Psychopharmacological Treatment for Cognitive Impairment in Survivors of Traumatic Brain Injury: A Critical Review

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Traumatic brain injury (TBI) is a growing national health issue that commonly results in clinically significant cognitive impairments. This article reviews and evaluates the many proposed psychopharmacological treatments for TBI-related cognitive impairment. A literature review was utilized to focus on stimulant and nonstimulant dopamine enhancing agents, acetylcholinesterase inhibitors, antidepressant agents, mood stabilizers, antipsychotics, and benzodiazepines. The most consistent evidence supports the use of dopamine enhancing medications. However, other medications such as acetylcholinesterase inhibitors and antidepressant agents may help select subgroups. A need remains for well designed, sufficiently powered studies that incorporate functionally relevant neuropsychological outcome measures.

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Traumatic brain injury (TBI) is a growing national health issue characterized by comorbid neuropsychiatric disturbances of mood, behavior, and cognition for which there are many proposed treatments but varying degrees of evidence. Approximately 1.4 million Americans sustain a TBI each year, which is likely an underestimate of the true incident burden.[1,2] Considering a peak injury age of 15 to 24 years, there is a substantial load of chronic disability.[2–5] As such, TBI results in significant morbidity, mortality, and a massive economic toll, with U.S. costs estimated to be 60 billion dollars in 2000.[1,2,6]

Traumatic brain injury is defined as a blow to the head or penetrating head injury that disrupts normal brain function.[6,7] It is classified according to whether or not the skull has been breached (penetrating versus nonpenetrating) and the severity of the initial impairment (mild, moderate or severe).[3,8–10] Severity is typically determined by the presenting Glasgow Coma Scale (GCS) and the duration of loss of consciousness and posttraumatic amnesia (Table 1).[1,8,10,11] Although mild TBI is most commonly diagnosed, there is active

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TABLE 1. TBI Severity Rating Scale

Severity	Glasgow Coma Scale Score	Duration of Loss of Consciousness	Duration of Posttraumatic Amnesia
Mild	13–15	<30 minutes and/or	<1 hour
Moderate	9–12	1–24 hours and/or	<24 hours
Severe	8 or less	>24 hours and/or	>24 hours

debate regarding whether *loss of consciousness* or an *alteration of consciousness* is the necessary criteria, which likely has diagnostic, treatment, and prognostic implications.

Cognition is divided into well-recognized but often overlapping domains of attention, executive function, memory, language, visuospatial and constructional abilities, and sensory-perceptual-motor skills.[4] Cognitive dysfunction can occur in multiple domains following TBI. These disturbances result from the combined effects of diffuse and focal damage typically to the anatomically vulnerable frontotemporal areas; thus memory, attention, and executive function deficits are most commonly observed.[4,11–13] Cognitive impairment is the most common chronic sequelae of TBI which can result in more persistent disability than the physical injury.[13] Sources have reported that TBI severity correlates with cognitive and functional outcomes.[3,10,12,14] For example, one prospective study (N=87) demonstrated that TBI severity moderately correlated with neuropsychological functioning (standardized coefficient=0.36, $p<0.05$) which correlated with functional outcome (standardized coefficient=0.52, $p<0.05$).[15] However, a key finding in this study was that cognitive impairment, particularly information processing speed, mediated the relationship between injury severity and functional decline (standardized coefficient=0.68, $p<0.05$).[16] This suggests that the restoration of functional autonomy is highly dependent on the resolution of cognitive deficits. However, there are no medications with an approved indication for treating TBI related cognitive impairment.

The purpose of this article was to systematically review the proposed psychopharmacological treatments for post-TBI cognitive impairment. We focused on commonly prescribed psychotropic medications to determine the relationship between pharmacological intervention and cognitive improvement in TBI survivors.

METHODS

Relevant articles published between 1950 and January 2008 were identified using Ovid MEDLINE. The following search terms were used: *traumatic brain injury* (then adding brain injuries to the populated list); *antidepressive agents*; *selective serotonin reuptake inhibitors* (then adding serotonin uptake inhibitors to the populated list); *antipsychotics* (then adding antipsychotic agents to the populated list); *CNS stimulants*; *benzodiazepines*; *mood stabilizers* (then adding valproic acid, antimanic agents, carbamazepine, and lithium to the populated list); and *cholinesterase inhibitors*. A second search from 1950 to October 2008 was later performed using *dopamine agonists* (then adding *bromocriptine* to the populated list); *amantadine*; and L-*dopa*. All terms were combined with *traumatic brain injury/brain injuries*.

We excluded nonhuman studies, non-English articles, reanalyses of previously published data sets, and case reports with fewer than five TBI subjects. We also excluded studies using the Glasgow Coma Scale as the only "cognitive" measure because it is not classically used as a cognitive outcome measure in the neuropsychological literature. Review articles detected by our literature searches identified additional sources.

Each study was reviewed by both authors and independently classified according to the grading system utilized by Warden et al.'s[4] Neurobehavioral Guidelines working group, which adapted their system from the Brain Trauma Foundation's Guidelines for the Management of Severe Head Injury. Each study was graded from class I to class III, with class I status being reserved for well-designed, double blind, placebo-controlled trials with reasonable subject recruitment (Table 2). A consensus conference was held to resolve differences in the classification schema for select articles.

Cognitive domains were defined and grouped according to the divisions noted by Warden's 2006 review which included attention, executive function, memory, language, sensory-perceptual-motor skills, and visuospatial and constructional abilities.[4] In addition, we included measures of global cognition, general intelligence, and arousal/orientation since they are relevant to TBI cognitive outcome. Funding sources were noted, and studies were considered "unfunded" if no mention of funding was made in

the article. The length of the study was determined by the amount of time subjects were exposed to the pharmacological intervention.

RESULTS

Using our search methods we identified 561 abstracts which resulted in 32 studies that met criteria for review. We identified four class I, eight class II, and 20 class III studies. Methylphenidate was the most commonly studied psychotropic intervention in randomized controlled trials (eight studies). A multitude of cognitive outcome measures were used (Table 3). Attention (25 studies), memory (21 studies), and executive function (15 studies) were the most commonly measured cognitive domains and were the most responsive to pharmacological intervention.

Stimulants

Methylphenidate was the only stimulant detected by our search. Methylphenidate promotes release of stored dopamine and norepinephrine from presynaptic vesicles and blocks the return of catecholamines into presynaptic nerve endings. Because TBI is associated with decreased dopamine activity, amplifying medications are likely to improve dopamine-dependent cognitive functions such as executive function.[17] The reviewed literature reports that methylphenidate has been used safely in adults and pediatric patients with all severities of TBI in acute, subacute, and long-term rehabilitation settings. Seven double-blind, randomized, placebo-controlled trials[18–24] which used cognitive measures as a primary outcome, as well as two other non-randomized trials,[25,26] reported that methylphenidate had positive effects on multiple cognitive domains including attention, memory, executive function, sensory-perceptual-motor skills, and global cognition. Attention was the most studied domain amenable to methylphenidate treatment. Only one small pediatric randomized, placebo-controlled trial (N=10) that used only 4 days of treatment reported no benefit with methylphenidate therapy.[27]

Nonstimulant Dopamine Enhancers

Nonstimulant dopamine enhancers increase dopamine neurotransmission by functioning as an agonist (bromocriptine and pramipexole) or dopamine precursor (carbidopa/L-dopa) or by unknown mechanisms (amantadine). As with stimulants, increased dopamine transmission appears to be the mechanism by which nonstimulant dopamine enhancers may improve post-TBI cognitive impairments, particularly nonmemory-based cognitions such as executive function, processing speed, and attention. While there was only one small negative randomized controlled trial of amantadine,[28] the remaining six out of seven prospective clinical trials, including two randomized, placebo-controlled trials,[29,30] and four non-randomized, placebo-controlled trials[31–34] reported that nonstimulant dopamine enhancers improve executive functioning, attention, global cognitive functioning, memory, language, and/or arousal. Only one did not use cognition as a primary outcome measure.[31] Improvements were demonstrated in adult and pediatric samples, subacute to remote injury, mild to severe injury, and inpatient and outpatient settings. Executive function seems to be the most amenable to nonstimulant dopamine enhancement. One study demonstrated increased prefrontal metabolism (the cortical region governing executive function) using positron emission tomography (PET) in patients treated with amantadine which correlated with executive performance (r=0.92, p=0.01).[33]

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors increase the availability of acetylcholine in the synaptic cleft by preventing its

TABLE 2. Classification of Study Evidence[4]

Class I	This is a well-designed and -conducted prospective, randomized, controlled trial. However, some trials may be downgraded due to poor design, insufficient patient numbers (n<20), or other methodological inadequacies.
Class II	This is a well-designed and -conducted clinical study in which the data were collected prospectively or retrospective analyses were based on clearly reliable data. Types of studies so classified include observational studies, cohort studies, prevalence studies, and case control studies. As mentioned above, class I design studies may be downgraded to class II evidence based on methodological flaws.
Class III	Most studies are based on retrospectively collected data. Evidence used in this class indicates well-designed and -conducted clinical series, databases or registries, case reviews, and case reports. Class I and II design studies may be downgraded to class III evidence due to methodological flaws. As mentioned above, although a class I study by design, a randomized, controlled trial could be downgraded by raters to class II or class III evidence or even be judged unusable based upon the degree of methodological flaws.

degradation. Because TBI is associated with a hypocholinergic state, this class may improve cognition by restoring normal cholinergic synaptic transmission.[12,17] Our literature review discovered three small positive prospective studies[35–36] and one small negative open label trial[38] using an acetylcholinesterase inhibitor for cognitive rehabilitation. Each prospective trial evaluated cognition as the primary outcome. Memory and attention were the most consistently improved cognitive domains. Although donepezil was the only acetylcholinesterase inhibitor studied prospectively, one retrospective cohort study (N=111) found no difference in efficacy or tolerability between donepezil, rivastigmine, or galantamine.[39]

Antidepressant Agents

Selective serotonin reuptake inhibitors (SSRIs) block presynaptic reuptake of serotonin in the neuronal synaptic cleft, thus enhancing serotonergic neurotransmission. There is evidence that serotonin activity decreases

TABLE 3. The Outcome Measures Used for Each Cognitive Domain

Cognitive Domains	Outcome Measures
Arousal and orientation	Galveston Orientation and Amnesia Test (GOAT); Orientation Log; Ranchos Los Amigos Cognitive Scale; Coma Near Coma Scale; Western Neurosensory Stimulation Profile
Language	Wechsler Adult Intelligence Scale–Revised (WAIS-R) Vocabulary; Controlled Oral Word Association Test (COWAT); Peabody Picture Vocabulary Test; Rapid Automatized Naming Test; Boston Naming Test
Executive function	Trail Making Test Part B; COWAT; Stroop Color and Word and Interference Test; Verbal and Non-Verbal (Design) Fluency Tests; Raven Progressive Colored Matrices; Sustained Arousal and Attention and Sustained Attention to Response Tasks ("go/no-go tasks"); Dysexecutive Questionnaire; Dual Task Counting and Digit Span; Wisconsin Card Sorting Test; Rey-Osterrieth Complex Figure; Behavior Rating Inventory of Executive Functioning; Tower of London Test
Attention/speed of processing	Choice Reaction Time (by itself or divided into Recognition/Motor/Total Reaction Time); Digit Symbol Substitution Test; Digit Span Test; Trail Making Test Part A; Letter Number Sequencing subscale of the WAIS; Stroop Color and Word Test; Digital Vigilance; Visual Search; Seashore Rhythm Test; Attention and Concentration Index of the Wechsler Memory Scale-Revised (WMS-R); Adult Activity Scale; (Ruff 2 & 7) Selective Attention Test; (Conners') Continuous Performance Test; Mental Control Sub-Test of the WMS-R; Symbol Search Sub-Test of the Wechsler Intelligence Scale III (WISC-III); Mesulam Verbal Cancellation Test; Paced Auditory Serial Addition Test; Sustained Arousal Task; Phasic Arousal Task; Distraction Task; Behavioral Inattention Task; Symbol Digit Modalities Test; Rapid Automatized Naming Test; Gordon Diagnostic System (Model 3); Woodcock-Johnson Psychoeducational Test Battery-Revised; Sustained Arousal and Attention Task; Dual Task; Test of Everyday Attention Task; Inattentive Behavior Task; Classroom Attentiveness; Sustained Attention to Response Task; Cognitive Failures Questionnaire; Two-Back Working Memory Task; Posner Paradigm; Test of Attentional Performance; Letter Cancellation Test; Mental Control Test
Memory including posttraumatic amnesia	GOAT; Functional Independence Measure-Cognitive; Sternberg Memory Scanning Test; WMS-R Learning Memory; Buschke Selective Reminding Test; Benton Visual Retention Test; WMS-R Logical Memory I/II and Visual Reproduction I/II; University of Southern California Repeatable Episodic Memory Test; Randt Memory Test; Sum or Recall, Sum of Consistent Long Term Recall and Recall Following 30 Minute Delay; Kimura Memory for Designs Test; Delayed Verbal and Visual Memory of the WMS-R; Porteus Maze; Pursuit Rotor Task; Sternberg Memory and Reaction Time Task; Sentence Repetition Task; Two-Back Working Memory Task; Global Memory Scale of the Memory Assessment Scale; Brief Visual Memory Test-Revised; Hopkins Verbal Learning Test; Memory Functioning Questionnaire; Auditory and Visual Immediate Indexes of the WMS-III; Rey Auditory Verbal Memory Test; Corsi Block Test; Reading Span Test; Spatial Delayed Response Task; Rivermead Behavioral Memory Test; Visual Memory Span; California Verbal Learning Test; Rey-Osterrieth Complex Figure
Sensory-perceptual-motor skills	Critical Flicker Fusion Threshold; Compensatory Tracking Test; Finger Tapping Test; Grooved Pegboard Test; Name Writing Test; Pursuit Rotor Task; Purdue Pegboard; Developmental Test of Visual Motor Integration
Global cognition and cognitive efficiency	Mini-Mental State Examination; Repeatable Battery for the Assessment of Neuropsychological Assessment
Visuospatial and constructional skills	WMS-R Visual Reproduction I/II; Porteus Maze; Corsi Block Test; Letter Cancellation Test; Rey-Osterreith Complex Figure
General intelligence	Raven Progressive Colored Matrices; WAIS Verbal and Performance Intelligence Quotients; Porteus Maze (Performance IQ); Wechsler Intelligence Scale for Children 3rd edition

after TBI, which may contribute to cognitive impairment.[17,40] SSRIs may improve post-TBI cognitive functioning by restoring the level of available serotonin which may influence expression of brain derived neurotrophic factor, resulting in remodeling and repair of the injured brain.[41] Four prospective clinical trials using sertraline (three studies) or fluoxetine (one study) measured cognition as a primary outcome.[18,40–42] These trials demonstrated mixed cognitive effects. Only sertraline was examined using a randomized clinical trial design[18,40] including one flawed negative trial (N=9).[37] The other negative study used a randomized, double-blind, placebo-controlled, parallel group design (sertraline [N=10], methylphenidate [N=10], and placebo [N=10]) which demonstrated that sertraline had inconsistent effects on attentional measures while offering no advantage over placebo on measures of global cognition, memory, attention, or sensory-motor-perceptual skills.[18] In contrast, two small prospective non-randomized, placebo-controlled trials reported improvements of multiple cognitive dimensions, including executive functioning, attention, memory, and sensory-perceptual-motor skills, in adult outpatients with concurrent depression when treated with either 8 months of fluoxetine (n=5) or 8 weeks of sertraline (n=15).[41,42] Neither study adjusted for the demonstrated concurrent improvements in depression.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) block reuptake of serotonin and norepinephrine, thus enhancing catecholamine neurotransmission. While norepinephrine and the coeruleo-cortical system may play a role in promoting neurological recovery by supporting neuroplasticity in animal models, its role in humans is still being investigated.[43] Only the cognitive effects of milnacipran, an SNRI recently approved for use in the United States, have been studied in TBI. This prospective 6-week non-randomized, placebo-controlled trial (N=10) examined cognition as a secondary outcome measure and reported that depressed TBI survivors treated with milnacipran had a modest two-point improvement in global cognition as measured by the Mini-Mental State Examination (MMSE).[44] Again, cognitive performance was not adjusted for improvement in depression.

Tricyclic antidepressants block presynaptic reuptake of norepinephrine, serotonin, and dopamine in addition to having multiple other pharmacological properties, most of which are associated with adverse effects. Tricyclic antidepressants' adrenergic and acetylcholine antagonist activity can lead to orthostatic hypotension and cognitive impairment in this vulnerable population. Moreover, the potential for decreased seizure threshold is also of great clinical concern, particularly in patients with brain injury. For example, one case series of 5 acquired brain injury patients described two incidents of generalized seizure activity when patients were treated with nortriptyline for mood impairments dosed between 50 and 100 mg daily.[45] No prospective clinical trials or retrospective medical record reviews have examined the impact of tricyclic antidepressants on cognition.

Mood Stabilizers

Mood stabilizers have various mechanisms of action that typically involve second messenger systems. There is little evidence to support their use for cognitive impairment in TBI patients, and in fact their use may be detrimental to cognitive recovery. For example, one randomized, placebo-controlled trial reported that long-term carbamazepine use for seizure prophylaxis in TBI patients had adverse effects on cognition including executive functioning, sensory-motor-perceptual skills, and attention in mixed pediatric and adult outpatients that resolved within 1 month of medication discontinuation.[46] Another randomized, placebo-controlled trial (N=379) reported that valproate had no effect on cognition compared to placebo when used for postinjury seizure prophylaxis.[47] In contrast, only small retrospective studies or case series, which did not use cognitive measures as a primary outcome, claimed cognitive benefit for carbamazepine in this population.[48,49] No prospective clinical trials, retrospective reviews, or case series with at least five TBI patients examining the impact of lithium on cognition in TBI survivors have been reported.

Benzodiazepines

Benzodiazepines reduce neuronal excitability by potentiating the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) throughout the brain. Because GABA plays an integral role in prefrontal subcortical circuit activity, the neural network known to govern executive function, it is theoretically possible that benzodiazepines could improve cognition in TBI patients with circuit lesions. However, there have been no prospective clinical trials proving this utility. Although concerns that benzodiazepines may impair cognitive recovery or result in behavioral disinhibition and par-

adoxical worsening of agitation have been suggested, these events have not been substantiated. In fact one retrospective cohort study of TBI patients evaluated on a trauma inpatient unit reported benzodiazepines had no effect on memory or length of post traumatic amnesia, suggesting that benzodiazepines may be a clinically attractive treatment for TBI-related behavioral disturbances.[50]

Antipsychotics

The utility of antipsychotic medication in TBI patients is highly controversial.[10] Given their antagonism of dopamine transmission, antipsychotics may impair cognitive recovery when used to treat TBI-related agitation since brain injury is associated with hypodopaminergic activity.[12,17] Review sources report that antipsychotics interfere with functional recovery, prolong posttraumatic amnesia, and worsen overall outcome.[10,12] When antipsychotics must be used for behavioral dyscontrol, these same sources recommend the use of atypicals over typicals due to a hypothesized lower relative risk of neurological adverse effects.

Cognitive instruments were used as secondary outcome measures in one prospective study designed to determine the benefit of quetiapine for TBI-related behavioral disturbances. This small prospective open label trial (N=7) reported that quetiapine had positive effects on global cognition.[51] However, the clinical significance of this finding is unclear given the small magnitude of cognitive improvement and the confounding significant large improvement in behavior. In contrast, one retrospective study using cognition as a primary outcome reported that neuroleptics were associated with an additional 7 days needed to clear posttraumatic amnesia.[50]

DISCUSSION

Given the sobering morbidity and economic sequelae of TBI, the dearth of well-designed randomized, placebo-controlled trials guiding the use of medications for TBI-related cognitive dysfunction is disheartening. Only 32 studies met criteria for review, of which 27 were prospective. Within this group only four achieved class I criteria, and with the exception of one valproate study, all enrolled fewer than 40 subjects.

While there is clearly a need for more well-designed randomized, placebo-controlled trials, current literature has the most evidence supporting the treatment of attentional impairments with stimulants, memory impairments with stimulants and cholinesterase inhibitors, and executive impairments with stimulant and nonstimulant dopamine enhancing agents. Nine of 10 studies observed multidimensional cognitive improvement with methylphenidate and six of seven studies observed similar improvements with dopamine enhancing agents. Stimulants have also been associated with an approximate 25% decreased length of hospitalization in moderate to severe TBI survivors.[20,25] Moreover, treatment of cognitive impairment with stimulant or nonstimulant dopamine enhancers is associated with improved functional performance.[20,25,30,32] Although the data are not nearly as robust, four of five studies using acetylcholinesterase inhibitors also report cognitive improvement.

The results are highly mixed for all other psychopharmacological interventions. Antidepressant agents may have a role in treating depression-related cognitive dysfunction. However, these studies are limited by very small sample sizes using multiple outcome measures, the usual absence of a placebo group, and a failure to use multivariable modeling to determine the effect of these medications on cognition independent of mood resolution. While valproate and benzodiazepines may be cognitively neutral agents in TBI patients, the current literature does not support their use or the use of other mood stabilizers or antipsychotics for post-TBI cognitive deficits. Moreover, the only randomized, placebo-controlled trial of valproate did not even demonstrate prophylactic seizure benefit and actually showed a trend toward increased mortality.[47]

There are several limitations of this review. Our selection methods may have been too conservative given that only 32 of 561 abstracts were analyzed. Furthermore, our review, like all reviews, is inherently limited by the search terms we utilized. Had we expanded our search, we would have noted many other novel treatments such as *N*-methyl-D-aspartic acid (NMDA)-receptor antagonists, statins, progesterone, erythropoietin, minocycline, kinin antagonists, toll-like receptor antagonists, synthetic cannabinoids, magnesium, cyclosporine-A, and thyrotropin releasing hormone which have all been studied for their possible attenuating effects of subsequent neurochemical, cellular, and metabolic alterations following the primary TBI insult.[52] However, the purpose of this article was to focus on the cognitive effects of commonly prescribed psychotropic medications used "off-label" for TBI. We believe the

studies we selected represent the most relevant published data for prescribing clinicians.

Treating TBI cognitive sequelae is complex and can be conceptualized along a continuum from acute to chronic care. TBI patients often have a variety of neuropsychiatric impairments and other comorbidities such as seizures, which are associated with cognitive impairment. As such, the acute and chronic management of TBI is interdisciplinary. This patient population often requires pharmacotherapy and/or rehabilitation services, which may also have cognitive benefits not addressed by this review.

Despite the propensity of certain focal areas to be injured with somewhat predicable neuropsychological disturbances, TBI is highly individualized. Subsequent neuropsychological impairments are dependent on biochemical disturbances, lesion locations, pre- and post-TBI neuropsychological status, and injury severity. The heterogeneity of brain injury certainly impacts therapeutic response to any given agent. This highlights the need for more controlled trials with narrower samples, which unfortunately limits generalization; however, this approach may lead to better treatment algorithms for specific TBI phenotypes.

Another limitation that future studies need to address is the multitude of neuropsychological testing utilized in these studies. Given that the long-range clinical goal is to restore functional status, perhaps the best approach is for investigators to choose neuropsychological measures that are consistently associated with functional outcomes in multivariable models. A recent review by the Committee on Research for the American Neuropsychiatric Association identified the Mattis Dementia Rating Scale-memory component and the Hopkins Verbal Learning Test as being particularly sensitive to memory-related functional impairment and the Executive Interview, Mattis Dementia Rating Scale-conceptualizations component, and Shipley Institute of Living Scale as being particularly sensitive to executive-function related functional impairment.[53] If the goal is to restore or preserve autonomy, then it only makes sense to use the measures that best correlate with functional status independent of mood, vigilance, and demographic confounders.

While our review suggests that dopaminergic psychotropic medications impart the most cognitive benefit to TBI patients among the commonly prescribed medications, there is a mounting volume of information regarding "second injury" processes involving the role of neuronal inflammation and apoptosis as molecular targets for future pharmacological intervention. Promising areas of study are currently measuring the effect of novel pharmacological agents in reducing inflammation while providing neuroprotection and brain remodeling via angiogenesis, neurogenesis, and synaptogenesis. We refer interested readers to a recent review of available literature by Vink and Nimmo[52] as well as to www.clinicaltrials.gov (search term *traumatic brain injury*) where they can find planned and in-progress Phase 1, 2, and 3 randomized clinical trials of NMDA-receptor antagonists, synthetic cannabinoids, progesterone, erythropoietin, and human growth hormone among other novel medications. This appears to be an exciting area of investigation that may yield benefits beyond classic psychopharmacological approaches.

The opinions expressed on this document are solely those of the authors and do not represent an endorsement by or the views of the United States Air Force, the Department of Defense, or the United States Government.

References

1. Powell JM, Ferraro JV, Dikmen SS, et al: Accuracy of mild traumatic brain injury diagnosis. Arch Phys Med Rehabil 2008; 89:1550–1555
2. Langlois JA, Ruthland-Brown W, et al: The epidemiology and impact of traumatic brain injury: a brief overview. J Head Trauma Rehabil 2006; 21:375–378
3. Kaufman DM: Clinical Neurology for Psychiatrists, 6th ed. Philadelphia, Saunders Elsevier, 2007, pp 537–548
4. Warden DL, Gordon B, McAllister TW, et al: Guidelines for the pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. J Neurotrauma 2006; 23:1468–1501
5. Kim E, Lauterbach EC, Reeve A, et al: Neuropsychiatric complications of traumatic brain injury: a critical review of the literature (a report by the ANPA Committee on Research). J Neuropsychiatry Clin Neurosci 2007; 19:106–127
6. Centers for Disease Control (CDC) and Prevention: Facts About Traumatic Brain Injury. Available at http://www.dvbic.org/TBI---The-Military/TBI-Facts.aspx
7. Defense and Veterans Brain Injury Center (DVBIC): Facts About Traumatic Brain Injury. Available at http://dvbic.org/index.html
8. National Institute of Health National Institute of Neurological Disorders and Stroke Publication No. 02–2478. Traumatic Brain Injury: Hope Through Research 2002. Available at www.ninds.nih.gov/disorders/tbi/tbi_htr.pdf
9. Sadock BJ, Sadock VA: Kaplan & Sadock's Synopsis of Psy-

chiatry Behavioral Sciences/Clinical Psychiatry, 10th ed. Philadelphia, Lippincott Williams & Wilkins, 2007, pp 363–364
10. Stern TA, Rosenbaum JF, Fava M, et al: Massachusetts General Hospital Comprehensive Clinical Psychiatry. Philadelphia, Mosby Elsevier, 2008, pp 1107–1121
11. Rao V, Lyketsos C: Neuropsychiatric sequelae of traumatic brain injury. Psychosomatics 2000; 41:95–103
12. Lee HB, Lyketsos CG, Rao V: Pharmacological management of the psychiatric aspects of traumatic brain injury. Int Rev Psychiatry 2003; 15:359–370
13. Rapoport MJ, McCullagh S, Shammi P, et al: Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. J Neuropsychiatry Clin Neurosci 2005; 17:61–65
14. Andreoli TE, Carpenter CC, Griggs RC, et al (eds): Cecil Essentials of Medicine, 5th ed. Philadelphia, WB Saunders, 2001, pp 953–955
15. Rassovsky Y, Satz P, Alfano MS, et al: Functional outcome in TBI I: neuropsychological, emotional, and behavioral mediators. J Clin Exp Neuropsychol 2006; 28:567–580
16. 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; 28:581–591
17. Jorge R, Robinson RG: Mood disorders following traumatic brain injury. Int Rev Psychiatry 2003; 15:317–327
18. Lee H, Kim SW, Kim JM, et al: Comparing effects of methylphenidate, sertraline, and placebo on neuropsychiatric sequelae in patients with traumatic brain injury. Hum Psychopharmacol Clin Exp 2005; 20:97–104
19. Gualtieri CT, Evans RW: Stimulant treatment for the neurobehavioral sequelae of traumatic brain injury. Brain Inj 1988; 2:273–290
20. Plenger PM, Dixon CE, Castillo RM, et al: Subacute methylphenidate treatment for moderate to moderately severe traumatic brain injury: a preliminary double-blind placebo-controlled study. Arch Phys Med Rehabil 1996; 77:536–540
21. 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; 76:440–450
22. Mahalick DM, Carmel PW, Greenberg JP, et al: Psychopharmacologic treatment of acquired attention disorders in children with brain injury. Pediatr Neurosurg 1998; 29:121–126
23. 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; 83:401–420
24. Kim YH, Ko MH, Na SY, et al: Effects of single-dose methylphenidate on cognitive performance in patients with traumatic brain injury: a double-blind placebo-controlled study. Clin Rehabil 2006; 20:24–30
25. Kaelin DL, Cifu DX, Matthies B: Methylphenidate effect on attention deficit in the acutely brain-injured adult. Arch Phys Med Rehabil 1996; 77:6–9
26. Hornyak JE, Nelson VS, Hurvitz EA: The use of methylphenidate in pediatric traumatic brain injury. Pediatric Rehabilitation 1997;1:15–17
27. Williams SE, Ris MD, Ayyangar R, et al: Recovery in pediatric brain injury: is psychostimulant medication beneficial? J Head Trauma Rehabil 1998; 13:73–81
28. Schneider WN, Drew-Cates J, Wong TM, et al: Cognitive and behavioral efficacy of amantadine in acute traumatic brain injury: an initial double-blind placebo-controlled study. Brain Inj 1999;13:863–872
29. McDowell S, Whyte J, D'Esposito M: Differential effect of a dopaminergic agonist on prefrontal function in traumatic brain injury patients. Brain 1998; 121:1155–1164
30. Meythaler JM, Brunner RC, Johnson A: Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. J Head Trauma Rehabil 2002; 17:300–313
31. Powell JH, Al-Adawi S, Morgan J, et al: Motivational deficits after brain injury: effects of bromocriptine in 11 patients. J Neurol Neurosurg Psychiatry 1996; 60:416–421
32. Patrick PD, Blackman JA, Mabry JL, et al: Dopamine agonist therapy in low-response children following traumatic brain injury. J Child Neurol 2006; 21:879–885
33. 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; 19:471–479
34. Beers SR, Skold A, Dixon CE, et al: Neurobehavioral effects of amantadine after pediatric traumatic brain injury: a preliminary report. J Head Trauma Rehabil 2005; 20:450–463
35. Morey CE, Cilo M, Berry J, et al: The effect of Aricept in persons with persistent memory disorder following traumatic brain injury: a pilot study. Brain Inj 2003; 17:809–815
36. Zhang L, Plotkin RC, Wang G, et al: Cholinergic augmentation with donepezil enhances recovery in short term memory and sustained attention after traumatic brain injury. Arch Phys Med Rehabil 2004; 85:1050–1055
37. Khateb A, Ammann J, Annoni JM, et al: Cognition-enhancing effects of donepezil in traumatic brain injury. Eur Neurol 2005; 54:39–45
38. Kaye NS, Townsend JB, Ivins R: An open-label trial of donepezil (Aricept) in the treatment of persons with mild traumatic brain injury. J Neuropsychiatry Clin Neurosci 2003; 15:383–385
39. Tenovuo O: Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury: clinical experience in 111 patients. Prog Neuropsychopharmacol Biol Psychiatry 2005; 29:61–67
40. Meythaler JA, Depalma L, Devivo MJ, et al: Sertraline to improve arousal and alertness in severe traumatic brain injury secondary to motor vehicle crashes. Brain Inj 2001; 15:321–331
41. Horsfield SA, Rosse RB, Tomasino V, et al: Fluoxetine's effects on cognitive performance in patients with traumatic brain injury. Int J Psychiatry Med 2002; 32:337–344
42. Fann JR, Uomoto JM, Katon WJ: Cognitive improvement with treatment of depression following mild traumatic brain injury. Psychosomatics 2001; 42:48–54
43. Reinhard DL, Whyte J, Sandel E: Improved arousal and initiation following tricyclic antidepressant use in severe brain injury. Arch Phys Med Rehabil 1996; 77:80–83
44. Kanetani K, Kimura M, Endo S: Therapeutic effects of milnacipran (serotonin noradrenaline reuptake inhibitor) on depression following mild and moderate traumatic brain injury. J Nippon Med School 2003; 70:313–320

45. Wroblewski BA, Joseph AB, Kupfer J, et al: Effectiveness of valproic acid on destructive and aggressive behaviors in patients with acquired brain injury. Brain Inj 1997; 11:37–47
46. Smith KR, Goulding PM, Wilderman D, et al: Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: a comparative study. Arch Neurology 1994; 51:653–660
47. Dikmen SS, Machamer MA, Winn HR, et al: Neuropsychological effects of valproate in traumatic brain injury. Neurology 2000; 54:895–902
48. Chatham-Showalter PE: Carbamazepine for combativeness in acute traumatic brain injury. J Neuropsychiatry Clin Neurosci 1996; 8:96–99
49. Persinger MA: Subjective improvement following treatment with carbamazepine (Tegretol) for a subpopulation of patients with traumatic brain injuries. Percept Mot Skills 2000; 90:37–40
50. Mysiw WJ, Bogner JA, Corrigan JD, et al: The impact of acute care medications on rehabilitation outcome after traumatic brain injury. Brain Inj 2006; 20:905–911
51. Kim E, Bijlani M: A pilot study of quetiapine treatment of aggression due to traumatic brain injury. J Neuropsychiatry Clin Neurosci 2006; 18:547–549
52. Vink R, Nimmo AJ: Multifunctional drugs for head injury. Neurotherapeutics 2009; 6:28–42
53. Royall DR, Lauterbach EC, Kaufer D, et al: The cognitive correlates of functional status: a review from the committee on research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2007; 19:249–265