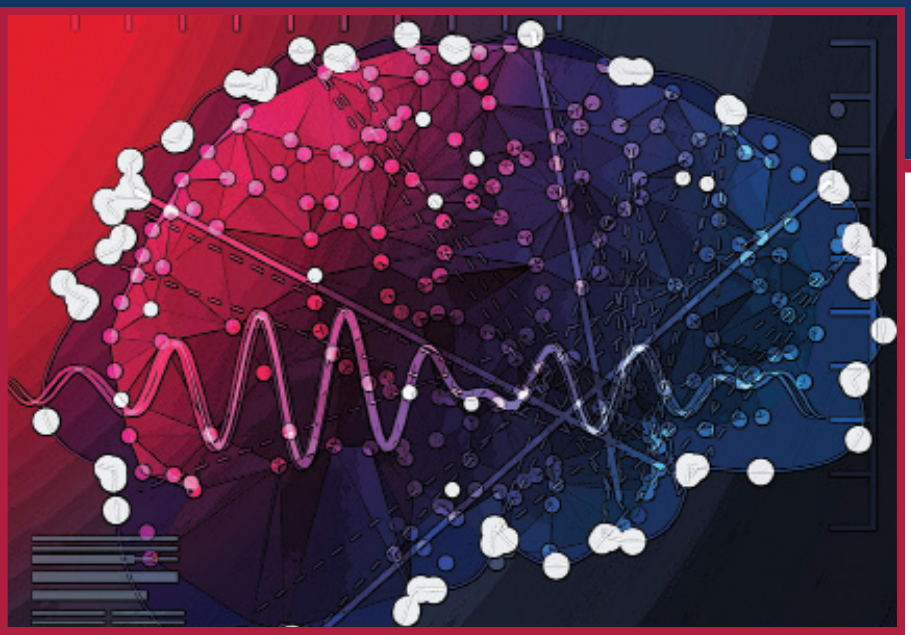
HOT Topics in Neuroscience

This ongoing column explores off-label or emerging treatment options, drug development trends, and theoretical concepts in the field of neuroscience.



Is Electroconvulsive Therapy a Treatment for Depression Following Traumatic Brain Injury?

ABSTRACT

Traumatic brain injury (TBI) can be caused by blunt or penetrating injury to the head. The pathophysiological evolution of TBI involves complex biochemical and genetic changes. Common sequelae of TBI include seizures and psychiatric disorders, particularly depression. In considering pharmacologic interventions for treating post-TBI depression, it is important to remember that TBI patients have a higher risk of seizures; therefore, the benefits of prescribing medications that lower the seizure threshold need to be weighed against the risk of seizures. When post-TBI depression is refractory to pharmacotherapy, electroconvulsive therapy (ECT) could provide an alternative therapeutic strategy. Data remain sparse on using ECT in this seizure-prone population, but three case reports demonstrated good outcomes. Currently, not enough evidence exists to provide clinical recommendations for using ECT for treating post-TBI depression, and more research is needed to generate guidelines on how best to treat depression in TBI patients. However, the preliminary data on using ECT in patients with TBI are promising. If proven safe, ECT could be a powerful tool to treat post-TBI depression.

KEYWORDS: Traumatic brain injury, TBI, mood disorders, depression, treatments, electroconvulsive therapy, ECT

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Traumatic brain injury (TBI) has a complex pathophysiology. The damage has great variability in the severity of injury and the neuroanatomical location. At the cellular level, the neurobiological response to TBI is divided into acute and chronic phases.[1]

Acutely, the mechanical forces from an injury can cause local depolarization, leading to glutamate excitotoxicity.[1,2] Locally compromised vasculature can also result in areas of ischemia. The resultant inability to remove waste products or deliver energy substrates causes dissolution of local ion gradients and tissue acidification by lactate buildup. Additionally, N-methyl-D-aspartate (NMDA)-dependent increases in intracellular calcium activate inflammatory and apoptotic pathways.[1] These biochemical processes play an important role in injury-associated cell death.

In the chronic phase of TBI, there is persistent inflammation with increased levels of proinflammatory cytokines in peripheral blood.[3,4] Astrocyte activation results in altered gene expression and astrogliosis. Cell death can continue for weeks to months after a TBI.[5] The mechanisms of neuroplasticity and tissue remodeling reinforce existing neuronal connections to maintain circuit function.[3,6]

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TBI-INDUCED DISORDERS

While the chronology of TBI has been established at a cellular level, it is difficult to interpret how such changes translate to the neurobehavioral and cognitive sequelae commonly reported after a TBI. In particular, people with TBI experience high rates of psychiatric disorders, including depression, anxiety, mania, irritability, aggression, panic or obsessive-compulsive tendencies, and drug abuse.[7,8] Depression has the highest prevalence in TBI-associated psychiatric impairment, with studies showing rates of 17 to 70 percent.[9-10] This wide range can be explained by the varying diagnostic criteria and amount of time elapsed since TBI. It has been shown that depression rates are highest during the first year following TBI and then decline,[10–12] though they remain elevated when compared to age-matched TBI-free controls.[10,12] Antidepressants are necessary for the treatment of depression in 11 to 44 percent of patients who are post-TBI.[10,11]

Up to 76 percent of patients with TBI also develop comorbid anxiety, and up to 54 percent suffer executive function impairments, such as aggression.[12] Preexisting depression, anxiety, and poor social functioning before a brain injury increase susceptibility for relapse or worsening of psychiatric symptoms after TBI.[7–12] However, rates of depression in patients with a TBI without a psychiatric history are still higher than in TBI-free matched controls.[11,12] Lower levels of education have also been linked to greater morbidity;[7–10] yet educational attainment does not always predict prognosis.[12]

While premorbid variables might predict mood disorders after a TBI, the anatomic severity and location of the injury are also contributing factors. Certain white matter tracts have been associated with TBI-related depression. For example, affective illness in patients following TBI has been linked to a reduction in microstructure of temporal and frontal white matter tracts when compared to those with TBI who did not develop a mood disorder.[10,13] The manifestations of TBI in persons with mood disorders follow established functional neuroanatomical relationships: damage to the left dorsolateral prefrontal cortex and left basal ganglia are associated with higher rates of post-TBI major depression, while right-sided hemispheric lesions are more often associated with anxious depression.[8] TBI severity is not correlated with risk for post-TBI depression,[10–11] suggesting that even minimal damage to the brain can precipitate psychiatric symptoms.

TABLE 1. Clinical data on post TBI depression and ECT therapy in three patients

TREATMENT CHARACTERISTICS	MARTINO[31]	RUEDRICH[32]	CROW[33]
Depression prior to TBI	Yes	Yes	Yes
Duration of depression	6.5 years (6 months before TBI, 6 years after TBI)	3 months	18 years
TBI etiology	Motor vehicle accident with closed head injury	Gunshot wound to the head	Gunshot wound to the head, 18 years prior
Therapies	Buproprion, fluoxetine, sertraline, citalopram, mirtazapine, imipramine, tranylcypromine, gabapentin, lamotrigine, olanzapine, lithium	Imipramine	Fluoxetine, amitriptyline, trazodone, lithium, haloperidol, despiramine, venlafaxine, levothyroxine, psychotherapy
Location and number of ECT treatments	12 bifrontal	17 bitemporal, brief pulse stimulation	8 right unilateral
Adverse events	None	None	None
Response	HAM-D score of 25 down to 7	Required further pharmacotherapy	BDI score of 20 down to 7
Duration of improvement	At 4 weeks, no mood symptoms	At 6 months, no relapse nor neurological deficits	Not described

TBI: traumatic brain injury; ECT: electroconvulsive therapy; HAM-D: Hamilton Rating Scale for Depression; BDI: Becks Depression Inventory

PHARMACOTHERAPY

When considering the treatment of mood disorders in patients with TBI, psychotropic drugs might have different effects in this population compared to those without TBI. Individuals with a history of TBI often have a low seizure threshold, resulting in a greater ictal risk.[14] Risks of medication-induced convulsions must be weighed against the potential psychiatric benefits of pharmacotherapy.

Evidence-based practice guidelines are lacking for treating patients with TBI-induced mood disorders. Sertraline and other selective serotonin reuptake inhibitors (SSRIs) appear to have the most documented evidence for improving mood and/or cognition.[7,8,15–18] In one study, 16 patients with post-TBI depression received an eight-week course of sertraline. The most common side effects were nausea, abdominal cramps, dizziness, and diarrhea; one subject dropped out as a result of side effects. In all participants, neurocognitive testing demonstrated significant improvement in sleep, emotional and social function, and ability to work. Other research substantiates these findings,[16] and sertraline has been documented to be effective in the treatment of depression in people with TBI.[8]

Recent research has assessed whether early sertraline therapy after TBI can prevent depression and improve TBI-associated cognitive impairments. Results do not indicate cognitive benefits in cases of TBI without depression, but do indicate that sertraline reduces the risk of post-TBI mood symptoms.[15,17] Cognitive impairments secondary to depression are unrelated to those resulting from TBI.

Other antidepressant drugs have been tested for the treatment of depression in

patients with TBI. Tricyclic antidepressants reportedly have less efficacy in relieving symptoms of post-TBI depression when compared to non-TBI depression and induce more unfavorable side effects. Prescribing the norepinephrine-dopamine reuptake inhibitor, bupropion, remains controversial because this medication decreases seizure thresholds; yet, a multicenter study did not reveal an increase in ictal events while utilizing this medication in patients following TBI. Despite pharmacotherapies for TBI-induced depression having been described,[8] more research is needed to identify those with the best efficacy.

ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is a powerful tool in the treatment of mood and psychotic disorders. It requires a short-term general anesthesia and paralysis prior to administering brief current pulses that induce a therapeutic convulsion.[18] Patients usually receive 6 to 12 treatments for full therapeutic benefit;[18,19] but the number of ECT applications is titrated individually for each case.

The precise mechanism underlying the efficacy of ECT remains unclear, but one theory is that it promotes neuroplasticity by optimizing or "resetting" existing brain networks.[20] Functional magnetic resonance imaging (MRI) research reveals symptom resolution correlating with changes in corticolimbic circuits following ECT; this supports the hypothesis of ECT-mediated neuroprotection and plasticity.[21] Similarly, certain functional brain networks are disrupted in patients with depression and normalize in those who experience a therapeutic response to ECT.[22]

ECT also induces neurogenesis and a release of trophic factors. An increase in the thickness of the gray matter of the cerebral cortex is documented in subjects with depression who have undergone ECT.[23] Animal studies have demonstrated neurogenesis in response to ECT in frontal limbic circuitry[24] and the hippocampus[25] and increases in expression of brain-derived neurotrophic factor[26] and vascular endothelial growth factor.[27] ECT also produces genetic and epigenetic changes.[28]

Current hypotheses regarding the mechanism of ECT 's actions in mood disorders include beneficial effects on various cellular and biochemical pathways.[29] However, it is notable that these proposed mechanisms of action have been based on studies limited to TBI-naïve animals and humans.

ECT FOR POST-TBI DEPRESSION

Since patients following a TBI have a reduced seizure threshold and a greater risk for developing post-traumatic epilepsy, there is some reluctance to apply ECT,[14] especially since it seems counterintuitive to induce convulsions for therapeutic advantage.[30] The stigma associated with ECT also diminishes the frequency of its application.

There is a dearth of information about the use of ECT in people with depression following TBI. There are no published investigations that demonstrate adverse effects of ECT in patients who are post-TBI; only three case reports document ECT use following a TBI, and each one describes amelioration of mood symptoms and neurocognitive improvement after ECT.[31–33] A 28-year-old man with TBI developed medication-resistant depression but experienced a good response to ECT.[31] He received it again for a relapse years later. At that time, neuropsychological testing documented that his cognitive performance did not deteriorate and even improved following ECT treatment. Similar clinical efficacy was evident following ECT treatment of depression in two individuals with gunshot-inflicted brain trauma.[32,33] These three clinical vignettes constitute the bulk of the current literature regarding ECT in treating patients with unipolar depression following a TBI. See Table 1 for a summary of the clinical circumstances in each case.

All three patients were diagnosed with major depression prior to their TBI, but mood symptoms significantly worsened after their injuries. Rates of post-TBI depression are higher in patients with a premorbid psychiatric history of an affective disorder.[7–12] However, those without depression prior to TBI still experience an increased risk of developing a post-TBI mood disorder during the first year following their brain injury.[11] There are no reports on ECT as treatment for new cases of depression following TBI.

There are reports of ECT's positive effects when used in patients with other organic neurological disorders, such as tumors or hydrocephalus, and these reports are sometimes referenced in support of ECT in the TBI population; however, such disorders are pathophysiologically distinct from TBI.[32] There is little data suggesting harm from utilizing ECT to treat persons with post-TBI mood disorders.

CONCLUSION

TBI is a distinct and complex pathophysiological entity. Neurocognitive deficits and mood disorders are common sequelae of TBI. While nonmodifiable factors influence risk of developing post-TBI depression, there is also evidence that biological factors are involved. People who have suffered TBI are at increased risk for ictal events and cognitive impairment. ECT has been documented to successfully treat patients with post-TBI mood symptoms in only three published cases. While these vignettes suggest that ECT might be a safe and effective therapeutic option in treating individuals with post-TBI depression, more research is needed to establish its safety and beneficial clinical outcomes among this patient population.

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