interest. Incidence rates of PTSD post-TBI have been reported to be 15–29%129,130 with prevalence rates ranging widely by study from 3% to 27%.131 Bryant and Harvey reported a frequency of 20% in individuals who had sustained a mild TBI in a motor vehicle accident,132 whereas Feinstein and coworkers reported an 84% rate of co-occurrence of mild TBI and PTSD.133 Also, the nature of military conflicts around the globe, more recently in Iraq and Afghanistan, has drawn attention to this relationship in military populations. Carlson and coworkers systematically reviewed the literature with regard to PTSD prevalence in a military sample, and found widely varying rates of combined mild TBI and PTSD.134 In a civilian sample, Hoffman and coworkers found that, among individuals with a mild TBI, risk factors for developing PTSD included Hispanic ethnicity, describing themselves as less happy pre-injury onset, and belief that they would be more affected by their injury.135

Given that PTSD involves persistent re-experiencing of a traumatic event, the question has been raised as to whether PTSD can occur in an individual who does not recall the traumatic event because of a brain injury. Warden and coworkers evaluated 47 soldiers who had sustained moderate TBI, none of whom could recall the traumatic event.136 Participants demonstrated some symptoms of PTSD such as elevated startle reflex, irritability, and avoidance of stimuli associated with the trauma. However, none reported any type of re-experiencing symptoms, and, therefore, they did not meet formal criteria for PTSD diagnosis. The authors concluded from that study that TBI accompanied by PTA and comorbid PTSD is very uncommon. In contrast, others have provided data and anecdotal observations to suggest that PTSD can occur in the absence of actual memories of the injury-producing event. For example, Bryant suggested that individuals can produce “pseudo-memories” of an event based on information they were told about the event, reading newspaper articles, or viewing pictures of the accident scene.137 These pseudomemories can serve as analogues to flashbacks and nightmares and can be experienced vividly and intensely. King presented a single-case study of an individual with no recollection of the injury who met full criteria for PTSD.138 He concluded that an individual can experience full PTSD via “islands” of memory of an event.

Other anxiety disorders have received some attention in the literature, including OCD, panic disorder, generalized anxiety disorder (GAD), specific phobia, and social phobia. However, research data involving individuals with brain injury are not nearly as abundant as is the case with PTSD. Moore and coworkers reviewed the literature with regard to these disorders coexisting with TBI.139 Generally speaking, they found widely disparate prevalence rates, and many single-case and anecdotal reports. Etiological mechanisms also vary between psychological and organic factors, with no clear evidence to support either type or cause in most cases. Regardless of the specific anxiety disorder, however, it appears that addressing and treating anxiety symptoms is paramount to recovery in individuals with brain injury, particularly those individuals with mild TBI. Fann and coworkers found that individuals with a mild TBI with comorbid anxiety were more functionally impaired, and perceived their cognitive deficits as more severe than did those without anxiety.5

PCS

The terms “post-concussional disorder” or “post-concussion syndrome” (PCS) have been given to the typical constellation of symptoms that occurs following mild TBI. Most individuals make a complete recovery from an uncomplicated mild TBI within 3 months.140 However, up to 44% of individuals report three or more symptoms 1 year following injury.141 As mentioned previously, PCS symptoms (e.g., headache, dizziness, cognitive complaints) are not specific to mild TBI, which complicates diagnosis.76,142 There is evidence in the literature that factors other than those specifically related to the injury are related to protracted recovery from mild TBI. For example, Meares and coworkers found that factors other than mild TBI were responsible for the presence of PCS symptoms.143 Those factors included the presence of pre-injury anxiety or depressive disorder, and acute PTSD. Further, the relationship between the severity of PTSD and PCS symptoms strengthened over time. Similarly, Hou and coworkers found that stress, anxiety, depression, and “all-or-nothing behavior” were associated with the risk of PCS symptoms beyond 3 months post-injury.144 Mittenberg and Strauman posited a neuropsychological theory of prolonged PCS that implicated anxiety as an important mechanism. In this model, typical symptom expectancies are activated following a mild TBI.145 Normally occurring premorbid symptoms are attributed to mild TBI. Selective attention to the inherent stress of the trauma subjectively magnifies these symptoms. Symptom expectations are confirmed, and anxiety about the significance of the symptoms receives selective attention in a cyclical relationship.

There is a dearth of studies that specifically address particular treatment regimens for anxiety in the context of TBI. The area that perhaps has received the most attention is in the treatment of persistent PCS. Mittenberg and coworkers presented results from a treatment study that included meeting with patients to review the nature and incidence of expected symptoms, presentation of the cognitive-behavioral model of symptom maintenance and treatment, techniques for reducing symptoms, and instructions for gradual resumption of premorbid activities.146 Patients in the treatment group demonstrated significantly shorter symptom duration and significantly fewer symptoms at follow-up. Al Sayegh and coworkers presented data supporting the efficacy of CBT in individuals with PCS.147 They concluded that information, education, and reassurance alone may not be as effective as was once thought. Some support was found for other types of treatment, including multifaceted programs with a psychotherapeutic element as well as mindfulness and relaxation. Bell and coworkers compared the effectiveness of standard level of care and a telephone intervention using a randomized control trial in reducing post-traumatic symptoms in patients with mild TBI.148 Both groups of patients received standard level of care with receipt of
instructional materials; however, the experimental group received scheduled telephone contacts (four or five sessions) over the initial 3 months post-injury aimed at education, symptom management, and encouragement to resume everyday activities. Patients receiving telephone intervention reported experiencing significant improvements in common post-concussive symptoms including sleep, fatigue, memory, and concentration, as well as reductions in experiences of dizziness, blurred vision, and sexual difficulties compared with patients in the control group. With regard to pharmacological treatment considerations, the use of anxiolytics in those with TBI is usually discouraged because of their sedating properties, as well as potential negative effects on cognitive functioning. In their review of the literature, Warden and coworkers reported insufficient evidence (class I and II studies) for or against the use of commonly used anxiolytics (e.g., tricyclics, benzodiazepines, and/or serotonin reuptake inhibitors) in the treatment of anxiety post-TBI.

**Substance Use Disorders (SUD)**

Numerous studies cite substance use and misuse, particularly of alcohol, as a major risk factor for sustaining a TBI. Intoxication at the time of injury has been associated with medical complications and extended lengths of stay during acute hospitalization. Continued substance use/misuse following discharge from rehabilitation has been shown to negatively impact vocational outcomes, reduce life satisfaction, increase risk for the development of mood disorders, increase the probability for re-injury, and increase mortality. For a subset of individuals with TBI, cognitive deficits (e.g., executive dysfunction) may combine with maladaptive coping and poor psychosocial adjustment to increase risk for the development of chronic substance use/misuse. Risk factors for continued post-injury substance use/misuse include pre-injury history of an SUD, intoxication at the time of injury, family history of an SUD, denial of dangers associated with continued substance use, younger age (i.e., < 25 years), male gender, fewer cognitive/physical impairments stemming from injury, less involvement in productive activities that produce income, and less community access.

The general term “substance abuse” has been used to define substance use, substance dependence, and/or SUD in much of the TBI literature. This failure to define terms accurately has been cited as a limitation in studies examining the relationship between TBI and substance use/misuse. In this section, the term “substance use” refers to the consumption of any amount of alcohol and/or other drugs, and does not imply illegal or unhealthy use. Consistent with Corrigan and coworkers, the term “substance misuse” will be applied to consumption that is risky or unhealthy, or that constitutes a limitation in studies examining the relationship between TBI and substance use/misuse.

The literature supports educating persons with TBI about the negative effects of continued substance use on recovery from TBI. Documented consequences of continued substance use include suppression of cognitive recovery, increased risk for seizures, potential interactive effects of alcohol and other drugs with prescribed medications, and increased risk for sustaining a second TBI. Studies suggest that presenting information using motivational interviewing techniques and multimedia psychoeducational materials may enhance retention of and receptiveness to the information. For example, Sander and colleagues randomized 104 adults with TBI into an experimental group using either motivational interviewing techniques or a standard level of care control group. The intervention group viewed a brief educational video that illustrated negative consequences associated with continued use of drugs and/or alcohol following TBI. Participants were then engaged in a brief session using motivational interviewing techniques and encouraged to consider risks associated with continued use. The control group received screening, information, and referral. At follow-up, there was no significant difference between the two groups in terms of substance use; however, the intervention was effective in educating participants on the negative impact of alcohol following TBI, and may have increased readiness to change.

A number of studies have also included firm recommendations regarding abstinence, at least for the 1st full year following injury. This recommendation alone may impact substance use following discharge from rehabilitation. Family education has been suggested as an integral part of substance use treatment for persons with TBI. In addition to receiving information regarding risks associated with continued substance use, families may support abstinence by encouraging lifestyle changes that are incompatible.
with substance use. For example, families can encourage activities and relationships that support abstinence, refuse to enable substance use, and require personal responsibility and accountability for behavior. Community supports such as Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) have also been suggested as helpful resources in providing education, social support, and promoting personal responsibility/accountability, although traditional programs do not always address the specific and unique issues that may be faced with those with TBI.

Pharmacological treatments of SUD in the TBI population have been recommended as an adjunct to traditional therapies, or when therapy alone has been unsuccessful.180 Naltrexone, acamprosate, and disulfiram (Antabuse) are United States Food and Drug Administration (FDA) approved medications for the treatment of alcohol use disorder. Naltrexone and acamprosate act to reduce alcohol cravings, whereas disulfiram operates via aversive counterconditioning. These medications should be initiated only after a period of abstinence of 7–10 days, and liver function tests are recommended with use of naltrexone. Naltrexone, methadone, and buprenorphine are FDA approved to treat opioid dependence. All three agents operate by reducing cravings.

### Caregiver Distress and Burden

Following community re-entry post-injury, family members become the de facto coordinators of care, assuming responsibility for patient adherence to complex self-care and medication regimens (e.g., medication management, activities of daily living, exercise, meeting appointments) in addition to the routine and rigors of family life (e.g., parenting, financial planning, meal preparation) and changes that may follow in the wake of a TBI (e.g., change in family roles, loss of income) without adequate professional support and intervention.178–180 Many caregivers feel overwhelmed and develop problems with stress, depression, anxiety, psychosomatic disorders, increased consumption of prescription and non-prescription drugs, financial difficulties, role changes, and poor social adjustment, with increasing social isolation that may require medical and mental health care services which they do not always receive.181,182 The evidence to date indicates that these issues are exacerbated over time when emotional and behavioral problems associated with psychiatric disorders and TBI persist.

A review of chronic family stress literature concluded that behavioral and emotional sequelae post-TBI impose greater stress on family members than injury severity or physical problems up to 15 years post-TBI.183 Heightened problems with depression, anxiety, behavioral and personality problems among individuals with TBI are directly associated with greater depression, anxiety, and burden among their family members. A study of caregivers, averaging 14 years post-injury, found behavioral disturbances are more likely to occur as the person with TBI becomes more distressed.197 Behavioral disturbances, in turn, were associated with greater caregiver burden.

We know families differ in their 1) personal and social resources, 2) perceived degree of distress imposed by an injury, 3) past medical and psychiatric histories, and 4) ability to cope with the changes they may encounter in everyday life. Consequently, families that maintain emotional bonds between family members and allow family members to adapt to changes in roles, relationships, and rules facilitate quality of life among persons with TBI over time.184 Individuals with TBI in families that report more abilities to communicate, solve problems, be emotionally responsive and involved, and have shared expectations for appropriate behavior exhibit less anxiety, anger, depression, inappropriate behavior, and psychosocial impairment than those in families lacking these abilities.185 These dynamics appear to be stable over time, with deleterious effects on the caregivers in the “unhealthy families.”186

Of particular concern is the emerging evidence concerning interpersonal aggression and violence that these families may experience in the post-acute period following TBI. We know that a significant minority of persons with TBI have recurring problems with agitation, irritability, impulse control, and emotional dysregulation soon after injury, and that these behaviors are often associated with overt verbal and physical aggression.187,188 Recent studies, literature reviews, and clinical commentary indicate that TBI is associated with a greater propensity for verbal and physical aggression.189–193 Unfortunately, in these scenarios, family members, particularly married partners, may experience physical abuse and aggression.193,194 The risk of physical abuse appears to be associated with increased alcohol and substance abuse.195

### Caregiver intervention

Brain injury rehabilitation programs routinely develop post-discharge plans for the patient and the designated caregiver. However, the long-term needs of the caregiver are not adequately addressed in progress updates or discharge planning sessions provided during the inpatient or outpatient rehabilitation program or in brief, infrequent outpatient visits with the patient’s care providers. Although several brain injury rehabilitation programs feature some degree of family training or counseling, there are no coordinated “programs of care” for family caregivers of persons with brain injury upon community re-entry following formal rehabilitation services. This situation exists in spite of the research evidence that caregivers who are distressed are more likely to develop severe problems with depression and ill health over the initial year of caregiving, and that families may need psychosocial and support services for many years following their injured loved-ones initial rehabilitation and outpatient service.182,196 The evidence is clear that “usual care” or “treatment as usual” is insufficient to prepare caregivers to cope with the problems they will face or to provide them with skills to resolve these issues following their return to community life.197

Recent work has demonstrated the feasibility and efficacy of extending psychoeducation and training to caregivers through in-home, telephone, or web-based conferencing.198–201 Randomized controlled trials using in-home and telephone-based problem solving training (PST) while implementing a predominant social problem solving model have been shown to be of low cost, and effective in decreasing caregiver depression.202 These effects have been observed among family caregivers of persons with stroke, spinal cord injury, and TBI, and there is also evidence that as caregivers benefit from PST, their care recipients experience less distress.199,203–205 The effects of PST for caregivers have been superior to those of educational programs (i.e., control group), and the effects have been observed over 3 months to 1 year later among community-residing caregivers. In a recent study of caregivers of persons with TBI varying in time since injury, Rivera and coworkers included a control group and a PST group.198 The control group received health-education materials that were sent to the participants in the mail, which were later reviewed over the telephone during structured telephone sessions. The experimental group received four in-home PST sessions over 1 year, with eight additional structured telephone sessions over the same time period. Outcome measures included self-report measures of depression, health complaints, well-being, caregiver burden, and social
problem-solving ability. Compared with participants in the control group, those individuals receiving PST experienced a decline in depression and health complaints by the 12th month of participation. These data suggest that families living with individuals with psychiatric disorder post-TBI may benefit from strategic, home and community-based interventions that address the immediate and pressing problems they identify.

Conclusions

Psychiatric disorder is common following TBI at all levels of injury severity. Neuroanatomical lesions may result in specific and persistent psychiatric, physical, personality and/or cognitive changes that can impact levels of participation in rehabilitation and functional independence in the community. Organic as well as psychological and psychosocial factors have been implicated in the development of psychiatric disorder following a TBI, particularly moderate to severe injury, and there is clear evidence that pre-morbid psychopathology and frontal lobe impairment may also have an influential role. Comorbid factors such as fatigue, sleep disturbance, pain, and degree of (and adjustment to) disability also come into play. Although substance use is a risk factor for sustaining a TBI, continued alcohol and other drug misuse after TBI has been associated with greater cortical atrophy, decreased life satisfaction, and poor functional outcomes, as well as chronic health conditions such as seizures and mood disorder.

Pharmacological treatments for psychiatric disorder post-TBI may help promote mood stability; however, a limitation is that most of the data on medication efficacy in patients with TBI and psychiatric disorder derive from case reports and series. Nonpharmacological treatments, such as CBT and cognitive rehabilitation, can aid in reducing the negative influence of mental distress and adjustment to disability. A multidisciplinary approach including comprehensive rehabilitation therapies (i.e., psychotherapy and cognitive rehabilitation) and pharmacological intervention may yield optimal benefit in the treatment of chronic psychiatric complications in patients with TBI. Further, interventional methods do exist and have been shown to be successful at reducing substance use disorders post-TBI. However, there are indications that such psychiatric and counseling services may be underutilized in this population, particularly those patients with depression or anxiety. Another important consideration is the impact of persistent psychiatric disease, particularly personality changes, executive dysfunction, and aggressive behaviors, can lead to increased caregiver burden and distress in the long term. Supportive psychoeducation and structured problem-solving interventions have been shown to reduce depression and stress, as well as increase development of necessary coping skills for the caregiver. Given that psychiatric symptoms are perceived as the most challenging for caregivers, effective treatments and interventions for both TBI patients and their caregivers is essential.

TBI can be viewed as a condition that is “disease causative and disease accelerative,” as it is well documented that TBI is associated with persistent cognitive and psychiatric symptoms. Recent estimates suggest that ~4,000,000 individuals in the United States experience a disability resulting from a TBI, with estimated direct and indirect annual costs surpassing $50 billion. The quality of life for those with TBI is poor compared with those without TBI on variables including physical health, emotional health, memory problems, and receiving welfare or disability payments. Patients with TBI and psychiatric disorders will require specific and long-term management of their symptoms, the costs of which are an ever-increasing economic toll on society. Ideally, services and programs that address these issues will promote the health and actual functioning of the individual for the long term in the community and in the home, and in this process, facilitate full participation in social and interpersonal roles in a manner commensurate with the World Health Organization model of disability. Increased participation in desired activities is a significant predictor of well-being and quality of life following TBI. Innovative community and home-based services that facilitate participation and quality of life may include use of long-distance, cost-effective technologies (e.g., telephone, videoconferencing) to treat issues such as depression and distress experienced by the patient and family caregivers. Similar applications may be used to promote self-management, health practices, and family functioning.

Acknowledgments

This work was funded by the generous support of the Moody Endowment.

Author Disclosure Statement

No competing financial interests exist.

References


Address correspondence to:
Dennis J. Zgaljardic, PhD, ABPP
Department of Neuropsychology
Transitional Learning Center
1528 Post Office Street
Galveston, TX 77550

E-mail: dzgaljardic@tlc–galveston.org
This article has been cited by: