Drug Therapies for the Neurobehavioral Sequelae of Traumatic Brain Injury

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Traumatic brain injury (TBI) is one of the most common causes of morbidity and mortality, especially in young adults. Recognition and early accurate diagnosis of neurobehavioral TBI sequelae are important in reducing the severity of postinjury symptoms. Sequelae of TBI include cognitive impairments, personality changes, aggression, impulsivity, apathy, anxiety, depression, mania, and psychosis.

Patients often present with nonspecific complaints of headache or dizziness after a head injury. Additional history taking and comprehensive mental status testing frequently reveal symptoms of depression or memory dysfunction, and psychiatric consultation may be sought. Because the neuropathology of TBI is diffuse and affects many areas of the brain, a multiplicity of neurobehavioral symptoms is common after TBI. This makes study of the post-TBI population challenging and may be the reason for the relatively few studies about treating neurobehavioral symptoms after TBI.

Although the following classification breaks down the manifestations of TBI according to psychiatric symptom dimensions that have an intuitive correlation with specific psychiatric interventions, a typical patient may require intervention with multiple medications to treat symptoms in various dimensions. On the other hand, after reviewing the following reasonable treatment options, a knowledgeable physician may choose a medication that targets multiple neurobehavioral sequelae of TBI (Table). However, medical management represents only one facet of the treatment of TBI; optimal treatment often will also require cognitive rehabilitation, behavioral training, counseling, and other individualized therapeutic modalities.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Medication</th>
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</thead>
<tbody>
<tr>
<td>Impaired memory</td>
<td>Acetylcholines inhibitor</td>
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<tr>
<td>Decreased arousal, apathy, amotivation</td>
<td>Amantadine</td>
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<td>Impaired processing/distract</td>
<td>Stimulant</td>
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<tr>
<td>Condition</td>
<td>Treatment</td>
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<td>-----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
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<tr>
<td>Depression</td>
<td>SSRI, SNRI</td>
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<tr>
<td>Depression with anergia/apathy</td>
<td>Bupropion</td>
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<tr>
<td>Mania/hypomania (bipolar)</td>
<td>Valproate, carbamazepine, lamotrigine; avoid lithium</td>
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<tr>
<td>Mania/hypomania (bipolar)</td>
<td>Valproate, carbamazepine, lamotrigine; avoid lithium</td>
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<tr>
<td>Bipolar disorder with psychosis and aggression</td>
<td>Atypical antipsychotic</td>
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<tr>
<td>Anxiety</td>
<td>SSRI, SNRI, beenzodiazepine</td>
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<tr>
<td>Anxiety with aggression</td>
<td>Buspirone, SSRI</td>
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<tr>
<td>Anxiety with depression</td>
<td>SSRI, SNRI</td>
</tr>
<tr>
<td>Psychosis</td>
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</tr>
<tr>
<td>Aggression</td>
<td>β-Blocker, valproate, carbamazepine, lamotrigine, atypical antipsychotic, SSRI, buspirone</td>
</tr>
</tbody>
</table>

SNRI, serotonin-norepinephrine reuptake inhibitor.

**Cognitive dysfunction after TBI**

*Memory impairment*. Memory impairment is a common problem after TBI. The sensitivity of the hippocampus to physiological stress and the mesial temporal predisposition to injury caused by the sphenoidal bony protuberances probably play a role. Acetylcholinesterase inhibitors have demonstrated promising results in the treatment of memory dysfunction after TBI. Donepezil has been the most studied acetylcholinesterase inhibitor. Zhang and colleagues\(^1\) conducted a prospective, randomized controlled study of donepezil in brain-injured patients in which significant improvements were achieved during the treatment phases on both
memory and concentration measures. Several other nonrandomized studies have evaluated cognitive impairment secondary to TBI and the open-label use of donepezil. These studies also support the finding that donepezil improves overall memory and attention.

**Diminished alertness, apathy, and lack of motivation.** Diminished alertness, apathy, and lack of motivation are common symptoms after TBI, particularly after diffuse axonal injury and bifrontal lobe injury. Patients often will not seek treatment themselves; family members usually bring them in for evaluation because of a decline in function. Patients may even present as abulic.

Amantadine is a dopaminergic medication that has been studied as a treatment for patients with TBI. It was initially proposed as a treatment because the frontal lobes are rich in dopaminergic neurons. Therefore, maximizing dopamine function in patients with bifrontal injury may result in improved function.

A prospective, randomized controlled study, conducted by Meythaler and colleagues, investigated the use of amantadine in patients with TBI and concluded that amantadine therapy was associated with a consistent trend toward improved neurorecovery with functional outcome measures. Other studies have demonstrated that amantadine specifically improved alertness, initiation, and motivation in patients with TBI.

**Decreased processing speed and distractibility.** Impaired processing speed and inattention are common symptoms after TBI and are probably attributed to the disconnection effects of diffuse axonal injury. Several prospective, randomized controlled studies showed that treatment with methylphenidate improved processing speed and inattention in patients with TBI.

**Affective symptoms after TBI**

**Depression.** Depression is probably the most commonly encountered disorder after TBI and is most likely caused by disruption of multiple neurotransmitter homeostasis. SSRIs—specifically sertraline—have been studied for the treatment of depression after TBI and have been found to be effective.

Although there is a lack of studies specifically investigating treatment of depression after TBI with this class of medications, the dual serotonergic and noradrenergic agents venlafaxine and duloxetine are reasonable alternative choices.

Bupropion is another treatment option, especially in a patient with depression who has significant anergia or apathy. Because of the anticholinergic effects that further impair cognitive function and increase the risk of delirium, tricyclic antidepressants should be avoided in those patients with TBI in whom cognitive dysfunction or delirium is a concern.

**Bipolar symptoms.** Variants of pure unipolar mania, as well as the opposite extreme of rapid cycling-type bipolar symptoms, can be observed in patients with TBI. Some reports suggest that these novel bipolar symptoms may correlate with temporal pole injury. Treatment with mood-stabilizing antiepileptic drugs has been shown to be effective in such patients.

Of the antiepileptics, valproate and divalproex sodium have been studied the most and are reported to be effective in treating posttraumatic bipolar symptoms. Carbamazepine has also been reported to be effective in treating bipolar symptoms in patients with TBI.

Although not specifically investigated for use in patients with TBI who have bipolar symptoms, lamotrigine is another reasonable treatment option that has been used for managing behavioral symptoms in TBI. Atypical antipsychotics may be another treatment option, especially in patients who have bipolar disorder accompanied by psychotic features.

Lithium carbonate should be avoided in patients with TBI. It lowers the seizure threshold, has the potential for neurotoxicity, and has a low therapeutic index. Furthermore, the monitoring required in cognitively impaired patients contributes to nonadherence.

**Anxiety symptoms after TBI**

Anxiety syndromes, specifically acute stress disorder, posttraumatic stress disorder (PTSD), panic disorder, generalized anxiety disorder, and obsessive-compulsive disorder, have been reported after TBI. Anxiety symptoms may be attributed to trauma of the amygdala, which, like the hippocampus, is prone to injury because of its mesial temporal location.

Limited data exist regarding the effectiveness of psychopharmacological agents for the treatment of anxiety disorders in patients with TBI; however, case reports support the use of SSRIs and venlafaxine.

Benzodiazepines should generally be avoided in patients with TBI because of the potential for further cognitive dysfunction, as well as behavioral disinhibition. In some severe cases of anxiety, low doses of benzodiazepines may be necessary until SSRIs become therapeutic. When benzodiazepines are used in this population, benefit may be derived from the cautious dosing of agents with long half-lives (eg, clonazepam) rather than those with short half-lives (eg, alprazolam).
Buspirone is another reasonable treatment option, especially in patients with anxiety and aggression. Bryant and colleagues suggested that early treatment of acute stress disorder with cognitive-behavioral therapy might also prevent the development of PTSD.

**Psychotic symptoms after TBI**

Although the development of chronic psychotic symptoms, such as hallucinations and delusions, is a relatively infrequent result of TBI, these symptoms are not uncommonly observed in the acute phase after TBI. When present, these symptoms can be quite debilitating.

Prefrontal and/or temporal lobe injury is thought to cause these posttraumatic psychotic symptoms. Although no randomized controlled trials have examined the treatment of secondary psychosis in TBI, treatment with atypical antipsychotics, such as risperidone, olanzapine, quetiapine, and ziprasidone, is generally considered first-line.

It should be noted that clozapine substantially lowers the seizure threshold, which can be problematic in brain-injured patients. Clozapine also has anticholinergic properties that can further impair cognitive function in this population and may provoke delirium.

Treatment with typical antipsychotic medications that have primarily dopamine receptor-blocking properties may cause a functional decline in patients with TBI who already have diminished dopaminergic circuits as a result of frontal lobe injury. Therefore, atypical antipsychotic agents—which have fewer dopamine-blocking properties than the typical antipsychotics and greater serotonergic action—are generally preferred.

**Aggression and impulsivity after TBI**

Aggression and impulsivity are commonly encountered after brain trauma, especially in the acute/subacute period. Orbitofrontal injury is strongly correlated with impulsive aggression. Several treatment strategies have been proposed. Randomized controlled trials have demonstrated the effectiveness of β-blockers such as propranolol for the management of agitation and aggression in brain-injured patients.

Valproate has also been reported to be effective in the treatment of aggression in patients with TBI. Atypical antipsychotics, SSRIs, lamotrigine, and buspirone also have been used for managing posttraumatic aggression.

**Personality changes after TBI**

The famous case of Phineas Gage illustrates the personality changes commonly observed after TBI, specifically frontal lobe injury. One study found that a personality disorder developed in 23.3% of patients as a result of TBI. Appropriate treatment of these personality disorders would involve a referral for psychotherapy. Medications such as SSRIs or mood stabilizers can be used to target specific symptoms, including aggression and emotional instability.

**Future treatment of TBI**

Early treatment with neuroprotecting agents may prevent some of the secondary excitotoxic injuries that lead to the demise of neurons in the days after the initial brain injury. N-methyl-d-aspartic acid receptor antagonists, such as memantine, may have potential as neuroprotectants, as suggested by experimental studies.

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