Current PSYCHIATRY

Traumatic brain injury: Pharmacotherapy options for cognitive deficits

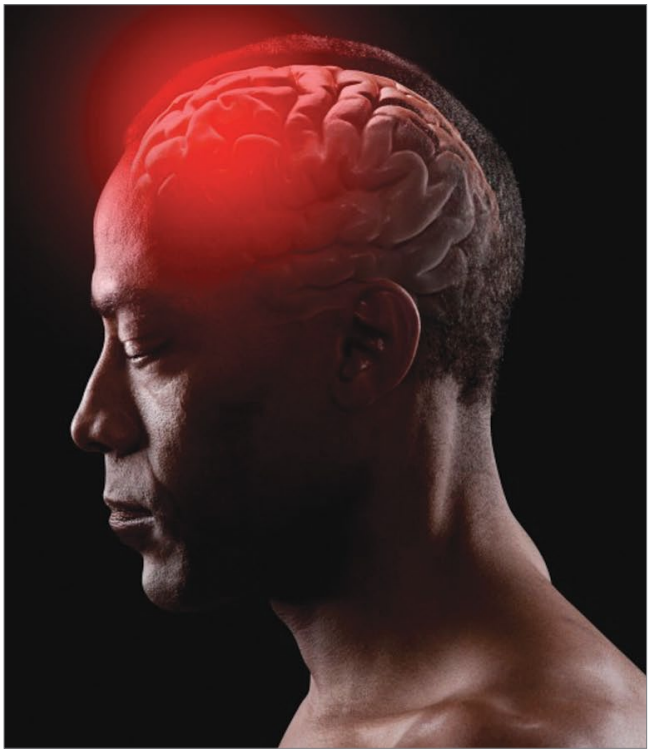
Different medication classes improve different areas of cognitive function

Mr. A, age 45, presents to the psychiatry clinic complaining of "ADHD." He says he is not able to sit through movies and often gets distracted while on his computer at work. He also is having problems in his relationship with his wife; she says having a conversation with him is difficult. He has seen a psychiatrist for depression, which is currently managed by his primary care physician (PCP), who prescribed sertraline, 100 mg/d. Mr. A feels that although his depression is now under control, the medication has had limited effect on improving his concentration.

With further discussion, Mr. A reveals that 6 months ago he was involved in a car accident and suffered a mild traumatic brain injury (TBI). He was hospitalized overnight and was encouraged to follow up with his PCP. During his only follow-up visit, Mr. A told his PCP that he was having difficulty concentrating since the accident. However, because Mr. A has a remote history of alcohol abuse, his physician was reluctant to give him additional medication and referred him to a psychiatrist.

TBI is increasingly common but often overlooked or not treated in the emergency room (ER). Each year at least 1.7 million people experience a TBI; 275,000 are hospitalized and 52,000 die.[1] The true incidence likely is greater because patients who do not present to the ER or hospital are not included in most studies, and the often-subtle psychiatric sequelae may preclude patients from seeking mental health treatment.

Psychiatric disorders are common among those who sustain a TBI (***Table 1, page 22***).[2] One prospective cohort



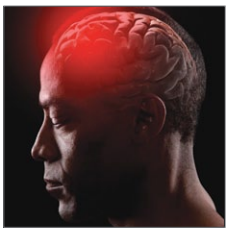
Lorin M. Scher, MD
Assistant Clinical Professor
Department of Psychiatry and Behavioral Sciences

Eleanor Loomis, BA
Medical Student (MS-4)

Robert M. McCarron, DO
Training Director
Internal Medicine/Psychiatry Residency
Department of Psychiatry and Behavioral Sciences
Department of Internal Medicine

• • • •

University of California, Davis
Sacramento, CA



TBI and cognitive deficits

Clinical Point

The Mini-Mental State Exam is not adequate to screen for subtle cognitive deficits in TBI patients

Table 1

Psychiatric symptoms: Common among TBI patients

Psychiatric symptom	Incidence
Aggression	30%
Anxiety	10% to 70%
Apathy	10%
Cognitive impairment	25% to 70%
Depression	25% to 50%
Mania	1% to 10%
Psychosis	3% to 8%

TBI: traumatic brain injury

Source: Adapted from reference 2

study found that patients with mild TBI are 2.8 times more likely than other patients to develop a psychiatric disorder.[3] Statistics regarding TBI and psychiatric illness often are limited because they rely on self-reports, chart review, or retrospective studies.[4]

TBI severity can be classified on the basis of Glasgow Coma Scale score and other factors (***Table 2***).[5] The correlation between severity of injury and resulting psychiatric illness or post-concussive symptoms is unclear.[6] There is evidence that cognitive defects are associated with decreased function. Cognitive dysfunction also has been associated with disability 10 years after moderate to severe TBI.[7] The association between cognitive dysfunction and outcome is more strongly correlated with moderate to severe TBI; there is no clear association in mild TBI.[7] Additionally, compared with patients with severe TBI, those with mild TBI were more likely to be employed. At all severity levels, function improves over time. Mild, moderate, and severe TBI have a similar recovery curve.[7]

Cognitive dysfunction and TBI

Cognitive dysfunction can be split into 3 categories:

- executive function
- memory
- processing speed.

The incidence of cognitive dysfunction after TBI is unclear. Several methods are used to quantify cognitive dysfunction in TBI patients; it is widely regarded that the Mini-Mental State Exam is not adequate to screen for subtle cognitive deficits.[6] However, there is no clear consensus on which tool should be used.[5]

Off-label pharmacotherapy

There are no FDA-approved medications for treating neuropsychiatric sequelae of TBI. Treatment should be symptom-based and employ the "start low, go slow" approach. Compared with patients without brain injury, TBI patients may experience increased adverse effects from psychotropics but may require standard doses. These patients also may have comorbidities such as seizure disorders, substance abuse, and depression that will affect treatment.[2] Different areas of cognitive function respond to different medication classes. Suggested medications include stimulant and nonstimulant catecholaminergic agents and cholinesterase inhibitors (***Table 3, page 33***).[8]

Executive function responds to nonstimulant catecholaminergics. In a review, Writer and Schillerstrom[5] found that TBI patients who received catecholaminergic augmentation showed improved function in 6 of 7 studies. In 2 randomized controlled trials (RCTs) and 4 nonrandomized, placebo-controlled trials, patients with mild to severe TBI showed improved executive function, attention, global cognitive function, memory, language, and/or arousal with use of bromocriptine, pramipexole, carbidopa/levodopa, or amantadine.[5] The greatest improvements were found in executive function. In 1 RCT, 10 patients with mild to severe TBI showed no functional improvement after 2 weeks of treatment.

Amantadine, 200 to 400 mg/d, has been shown to safely improve arousal and cognitive function in patients with moderate to severe TBI when started 3 days to 5 months after injury.[9] Amantadine, 400 mg/d, also improves executive function measures without significant benefit in attention or memory in patients with mild to severe TBI 6 months post-injury.[10]

Table 2

Classifying severity of traumatic brain injury

Severity	GCS score	LOC duration	PTA*
Mild	13 to 15	<30 minutes	<1 hour
Moderate	9 to 12	1 to 24 hours	1 to 24 hours
Severe	<8	>24 hours	>24 hours

*Includes loss of memory immediately before or after the accident

GCS: Glasgow Coma Scale; LOC: loss of consciousness; PTA: posttraumatic amnesia

Source: Reference 5

Memory responds to cholinesterase inhibitors. Memory deficits secondary to TBI affect immediate and delayed memory. The cholinesterase inhibitor donepezil is approved for treating Alzheimer's disease (AD) in the United States and Canada, and research suggests memory deficits after TBI may be similar to those seen in AD.[11] This includes deficits in long-term memory storage, which likely is associated with the cholinergic system.[11] Post-mortem studies have found similarities in traumatically injured brains and those of AD patients.[11]

Three small prospective studies of donepezil have shown improved memory and attention in TBI patients when cognition is the primary outcome, with 1 small negative open-label trial.[7] In a study of 53 patients, Whelan et al[12] found that donepezil improved patients' intelligence quotient and clinician-based assessment of cognition over 2 years. Taverni et al[13] found memory improvement in 2 TBI patients within 3 weeks of starting donepezil. These results suggest that donepezil may be used in acute and late phases of memory deficits following mild, moderate, or severe TBI.[6] All studies titrated donepezil from 5 to 10 mg/d over several weeks. Dosing guidelines for donepezil in AD suggest 5 mg/d for 4 to 6 weeks, which may be increased to 10 mg/d if needed.[8]

Rivastigmine (3 to 6 mg/d) has been shown to be effective in mild TBI when started 1 year after injury and safe for 12 to 38 weeks of treatment.[14,15] One retrospective cohort study of 111 patients with chronic TBI found no difference among donepezil, rivastigmine, or galantamine, with mean doses of 7.2 mg/d, 10 mg/d, and 2.3 mg/d, respectively.[16] Sixty-one percent of patients showed improvement and the remainder had modest or no response. This study suggests that positive response on cognition may be similar among cholinesterase inhibitors. In case reports, physostigmine has offered some benefit[17,18]; however, cardiovascular and autonomic side effects restrict its use.[11] Tacrine is associated with problematic gastrointestinal and hepatic side effects.[11]

Processing speed responds to stimulant catecholaminergics. Although the incidence of psychiatric illness is not correlated with TBI severity, evidence suggests that speed of processing mediates the relationship between injury severity and functional decline.[19] Therefore, aggressively treating these deficits may help improve function.

Methylphenidate improves attention and processing speed after TBI. A review of 7 randomized trials and 2 nonrandomized trials indicated that patients with mild to severe, chronic TBI experienced significantly improved cognitive function after methylphenidate treatment.[5] Willmott and Ponsford[20] found significant enhancement in information processing speed within 2 weeks of methylphenidate treatment in 40 patients with moderate or severe TBI. Methylphenidate increased the rate of recovery and led to improvement in acute[21] and post-acute phases.[22] In addition, methylphenidate may improve processing speed even in the absence of significant changes in attention.[23]

The standard methylphenidate dose used in most studies, 0.3 mg/kg twice daily, is safe and effective. Dosing usually is started at 5 mg/d and titrated to symptomatic relief. Because methylphenidate

continued on page 33

Clinical Point

Catecholaminergics improved TBI patients' cognitive function in 2 randomized and 4 nonrandomized trials

continued from page 23

Table 3

Recommended treatments for mild TBI-related cognitive deficits

Deficit	First-line medication	Side effects	Contraindications	Other treatments
Memory	Donepezil (5 to 10 mg/d)	Diarrhea, nausea, vomiting, muscle cramps, fatigue, anorexia	Hypersensitivity to donepezil or piperidine derivatives	Rivastigmine, galantamine, physostigmine, CDP-choline
Speed of processing	Methylphenidate (0.3 mg/kg twice daily)	Headache, insomnia, decreased appetite, nausea, vomiting, anxiety, irritability	Hypersensitivity to methylphenidate, glaucoma, history of Tourette syndrome or tics, use of MAOI within 14 days	Dextroamphetamine
Executive function	Amantadine (200 to 400 mg/d)	CNS depression, orthostatic hypotension, peripheral edema, agitation, nausea, anorexia	Hypersensitivity to amantadine	Bromocriptine, pramipexole, carbidopa/levodopa

CDP-choline: cytidinediphosphocholine; MAOI: monoamine oxidase inhibitor

Source: Reference 8

does not lower the seizure threshold, it is safe for patients at high risk for seizure.[24] Methylphenidate also significantly improves attention and speed of processing in pediatric head trauma.[25,26]

Dextroamphetamine also is used to treat speed of processing dysfunction after TBI, but is less studied than methylphenidate. Dextroamphetamine, 5 to 30 mg/d, was found to effectively treat attention problems that interfered with rehabilitation in patients with severe TBI.[27]

Nonpharmacologic treatments

In addition to pharmacotherapy, nonpharmacologic interventions also should be a mainstay of treatment. Compensatory training and cognitive exercise may improve patients' cognitive deficits and return some sense of control. Individual and family psychotherapy, including cognitive-behavioral therapy, also may be beneficial.[2] Review sources have identified the importance of validating patients' symptoms and developing a goal-based treatment plan.[6]

CASE CONTINUED

Improvement with stimulants

Unlike many TBI patients who do not recognize the often-subtle psychiatric sequelae of their injury, Mr. A is aware of his difficulty concentrating, which is temporally linked with his accident. After exploring the association between Mr. A's symptoms and his injury, his psychiatrist concludes that Mr. A's cognitive deficits likely are associated with his TBI. Mr. A's history of alcohol abuse raises concerns about prescribing stimulants. However, after assuring that Mr. A's depression is well controlled and addressing his risk of substance abuse, his psychiatrist prescribes methylphenidate titrated to 30 mg/d. When he returns to the clinic several weeks later, Mr. A reports improved attention and functioning at work, and continues to follow up with the psychiatrist without requiring changes to his medication regimen.

Clinical Point

Memory deficits after TBI may be similar to those seen in Alzheimer's disease

References

1. Faul M, Xu L, Wald MM, et al. Traumatic brain injury in the United States; emergency department visits, hospitalizations, and deaths, 2002-2006. Atlanta, GA: Centers for Disease Control and Prevention; 2010. Available at: http://www.cdc.gov/traumaticbraininjury/tbi_ed.html. Accessed December 1, 2010.
2. Vaishnavi S, Rao V, Fann JR. Neuropsychiatric problems after traumatic brain injury: unraveling the silent epidemic. Psychosomatics. 2009;50(3):198-205.
3. Fann JR, Burington B, Leonetti A, et al. Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. Arch Gen Psychiatry. 2004;61(1):53-61.
4. Bryant RA, O'Donnell ML, Creamer M, et al. The psychiatric sequelae of traumatic injury. Am J Psychiatry. 2010;167(3):312-320.
5. Writer BW, Schillerstrom JE. Psychopharmacological treatment for cognitive impairment in survivors of traumatic brain injury: a critical review. J Neuropsychiatry Clin Neurosci. 2009;21(4):362-370.

continued on page 37

continued from page 33

6. Arciniegas DB, Anderson CA, Topkoff J, et al. Mild traumatic brain injury: a neuropsychiatric approach to diagnosis, evaluation, and treatment. Neuropsychiatr Dis Treat. 2005;1(4):311-327.
7. Sigurdardottir S, Andelic N, Roe C, et al. Cognitive recovery and predictors of functional outcome 1 year after traumatic brain injury. J Int Neuropsychol Soc. 2009;15(5):740-750.
8. Physicians' desk reference. 64th ed. Montvale, NJ: Thomson Reuters; 2010.
9. Sawyer E Mauro LS, Ohlinger MJ. Amantadine enhancement of arousal and cognition after traumatic brain injury. Ann Pharmacother. 2008;42(2):247-252.
10. Kraus MF, Smith GS, Butters M, et al. Effects of the dopaminergic agent and NMDA receptor antagonist amantadine on cognitive function, cerebral glucose metabolism and D2 receptor availability in chronic traumatic brain injury: a study using positron emission tomography (PET). Brain Inj. 2005;19(7):471-479.
11. Griffin SL, van Reekum R, Masanic C. A review of cholinergic agents in the treatment of neurobehavioral deficits following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2003;15(1):17-26.
12. Whelan FJ, Walker MS, Schultz SK. Donepezil in the treatment of cognitive dysfunction associated with traumatic brain injury. Ann Clin Psychiatry. 2000;12(3):131-135.
13. Taverni JP, Seliger G, Lichtman SW. Donepezil medicated memory improvement in traumatic brain injury during post acute rehabilitation. Brain Inj. 1998;12(1):77-80.
14. Silver JM, McAllister TW, Arciniegas DB. Depression and cognitive complaints following mild traumatic brain injury. Am J Psychiatry. 2009;166(6):653-661.
15. Silver JM, Koumaras B, Chen M, et al. Effects of rivastigmine on cognitive function in patients with traumatic brain injury. Neurology. 2006;67(5):748-755.
16. Tenovuo O. Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury—clinical experience in 111 patients. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(1):61-67.
17. Goldberg E, Gerstman LJ, Mattis S, et al. Selective effects of cholinergic treatment on verbal memory in posttraumatic amnesia. J Clin Neuropsychol. 1982;4(3):219-234.
18. Eames P, Sutton A. Protracted post-traumatic confusional state treated with physostigmine. Brain Inj. 1995;9(7):729-734.
19. Rassovsky Y, Satz P, Alfano MS, et al. Functional outcome in TBI II: verbal memory and information processing speed mediators. J Clin Exp Neuropsychol. 2006;28(4):581-591.
20. Willmott C, Ponsford J. Efficacy of methylphenidate in the rehabilitation of attention following traumatic brain injury: a randomised, crossover, double blind, placebo controlled inpatient trial. J Neurol Neurosurg Psychiatry. 2009;80(5):552-557.

Related Resource

- Konrad C, Geburek AJ, Rist F, et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. Psychol Med. 2010;22:1-15.

Drug Brand Names

Amantadine • Symadine, Symmetrel
Bromocriptine • Parlodel
Carbidopa/levodopa • Sinemet
Dextroamphetamine • Dexedrine
Donepezil • Aricept
Galantamine • Razadyne
Methylphenidate • Ritalin, Methylin, others
Physostigmine • Antilirium
Pramipexole • Mirapex
Rivastigmine • Exelon
Sertraline • Zoloft
Tacrine • Cognex

Disclosures

Dr. Scher and Ms. Loomis report no financial relationship with any company whose products mentioned in this article or with the manufacturers of competing products.

Dr. McCarron is a speaker for Eli Lilly and Company.

21. Kaelin DL, Cifu DX, Matthies B. Methylphenidate effect on attention deficit in the acutely brain-injured adult. Arch Phys Med Rehabil. 1996;77(1):6-9.
22. Whyte J, Hart T, Vaccaro M, et al. Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. Am J Phys Med Rehabil. 2004;83(6):401-420.
23. Whyte J, Hart T, Schuster K, et al. Effects of methylphenidate on attentional function after traumatic brain injury. A randomized, placebo-controlled trial. Am J Phys Med Rehabil. 1997;76(6):440-450.
24. Wroblewski BA, Leary JM, Phelan AM, et al. Methylphenidate and seizure frequency in brain injured patients with seizure disorders. J Clin Psychiatry. 1992;53(3):86-89.
25. Mahalick DM, Carmel PW, Greenberg JP, et al. Psychopharmacologic treatment of acquired attention disorders in children with brain injury. Pediatr Neurosurg. 1998;29(3):121-126.
26. Hornyak JE, Nelson VS, Hurvitz EA. The use of methylphenidate in paediatric traumatic brain injury. Pediatr Rehabil. 1997;1(1):15-17.
27. Hornstein A, Lennihan L, Seliger G. Amphetamine in recovery from brain injury. Brain Inj. 1996;10(2):145-148.

Bottom Line

Cognitive dysfunction as a result of traumatic brain injury may be misdiagnosed and undertreated. Memory, executive function, and speed of processing show significant improvement in response to catecholaminergic and cholinergic augmentation. Nonpharmacologic interventions also should be a mainstay of treatment.

Clinical Point

Nonpharmacologic interventions such as compensatory training also should be a part of treatment for TBI patients