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Treatment of Post-Traumatic Cognitive Impairments

Hal S. Wortzel, MD[1,2,3] and **David B. Arciniegas, MD**[2,3]

[1]VISN 19 Mental Illness Research, Education, and Clinical Center, Denver Veterans Affairs Medical Center, Denver, CO

[2]Neurobehavioral Disorders Program, Department of Psychiatry, University of Colorado School of Medicine, Aurora, CO, USA

[3]Behavioral Neurology Section, Department of Neurology, University of Colorado School of Medicine, Aurora, CO, USA

Abstract

Opinion statement

- Cognitive impairment is a common consequence of traumatic brain injury (TBI) and a substantial source of disability. Across all levels of TBI severity, attention, processing speed, episodic memory, and executive function are most commonly affected.
- The differential diagnosis for posttraumatic cognitive impairments is broad, and includes emotional, behavioral, and physical problems as well as substance use disorders, medical conditions, prescribed and self-administered medications, and symptom elaboration. Thorough neuropsychiatric assessment for such problems is a pre-requisite to treatments specifically targeting cognitive impairments.
- First-line treatments for posttraumatic cognitive impairments are non-pharmacologic, including education, realistic expectation setting, environmental and lifestyle modifications, and cognitive rehabilitation.
- Pharmacotherapies for posttraumatic cognitive impairments include uncompetitive N-methyl-D-aspartate receptor (NMDA) antagonists, medications that directly or indirectly augment cerebral catecholaminergic or acetylcholinergic function, or agents with combinations of these properties.
- In the immediate post-injury period, treatment with uncompetitive NMDA receptor antagonists reduces duration of unconsciousness. The mechanism for this effect may involve attenuation of neurotrauma-induced glutamate-mediated excitotoxicity and/or stabilization of glutamate signaling in the injured brain.
- During the sub-acute or late post-injury periods, medications that augment cerebral acetylcholinergic function may improve declarative memory. Among responders to this treatment, secondary benefits on attention, processing speed, and executive function impairments as well as neuropsychiatric disturbances may be observed. During these post-injury periods, medications that augment cerebral catecholaminergic function may improve hypoarousal, processing speed, attention, and/or executive function as well as comorbid depression or apathy.

Corresponding Author Address: Hal S. Wortzel, MD, VISN 19 MIRECC, Denver VAMC, 1055 Clermont Street, Denver, CO 80220 USA, Phone: 303-399-8020 x5644, hal.wortzel@ucdenver.edu.

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- When medications are used, a “start-low, go-slow, but go” approach is encouraged, coupled with frequent reassessment of benefits and side effects as well as monitoring for drug-drug interactions. Titration to either beneficial effect or medication intolerance should be completed before discontinuing a treatment or augmenting partial responses with additional medications.

Keywords

Traumatic brain injury; Cognitive disorders; Rehabilitation; Drug therapy; Post-traumatic cognitive impairments; Treatment

Introduction

Traumatic brain injury (TBI) is a common problem in the United States, affecting more than 1.5 million individuals each year [1, 2]. Injury-event related cognitive impairments, including loss of consciousness, attention and memory impairments, and/or other alterations of consciousness, are typical manifestations of biomechanically-induced alterations of brain function. They are so common that they are embedded in most clinical case definitions of TBI [3–6]. In the subacute and late post-injury periods after severe TBI, impairments of attention, processing speed, episodic memory, and executive function are common [7]. After moderate TBI, processing speed, episodic memory, and executive function also are commonly affected in both the early and late post-injury periods. Fortunately, long-term cognitive impairments of these types are not universal nor are deficits in these domains uniform within or across individuals with such injuries [8]. When such long-term impairments occur, however, they contribute to disability [9, 10] and often are distressing to the person with TBI and his or her family [11].

Most individuals who sustain mild TBI recover fully and do not experience long-term cognitive impairments [12, 13, 7]. However, a non-trivial minority of these individuals develop persistent cognitive complaints and/or impairments [14], the nature and etiology of which are subjects of considerable controversy [7, 15]. In some cases, comorbid neuropsychiatric conditions, substance use disorders, medical conditions, medications, pre-injury factors (including neurodevelopmental conditions and neurogenetics), and post-injury psychosocial issues (including litigation) may contribute to the development and persistence of cognitive complaints and/or impairments [12, 13]. Other patients may experience long-term cognitive problems that are misattributed to mild TBI when in fact the index injury is more than mild [16–18] or preceded by prior TBI that confer vulnerability to adverse cognitive outcomes [19]. There also may be a small subset of individuals for whom other conditions are not explanatory and whose long-term cognitive impairments reflect neurotrauma-induced disruptions of brain structure and function [20].

Prior to initiating treatment specifically targeting posttraumatic cognitive impairments, a comprehensive neuropsychiatric evaluation is needed to: a) establish that an injury occurred that meets the widely-accepted definition of TBI [3]; and b) to determine whether cognitive difficulties experienced in the post-injury period are best accounted for by TBI, another neuropsychiatric condition, iatrogenic factors (including prescribed medications), or some combination of these and other factors. Identifying and treating comorbid neuropsychiatric conditions is essential. Additionally, estimating pre-injury cognitive function, premorbid neuropsychiatric health, the role of TBI in symptom development, the effects of bodily injuries on cognitive and psychological function, the psychosocial context in which the recovery occurred, and the effects (or lack) of any treatments provided must be ascertained. It is imperative that clinicians attend to more than superficially compelling temporal relationships when evaluating persons with posttraumatic cognitive impairments. When

interpreting injury history and current symptoms, care must be taken to avoid the logical fallacies of *post hoc ergo propter hoc* (after TBI, therefore because of TBI) or *post hoc ergo cum hoc* (with TBI, therefore because of TBI) in order to ensure that opportunities to identify and treat other causes of cognitive complaints and/or impairments are not missed.

The evidence base for nonpharmacologic and pharmacologic treatments has developed substantially over the last 20 years, and especially in the last decade [21–40]. Although there are no United States Food and Drug Administration (FDA) approved treatments for cognitive impairments due to TBI, the published literature provides a useful guide to the treatment of such problems. Where evidence for the treatment of a specific type of posttraumatic cognitive impairment is lacking, modeling treatment after phenomenologically similar but etiologically distinct conditions (e.g., stroke, multiple sclerosis, neurodegenerative disorders, attention deficit hyperactivity disorder) also may be useful. The limitations of such treatments-by-analogy necessitate a measure of caution when prescribing medications or offering rehabilitative interventions to persons with posttraumatic cognitive impairments, especially with respect to treatment tolerability, safety, and cost-effectiveness. Nonetheless, clinicians are better positioned today to offer potentially useful treatments to individuals with these problems than at any time in the past.

The current treatment options described in this article are of two general types: cognitive rehabilitation and pharmacotherapy. Consistent with the citation style and clinical practice-oriented focus of this journal, evidence-based reviews, systematic reviews, meta-analyses, and other synthetic works are cited here when they serve to establish the evidence class associated with the treatment described and/or when they summarize large numbers of case reports, case series, uncontrolled studies, and expert opinions. Among those cited, a few recent articles of particular importance also are identified. Other interventions (e.g., education and counseling, technology-based interventions) are not addressed at length; interested readers are referred elsewhere [41, 42] for detailed reviews of these subjects.

Treatment

Diet and lifestyle

- Pre-treatment assessment includes working with the patient and/or caregiver to identify and modify (i.e., eliminate, minimize, or anticipate) environmental antecedents to cognitive failures.
- Additionally, the relationship between cognitive failures and emotional/behavioral disturbances requires clarification. If cognitive failures precipitate emotional/behavioral responses, then treatment of cognitive impairments may obviate interventions directed specifically at emotion and/or behavior. Conversely, if emotional and behavioral disturbances are primary problems and interfere with cognition, then treatment of those disturbances takes precedence over, and may reduce the need for, treatment of cognitive impairments.
- Developing adaptive and compensatory strategies that limit the adverse effects of cognitive impairment on functional performance is an essential element of treatment. Effectively developed and deployed, such strategies may reduce the need for additional cognitive rehabilitation or pharmacotherapeutic interventions.
- Adaptive strategies include reducing environmental or internal sources of distraction before engaging in cognitive tasks; evaluating and, where necessary, modifying the cognitive complexity of tasks that the patient is asked to perform; scheduling cognitively challenging daily events to coincide with periods during which the patient is well rested and refreshed; resetting the patient’s and others’

expectations regarding the timing of and time needed to complete cognitively challenging tasks; encouraging patience when awaiting a patient's verbal responses; and teaching others not to respond on behalf of the patient unless asked to do so.

- Compensatory strategies include 'cognitive prosthetics' such as memory notebooks, timers with alarms and messages, task lists, and verbal and/or non-verbal cues from others (or by signage posted in the patient's environment). These strategies, once they are made automatic over many rehearsals and through positive reinforcement, may improve functional use of remaining cognitive abilities. Assistive technologies, including communication devices, 'smart phones,' electronic day planners, global positioning devices, and so forth also may compensate for impairments in attention, working memory, language and communication, episodic memory, topographical orientation, and executive function.
- Consultation with speech and occupational therapists experienced in the selection and use of adapative and compensatory strategies may facilitate their development.
- Persons with TBI and/or their caregivers may benefit from participating in brain injury support groups as well as the education, information, referral, and other resources of the Brain Injury Association of America and their local affiliates (http://www.biausa.org/).
- There is no evidence to support specific diets or other nutritional programs as treatments for posttraumatic cognitive impairments, with the exception of the nutriceutical cytidine 5 -diphosphocholine (CPD-choline or citicholine); this intervention is discussed later in this article.

Cognitive Rehabilitation

- Cognitive rehabilitation is a systematic program of interventions designed to improve cognitive abilities and the application of cognition to everyday function. These interventions may re-establish or reinforce previously learned skills, develop compensatory strategies for cognitive deficits, and/or facilitate adaptation to irremediable cognitive impairments.
- Cognitive rehabilitation includes general interventions as well as cognitive domain-specific interventions.
- The American Congress of Rehabilitation Medicine [21–23] and European Federation of Neurological Societies [25, 26] performed systematic review and analysis of the cognitive rehabilitation literature for the purpose of developing evidence-based recommendations for the treatment of cognitively-impaired persons with TBI or stroke. Their recommendations include Practice Standards (based on one or more Class I studies with support from additional Class II or III studies), Practice Guidelines (based on one or more Class I studies with methodological limitations or one or more well-designed Class II studies), and Practice Options (based on one or more Class II, III, or IV studies). These practice recommendations correspond closely to the Class I, Class II–III, and Class IV evidence ratings used in this journal, and will be translated as such in this article. Additionally, only those interventions relevant to the cognitive rehabilitation of persons with TBI are presented.
- The cost-effectiveness of these treatments is not established.

General Cognitive Rehabilitation Interventions: Comprehensive-holistic neuropsychological rehabilitation is recommended during post-acute rehabilitation to reduce cognitive and functional disability for persons with moderate to severe TBI ([23], Class I). This treatment approach encompasses cognitive rehabilitation, discipline-specific therapies (physical, occupational, and speech therapies), as well as individual and group therapies directed at metacognitive, emotional, interpersonal, and functional skills. In this context, individual and group psychotherapies emphasizing emotional, behavioral, and interpersonal function may facilitate the success of cognition-specific interventions ([23], Class II).

Self-regulation and self-monitoring instruction may contribute to the rehabilitation of a broad range of cognitive impairments, including attention, declarative memory, visuospatial function (spatial attention), executive function, and emotional regulation impairments ([23], Class IV). Compensatory strategy training may contribute usefully to cognitive rehabilitation after TBI. However, its use among persons with severe memory impairment should be applied to specific functional activities and offered after emergence from posttraumatic amnesia ([23], Class II).

There is no evidence demonstrating that computer-based tasks administered without therapist involvement (i.e., rote practice or task repetition on a computer) are beneficial, and their use therefore is specifically discouraged ([23], Class IV).

Attention: There is insufficient evidence to establish that attention training provided during the acute recovery period provides benefits above and beyond those associated with spontaneous recovery alone or from more general cognitive rehabilitation interventions. Accordingly, attention training during the early post-injury period is not recommended ([23, 26], Class IV).

Direct attention training and metacognitive training targeting the development of compensatory strategies is recommended during the postacute rehabilitation period. Direct attentional training may improve complex attention and reduce emotional distress ([43, 44], Class I). Repetition of working memory tasks may also improve attention benefits ([45], Class IV).

Clinician-guided computer-based attention training may be used as an adjunct to other cognitive rehabilitation interventions for attention. However, this adjunctive strategy should not consist solely of repeated exposure to computer-based training tasks ([23], Class II).

Memory: Compensatory strategy training, including internalized strategy training (e.g., visual imagery) and external memory compensations (e.g., memory notebooks), is a useful treatment for posttraumatic memory impairments generally ([23], Class I; [26], Class II). Individuals with relatively mild memory impairments, relatively preserved functional independence, and sufficient motivation to engage in and rehearse these compensatory strategies are most likely to benefit from this type of intervention ([21, 23], Class I). For individuals with more severe memory impairments, functionally relevant external memory compensations (e.g., memory notebooks) may be useful ([23], Class II).

Errorless learning may facilitate compensatory strategies training targeting personally relevant memory problems ([46], Class I). Errorless learning may be a useful strategy for teaching specific information or procedures to individuals with memory impairment and no more than mild executive dysfunction ([47, 23], Class IV). Transfer of training acquired by persons with severe posttraumatic memory impairments through errorless learning to novel tasks or functional use of memory is modest ([23], Class IV).

Group-based interventions also may be useful for the treatment posttraumatic memory impairments ([23], Class IV).

Language and Communication: Incorporating cognitive-linguistic therapies in postacute rehabilitation may facilitate cognitive and functional progress among individuals with posttraumatic language impairments ([23], Class IV). Errorless learning and self-instruction training also may provide communication benefits through improvements in emotional perception abilities ([48], Class II).

Evidence supports the efficacy of social communication skills training, incorporating pragmatic conversational skills, social behaviors, and cognitive abilities necessary for successful social interaction, in the postacute period (more than one year) following injury ([49, 50], Class I). Group-based interventions may be particularly useful methods of rehabilitating social communication skills after TBI ([23], Class IV).

Executive Function: Metacognitive strategy training entails treatments directed at improving self-monitoring and self-regulation, including emotional self-regulation. These inventions emphasize internalizing control of the skill to be learned. This can be accomplished by structured and repetitive cueing, or by encouraging ongoing self-monitoring and assessment. Such interventions typically require a high degree of individualization to the subject, his or her strengths and deficits, and the context in which those deficits occur. Metacognitive training is useful for the treatment of posttraumatic executive dysfunction ([23], Class I) and may contribute usefully to the treatment of posttraumatic attention and memory impairments ([23], Class I). Patients with relatively mild to moderate impairments in executive function are likely to benefit most from this form of cognitive rehabilitation. Awareness-training, incorporating feedback to increase the patient's appreciation for intact abilities and exercises involving predicting, self-monitoring, and self-evaluating performance, may improve self-awareness as well as cognitive aspects of instrumental activities of daily living performance ([51, 52], Class I). Patients with severely impaired executive function may need substantial, ongoing external interventions to compensate for such problems in even a limited fashion ([53, 54], Class IV).

Programmatic interventions for problem-solving deficits (focused training on problem-solving strategies) during the postacute rehabilitation period may improve function, especially when strategy training is directed at personally relevant everyday situations and functional activities ([55, 56], Class II). Autobiographical memory queuing may improve performance on planning tasks and support the development of problem-solving techniques ([57], Class III). Group-based problem-solving interventions also may be useful for the treatment of posttraumatic executive dysfunction ([23], Class IV).

Pharmacologic treatment

- Pharmacotherapy of cognitive impairment secondary to TBI is best regarded as adjunctive to nonpharmacologic interventions.
- Many medications are potentially useful treatments of posttraumatic cognitive impairments. However, the number for which there is evidence sufficient to support general treatment recommendations remains relatively limited. The discussion of pharmacotherapies for posttraumatic cognitive impairments offered here therefore focuses on medications with treatment effects that have been demonstrated in well-designed clinical trials or replicated in two or more studies published in peer-reviewed journals.

Uncompetitive N-Methyl-D-Aspartate Receptor Antagonists

Amantadine: Amantadine and memantine belong to the adamantanamine group of compounds. Their principal mechanism of action is uncompetitive antagonism at the NMDA receptor complex through the phencyclidine binding site inside the receptor-associated ion-channel. Antagonism of glutamatergic inhibitory inputs on presynaptic dopaminergic neurons secondarily enhances dopaminergic neurotransmission. These agents also are purported to have multiple additional effects on dopaminergic neurotransmission, including enhanced dopamine release, decreased presynaptic dopamine reuptake, stimulation of dopamine receptors, and/or enhanced postsynaptic dopamine receptor sensitivity. However, the strengths and relative contributions of direct dopaminergic modulatory properties on the clinical effects produced by amantadine and memantine when prescribed at typical doses (see below) remain uncertain [36, 58].

Treatment with amantadine within the first few days following TBI improves arousal at one-week post-injury ([59, 39], Class IV). This clinical effect appears more likely to reflect its attenuation of traumatically-induced glutamate excitotoxicity during the early post-injury period than facilitation of dopamine release, since functionally disruptive excesses of cerebral dopamine are characteristic of the early post-injury neurochemical disturbances incited by biomechanical neurotrauma [36, 60, 61].

By contrast, amantadine-mediated improvements in the rate of cognitive recovery during the subacute post-injury period following TBI ([62], Class I) as well as accelerated rate of functional recovery during subacute treatment of posttraumatic disorders of consciousness ([63], Class I) most likely reflect the indirect and/or direct dopamine-facilitating effects of this medication. Similarly, these effects are most likely to account for the beneficial effects of amantadine on attention, visuospatial function (constructional praxis), executive function, and general cognitive function during the subacute and late post-injury periods following moderate to severe TBI ([35], Class IV).

Standard dosage: 25–200 mg twice daily (total daily dose not to exceed 400 mg per day).

Contraindications: Use during pregnancy and breastfeeding are contraindicated. Patients with a history of seizures should be carefully monitored for change in seizure activity. Patients with congestive heart failure also require careful monitoring.

Main drug interactions: Amantadine may potentiate the effects of anticholinergic agents and other psychostimulants. Triamterene/hydrochlorothiazide may decrease renal excretion of amantadine.

Main side effects: Headache, nausea, diarrhea, constipation, anorexia, dizziness, lightheadedness, orthostatic hypotension, anxiety, irritability, depression, and hallucinations may occur during amantadine treatment. Psychosis and confusion may occur with high doses. Abrupt withdrawal has been associated (rarely) with neuroleptic malignant syndrome.

Cost: 100 mg = $1.78 ea.

Catecholamine Augmentation

Methylphenidate: Methylphenidate, like dextroamphetamine and other mixed amphetamine salts, augments cerebral levels of dopamine and norephinephrine via promotion of their release and, at higher doses, blocks monoamine reuptake and confers a modest degree of monoamine oxidase inhibition. Although dextroamphetamine [64, 65] and other mixed amphetamine salts are sometimes used to treat posttraumatic cognitive

impairments, the literature describing the efficacy, tolerability, and safety of methylphenidate for this purpose is much more fully developed. Accordingly, when a stimulant is used in this population, methylphenidate is the first-line medication from this class [36].

During the subacute and late post-injury periods, methylphenidate may improve hypoarousal ([28], Class I), attention and processing speed ([29, 31], Class I; [35], Class II), and general cognitive function ([35], Class IV). Methylphenidate also appears to improve cognitive function and to reduce daytime sleepiness in the context of depression during the subacute period following TBI, and is comparably effective to sertraline as an antidepressant ([66], Class II).

Standard dosage: Treatment typically begins at 5 mg twice daily, with doses given in the morning and mid-day. Doses are increased by 5 mg twice-daily increments every 2–3 days, as tolerated, to a target dose of 0.3 mg per kg twice daily (e.g., for a 70 kg patient, dosing is approximately 20 mg twice daily).

Contraindications: Concomitant use of an MAOI, pregnancy, and breastfeeding. Methylphenidate may exacerbate anxiety, psychosis, Tourette's syndrome and other tics or dyskinetic movements, glaucoma, hypertension, cardiovascular problems, and symptomatic hyperthryoidism.

Main drug interactions: Methylphenidate may decrease the metabolism of tricylic antidepressants, warfarin, primidone, phenytoin, phenobarbital, and phenylbutazone, and may decrease the effectiveness of antihypertensive agents.

Main side effects: Anxiety, irritability, insomnia, and dysphoria. Methylphenidate may suppress appetite, and cause mild increases in heart rate and blood pressure.

Special considerations: Methylphenidate does not predictably lower seizure threshold among TBI patients with seizures ([32, 27], Class I; [67], Class IV) and appears to be a generally safe treatment in this population ([32, 27], Class I).

Cost: 5 mg = $0.33 ea.; 10 mg = $0.47 ea.; 20 mg = $0.68 ea.

Bromocriptine: Bromocriptine acts directly on dopamine type 2 (D2) receptors. At low doses, bromocriptine acts as a pre-synaptic D2 receptor agonist, thereby reducing dopaminergic release and the function of dopaminergically-dependent neural systems. At mid-range doses, post-synaptic effects at D2 receptors predominate and, on balance, bromocriptine augments the function of the neural networks in which dopamine-responsive neurons participate [36].

In the subacute and late periods following complicated mild to severe TBI, bromocriptine improves executive function ([68], Class I). It also may improve "cognitive initation" (i.e., diminished motivation, or apathy) in the late post-injury period ([69, 70], Class IV). Bromocriptine does not appear to improve working memory ([68], Class I) or attention ([30], Class I) during the subacute or late periods following TBI, and its administration in this context is associated with clinically concerning adverse effects ([30], Class I).

The effects of bromocriptine on arousal among persons with disorders of consciousness are inconsistent ([70, 71], Class IV). In light of the evidence favoring amantadine for this purpose ([63], Class I), bromocriptine is at best a second-line intervention for the treatment of posttraumatic disorders of consciousness.

Standard dosage: 2.5–7.5 mg twice daily; package insert suggests that bromocriptine may be administered safely up to doses of 100 mg daily, although safety of such dosing among persons with TBI is not established.

Contraindications: Uncontrolled hypertension and hypersensitivity to ergot alkaloids are strict contraindications. Although breastfeeding is contraindicated, use during pregnancy does not appear to be associated with significant increased adverse events or outcomes.

Main drug interactions: Bromocriptine decreases the effectiveness of antidopaminergic agents.

Main side effects: Dizziness, drowsiness, faintness, syncope, nausea, vomiting, abdominal cramps, constipation, and diarrhea may occur frequently, though they are generally of mild severity.

Cost: 2.5 mg = $2.18 ea.

Cholinergic Augmentation—Treatment with cholinesterase inhibitors may contribute usefully to the treatment of persons with posttraumatic memory impairments during the subacute and late post-injury periods [35, 36, 38, 40, 61]. Although physostigmine has been used for this purpose [72], newer and better-tolerated cholinesterase inhibitors have supplanted it as a cholinergically-augmenting pharmacotherapy for posttraumatic cognitive impairments.

Donepezil: Donepezil is a centrally-selective acetylcholinesterase inhibitor. Treatment with donepezil improves attention and memory impairments during the subacute post-injury period ([33], Class I). In the late post-injury period, donepezil may improve subjective attention and memory complaints ([20], Class II; [73], Class IV), sensory gating impairments ([20], Class II), declarative memory impairments ([35, 40], Class III), and related neurobehavioral disturbances ([73, 74], Class IV).

Standard dosage: 5–10 mg daily.

Contraindications: Known hypersensitivity to donepezil or piperidine derivatives, pregnancy, and breastfeeding.

Main drug interactions: Agents that inhibit hepatic metabolism (CYP450, 3A4, and 2D6) such as ketoconazole and quinidine may increase blood levels of donepezil. Inducers of hepatic metabolism (phenobarbital, phenytoin, carbamazepine, dexamethasone, rifampin) may decrease blood levels. However, little is presently known about the drug-drug interactions of this agent.

Main side effects: Headache, nausea, diarrhea, vomiting, fatigue, insomnia, muscle cramping, pain, and abnormal dreams.

Cost: 5 mg = $7.87 ea.

Rivastigmine: Rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase; the former provides its mechanism of action on cerebral cholinergic function. Treatment with rivastigmine in the late post-injury period may improve attention and working memory ([75], Class I), although this effect was not observed in a similarly large study of this population ([34], Class I). In a planned secondary analysis of persons with persistent

posttraumatic memory impairments, rivastigmine improved declarative memory and secondarily improved attention, processing speed, executive function, and neuropsychiatric status ([34], Class II;[37], Class IV). Subjective improvements in attention, memory, motivation, and fatigue also are reported ([73], Class IV).

Standard dosage: 1.5–6 mg twice daily.

Contraindications: Known hypersensitivity to carbamates, pregnancy, and breastfeeding.

Main drug interactions: Rivastigmine may increase the effects of anesthetics and should be discontinued prior to surgery. Bradycardia may occur if combined with beta-blockers. Potential synergistic effects if co-administered with cholinomimetics.

Main side effects: Headache, nausea, diarrhea, vomiting, fatigue, appetite loss, dizziness, asthenia, sweating.

Cost: 3 mg = $2.50 ea.

Mixed Catecholamine and Cholinergic Augmentation

Cytidine 5′-Diphosphocholine (citicholine): Cytidine 5′-diphosphocholine (citicholine, or CDP-choline) is an essential intermediate in the biosynthetic pathway of phospholipids incorporated into cell membranes. It appears to activate the biosynthesis of structural phospholipids in neuronal membranes, increase cerebral metabolism, and enhance activity of dopamine, norepinephrine, and acetylcholine ([76–78]).

Treatment with citicholine during the early period after mild to moderate TBI may reduce postconcussive symptoms and improve recognition memory ([79], Class I). Among persons with moderate to severe TBI receiving inpatient rehabilitation, citicholine improves cognitive, motor, and psychiatric disturbances and shortens length of stay ([80], Class I).

Standard dosage: Up to 1–2 grams daily.

Contraindications: There are no known contraindications; given the limited available data, use during pregnancy or when breastfeeding is discouraged.

Main drug interactions: There are no known drug interactions with citicholine.

Main side effects: Side effects are uncommon, but may include insomnia, blurred vision, headache, nausea, diarrhea, blood pressure alterations, and chest pain.

Cost: 250 mg = $0.67 ea.

Additional Medication Considerations

- Patients with TBI are particularly susceptible to the adverse cognitive effects of antipsychotic medications ([36, 60, 38], Class IV). In general, these effects remit upon discontinuation of these agents.
- Antiepileptic drugs may contribute to cognitive impairment subsequent to TBI ([35, 36, 81], Class IV). Prophylactic treatment with phenytoin ([82, 83], Class I) or carbamazepine ([83], Class I) after the first week post-injury produces cognitive impairments. Valproate appears to be cognitively neutral during this period and

may be preferable when either continued prophylaxis or treatment of posttraumatic seizures is required ([84], Class I).

- Benzodiazepines as well as atypical gamma-aminobutyric acid (GABA) agonists may exacerbate cognitive disturbances in TBI patients ([64], Class III; [85], Class IV). Additionally, GABA agonists may negatively impact neuroplasticity, arguing against their use during the acute recovery period [85].
- Medications with anticholinergic properties may produce cognitive impairments (especially memory, attention, and executive function disturbances) at doses that are likely to be innocuous among persons without TBI ([61], Class IV).

Education

- Early education and counseling regarding TBI, postconcussive symptoms, expected course and typical outcomes is among the most effective interventions with which to reduce the risk of atypical recovery and persistent postconcussive symptoms after mild TBI ([86, 87], Class I) as well as moderate to severe TBI ([88], Class I).

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•• Of major importance

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