Cognitive Impairment Following Traumatic Brain Injury

*David B.Arciniegas, MD**
Kerri Held
Peter Wagner, MD

Address
*Denver Veterans Affairs Medical Center, 1055 Clermont Street, Denver, CO 80220, USA.
E-mail: David.Arciniegas@UCHSC.edu

Current Treatment Options in Neurology 2002, 4:43–57
Current Science Inc. ISSN 1092-8480

Opinion statement

- Cognitive impairments due to traumatic brain injury (TBI) are substantial sources of morbidity for affected individuals, their family members, and society. Disturbances of attention, memory, and executive functioning are the most common neurocognitive consequences of TBI at all levels of severity. Disturbances of attention and memory are particularly problematic, as disruption of these relatively basic cognitive functions may cause or exacerbate additional disturbances in executive function, communication, and other relatively more complex cognitive functions.
- Because of the high rate of other physical, neurologic, and psychiatric syndromes following TBI, a thorough neuropsychiatric assessment of the patient is a prerequisite to the prescription of any treatment for impaired cognition.
- Psychostimulants and other dopaminergically active agents (*eg,* methylphenidate, dextroamphetamine, amantadine, levodopa/carbidopa, bromocriptine) may modestly improve arousal and speed of information processing, reduce distractibility, and improve some aspects of executive function.
- Cautious dosing (start-low and go-slow), frequent standardized assessment of effects and side effects, and monitoring for drug-drug interactions are recommended.
- Cognitive rehabilitation is useful for the treatment of memory impairments following TBI. Cognitive rehabilitation may also be useful for the treatment of impaired attention, interpersonal communication skills, and executive function following TBI. This form of treatment is most useful for patients with mild to moderate cognitive impairments, and may be particularly useful for those who are still relatively functionally independent and motivated to engage in and rehearse these strategies.
- Psychotherapy (*eg,* supportive, individual, cognitive-behavioral, group, and family) is an important component of treatment. For patients with medication- and rehabilitation-refractory cognitive impairments, psychotherapy may be needed to assist both patients and families with adjustment to permanent disability.

Introduction

Traumatic brain injury (TBI) is a common problem in the US, with hospital-based catchment surveys conservatively estimating an incidence of 200 per 100,000 persons per year, or about 550,000 new injuries per year [1]. An additional 1.7 million persons experience a mild TBI requiring the attention of a physician [2]. Many more do not come

to medical attention in the immediate post-injury period, and may be unaccounted for epidemiologically [3]. The most common causes of TBI are motor vehicle accidents, falls, and assaults [1]. Alcohol or other substances may be causally involved in as many as 50% of these injuries [4]. The incidence of TBI is bimodally distributed, peaking in the second and third decades of life and increasing again after the seventh decade. Men are injured two to three times more often than women in younger age groups, whereas both sexes are equally at risk after age 65 [5]. Mild injuries account for the majority of TBI (80%), followed next by moderate (10% to 13%) and then severe injuries (7% to 10%).

At least 85,000 persons who experience TBI each year develop persistent cognitive, emotional, behavioral, or somatic disability [6]. Neuropsychiatric sequelae such as mood and anxiety disorders, postconcussive syndrome, personality change, aggression, and psychosis are among the most common problems after a significant TBI and produce significant morbidity among TBI survivors [7]. Whether one regards the development of neuropsychiatric problems following TBI as direct consequences of neurologic damage, pre- or post-TBI emotional and psychosocial issues, or a complex interaction of these factors, it is clear that such problems do develop, interfere with recovery and rehabilitation, and require treatment.

Cognitive impairments due to TBI are substantial sources of morbidity for affected individuals, their family members, and society [8]. Disturbances of attention, memory, and executive functioning are common consequences of TBI at all levels of severity [9,10].

Selective attention and sustained attention (vigilance or concentration) are relatively basic cognitive functions. Selective attention refers to the direction of attentional processing towards a single stimulus, and sustained attention refers to the maintenance of attentional processing on a single stimulus. Ideally, an individual is able to develop multiple attentional processing streams simultaneously (divided attention or "multitasking") and shift flexibly between attentional sets. Relatively intact attention is also required for new learning (encoding new memories).

These attentional processes are subserved by a large, selective, distributed neural network [11]. This network is comprised of multiple central nervous system structures including the reticular formation, thalamus, hippocampal and entorhinal areas, the frontal and right parietal lobes, and the axonal connections between these areas. Marked disruptions in the structure or functioning of this network produce a range of clinical symptoms, with coma and delirium at the severe end of the continuum and mild inattention and related disturbances in new learning at the other.

Complex cognitive functions, including executive function, comportment ("social intelligence"), and motivation are also frequently impaired after TBI. Executive function refers to a collection of abilities including categorization and abstraction; systematic memory searching and information retrieval; problem solving; self-direction; planning and organization of cognition and behavior; independence from external environmental contingencies; maintenance of and fluent shifting between information or behavior sets; and use of language to guide behavior. These are the functions that are most immediately regarded as "intelligence" by patients, their families, and their care providers. Executive function is most often ascribed to the function of dorsolateral prefrontal-subcortical circuit [12], and in particular its ability to integrate the processing and interaction of more "basic" cognitive processes carried on elsewhere in the brain. Executive dysfunction is a relatively common consequence of TBI, and may arise as a direct effect of injury to the frontal lobes or instead as a consequence of disturbances in the more basic aspects of cognition [13].

Comportment describes the manner in which one interacts with others. This term refers to the ability to understand and integrate self-assessment with social cueing, or the process of generating socially appropriate and adaptive behavior. This function is most often ascribed to the lateral orbitofrontal-subcortical circuit [12] and its ability to integrate limbic-paralimbic information with other socially or environmentally relevant information. Impairments in this cognitive domain are common consequences of TBI, both acutely and chronically [14]. Because such impairments typically present as behavioral disturbances (*ie,* aggression, disinhibition, social inappropriateness), and not as disturbances of cognition per se, treatment of these problems is not discussed in this article. For additional information on the treatment of these problems, readers are referred to reviews by Arciniegas *et al.* [15] and Silver and Yudofsky [14].

Motivation refers to the process of generating, directing, and sustaining goal-directed cognition, emotion, and behavior. Dysfunction of this process results in diminished motivation (or, in increasingly extreme forms, apathy or abulia)—a reduction in goal-directed motor, emotional, and cognitive activity. Motivation is most often ascribed to the anterior cingulate-subcortical circuit [12]. Diminished motivation is a common consequence of severe TBI, although it may also be seen following relatively milder injuries. Although the treatment of diminished motivation overlaps substantially with the treatment of impaired cognition, it will not be more specifically addressed in this paper. Readers interested in a more thorough review of this subject alone are referred to an article by Campbell and Duffy [16].

The neural substrates of complex cognition are comprised by a series of relatively discrete, parallel, distributed, and reciprocally interconnected frontal-subcortical networks. These networks are anatomic and functional extensions of those subserving basic cognition. Conse-

Table 1. Medications and their dose ranges and typical dosing schedules commonly used in the treatment of cognitive impairment due to traumatic brain injury

Medcation	Adult dose range, *mg/day*	Typical dosing schedule
Methylphenidate	5 to 80	Two to four times daily
Dextroamphetamine	5 to 60	Two to four times daily
Amantadine	50 to 400	One to two times daily
Bromocriptine	2.5 to 7.5	Three times daily
Levodopa/carbidopa	10/100 to 25/100	Two to four times daily
Donepezil	5 to 10	Once daily
Protriptyline	5 to 60	Once in the morning

quently, these "higher" cognitive (*eg,* executive) functions are to some degree predicated on relatively normal "lower" cognitive functions (*eg,* attention, language, new learning). Of note, disturbances in complex cognition may also impair the function of (or at least ability to make use of) more basic cognitive functions.

Although cognitive deficits arising from penetrating or focal trauma are often understandable given the functions known to be subserved by the site of injury (*eg,* disinhibition following bilateral orbitofrontal contusion) [17], the etiology of cognitive impairments following nonpenetrating (or "nonfocal") injuries is relatively less well understood. It is known that cytotoxic processes (*ie,* calcium and magnesium dysregulation, free radical injury, neurotransmitter excitotoxicity) [18] and diffuse axonal injury due to straining and shearing biomechanical forces [18,19] result from nonpenetrating, noncontusional injuries. These processes functionally and structurally disrupt the neural networks subserving cognition, and may by this mechanism produce cognitive impairment.

Because there are no US Food and Drug Administration (FDA) approved treatments for cognitive impairment due to TBI, pharmacotherapies are generally modeled after those for patients with phenomenologically similar, but etiologically distinct disorders (*ie,* attention-deficit hyperactivity disorder, Alzheimer's disease, and others). For example, the attention deficits of persistently impaired TBI survivors sometimes superficially resemble those of patients with attention-deficit hyperactivity disorder (ADHD). Given this similarity, some authors suggest that psychostimulants (*eg,* methylphenidate, dextroamphetamine, amantadine, and others) may be useful for hypoarousal, slowed information processing, and distractibility following TBI.

The clinical effectiveness of these agents might suggest that catecholaminergic dysfunction underlies such deficits after TBI. However, few studies [20–22] offer support for the hypothesis that cerebral catecholamine levels are chronically altered by TBI; instead, most suggest only that acute elevations of striatal dopamine are predictive of poor recovery from TBI [23–25]. However, no human studies have demonstrated a clear relationship between in vivo markers of dopaminergic function and long-term cognitive deficits in traumatically brain-injured humans.

A more consistent and often pursued hypothesis in basic and clinical neuroscience relates cognitive impairment following TBI to acute and long-term alterations in cortical cholinergic function. Animal studies [26–28] demonstrate chronic alterations in hippocampal cholinergic function following experimentally-induced TBI, and the relationship of such alterations to persistent cognitive impairments. Human postmortem [29,30] studies also demonstrate that TBI produces cortical cholinergic dysfunction via loss of cortical cholinergic afferents; these studies also demonstrate that post-synaptic muscarinic and nicotinic receptors are not reduced by TBI.

A cholinergic hypothesis of attention and memory impairment following TBI is formulated readily based on 1) the role of acetylcholine in attention and memory; 2) the strong relationship between cholinergic deficits and cognitive impairment following experimentally-induced injury in animals; and 3) observed losses of cortical cholinergic afferents following TBI in humans [31,32]. Multiple studies have demonstrated that cholinergic augmentation, generally using one of several cholinesterase inhibitors (*eg,* physostigmine, donepezil), can improve TBI-induced memory deficits even in the late postinjury period (longer than 1 year) in some TBI survivors [33–39•].

It may be that both cholinergic and dopaminergic dysfunction, including dopaminergic dysfunction secondary to reduced cortical cholinergic function, contribute to cognitive impairments following TBI. Although the literature demonstrating reduced cortical cholinergic function following TBI is robust, clinical evidence suggests a role for augmentation of either or both neurotransmitter systems in persistently impaired TBI survivors (*see* Table 1 for a list of typically used agents, doses, and dosing schedules). However, the interindividual response to such agents is not uniform [40]. Some patients respond to psychostimulants, some to cholinesterase inhibitors, some to either, and others to neither class of medication. Selecting an appropriate treatment for a given patient might be done more easily if clinical markers (neurophysiologic, neuroimaging, or

specific symptoms) of dysfunction in these systems were available. However, no simple and inexpensive methods of indexing either dopaminergic or cholinergic function in humans are available.

Despite the high frequency of neuropsychiatric problems following TBI, there is a relative paucity of rigorously conducted clinical studies on which to base treatment decisions. Treatment of cognitive impairment due to TBI is the most extensively studied area, but even here there are limitations regarding both treatment methods and their cost effectiveness. The recommendations made in this article are derived from an extensive review of two major modes of treatment for cognitive impairment following TBI—pharmacotherapy and cognitive rehabilitation. Other issues (*eg*, diet and lifestyle, psychotherapy) will receive brief comments, but readers should bear in mind that there are no studies to offer guidance about the effectiveness (or cost effectiveness) of these "alternative" treatments of cognitive dysfunction due to TBI.

Treatment

Diet and lifestyle

- Persistently symptomatic patients, whether suffering from cognitive, emotional, behavioral, or somatic problems following TBI, should be encouraged to participate in TBI support groups and to make use of the local and national brain injury associations for education, information, and general support. For convenience, the internet address for the national Brain Injury Association is www.biausa.org.
- There is no evidence to support benefit a role for specific diets or other nutritional programs on cognitive performance following TBI. One possible exception is the nutritional supplement cytidine 5′-diphosphocholine (CPD-choline or citicholine), which is discussed in the next section.

Pharmacologic treatment

Psychostimulants

Methylphenidate

In the acute rehabilitation setting, methlyphenidate may improve the rate of functional recovery and attention [41, Class I]. Studies suggest that methylphenidate may be used during the postacute recovery period after TBI to increase the rate of recovery, an effect that may facilitate increased involvement and compliance with acute rehabilitation and perhaps earlier hospital discharge.

In a study of 10 patients undergoing acute rehabilitation, Kaelin *et al.* [42••, ClassIIa] demonstrated improved attention, as assessed by the Digit Span, Mental Control subscale of the Wechsler Memory Test-Revised, and Symbol Search scores, and improved function as assessed by Disability Rating Scores (DRS).

Mood and cognitive performance may also respond to methylphenidate [43, Class I], although it is not clear whether or for how long such benefits are sustained by this treatment. Additionally, it may be that cognitive improvements occurring in the context of concurrently improved mood may be attributable to this latter improvement alone.

Arousal and speed of information processing may be also improved by methylphenidate, even where no significant effects are observed on other aspects of attention, including motor speed, distractibility, and vigilance performance [44••, Class I].

Methylphenidate does not significantly reduce seizure threshold in traumatically brain-injured patients, including those with active seizure disorders [45•, Class IIIa2].

In summary, methylphenidate may improve arousal, speed of information processing, and some aspects of basic attention. However, treatment response to methylphenidate is not universal among TBI patients [46, Class I]. It may be most helpful to patients whose deficits are in the specific domains of cognition already demonstrated to respond to this treatment.

Standard dosage	5 to 80 mg per day; higher doses may be needed and safely tolerated. Doses may be divided into two, three, or four times daily doses, if necessary. Sustained-release preparations are available, and may be useful, but have no to-date studies in this population.
Contraindications	Concomitant use of a monoamine oxidase inhibtor (MAOI), pregnancy, and breast-feeding. May exacerbate anxiety, psychosis, Tourette's syndrome and other tics, glaucoma, hypertension, cardiovascular problems, and symptomatic hyperthryoidism.
Main drug interactions	May decrease the metabolism of tricyclic antidepressants (TCAs), warfarin, primidone, phenytoin, phenobarbital, and phenylbutazone. May decrease the effectiveness of antihypertensive agents.
Main side effects	Anxiety, irritability, insomnia, and dysphoria. May suppress appetite, and cause mild increases in heart rate and blood pressure.
Special points	Methylphenidate does not predictably lower seizure threshold among TBI patients with seizures, and is a potentially useful and safe treatment in this population [47, Class IIIa2].
Cost/cost effectiveness	5 mg costs $0.29 each; 10 mg costs $0.40 each; 20 mg costs $0.59 each.

Dextroamphetamine

	Dextroamphetamine is frequently used in the treatment of attention and memory impairment following TBI, and is thought to have beneficial effects on depression, anergia, and impaired motivation. However, a thorough Medline search yielded only a single Class IIIb report to support its use in this population [48]. This report describes improvement in verbal memory and learning skills in response to treatment with either this agent or methylphenidate in a single adult male treated in the late post-injury period.
Standard dosage	5 to 60 mg per day. Doses may be divided into two, three, or four times per day doses, if necessary.
Contraindications	Concomitant use of breast-feeding is an absolute contraindication. Pregnancy, hyperthyroidism, moderate to severe hypertension, glaucoma, symptomatic cardiovascular disease, and a history of stimulant abuse are relative contraindications and warrant caution. Dextroamphetamine may also exacerbate or produce (rare) psychosis, worsening Tourette's syndrome and other tics, and exacerbate dystonia and dyskinesia.
Main drug interactions	Acidifying agents lower absorption of dextroamphetamine, and alkalinizing agents increase its absorption. The effects of antihypertensive agents may be antagonized. These agents may also potentiate the effects of phenobarbital and phenytoin by delaying gastrointestinal absorption, increase the noradrenergic effects of TCAs, increase the dopaminergic effects of antiparkinsonian agents, and potential the analgesic properties of meperidine. Haloperidol and lithium may decrease the effectiveness of dextroamphetamine.
Main side effects	Headache, hyperactivity, insomnia, restlessness, talkativeness, palpitations, tachycardia, mild increases in blood pressure, dry mouth, constipation, or diarrhea.
Cost/cost effectiveness	5 mg costs $0.25.

Amantadine

	Amantadine has significant dopaminergic properties and has been suggested to be of benefit for many of the same problems for which the other psychostimulants are used [49,50, Class IIIa1]. Amantadine may reduce agitation, aggression, affective lability, and may improve motivation (apathy). With regard to cognitive performance, amantadine may improve arousal, speed of information processing and vigilance [51, Class IIIb; 52, Class IIIa], and may also reduce perseveration [51, Class IIIb].
Standard dosage	50 to 400 mg per day.
Contraindications	Use during pregnancy and breast-feeding are contraindicated. Patients with a history of seizures should be carefully monitored for change in seizure activity during treatment with amantadine. Patients with congestive heart failure also require careful monitoring when amantadine is used.

Main drug interactions	Amantadine may potentiate the effects of anticholinergic agents and other psychostimulants. Triamterene and 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 (rare) with neuroleptic malignant syndrome.
Cost/cost effectiveness	100 mg costs $0.18 each tablet.

Bromocriptine

	Bromocriptine may also improve impaired executive function and diminished motivation due to TBI [53, Class I]. However, unlike the other psychostimulants, bromocriptine has not been demonstrated to have a consistent effect on affective lability or mood disorders due to TBI.
Standard dosage	2.5 to 7.5 mg per day.
Contraindications	Uncontrolled hypertension and hypersensitivity to ergot alkaloids are strict contraindications. Although breast-feeding is contraindicated, use during pregnancy does not appear to be associated with significant increased adverse events or outcomes.
Main drug interactions	Bromocriptine will decrease 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/cost effectiveness	2.5 mg costs $1.69 each tablet.

Levodopa/carbidopa

	Levodopa/carbidopa may also be useful for patients with impaired motivation, hypoarousal and inattention, and executive dysfunction, independent of the presence of motor dysfunction, with effective doses ranging between 10/100 and 25/250 tablets four times per day [54, Class IIIa1].
Standard dosage	10/100 twice daily to 25/250 four times daily.
Contraindications	Concomitant use of a MAOI, narrow-angle glaucoma, pregnancy, breast-feeding, and melanoma (or suspicious but undiagnosed skin lesions).
Main drug interactions	Significant postural hypotension may develop in patients concurrently treated with antihypertensive agents. Antidopaminergic agents predictably decrease the effectiveness of levodopa/carbidopa. Hypertension and dyskinesias have also been reported during concurrent treatment with TCAs.
Main side effects	Involuntary choreiform movements, dystonia, other involuntary movements, paranoia, hallucinations, and depression may occur. Nausea, vomiting, orthostatic hypotension, dizziness, nightmares, anxiety, and headache may occur.
Cost/cost effectiveness	10/100 mg costs $0.26 each; 25/100mg costs $0.28 each; 25/250 mg costs $0.33 each.

Procholinergic agents

- Traumatic brain injury may produce cognitive impairments via disruption of cholinergic function [55,56]. As noted, animal and human studies both support this suggestion. Additionally, the sensitivity of TBI patients the anticholinergic effects of many commonly prescribed medications also suggests that these individuals may have a relatively reduced reserve of cholinergic function.
- Several reports describe cognitive improvements following administration of physostigmine, both in the acute [33, Class IIIa1] and postacute [34,35, Class IIIb] injury period. Levin *et al.* [36, Class I] performed a double blind, placebo-controlled study of combined oral physostigmine and lecithin in 16 patient with moderate to severe TBI demonstrating cognitive impairments

during inpatient rehabilitation. Although the results generally indicated no difference in the effects of the physostigmine-lecithin combination as compared to lecithin alone, sustained attention on the continuous performance test was more efficient under physostigmine than placebo. Similarly, Cardenas *et al.* [37, Class I] performed a double blind, placebo-controlled, crossover design study of physostigmine, placebo, and scopolamine (a cholinergic antagonist) in 36 men with memory impairment of at least 3 months duration following TBI. Improvement in memory scores occurred in 44% of subjects while taking oral physostigmine but not placebo or scopolamine, particularly on the long-term storage component of the Selective Reminding Test.

- Although physostigmine may be of benefit to cognitively impaired TBI survivors, the systemic toxicity associated with this medication limits its acceptability as a treatment in this population. Given the availability of other, safer, orally administered cholinesterase inhibitors, the authors do not recommend using physostigmine.
- Among the second-generation cholinesterase inhibitors (*eg,* tacrine, donepezil, rivastigmine, galantamine), donepezil is the only agent for which there are published reports supporting use in the TBI population. Although there is no reason to suspect that the other cholinesterase inhibitors might not also be similarly useful, at present there is no evidence to support their use.

Donepezil hydrochloride

Donepezil hydrochloride, a centrally selective cholinesterase inhibitor with relatively limited systemic effects, may also be of benefit for cognitive impairment following TBI. Taverni *et al.* [38, Class IIIa1] described improvements in refractory memory impairments as assessed by the Rivermead Behavioral Memory Test and Ross Immediate Processing Assessment in the late post-injury period in two traumatically brain-injured patients. Improvement occurred after approximately 3 weeks of treatment at 5 mg per day.

Whelan *et al.* [39•, Class IIIa1] performed an open-label study of donepezil in 53 outpatients receiving care for long-term neuropsychiatric sequelae of TBI, including cognitive impairment. Patients were treated with donepezil 5 to 10 mg daily for an average of 12 months. Assessments of cognition with the Wechsler Adult Intelligence Scale-Revised and the Hooper Visual Organization Test were obtained on a subset of 22 patients, and clinician assessment ratings were obtained for the entire sample. Improvements in full-scale intelligence quotient (IQ) and clinician-based ratings were observed. These improvements occurred well after the period during which spontaneous recovery and "practice effects" might offer better explanations for them.

Blokland [31] suggests that acetylcholine may also play a pivotal role in the modulation of attentional processes. Arciniegas *et al.* [57, Class IIIa1] describe improvement in auditory sensory gating (a pre-attentive function that facilitates filtering of sensory information and therefore selective attention) and related evoked potentials in eight of 10 patients treated with donepezil hydrochloride 5 mg per day.

Standard dosage 5 to 10 mg per day.

Contraindications Known hypersensitivity to piperidine derivatives, pregnancy, and breast-feeding.

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, and 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/cost effectiveness 5 mg costs $4.28 each tablet.

Tricyclic antidepressants

- In general, TCAs should not be prescribed for any reason in patients with significant cognitive impairment due to TBI; the significant anticholinergic and antihistaminergic effects of these agents predictably further impairs cognition in this population [15, ClassIIIc].
- The development of seizures during treatment with any TCA in this population is particularly concerning, and has been reported to occur in nearly 20% of TBI patients treated with these agents [59, Class IIIa2].

Protriptyline

Protriptyline, a secondary amine TCA, may be an exception to the recommendation discussed previously. This agent has been suggested to have sufficient stimulant properties to permit its use for anergia and diminished motivation in TBI patients [58, Class IIIa1]. However, this agent does not appear to confer any benefit on cognition beyond that afforded by improved arousal and motivation alone. Additionally, the authors of the report described the use of protriptyline in this population as best considered as an alternative treatment option only when other standard psychostimulants have not proven effective.

Standard dosage 5 to 60 mg per day.

Contraindications Concurrent use of a MAOI is absolutely contraindicated. Early postacute myocardial infarction, narrow-angle glaucoma, prostatic hypertrophy, and seizure disorders are also general contraindications.

Main drug interactions May decrease the effects of clonidine and indirect-acting sympathomimetics, and increase the effects of direct-acting sympathomimetics, sedatives (*eg,* alcohol, barbiturates, benzodiazepines, and central nervous system depressants).

Main side effects Anticholinergic effects (*eg,* dry mouth, blurred vision, mild tachycardia, urinary retention, constipation), orthostatic hypotension, and sedation are most common. Rare effects include agranulocytosis, thrombocytopenia, eosinophilia, leukopenia, paralytic ileus, hepatitis, and significant QRS interval prolongation.

Special points Seizure risk in the acute rehabilitation setting may preclude use of this medication.

Cost/cost effectiveness 5 mg costs $0.47 each; 10 mg costs $0.68 each.

Cytidine 5'-diphosphocholine

Cytidine 5'-diphosphocholine (CDP-choline or citicoline) is an essential intermediate in the biosynthetic pathway of phospholipids incorporated into cell membranes. Orally ingested CDP-choline is metabolized into its two principle components, cytidine and choline. CDP-choline appears to activate the biosynthesis of structural phospholipids in neuronal membranes, increase cerebral metabolism, and enhance activity of dopamine, norepinephrine, and acetylcholine [60•,61]. As such, it has been suggested that CDP-choline may improve neuropsychologic performance among cognitively impaired TBI survivors.

One single blind randomized study conducted in 216 patients with severe or moderate TBI suggests that CDP-choline may improve global outcome of patients, including improvement in motor, cognitive, and psychiatric problems [62, Class Iia]. The CDP-choline group also had a decreased length of stay in the hospital.

Levin [63, Class I] performed a double blind placebo-controlled study of 14 patients to evaluate the efficacy of CDP-choline for treating post-concussion symptoms in the first month after mild to moderate TBI. Oral CDP-choline (1 g) and placebo control groups were matched for age, education, and severity of initial injury (as assessed by impairment of consciousness). CDP-choline reduced the severity of post-concussion symptoms and improved recognition memory for designs. Other aspects of neuropsychologic performance were not significantly influenced by this treatment.

CDP-choline is available in the US as a nutritional supplement, and is most commonly formulated as 250 mg capsules (the cost of each capsule is about $0.25). The articles noted suggested that doses approaching 1 g per day may be

required to effect cognitive improvement among TBI survivors. A meta-analysis of studies using CDP-choline in elderly patients suggests that it is associated with less adverse effects than placebo [64], and there are no reports of serious adverse events in the TBI population. At present, the limited scope of the relevant literature and the lack of rigorous FDA scrutiny of the safety, tolerability, and efficacy of this agent preclude recommending routine use CDP-choline in this population. However, for patients unwilling or unable to take other prescribed medications, CDP-choline may be a "nutritional supplement" that some patients may find more acceptable and which may be of modest benefit.

Additional medication considerations

- Patients with TBI are particularly susceptible to the adverse effects of antipsychotic medications [65, Class IIIa]. Typical antipsychotic agents, and in particular low-potency neuroleptics, have been shown to produce significant cognitive impairments in TBI patients; such impairments improve on discontinuation of these agents [66, Class IIIa1].
- In a double blind placebo-controlled study of the cognitive and emotional effects of phenytoin (40 patients) and carbamazepine (42 patients) in TBI patients being treated with these medications for seizure prophylaxis, Smith *et al.* [67, Class I] noted that both of these medications (but particularly carbamazepine) produced significantly more cognitive and motor slowing than did placebo. Dikmen *et al.* [68, Class I] also described greater cognitive impairment during treatment with phenytoin for prophylaxis of posttraumatic seizures when compared with placebo in a study with 244 patients with TBI. Additionally, phenytoin conferred no benefit against the development of post-traumatic seizures when used after the first week post-TBI. Both studies suggest that careful monitoring of cognition during treatment with anticonvulsants in brain-injured patients is warranted, and that such treatment should be reserved for patients with established seizure disorders.

Other treatments

Cognitive rehabilitation

- Cognitive rehabilitation is a systematic, functionally oriented program of interventions designed to improve neuropsychologic performance. Following a thorough neuropsychologic assessment of a patient's cognitive strengths and deficits, interventions are designed to reestablish or reinforce previously learned skills, develop compensatory strategies for cognitive deficits, or facilitate adaptation to irremediable cognitive impairments. Regardless of the specific type of intervention, cognitive rehabilitation is intended to promote functional improvement, and limit the impact of permanent cognitive disabilities on everyday functioning and quality of life.
- Cognitive rehabilitation is often multimodal, but each component is directed towards the improvement of a specific cognitive domain or ability. Programs targeting impairments in attention, language and communication, memory, visuospatial function, and executive function have been studied in TBI patients. The literature regarding cognitive rehabilitation is complex, and interpretation of treatment studies is challenging. Interested readers should refer to Cicerone *et al.* for a detailed review of this subject [69••]. This report describes an exhaustive review of the published literature available via MedLine performed by the Cognitive Rehabilitation Committee (a subcommittee of the American Congress of Rehabilitation Medicine's Brain Injury—

Interdisciplinary Special Interest Group). In their report, studies of cognitive rehabilitation delivered to patients with either TBI or stroke are discussed. The authors of this paper will discuss only the studies pertaining to TBI, and will draw on the recommendations of Cicerone *et al.* and the authors' own interpretation of the literature in making comments herein. The authors' review and recommendations are summarized according to domain of cognition. Of note, there is no data regarding the cost effectiveness of these treatments.

Attention

Inventions for attentional impairments generally employ repetition of drills focused on speed of information processing, selective attention, sustained attention (concentration, vigilance), and divided attention. These drills appear to be designed to improve performances through practice, although ongoing feedback, reinforcement, and strategy education are sometimes incorporated, as well.

Studies performed to-date do not support the use of attention training interventions during the acute recovery period following TBI [70, Class I; 71, Class IIa1], and the limited evidence of benefit from such programs appears to be entirely accounted for by spontaneous recovery, practice effects or both, and such therapies do not appear to alter the rate of recovery. Additionally, attention training interventions in the acute recovery period do not appear to effect improvements in neuropsychologic functioning or activities of daily living that exceed those conferred by standard acute rehabilitation.

In the postacute and late post-injury period, attention training directed at improvement of selective and divided attention may be beneficial [72, Class I]. Treatments targeting reaction time and vigilance appear to be less effective [71, Class IIa1; 73, Class IIIa]. Additionally, there is limited evidence that the benefits of attention training generalize beyond the specific task of the training exercises. Additional research is required to ascertain whether strategy education and feedback facilitate generalization of such training to everyday functions or activities of daily living.

Memory

Memory training typically focuses on rehabilitation of deficits in new learning (encoding) and information retrieval (recall) in either the acute or postacute injury periods. Typical interventions include use of compensatory aids (notebooks, computers, pagers, reminder alarms), environmental adaptations (including restructuring of patient, family, and social interactions), and compensatory strategies (rehearsal, organization, visual imagery, verbal labeling, mnemonics).

Compensatory strategy training for memory impairments is useful [74–76, Class I], particularly when such training includes individualized strategies targeting everyday memory problems [74, Class I], rehearsal and visual imagery [75, Class I], and memory notebooks [76, Class I]. These studies suggest that patients 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.

Patients with moderate to severe memory impairments may benefit from compensatory strategies targeting learning of specific skills and information, particularly when related to work skills [77, Class II; 78,79, Class IIIa; 80, Class IIIb]. However, there is no evidence to suggest that memory rehabilitation permits more severely impaired patients to extend their compensatory strategies beyond the specific tasks rehearsed during rehabilitation.

Language and communication

Deficits in language include any of the aphasias; such deficits are very uncommon consequences of nonpenetrating TBI and occur only when relevant language areas are contused or functionally disconnected from the neural networks in which they

participate. More subtle deficits in communication related to self- and interpersonal awareness (forms of "social cognition") are relatively more common consequences of TBI.

There is limited literature supporting the use of rehabilitation strategies targeting interpersonal communication skills. In a study of 16 patients with functional communication deficits in the acute rehabilitation period, Helffenstein and Wechsler [81, Class I] demonstrated improvements in self-concept, interpersonal communication skills, and improved everyday interpersonal communication using systematic feedback based on videotapes of patients' interpersonal interactions. Similar benefits may be obtained from focused communication skill rehabilitation in the late post-injury period [82, Class IIIa1], although additional research is required to confirm this suggestion and the generalizability of improvements facilitated by such training.

Executive function

Executive function includes categorization and abstraction; systematic memory searching and information retrieval; self-reflection; problem solving; judgment; freedom from external environmental contingencies; maintenance of and fluent shifting between information or behavior sets; use of language to guide behavior; organization and planning or cognition and behavior; and behavioral adaptation. Deficits in these areas may produce marked difficulties in everyday problem solving, reasoning, decision making, and functional independence. Interventions for such deficits may be predominantly behavioral (specific skill-based training), cognitive (strategies for initiation and self-monitoring of skills), or both. Importantly, deficits in relatively more basic aspects of cognition (attention, memory) should be remediated prior to intensive rehabilitation of executive function, and deficits in the latter area may be predicated on deficit in the former areas.

Two small Class IIa studies [83,84] suggest that programmatic interventions for problem solving deficits (focused training on problem-solving strategies) and application of such to everyday situations and functional activities may be useful. These inventions should emphasize internalization of 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 are manifested.

Patients with relatively mild to moderate impairments in executive function are likely to benefit most from this form of cognitive rehabilitation. Patients with severely impaired executive function may need substantial, ongoing external interventions to compensate for such problems in even a limited fashion [85, Class IIIb; 86, Class III].

Education

- A brief educational intervention regarding the types of symptoms and course of recovery should be offered to patients with mild TBI in the immediate postacute injury period (within 3 weeks). This intervention appears to reduce postconcussive symptom formation and improve functional outcome just as effectively as longer educational and treatment programs [87, Class II]. It is not clear whether such brief educational interventions reduce symptoms of mild neurocognitive dysfunction more specifically. To the extent that other postconcussive symptoms and psychologic overlay contribute to cognitive dysfunction, brief educational interventions may reduce the likelihood of additional cognitive disability caused by these other neuropsychiatric sequelae.

Psychotherapy

- In the postacute injury period, cognitive group therapy during inpatient rehabilitation may be particularly useful for improving social interaction skills among more severely injured patients [88, Class IIIa1]. Such treatment may mitigate the potentially negative impact of TBI on the patient's interactions with caregivers, family, and other social supports. Importantly, family members should be included in these therapies because they both experience adverse effects of a patient's TBI and sometimes inadvertently contribute to persistent emotional and behavioral problems following TBI [89, Class IIIa1].
- Brief cognitive behavioral therapy has been suggested to be of particular benefit in the treatment of postconcussive symptoms, and may limit the potential impact of iatrogenic development of persistent cognitive and emotional symptoms following mild TBI [90, Class IIIc].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kraus JF, Sorenson SB: **Epidemiology.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudofsky SC, Hales RE. Washington, DC: American Psychiatric Press; 1994:3–41.
2. Waxweiler RJ, Thurman D, Sniezek J, *et al.*: **Monitoring the impact of traumatic brain injury: a review and update.** *J Neurotrauma* 1995, **12:**509–516.
3. Fife D: **Head injury with and without hospital admission: comparison of incidence and short–term disability.** *Am J Public Health* 1987, **77:**810–812.
4. Miller NS: **Alcohol and Drug Disorders.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudosfsky SC, Hales RE. Washington, DC: American Psychiatric Press; 1994:471–512.
5. Fogel BS, Duffy J: **Elderly Patients.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudofsky SC, Hales RE. Washington, DC: American Psychiatric Press; 1994:413–441.
6. Kraus JF, Nourjah P: **The epidemiology of mild head injury.** In *Mild Head Injury.* Edited by Levin HS, Eisenberg HM, Benton AL. New York: Oxford University Press; 1989:8–22.
7. McAllister TW: **Neuropsychiatric sequelae of head injuries.** *Psychiat Clin N Am* 1992, **15:**395–413.
8. Max W, MacKenzie E, Rice D: **Head injuries: costs and consequences.** *J Head Trauma Rehabil* 1991, **6:**76–91.
9. O'Shanick GJ, O'Shanick AM: **Personality and Intellectual Changes.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudofsky SC, Hales RE. Washington, D.C.: American Psychiatric Press, Inc.; 1994:163–188.
10. Lovell MR, Franzen MD: **Neuropsychological Assessment. In** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudofsky SC, Hales RE. Washington, D.C.: American Psychiatric Press, Inc.; 1994:133–160.
11. Mesulam M-M: *Principles of Behavioral and Cognitive Neurology,* edn 2. Philadelphia: FA Davis; 2000.
12. Mega MS, Cummings JL: **Frontal-subcortical circuits and neuropsychiatric disorders.** *J Neuropsychiat Clin Neurosci* 1994, **6:**358–370.
13. Spikman JM, Deelman BG, Van Zomeren AH: **Executive functioning, attention and frontal lesions in patients with chronic CHI.** *J Clin Exp Neuropsychol* 2000, **22:**325–338.
14. Silver JM, Yudofsky SC: **Aggressive Disorders.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by: Silver JM, Yudosfky SC, Hales RE. Washington, DC: American Psychiatric Press; 1994:313–353.
15. Arciniegas DB, Topkoff J, Silver JM: **Neuropsychiatric Aspects of Traumatic Brain Injury.** *Curr Treat Options Neurol* 2000, **2:**167–186.
16. Campbell JJ, Duffy JD: **Treatment strategies in amotivated patients.** *Psychiatr Ann* 1997, **27:**44–49.
17. Cassidy JW: **Neuropathology.** In *Neuropsychiatry of Traumatic Brain Injury.* Edited by Silver JM, Yudofsky SC, Hales RE. Washington, DC: American Psychiatric Press; 1994:43–79.
18. McIntosh TK, Juhler M, Raghupathi R, *et al.*: **Secondary brain injury: neurochemical and cellular mediators.** In *Traumatic Brain Injury.* Edited by Marion DW. New York: Thieme Medical Publishers; 1999:39–54.
19. Halliday AL: **Pathophysiology.** In *Traumatic Brain Injury.* Edited by Marion DW. New York: Thieme Medical Publishers; 1999:29–38.
20. Tang YP, Noda Y, Nabeshima T: **Involvement of activation of dopaminergic neuronal system in learning and memory deficits associated with experimental mild traumatic brain injury.** *Euro J Neurosci* 1997, **9:**1720–1727.

21. Eghwrudjakpor PO, Miyake H, Kurisaka M, Mori K: **Central nervous system bioaminergic responses to mechanical trauma: an experimental study.** *Surg Neurol* 1991, **35:**273–279.
22. Kmeciak-Kolada K, Felinska W, Stachura Z, *et al.*: **Concentration of biogenic amines and their metabolites in different parts of brain after experimental cerebral concussion.** *Pol J Pharmacol Pharm* 1987, **39:**47–53.
23. Donnemiller E, Brenneis C, Wissel J, *et al.*: **Impaired dopaminergic neurotransmission in patients with traumatic brain injury: a SPECT study using 123I–beta–CIT and 123I–IBZM.** *Eur J Nuclear Med* 2000, **27:**1410–1414.
24. Hamill RW, Woolf PD, McDonald JV, *et al.*: **Catecholamines predict outcome in traumatic brain injury.** *Ann Neurol* 1987, **21:**438–443.
25. Woolf PD, Hamill RW, Lee LA, *et al.*: **The predictive value of catecholamines in assessing outcome in traumatic brain injury.** *J Neurosurg* 1987, **66:**875–882.
26. Dixon CE, Bao J, Bergmann JS, Johnson KM: **Traumatic brain injury reduces hippocampal high–affinity [3H]choline uptake but not extracellular choline levels in rats.** *Neurosci Letters* 1994, **180:**127–130.
27. Saija A, Robinson SE, Lyeth BG, *et al.*: **The effects of scopolamine and traumatic brain injury on central cholinergic neurons.** *J Neurotrauma* 1988, **5:**161–170.
28. DeAngelis MM, Hayes RL, Lyeth BG: **Traumatic brain injury causes a decrease in M2 muscarinic cholinergic receptor binding in the rat brain.** *Brain Res* 1994, **653:**39–44.
29. Murdoch I, Perry EK, Court JA, *et al.*: **Cortical cholinergic dysfunction after human head injury.** *J Neurotrauma* 1998, **15:**295–305.
30. Dewar D, Graham DI: **Depletion of choline acetyltransferase but preservation of M1 and M2 muscarinic receptor binding sites in temporal cortex following head injury: a preliminary human postmortem study.** *J Neurotrauma* 1996, **13:**181–187.
31. Blokland A: **Acetylcholine: a neurotransmitter for learning and memory?** *Brain Res Brain Res Rev* 1995, **21:**285–300.
32. Aigner TG: **Pharmacology of memory: cholinergic–glutamatergic interactions.** *Curr Opin Neurobiol* 1995, **5:**155–160.
33. Bogdanovitch UJ, Bazarevitch GJ, Kirillov AL: **The use of cholinesterase in severe head injury.** *Resuscitation* 1975, **4:**139–141.
34. Eames P, Sutton A: **Protracted post-traumatic confusional state treated with physostigmine.** *Brain Inj* 1995, **9:**729–734.
35. Goldberg E, Gerstman LJ, Hughes JE, *et al.*: **Selective effects of cholinergic treatment on verbal memory in posttraumatic amnesia.** *J Clin Neuropsychol* 1982, **4:**219–234.
36. Levin HS, Peters BH, Kalisky Z, *et al.*: **Effects of oral physostigmine and lecithin on memory and attention in closed head–injured patients.** *Cent Nerv Sys Trauma* 1986, **3:**333–342.
37. Cardenas DD, McLean A, Farrell-Roberts L, *et al.*: **Oral physostigmine and impaired memory in adults with brain injury.** *Brain Inj* 1994, **8:**579–587.
38. Taverni JP, Seliger G, Lichtman SW: **Donepezil mediated memory improvement in traumatic brain injury during post acute rehabilitation.** *Brain Inj* 1998, **12:**77–80.
39.• Whelan FJ, Walker MS, Schultz SK: **Donepezil in the treatment of cognitive dysfunction associated with traumatic brain injury.** *Ann Clin Psych* 2000, **12:**131–135.

This article is describes the largest study of donepezil for the treatment of the neuropsychiatric sequelae of TBI performed to-date, and offers evidence to support use of this medication in this population.

40. Speech TJ, Rao SM, Osmon DC, Sperry LT: **A double-blind controlled study of methylphenidate treatment in closed head injury.** *Brain Inj* 1993, **7:**333–338.
41. 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 Rehab* 1996, **77:**536–40.
42.•• Kaelin DL, Cifu DX, Matthies B: **Methylphenidate effect on attention deficit in the acutely brain–injured adult.** *Arch Phys Med Rehab* 1996, **77:**6–9.

This study provides strong evidence of a beneficial effect of methylphenidate on several measures of attention.

43. Gualtieri CT, Evans RW: **Stimulant treatment for the neurobehavioral sequelae of traumatic brain injury.** *Brain Inj* 1988, **2:**273–290.
44.•• 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 Rehab* 1997, **76:**440–450.

This excellent Class I study suggests that the primary benefits afforded by methylphenidate in cognitively impaired TBI survivors are increased arousal and improved processing speed.

45.• Wroblewski BA, Leary JM, Phelan AM, *et al.*: **Methylphenidate and seizure frequency in brain injured patients with seizure disorders.** *J Clin Psych* 1992, **53:**86–89.

Although now nearly a decade old, this article offers evidence that methylphenidate does not increase risk of seizures in this population.

46. Speech TJ, Rao SM, Osmon DC, Sperry LT: **A double-blind controlled study of methylphenidate treatment in closed head injury.** *Brain Inj* 1993, **7:**333–338.
47. Wroblewski BA, Leary JM, Phelan AM, *et al.*: **Methylphenidate and seizure frequency in brain injured patients with seizure disorders.** *J Clin Psych* 1992, **53:**86–89.
48. Evans RW, Gualtieri CT, Patterson D: **Treatment of chronic closed head injury with psychostimulant drugs: a controlled case study and an appropriate evaluation procedure.** *J Nerv Ment Dis* 1987, **175:**106–110.
49. Gualtieri T, Chandler M, Coons TB, Brown LT: **Amantadine: a new clinical profile for traumatic brain injury.** *Clin Neuropharmacol* 1989, **12:**258–270.

50. Kraus MF, Maki PM: **Effect of amantadine hydrochloride on symptoms of frontal lobe dysfunction in brain injury: case studies and review.** *J Neuropsych Clin Neurosci* 1997, **9:**222–230.
51. Van Reekum R, Bayley M, Garner S, *et al.*: **N of 1 study: amantadine for the amotivational syndrome in a patient with traumatic brain injury.** *Brain Inj* 1995, **9:**49–53.
52. Nickels JL, Schneider WN, Dombovy ML, Wong TM: **Clinical use of amantadine in brain injury rehabilitation.** *Brain Inj* 1994, **8:**709–718.
53. 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.
54. Lal S, Merbtiz CP, Grip JC: **Modification of function in head–injured patients with Sinemet.** *Brain Inj* 1988, **2:**225–233.
55. Arciniegas D, Adler L, Topkoff J, *et al.*: **Attention and memory dysfunction after traumatic brain injury: cholinergic mechanisms, sensory gating, and a hypothesis for further investigation.** *Brain Inj* 1999, **13:**1–13.
56. Whitlock JA: **Brain injury, cognitive impairment, and donepezil.** *J Head Trauma Rehab* 1999, **1:**424–427.
57. Arciniegas DB, Topkoff JL, Anderson CA, *et al.*: **Normalization of P50 physiology by donepezil hydrochloride in traumatic brain injury patients.** *J Neuropsychiat Clin Neurosci* 2001, **13:**140.
58. Wroblewski B, Glenn MB, Cornblatt R, *et al.*: **Protriptyline as an alternative stimulant medication in patients with brain injury: a series of case reports.** *Brain Inj* 1993, **7:**353–362.
59. Wroblewski BA, McColgan K, Smith K, *et al.*: **The incidence of seizures during tricyclic anti-depressant drug treatment in a brain-injured population.** *J Clin Psychopharmacol* 1990, **10:**124–128.
60.• Secades JJ, Frontera G: **CDP-choline: pharmacological and clinical review.** *Methods Find Exp Clin Pharmacol* 1995, **17(suppl):**1–54.

This article is one of the most frequently cited reviews of CDP-choline, and will be of particular use to those considering recommending this agent to their patients.

61. Dixon CE, Ma X, Marion DW: **Effects of CDP-Choline treatment on neurobehavioral deficits after TBI and on hippocampal and neocortical acetylcholine release.** *J Neurotrauma* 1997, **14:**161–169.
62. Calatayud M, Calatayud V, Perez JB, Aso EJ: **Effects of CDP-choline on the recovery of patients with head injury.** *J Neurol Sci* 1991, **103(suppl):**S15–S18.
63. Levin HS: **Treatment of postconcussional symptoms with CDP-choline.** *J Neurol Sci* 1991, **103:**S39–S42.
64. Fioravanti M, Yanagi M: **Cytidinediphosphocholine (CDP choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly.** The Cochrane Database of Systematic Reviews 1[1]. 2001.
65. Pourcher E, Baruch P, Bouchard RH, *et al.*: **Neuroleptic associated tardive dyskinesias in young people with psychoses.** *Brit J Psych* 1995, **166:**768–772.
66. Stanislav SW: **Cognitive effects of antipsychotic agents in persons with traumatic brain injury.** *Brain Inj* 1997, **11:**335–341.
67. Smith KR, Jr, Goulding PM, Wilderman D, *et al.*: **Neurobehavioral effects of phenytoin and carbamazepine in patients recovering from brain trauma: a comparative study.** *Arch Neurol* 1994, **51:**653–660.
68. Dikmen SS, Temkin NR, Miller B, *et al.*: **Neuro-behavioral effects of phenytoin prophylaxis of posttraumatic seizures.** *JAMA* 1991, **265:**1271–1277.
69.•• Cicerone KD, Dahlberg C, Kalmar K, *et al.*: **Evidence-based cognitive rehabilitation: recommendations for clinical practice.** *Arch Phys Med Rehab* 2000, **81:**1596–1615.

This article reviews the literature regarding cognitive rehabilitation is substantial detail, and will be very useful for those wishing to quickly survey the literature regarding the effectiveness of cognitive rehabilitation for patients with TBI or stroke.

70. Novack TA, Dillon MC, Jackson WT: **Neurochemical mechanisms in brain injury and treatment: a review.** *J Clin Exp Neuropsychol* 1996, **18:**685–706.
71. Ponsford JL, Kinsella G: **Evaluation of a remedial programme for attentional deficits following closed–head injury.** *J Clin Exp Neuropsychol* 1988, **10:**693–708.
72. Gray JM, Robertson I, Pentland B, Anderson S: **Microcomputer-based attentional retraining after brain damage: a randomized group controlled trial.** *Neuropsychol Rehab* 1992, **2:**97–115.
73. Ethier M, Braun CM, Baribeau JM: **Computer-dispensed cognitive-perceptual training of closed head injury patients after spontaneous recovery. Study 1: speeded tasks.** *Can J Rehabil* 1989, **2:**223–233.
74. Berg I, Konning-Haanstra M, Deelman B: **Long-term effects of memory rehabilitation: a controlled study.** *Neuropsychol Rehab* 1991, **1:**97–111.
75. Ryan TV, Ruff RM: **The efficacy of structured memory retraining in a group comparison of head trauma patients.** *Arch Clin Neuropsychol* 1988, **3:**165–179.
76. Schmitter-Edgecombe M, Fahy J, Whelan J, Long C: **Memory remediation after severe closed head injury. Notebook training versus supportive therapy.** *J Consult Clin Psychol* 1995, **63:**484–489.
77. Wilson BA, Evans JJ, Emslie H, Malinek V: **Evaluation of NeuroPage: a new memory aid.** *J Neurol Neurosurg Psychiatry* 1997, **63:**113–115.
78. Zencius A, Wesolowski MD, Burke WH: **A comparison of four memory strategies with traumatically brain–injured clients.** *Brain Inj* 1990, **4:**33–38.
79. Burke JM, Danick JA, Bemis B, Durgin CJ: **A process approach to memory book training for neurological patients.** *Brain Inj* 1994, **8:**71–81.
80. Kime SK, Lamb DG, Wilson BA: **Use of a comprehensive programme of external cueing to enhance procedural memory in a patient with dense amnesia.** *Brain Inj* 1996, **10:**17–25.

81. Helffenstein D, Wechsler R: **The use of interpersonal process recall (IPR) in the remediation of interpersonal and communication skill deficits in the newly brain injured.** *Clin Neuropsychol* 1982, **4:**139–143.

82. Gajar A, Schloss PJ, Schloss CN, Thompson CK: **Effects of feedback and self-monitoring on head trauma youths' conversation skills.** *J Appl Behav Anal* 1984, **17:**353–358.

83. Fox RM, Martella RC, Marchand-Martella NE: **The acquisition, maintenance and generalization of problem solving skills by closed head injured adults.** *Behav Ther* 1989, **20:**61–76.

84. Cicerone KD, Giacino JT: **Remediation of executive function deficits after traumatic brain injury.** *Neurorehabilitation* 1992, **2:**12–22.

85. Sohlberg MM, Sprunk H, Metzelaar K: **Efficacy of an external cueing system in an individual with severe frontal lobe damage.** *Cognit Rehab* 1988, **6:**36–41.

86. Evans JJ, Emslie H, Wilson BA: **External cueing systems in the rehabilitation of executive impairments of action.** *J Int.Neuropsychol Soc* 1998, **4:**399–408.

87. Paniak C, Toller-Lobe G, Durand A, Nagy J: **A randomized trial of two treatments for mild traumatic brain injury.** *Brain Inj* 1998, **12:**1011–1023.

88. Lundgren CC, Persechino EL: **Cognitive group: a treatment program for head–injured adults.** *Am J Occ Ther* 1986, **40:**397–401.

89. Uomoto JM, Brockway JA: **Anger management training for brain injured patients and their family members.** *Arch Phys Med Rehab* 1992, **73:**674–679.

90. Miller LJ, Mittenberg W: **Brief cognitive behavioral interventions in mild traumatic brain injury.** *App Neuropsychol* 1998, **5:**172–183.