Mood Disorders Following Traumatic Brain Injury

This article provides an update on mood disorders, including depressive disorder and anxiety disorders along with accompanying symptoms, following TBI.

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Mood disorders are among the most common consequences of traumatic brain injury (TBI). TBI is known to be associated with the development of a wide range of affective symptoms, with an annual prevalence range of 7% to 66%.[1] The presence of mood disorders after TBI can have profound consequences for rehabilitation outcomes and severely affect interpersonal, occupational, and social functioning.[2] Disability from these mood disorders can impair activities of daily living and overall quality of life, in addition to increasing the lifetime risk for suicide.[1-3]

The most common mood disorders after TBI are major depressive disorder and anxiety disorders, with prevalence ranges of 13% to 53% and 11% to 70%, respectively.[4-6] Prominent depressive symptomatology after TBI includes feelings of sadness, loss of interest, feelings of hopelessness, low self-worth, guilt, lethargy, lack of motivation, sleep disturbance, appetite changes, irritability, and suicidal thoughts. Because of dysregulation of frontotemporal circuits, depressive symptoms also may be accompanied by symptoms of agitation, aggression, and disinhibition.[7] Population studies have revealed that anxiety symptoms most commonly seen after TBI—particularly in those with comorbid body injury—include reexperiencing, hypervigilance, persistent worry, and autonomic arousal.[6,8] In contrast to depressive disorders, bipolar and related disorders are less frequent after TBI, with prevalence rates consistent with population prevalence of idiopathic bipolar disorder. Rates of up to 1% to 9% have been reported in some early TBI studies,[1,9] although it is probable (based on clinical experience and discussions with other TBI experts) that actual rates may be closer to 1% to 2%. Secondary mania also has been reported in individuals with closed head trauma, and such episodes are associated with posttraumatic seizures.[10] Whereas diagnosis of a mood disorder involves recognition of signs and symptoms presented in a clustered, episodic nature, the presence of substance use and delirium or encephalopathy must first be ruled out.[11]

Pathophysiology

In recent decades, it has been established that the pathophysiology of mood disorders after TBI involves an interplay of factors that (1) precede trauma (e.g., genetic loading, previous psychiatric history); (2) associate with trauma (e.g., severity of injury, location, mechanism, symptom duration, context of injury); and (3) follow trauma (e.g., psychosocial support, employment, resources available for recovery).[1,12,13] Current evidence also suggests that development of mood symptoms in the early TBI period is associated with disruption to neural networks, whereas psychosocial impairment may be associated with symptoms in the chronic phase of injury.[1] The most recent advances in TBI neuroimaging reveal that mood disorders (in particular depression) after TBI are associated with lower gray matter measures (volume, thickness, or density) and greater white matter damage. Specific regions of interest that have been implicated in the development of mood disorders can be found in Figure 1.[14] Poor pre-TBI psychosocial function, lower education, and female sex also have been established as risk factors for the development of mood symptoms after TBI.[15,16]

Assessment

When making a formal neuropsychiatric assessment in a person with TBI, it is important to consider life events the

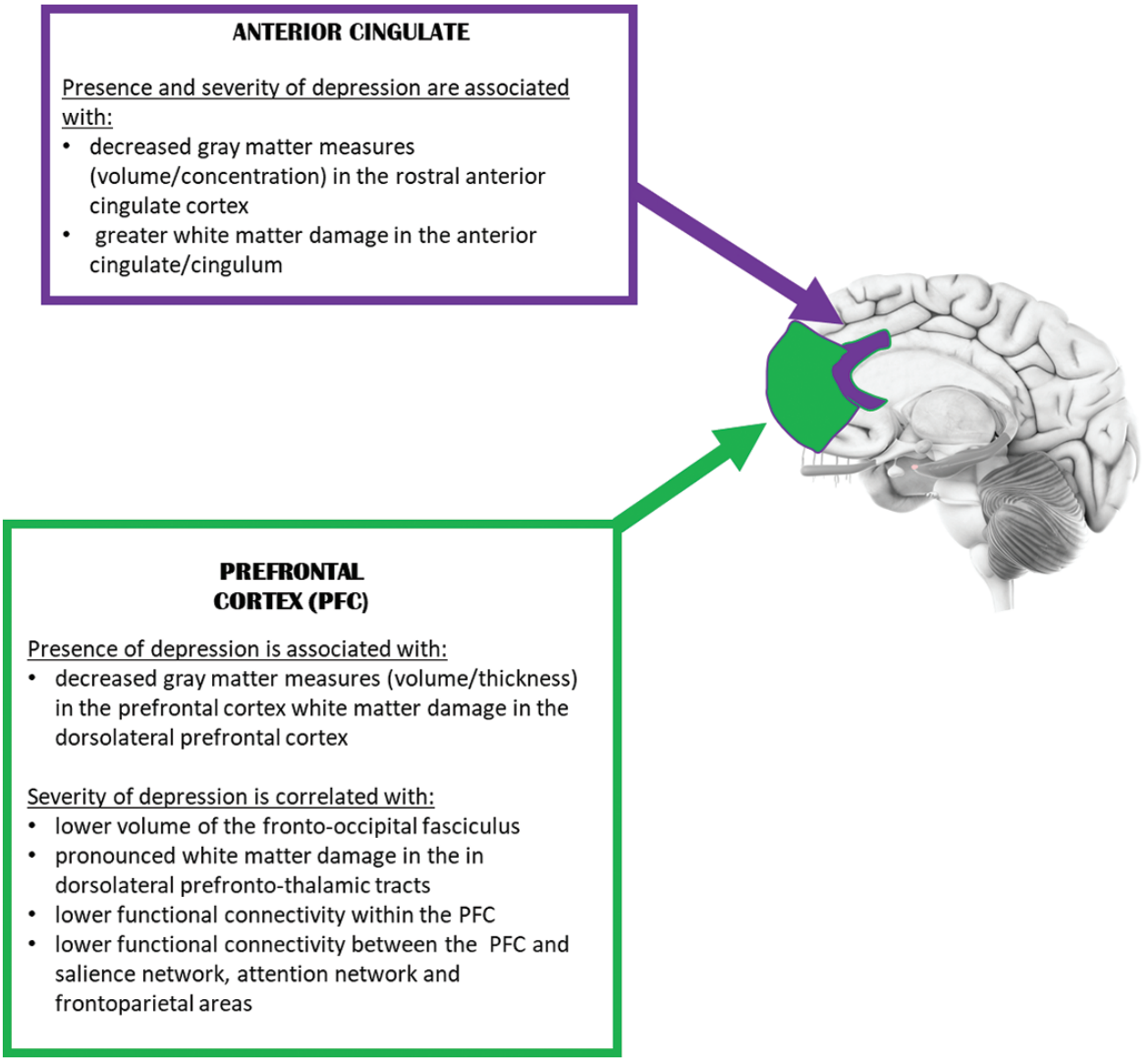

Figure 1. Regions of interest that have been implicated in the development of mood disorders.

individual has encountered, the individual's personality and temperament, the individual's behavior, and components of the brain disease process.[17] It is critical to consider medical comorbidities and perform a thorough exploration of how much symptomatology can be explained by TBI vs preinjury psychiatric illness. Including a broad differential diagnosis in determining syndrome and choosing the mostly likely diagnosis can facilitate a more focused treatment approach. A stepwise assessment includes (1) comprehensive psychiatric evaluation, (2) brief neurologic examination, (3) problem-focused medical workup, (4) ancillary studies to help establish diagnosis such as cognitive testing, (5) multipronged formulation, (6) multidisciplinary treatment, and (7) consultations and referrals.

Treatment

Pharmacologic Interventions

General guidelines for pharmacologic treatment of neuropsychiatric disturbances after TBI should include (1) choosing a medication, starting with a low dose and titrating slowly; (2) allowing for a therapeutic trial of all medications; (3) reassessing clinical condition throughout; (4) monitoring drug-drug interactions; (5) avoiding polypharmacy; and (6) considering coexisting medical problems. Avoidance of benzodiazepines and first-generation neuroleptics is important as these can impair neuronal growth.

Depression

Despite minimal progress in pharmacologic evidence in

Table 1. PHARMACOLOGIC AGENTS USED IN TREATMENT OF MOOD DISORDERS AFTER TBI

Disorder	First-line medications	Standard dosage (mg/d)	Cautions
Depression	Sertraline	50-150	In persons with vulnerability to experiencing mania and hypomania, it can potentiate a switch to these mood states.
	Citalopram	5-20	
Mania: acute	Quetipiane	25-300	Orthostasis, weight gain,metabolic syndrome
Mania: maintenance	Valproate	250-1500, in 2 divided doses	Can increase levels of other anticonvulsants (eg, lamotrigine and carbamezapine), thereby decreasing their clearance
PTSD	Sertraline	50-150	In persons with vulnerability to experiencing mania and hypomania, it can potentiate a switch to these mood states.

the past 10 years, the most robust evidence for treatment of depression after TBI involves therapy with selective serotonin reuptake inhibitors (SSRIs). Randomized controlled trials using SSRIs to treat depression after TBI generally have been designed with strong rigor and with sufficient numbers of participants compared with other treatment trials investigating other psychotropic drug classes. Sertraline and citalopram have showed the most evidence for improvement in depressive symptoms within a year after injury when compared with placebo.[18-20] Pharmacologic interventions using methylphenidate to target the dopaminergic deficits also have shown reduction in TBI depressive symptomatology and prove a viable alternative to SSRIs; however, an adjuvant role of stimulants alongside antidepressant use in TBI has not been an area of research focus.[21] Table 1 summarizes pharmacologic treatment interventions commonly used for treatment of depression after TBI.

Of the neuromodulatory interventions available for use in TBI, repetitive transcranial direct current stimulation has shown the most promise in reduction of TBI depressive symptoms.[22] Electroconvulsive therapy also has been proposed as a treatment option for people who do not respond to antidepressants, but studies in this area are limited.[22] Future studies focused on large-sample randomized controlled trials using head-to-head pharmacologic comparisons, neuromodulation, or combination treatment using augmentation strategies should incorporate premorbid psychosocial functioning, preinjury psychiatric disease, cognitive deficits, and functional recovery when examining outcomes.

Anxiety

Paroxetine and sertraline are the two most-studied SSRIs for treatment of anxiety after TBI, primarily in veterans with posttraumatic stress disorder.[23] SSRIs such as citalopram have a lower side effect burden and might be better tolerated than others in this class. Lithium, primarily used for treatment of idiopathic bipolar disorder, has been trialed in case reports of aggression in bipolar disorder but lacks evidence for use in bipolar mania or depression. Other mood-stabilizing agents (eg, valproic acid, lamotrigine, oxcarbazepine) and second-generation neuroleptics (eg, aripiprazole, lurasidone, olanzapine, ziprasidone, risperidone) may be useful in treatment, but the effects on cognition (eg, processing speed, alertness, and memory) with mood stabilizers and extrapyramidal symptoms as well as metabolic syndrome with neuroleptics must be considered.[1]

Nonpharmacologic Interventions

Apart from medications, other interventions such as psychotherapy, neurorehabilitation, and psychosocial rehabilitation are useful in the management of neuropsychiatric symptoms in the subacute phase of TBI. Psychotherapy typically involves supportive therapy, behavioral therapy, and cognitive-behavioral therapy, and engaging patients alongside family members and caregivers often bodes well for prognosis.[24] Neurorehabilitation includes cognitive rehabilitation and occupational, physical, and speech/language therapy. Combined, these therapies have strong evidence for improving processing speed, working memory, visual processing, and compensatory measures for memory loss.[25] Psychosocial rehabilitation can involve rehabilitation of vocation, education, and building social supports.[25]

Future Directions

Many mood disorders that develop after TBI do not improve despite pharmacologic and nonpharmacologic interventions. Alternative modalities of treatment including approaches in neuromodulation show promise. Resting-state functional MRI-guided neurostimulation may prove efficacious in more targeted interventions for people with treatment-resistant symptoms.[14] Physical therapy for vestibular dysfunction as well as therapeutic aerobic exercise have shown promise. Metabolic supplements and medical can-

nabis are other alternatives that are being explored.[25] Much is yet to be learned about aberrant pathways implicated in post-TBI mood disorders and how they differ from idiopathic psychiatric illness; more studies are needed urgently. ■

1. Jorge RE, Arciniegas DB. Mood disorders after TBI. *Psychiatr Clin North Am*. 2014;37(1):13-29.
2. Kalpakjian CZ, Lam CS, Toussaint LL, et al. Describing quality of life and psychosocial outcomes after traumatic brain injury. *Am J Phys Med Rehabil.* 2004;83(4):255-265.
3. Oquendo MA, Friedman JH, Grunebaum MF, et al. Suicidal behavior and mild traumatic brain injury in major depression. *J Nerv Ment Dis.* 2004;192(6):430-434.
4. Jorge RE. Mood disorders. *Handb Clin Neurol.* 2015;128:613-631. doi:10.1016/B978-0-444-63521-1.00038-8
5. Howlett JR, Nelson LD, Stein MB. Mental health consequences of traumatic brain injury. *Biol Psychiatry*. 2022;91(5):413-420.
6. Riggio S. Traumatic brain injury and its neurobehavioral sequelae. *Neurol Clin.* 2011;29(1):35-vii.
7. Arciniegas DB, Wortzel HS. Emotional and behavioral dyscontrol after traumatic brain injury. *Psychiatr Clin North Am.* 2014;37(1):31-53.
8. Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA.* 2007;298(18):2141-2148.
9. Robert S. Traumatic brain injury and mood disorders. *Ment Health Clin*. 2020;10(6):335-345.
10. Shukla S, Cook BL, Mukherjee S, Godwin C, Miller MG. Mania following head trauma. *Am J Psychiatry*. 1987;144(1):93-96.
11. Bajamundi-Plyler C, Hatfield R, Rosier JT, Roy D. A case study on the management of the behavioral sequelae of traumatic brain injury. *J Acad Consult Liaison Psychiatry.* 2022;63(4):316-323.
12. Roy D, Koliatsos V, Vaishnavi S, Han D, Rao V. Risk factors for new-onset depression after first-time traumatic brain injury. *Psychosomatics*. 2018;59(1):47-57.
13. Roy D, Ghosh A, Yan H, et al. Prevalence and correlates of depressive symptoms within 6 months after first-time mild traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* 2022;34(4):367-377.
14. Medeiros GC, Twose C, Weller A, et al. Neuroimaging correlates of depression after traumatic brain injury: a systematic review. *J Neurotrauma.* 2022;39(11-12):755-772.
15. Lavoie S, Sechrist S, Quach N, et al. Depression in men and women one year following traumatic brain injury (TBI): a TBI model systems study. *Front Psychol.* 2017;5:634.
16. Ouellet MC, Beaulieu-Bonneau S, Sirois MJ. Depression in the first year after traumatic brain injury. *J Neurotrauma.* 2018;35(14):1620-1629.
17. McHugh PR, Slavney PR. The Perspectives of Psychiatry. Baltimore, MD: Johns Hopkins University Press; 1998.
18. 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;90:733-740.
19. Fann JR, Bombardier CH, Temkin N, et al. Sertraline for major depression during the year following traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil*. 2017;32(5):332-342.
20. Rapoport MJ, Chan F, Lanctot K, Herrmann N, Feinstein A. An open-label study of citalopram for major depression following traumatic brain injury. *J Psychopharmacol.* 2008;22(8):860-864.
21. Lee H, Kim S-W, Kim J-M, Shin I-S, Yang S-J, Yoon J-S. Comparing effects of methylphenidate, sertraline and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. *Hum Psychopharmacol.* 2005;20(2):97-104.
22. Narapareddy BR, Narapareddy L, Lin A, et al. Treatment of depression after traumatic brain injury: a systematic review focused on pharmacological and neuromodulatory interventions. *Psychosomatics.* 2020;61(5):481-497.
23. McAllister TW. Psychopharmacological issues in the treatment of TBI and PTSD. *Clin Neuropsychol*. 2009;23(8):1338-1367.
24. Fann JR, Quinn DK, Hart T. Treatment of psychiatric problems after traumatic brain injury. *Biol Psychiatry*. 2022;91(5):508-521.
25. National Institutes of Health. Consensus development panel on rehabilitation of persons with traumatic brain injury. *JAMA*. 1999;282:974-983..

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