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Pharmacological interventions for traumatic brain injury

Psychostimulants, antidepressants, and other agents may speed the recovery of patients suffering from the functional deficits that follow an insult to the brain.

ABSTRACT: Traumatic brain injury is common in North America and has dramatic and wide-ranging effects on survivors' quality of life. Those who survive traumatic brain injury may experience anxiety, agitation, memory impairments, and behavioral changes. When managing the immediate and long-term consequences of such injuries, clinicians have many pharmacological options, including psychostimulants, antidepressants, antiparkinsonian agents, and anticonvulsants. These and other agents can play a role in managing the neuropsychiatric, neurocognitive, and neurobehavioral sequelae of injury to the brain.

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Traumatic brain injury (TBI) is commonly defined as an insult to the brain from an external force that causes temporary or permanent impairment in functional, psychosocial, or physical abilities.[1] It is a significant cause of morbidity and mortality, and the leading cause of death and disability among young adults. Common causes of TBI include motor vehicle accidents, falls, sports injuries, and violence,[1] and it is recognized increasingly in war zone injury.[2] In the US, approximately 2 million people will sustain a TBI each year, one-quarter of whom will require hospitalization, leading to a conservative estimate of direct and indirect costs of $50 billion to $100 billion annually.[3] With advances in the management of head trauma, an increasing number of patients are surviving with residual neurological impairments. A National Institute of Health panel estimates that 2.5 to 6.5 million Americans currently live with TBI-related disabilities.[4]

The effective treatment of TBI requires input from multiple disciplines and professions starting at the time of injury and continuing through the rehabilitation phase. Despite the prevalence and cost of TBI-related disabilities there is a paucity of literature reviewing modern approaches to pharmacotherapy. There is, however, growing evidence that medications may speed recovery by enhancing some neurological functions without impacting others. Pharmacotherapy is increasingly being used in both the subacute (less than 1 month post-TBI) and chronic (more than 1 month post-TBI) phases.

Disabilities arising from TBI that have a direct impact on functioning and rehabilitative potential can be broadly classified into four main categories: decreased level of consciousness (LOC), and neuropsychiatric, neurocognitive, and neurobehavioral

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Table. Agents and indications to consider when managing sequelae of traumatic brain injury.

	Neuropsychiatric sequelae	Neurocognitive sequelae	Neurobehavioral sequelae	Decreased level of consciousness
Acute phase (< 1 month post-TBI)	selective serotonin reuptake inhibitors	methylphenidate (attention, processing speed, memory deficits)	amantadine (agitation, anxiety)	bromocriptine (vegetative state, akinetic mutism)
		amantadine (attention, concentration, alertness, mobility deficits)	selective serotonin reuptake inhibitors (anxiety)	methylphenidate (coma, minimally conscious state)
		donepezil (attention, memory deficits)		amantadine (minimally conscious state)
Chronic phase (> 1 month post-TBI)	selective serotonin reuptake inhibitors	methylphenidate (attention, memory deficits)	methylphenidate (agitation, impulsivity)	bromocriptine (vegetative state, akinetic mutism)
		modafinil (memory, motor, attention deficits)	amantadine (agitation, anxiety)	levodopa combined with carbidopa (vegetative state, coma)
	valproic acid	amantadine (attention, concentration, alertness deficits)	beta-blockers (agitation, aggression)	amantadine (minimally conscious state)
		bromocriptine (initiation, speech deficits)	selective serotonin reuptake inhibitors (anxiety, agitation)	amitriptyline (minimally conscious state)
		selective serotonin reuptake inhibitors (motor speed, recent memory deficits)	amitriptyline (agitation)	
		valproic acid (problem-solving, recent memory deficits)	bromocriptine (restlessness)	
			bupropion (restlessness)	
			valproic acid (agitation, impulsivity, restlessness)	
			antiandrogens (inappropriate sexual behavior)	

sequelae.[5-8] Decreased level of consciousness refers to a diverse range of clinical states including coma, vegetative states, akinetic mutism, and locked-in states. Neuropsychiatric symptoms may present as mood disorders, posttraumatic stress disorder, and personality changes characterized by disinhibition and egocentricity. Neurocognitive injuries vary, but most frequently involve impaired attention, memory, and executive functioning. Neurobehavioral deficits distinct from neuropsychiatric sequelae may take the form of irritability, hyperexcitability, nervousness, disinhibition, poor impulse control, restlessness, and aggression, with aggression and agitation seen in as many as 30% of brain-injured patients.[5-8]

Depending on the location of injury, damage can occur to a variety of neurotransmitter networks critical to cognitive processes. Investigation has focused on the loss of dopaminergic neurons that regulate executive functioning, as well as deficits in norepinephrine and acetylcholine, which limit attention—a critical function for effective rehabilitation.[9] Fortunately, a number of pharmacological interventions show promise in helping patients cope with these losses and deficits.

Although insufficient evidence exists to establish guidelines for optimal pharmocotherapy, medications may be used to support recovery. Examples are shown in the accompanying **Table**, which summarizes the pharmacological approaches discussed in more detail below. When problematic TBI symptoms are identified, clinicians can use this information to determine pharmacological options and integrate them with non-pharmacological options such as physical therapy, occupational therapy, physiatry, and the patient's support network.

Planning a pharmacological intervention strategy

The decision to use pharmacological intervention should be the result of multidisciplinary collaboration and made with the patient or his or her substitute decision maker. Goals of therapy should be clarified, and outcomes and adverse events should be reliably tracked, particularly so medications that are ineffective or cause adverse events can be discontinued and unnecessary polypharmacy can be avoided. Selecting the most appropriate agent requires careful analysis of the neurological disabilities present, the nature of the underlying lesion, and the time elapsed since the injury.

Psychostimulants

Psychostimulants such as methylphenidate are most commonly used to treat attention deficit hyperactivity disorder (ADHD), a condition that involves problems with executive functioning and can be characterized as similar to brain injury both in terms of symptoms and neurotransmitter aberrations.[10]

Although the complete mechanism of action of methylphenidate remains unknown, this agent is thought to bind dopamine transporters, thereby blocking reuptake and increasing extracellular dopamine levels, particularly in the frontal cortex.[11] It is also thought to increase norepinephrine and serotonin levels. In the majority of studies, methylphenidate has been administered twice daily, either at a fixed dose of 10 to 15 mg or at a dose of 0.3 mg/kg.[12-15]

In the acute phase after a TBI, methylphenidate-treated patients demonstrated better attention, concentration, and performance on motor memory tasks at 1 month, but these benefits did not persist at 3 months. Thus, it has been suggested that while methylphenidate may shorten recovery time, it does not change morbidity.[12]

In the chronic phase after a TBI, patients have reported improvements in mood, work performance, and alertness, with more limited evidence suggesting an improvement of fluency and selective attention. The impact of methylphenidate on chronic attention is more ambiguous: one study suggests improvement in long-term processing speed and attention to tasks but not increased sustained attention or decreased susceptibility to distraction.[12] Two separate studies have suggested methylphenidate is effective in the treatment of agitation and seizures,[16,17] while another demonstrated no neurobehavioral benefit.[18]

Despite the accumulation of controlled clinical trials, there is no consensus on the use of stimulants in treating TBI-induced impairments in arousal and motor activity. It should be noted that one recent review concluded "at present there is insufficient evidence to support routine use of methylphenidate or other amphetamines to promote recovery from TBI,"[19] while another review noted that at least 10 clinical trials have demonstrated a role for methylphenidate in both adult and pediatric brain injury patients suffering from neurocognitive deficits, particularly in attention, memory, cognitive processing, and speech.[20]

Methylphenidate has a quick onset of action and relatively benign side effect profile, and we believe it to be useful in both the acute and chronic phase of TBI.

Antidepressants

Despite potentially severe consequences, post-TBI psychiatric sequelae are underdiagnosed and undertreated. Fortunately, current evidence suggests that antidepressants can be used to manage both neuropsychiatric and additional neurological deficits persisting from brain injury.

Selective serotonin reuptake inhibitors (SSRIs) have been found useful in treating behavioral syndromes in TBI patients, particularly in the subacute stages of recovery[21] but also in chronic settings. The majority of studies suggest that SSRIs improve neurobehavioral, neurocognitive, and neuropsychiatric deficits, specifically agitation, depression, psychomotor retardation, and recent memory loss; however, most data originates from nonrandomized trials.

Sertraline administered at an average dose of 100 mg daily for 8 weeks has been found to be beneficial for agitation, depressed mood, and deficits in psychomotor speed and recent memory; shorter treatment durations have demonstrated no benefit.[21]

Similarly, 60 mg daily of fluoxetine for 3 months was shown to be effective in the treatment of obsessive-compulsive disorder caused by brain injury.[22] Finally, paroxetine or citalopram, at a dose of 10 to 40 mg daily, was shown by another study to be equally effective in the treatment of pathological crying.[23] None of the reviewed studies addressed neurocognitive deficits.

The highest concentration of serotonergic and adrenergic fibres is located near the frontal lobes, the most common site of traumatic contusion.[24] Consequently, these fibres are commonly injured in TBI, suggesting that newer antidepressants with effects on both norepinephrine and serotonin, such as mirtazapine and venlafaxine, may also be effective in the treatment of TBI sequelae; however, clinical data with these agents in TBI is lacking. Similarly, bupropion increases both dopamine and norepinephrine levels and is a weak inhibitor of serotonin reuptake. At 150 mg daily, this agent has been useful in treating restlessness.[25]

Antiparkinsonian drugs

The antiparkinsonian drugs amantadine, bromocriptine, and levodopa combined with carbidopa (e.g., Sinemet) have varied mechanisms of action, but all ultimately serve to increase dopamine levels in the brain.

Amantadine acts presynaptically to enhance dopamine release or inhibit its reuptake, and can act postsynaptically to increase the number, or alter the configuration of, dopamine receptors.[26] It is also a noncompetitive NMDA receptor antagonist and may provide protection against possible glutamate-mediated excitotoxicity in the context of TBI.[27] Bromocriptine is a dopamine receptor agonist affecting primarily D2 receptors and to a lesser extent D1 receptors.[28] The use of levodopa and carbidopa in combination directly increases dopamine levels: levodopa becomes dopamine once decarboxylated, while carbidopa inhibits L-amino decarboxylase, allowing levodopa to reach the central nervous system.[28]

Multiple studies of amantadine at a dose of 100 to 300 mg daily have suggested its effectiveness in both the acute and chronic care phases after TBI, particularly in diffuse, frontal, or right-sided brain injury. Currently, the evidence suggests neurocognitive or neurobehavioral deficits, particularly cognition difficulties and agitation, are primary indications for amantadine use.[26,29,30] Amantadine-treated patients demonstrated improvements in motivation; decreased level of apathy; increased attention, concentration, and alertness; improved executive functioning; decreased processing time; reduced agitation, distractibility, fatigue, aggression, and anxiety. In addition, patients treated with amantadine demonstrated changes in outcome LOC, specifically improved arousal and LOC as measured by the Glasgow Coma Scale. Interestingly, one study also suggested decreased mortality.[31] To date, no study has shown an improvement in memory.

Three case reports using 5 to 45 mg of bromocriptine daily,[32] and one study using a combination of 100 mg of bromocriptine with 100 mg of ephedrine,[33] showed improvement in akinetic mutism, while another study using 5 mg of bromocriptine combined with sensory stimulation led to improvements in patients with vegetative or minimal consciousness.[34]

The evidence is similarly limited for levidopa and carbidopa medications where nonrandomized studies suggest that they might be useful in the chronic phase of TBI with diffuse injury and persistent vegetative state.[35]

Combining agents has also been tried in one study that found improvements in neuropsychiatric deficits with the daily administration of 25 mg/200 mg of levodopa/carbidopa three times daily, 250 mg of amantadine, and 5 mg of bromocriptine twice daily.[36]

Anticonvulsants

Anticonvulsants have been used with varying results for treating symptoms of TBI. Valproic acid, for example, enhances inhibitory control mediated by the neurotransmitter GABA, thereby promoting general central nervous system stabilization, but findings thus far have been mixed. Investigations utilizing 600 to 2250 mg of valproic acid daily (resulting in serum levels of 40 to 100 μg/mL), have demonstrated positive neurocognitive effects, including improved recent memory and problem-solving, as well as ameliorating neuropsychiatric and neurobehavioral symptoms such as depression, mania, destructive and aggressive behavior, restlessness, disinhibition, impulsivity, lability, and alertness.[37-41] Conversely, one controlled trial found valproic acid negatively impacted decision-making speed, and another suggested an increased mortality rate with valproic acid use.[37-41]

Other agents

Modafinil is a vigilance-promoting drug commonly used to treat narcolepsy and idiopathic hypersomnia, illnesses that can present with symptoms similar to those seen in TBI: excessive daytime sleepiness, inattention, and decreased ability to perform social activities. The precise mechanism of action remains unknown, although it is believed that modafinil can inhibit GABA or increase glutamate levels in the nondopaminergic anterior hypothalamus, hippocampus, and amygdale.[42,43] Two studies that investigated the role of modafinil in chronic TBI showed an improvement in neurocognitive deficits, specifically memory and attention, as well as improving daytime somnolence at doses between 100 and 400 mg.[44,45]

Four randomized control trials examining the use of beta-blockers, specifically propranolol and pindolol, have demonstrated beneficial effects on neurobehavioral symptoms of aggression and agitation in both the chronic and subacute phase. This class of drugs deserves further attention for the management of both neuropsychiatric and neurobehavioral sequelae of TBI.[46]

Neuroleptics are being used increasingly in the setting of delirium, and one might consider using them in an attempt to allow the brain to recalibrate neurotransmitter levels. However, it should be noted that there is some evidence that dopamine blockade may negatively affect recovery.[47,48] There are also a number of animal studies examining drugs that have the potential to adversely affect brain recovery following TBI. These studies typically use a stroke model, so generalizing to TBI may not be possible.

Nevertheless, the evidence currently does not support the use of neuroleptics, benzodiazepines, phenytoin, prazosin, trazodone, and similar agents because of their potential adverse effect on recovery, presumably through the impacts they have on neurotransmitters such as dopamine, norepinephrine, or GABA.[49-51]

Preliminary evidence suggests cholinesterase inhibitors such as donepezil may improve long-term cognitive outcomes, particularly in domains such as memory and attention when administered early, and further investigation with these agents is also warranted.[52,53]

Finally, antiandrogenic medications, such as estrogen and medroxyprogesterone, may have a role to play in reducing inappropriate sexual behavior in patients with TBI. In a case study and one small trial, these drugs demonstrated effectiveness.[54]

Summary

The nature of TBI sequelae, whether psychiatric, cognitive, or behavioral, is poorly understood. Likewise, the use of pharmacological interventions to improve symptoms, function, and outcome is still under development. There are, however, a number of agents that inspire optimism. When treating neurological deficits medically, there is evidence to support the tailored use of these agents for particular TBI clinical scenarios. The timing and nature of symptoms, along with whether agents are administered in the acute or chronic phase after TBI, are all relevant factors for determining proper use.

With insufficient evidence to establish guidelines for optimal treatment, care must be taken when choosing pharmacological interventions for TBI. If the decision is made to use medications to promote TBI recovery or treat its attendant disabilities, clinicians should thoroughly document the goals of pharmacotherapy and closely monitor for side effects. Future studies will undoubtedly add to the clinician's armamentarium for the care of TBI patients.

Competing interests

None declared.

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