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Guidelines for the Pharmacologic Treatment of Neurobehavioral Sequelae of Traumatic Brain Injury

NEUROBEHAVIORAL GUIDELINES WORKING GROUP MEMBERS

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ABSTRACT

There is currently a lack of evidence-based guidelines to guide the pharmacological treatment of neurobehavioral problems that commonly occur after traumatic brain injury (TBI). It was our objective to review the current literature on the pharmacological treatment of neurobehavioral problems after traumatic brain injury in three key areas: aggression, cognitive disorders, and affective disorders/anxiety/psychosis. Three panels of leading researchers in the field of brain injury were formed to review the current literature on pharmacological treatment for TBI sequelae in the topic areas of affective/anxiety/psychotic disorders, cognitive disorders, and aggression. A comprehensive Medline literature search

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was performed by each group to establish the groups of pertinent articles. Additional articles were obtained from bibliography searches of the primary articles. Group members then independently reviewed the articles and established a consensus rating. Despite reviewing a significant number of studies on drug treatment of neurobehavioral sequelae after TBI, the quality of evidence did not support any treatment standards and few guidelines due to a number of recurrent methodological problems. Guidelines were established for the use of methylphenidate in the treatment of deficits in attention and speed of information processing, as well as for the use of beta-blockers for the treatment of aggression following TBI. Options were recommended in the treatment of depression, bipolar disorder/mania, psychosis, aggression, general cognitive functions, and deficits in attention, speed of processing, and memory after TBI. The evidence-based guidelines and options established by this working group may help to guide the pharmacological treatment of the person experiencing neurobehavioral sequelae following TBI. There is a clear need for well-designed randomized controlled trials in the treatment of these common problems after TBI in order to establish definitive treatment standards for this patient population.

Key words: aggression; brain injury; cognition; evidence based reviews; neurobehavior; pharmacology; psychiatric disorders

INTRODUCTION

TRAUMATIC BRAIN INJURY (TBI) is a principal cause of death and disability in active young adults today. Approximately 5 million Americans live with disability as a result of brain injury, with an estimated cost to society of $48.3 billion annually.[1,2]

Neurobehavioral problems commonly seen after TBI include psychiatric disorders, cognitive problems and aggression. It is well recognized that neurobehavioral problems are the most debilitating sequelae to individuals with TBI attempting to reestablish family and work relationships.[3] These sequelae may also impede the rehabilitation and recovery process, contribute to sub-optimal follow-up, and ultimately negatively affect overall outcomes. Such symptoms may interfere with return to work and quality of life and the cost to the nation in care expenditures, lost productivity and family disruption is staggering.[4]

While many small clinical trials and case studies have been conducted of the effectiveness of pharmacologic therapy for these problems after TBI, a comprehensive review to form evidence based practice guidelines has not been conducted.

I. Affective Disorders, Anxiety, and Psychosis after TBI

A significant body of evidence suggests that TBI results in an increased relative risk of developing various psychiatric disorders including mood and anxiety disorders, as well as psychotic syndromes.[5–8] Despite this, there is little consensus about the treatment of these disorders. In the absence of good evidence, a body of clinical lore has developed which suggests that individuals with TBI are more refractory to treatment, more prone to the various side effects of psychotropic agents, and may not respond to traditional psychotropic agents.[9] In fact some clinicians feel very strongly that some standard agents are ineffective, or that they may be associated with excess toxicity in the brain injured population.

Depression after TBI is very common, with best estimates suggesting that 25–60% of individuals with TBI develop a depressive episode within eight years of their injury.[6,10,11] Depression is associated with poorer social and functional outcome.[11] Anxiety occurs frequently with depression,[4,6,11,12] and may occur as an independent disorder. Van Reekum and colleagues have suggested that individuals with TBI have increased relative risks of generalized anxiety disorder, obsessive compulsive disorder (OCD), panic disorder, and post-traumatic stress disorder (PTSD) of 2.3, 2.6, 5.8, and 1.8, respectively. PTSD and depression are common disorders in those who have persistent postconcussive symptoms.[13,14]

Although psychosis is a relatively rare complication of TBI, psychotic syndromes do occur more frequently in individuals who have had a TBI than in the general population.[8,15–17] Psychosis is a good example of a low frequency, high impact complication of TBI, causing enormous distress to individuals and their caregivers.[15] Psychotic syndromes following TBI can occur during the period of post-traumatic amnesia, as a complication of post-traumatic epilepsy, in the context of TBI-related mood disorders, or associated with a chronic, schizophrenia-like syndrome. Bearing these contexts in mind when assessing the etiology of psychosis helps to guide appropriate interventions.

Thus, considering that depression, anxiety, and psychotic disorders occur at increased rates in individuals

with TBI, and that 1–2 million Americans sustain a TBI each year, it is important to clarify the state of evidence with respect to the pharmacologic treatments of these disorders in the TBI population.

II. Cognitive Deficits after TBI

The cognitive effects of TBI become evident after resolution of posttraumatic amnesia and have been well documented.[18,19] Although cognitive deficits vary with severity of injury, these generally include problems with attention/concentration, memory, and executive functioning, e.g., problem solving, mental flexibility, and initiation. These deficits are found within the overall picture of diffuse brain injury and, in particular, damage to frontotemporal regions commonly seen in TBI. Cognitive complaints are common even after mild TBI both acutely and at later follow-up. Prevalence rates for memory and attention complaints after mild TBI vary but have been reported to range from 40 to 60% at 1–3 months post-injury.[20] Deficits can result in significant long-term morbidity even in those with more mild injuries. The development of effective treatment strategies for these cognitive sequelae is critical. Medications are frequently used to treat neurobehavioral sequelae.[21,22] However, evidence-based clinical guidance has been lacking.

In considering the possible effects of pharmacologic treatment on the cognitive deficits that can follow TBI, at least three complexities have to be kept in mind. One is that cognition is not a single ability; it is now known to be made up of components that are separable on functional, neural, and pathological grounds. Another complexity is that the components of cognition cannot be measured in pure form by any available test, so that the translation from actual test results to componential function is rarely exact. The third complexity is that TBI need not respect the componential boundaries and may cause functional deficits that are greater or less than the sum of the component deficits.

Cognitive components (domains). The usual division of cognitive domains separates them into the following components: attention, executive function, memory, language, visuospatial and constructional abilities, and sensory-perceptual-motor skills. Although the traditional definitions of each domain is well recognized, rapidly expanding research has elaborated further complexity with respect to domain subcomponents and the interrelationship of the neural networks that subserve these domains. For the purpose of our review of outcomes in TBI pharmacologic treatment research, we have defined these domains using the following framework.

Attention and speed of processing. The diffuse damage that accompanies traumatic brain injury tends to diminish attention/concentration, mental processing speed, and cognitive efficiency. Related to these decreased abilities, patients' complaints include inability to concentrate, distractibility, difficulty performing more than one task at a time, confusion and perplexity in thinking, irritability, fatigue, and increased time and effort to perform even simple tasks.[18,23,24]

Memory. Problems with memory are among the most common cognitive complaints in persons with TBI. Memory can be fractionated into a variety of processes and subdomains that fit along a number of overlapping dimensions. The studies reviewed for this report that cover memory functions largely consider declarative memory processes (i.e. recall of facts and events) and associated subdomains. Memory processes are highly related to attention and executive functioning, and problems in these domains may affect the efficiency of encoding and retrieval.

Executive functions. Prefrontal brain systems are vulnerable to diffuse and focal damage after TBI; consequently, problems in executive capacities such as reasoning, planning, inhibiting, organizing and sequencing are common in persons with TBI. Again, a number of subdomains within this category of cognition are interdependent with other cognitive domains and emotional functioning.

III. Aggression after TBI

Explosive and violent behavior has long been associated with focal brain lesions, as well as with diffuse damage to the central nervous system (CNS).[25] Agitation that occurs during the acute stages of recovery from brain injury can endanger the safety of patients and their caregivers. Agitation may be predictive of longer length of stay and decreased cognition.[26] Subsequently, low frustration tolerance and explosive behavior may develop that can be set off by minimal provocation or occur without warning. Aggression and irritability are major causes of disability to individuals with brain injury and sources of stress to their families. These episodes range in severity from irritability to outbursts that result in damage to property or assaults on others. Aggressive and agitated behaviors may be treated in a variety of settings, ranging from the acute brain injury unit in a general hospital, to a "neurobehavioral" unit in a rehabilitation facility, to outpatient environments including the home setting. However, in severe cases, affected individuals cannot remain in the community or with their families, and require care in long-term psychiatric or neurobehavioral facili-

ties. In a survey of all skilled nursing facilities in Connecticut, 45% of facilities had individuals with a primary diagnosis of TBI who met the definition of agitation.[27]

It has been reported that during the acute recovery period, 35–96% of individuals with brain injury exhibit agitated behavior.[28,29] After the acute recovery phase, irritability or bad temper is common, particularly following moderate to severe injury. In the two prospective studies of the occurrence of aggression, agitation, or restlessness that have been monitored by an objective rating instrument, the Overt Aggression Scale, 11–34% of TBI patients were found to be agitated or have aggressive behavior.[30,31] In studies that have followed patients from 1 to 15 years after injury, irritability has occurred in up to 71%, and agitation in up to 67%.[32–42] In one study, increased irritability has also been linked to the number of traumatic brain injuries and the presence of loss of consciousness.[43]

Although there is no medication that is approved by the FDA specifically for the treatment of aggression, medications are widely used in the management of patients with acute or chronic aggression. The reported effectiveness of these medications is highly variable, as are the reported rationales for their prescription.

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METHODS

General Methodology and Search Strategy

The guidelines group accomplished the evidence based review of the literature over several meeting sessions. Subgroups based on topic area were identified during the first meeting held in January 2000. Search parameters for each topic were also identified at that time. The primary comprehensive literature search was conducted at the meeting held in July 2000. The search engine OVID was used to explore the Medline database from 1960 to the present. In brief, the overall approach used was to define the proper terms for brain injury, the behavioral syndromes of interest, and the therapies of interest. The term *Craniocerebral Trauma* was the broadest appropriate term in the OVID program for generating articles relevant to traumatic brain injury. This includes such areas as brain injuries, coma, post-head injury, head injuries (closed and penetrating), and intracranial hemorrhage (traumatic). Each of these terms in turn has several subheadings. OVID allows these terms to be "exploded" which means that the search will include all of the subheadings under the main heading. For example, an "exploded" search of *Craniocerebral Trauma* resulted in 59,780 references. The addition of key words "brain injury, head injury, head injuries" resulted in a total of 63,702 references. The terms used to generate the brain injury and behavioral syndromes were then combined and filtered to include humans (as opposed to animals) and English language articles.

These terms, along with the syndromes of interest, therapies of interest, and other key words were combined to generate a bibliography of articles to be further evaluated. Subject review articles were included solely for a review of bibliographies in order to capture any relevant articles that may have been missed by the computer review. References from research articles were also reviewed for inclusion. Similarly, all members of the guidelines group were asked to review their personal files for any pertinent articles that may not have been identified by the Medline search. Titles of research articles were reviewed initially for relevance to the topic. When a decision could not be made, abstracts were obtained. Based

on review of the article titles and abstracts, two group members reduced the list of papers to be read by the working group. If the title or abstract appeared to be relevant to the topic, the full text article was reviewed.

This review confined itself to research done on individuals with TBI and a review of other therapies commonly used for TBI sequelae but with published literature only in other patient populations was beyond the scope of the project. However, readers should not lose sight of the fact that evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.

Article Scoring

Papers were read and scored by at least two of the group members independently. Both committee members completed data extraction forms. Articles were scored based on methodology with consideration to limitations/potential confounds that would affect the interpretation of results. A consensus review was then completed for each paper, and the level of evidence decided upon by the two primary reviewers. When the two primary reviewers could not reach agreement, the other group members were consulted to achieve a consensus rating. Evidence tables were generated using the scoring results on this final group of papers.

The scoring method was adapted from the Brain Trauma Foundation's Guidelines for the Management of Severe Head Injury[1]:

Class I evidence. This is well-designed and conducted prospective randomized controlled trials (RCT)—the gold standard of clinical trials. However, some may be downgraded due to poor design, insufficient patient numbers, or other methodological inadequacies.

Class II evidence. This is well-designed and conducted clinical studies in which the data were collected prospectively, or retrospective analyses based on clearly reliable data. Types of studies so classified include: observational studies, cohort studies, prevalence studies, and case control studies. As mentioned above, class I design studies may be downgraded to class II evidence based on methodological flaws.

Class III evidence. Most studies are based on retrospectively collected data. Evidence used in this class indicates well-designed and conducted clinical series, databases or registries, case reviews, and case reports. Class I and II design studies may be downgraded to class III evidence due to methodological flaws.

As mentioned above, although a class I study by design, a RCT could be downgraded by raters to class II or class III evidence or even be judged unusable based upon the degree of methodological flaws. Articles were also rated unusable if no measurement data were provided, patients had acquired rather than traumatic brain injury or if a mixed population was reported for which separate data for patients with TBI were not given. In an effort to minimize confusion, throughout this document classes I, II and III refer to classes of evidence (the final decision of the group based upon study design and downgrades for methodological flaws) rather than study design, except where specifically noted in the text.

Recommendations for standards, guidelines and options were based upon the level of evidence described in the Table 1 (adapted from Cicerone et al., 2000[2]).

I. Affective Disorders, Anxiety, and Psychosis

The Affective Disorders, Anxiety, and Psychosis work group initially determined their focus to be a review of evidence for the pharmacologic treatment of depression and anxiety. After further discussion and an initial review of available literature from preliminary searches, it was felt that the review should be expanded to include evidence for the treatment of other mood disorders includ-

Table 1. Criteria for Determining the Level of Recommendation

Standards	*Guidelines*	*Options*
Based on at least 1, well-designed class I study with an adequate sample, or overwhelming class II evidence, that directly addresses the effectiveness of the treatment in question, providing good evidence to support a recommendation as to whether the treatment be specifically considered for persons with traumatic brain injury.	Based on well designed class II studies with adequate samples, that directly addresses the effectiveness of the treatment in question, providing fair evidence to support a recommendation as to whether the treatment be specifically considered for persons with traumatic brain injury.	Based on class II or class III studies, with additional grounds to support a recommendation as to whether the treatment be specifically considered for persons with traumatic brain injury.

ing mania, as well as the treatment of psychotic syndromes. Other behavioral syndromes (such as pathological affect or affective lability, PTSD, substance abuse) were not included in this effort. The terms *anxiety disorders, mood disorders, mania, bipolar disorder, schizophrenia and disorders with psychotic features* were used by the Affective Disorders/Anxiety/Psychosis working group were used in the Medline search to describe the psychiatric disorders of interest. The terms *antidepressive agents, antipsychotic agents, anti-anxiety agents, anticonvulsants, electroconvulsive therapy, electromagnetics, phototherapy, drug therapy* were used to encompass the therapies of interest. In an effort to be sure that papers exploring the use of newer atypical antipsychotics and other new biological interventions were identified, the key words clozapine, olanzapine, quetiapine, and transcranial magnetic stimulation were added. The working group reviewed a total of 150 papers including those in the initial medline search and those identified by group members and from bibliography searches. The majority of these articles were review papers or not within the topic area and thus were subsequently excluded after bibliography review was conducted. However, 43 remaining articles were considered for evidence.

II. Cognitive Disorders

A preliminary list of search terms was generated by the subgroup members through a discussion on cognitive impairments secondary to traumatic brain injury. Group members were able to generate this list from their clinical expertise and knowledge within their respective disciplines. From this discussion, a list of 188 clinical terms to describe these impairments was generated, in addition to a list of pharmacological agents. These clinical terms were submitted for the initial MESH term search. Two subject heading specialists from the Medical Subject Heading Department, Jacqueline Shoalman and Doug Johnston, were consulted via telephone. Many of the terms selected did not have exact matches, and the initial search yielded thousands of additional possible families of search terms. This new list of terms to consider was circulated to all members of the subgroup, who systematically eliminated various terms that were considered irrelevant for the purposes of the project. The search process also revealed that pharmacologic treatments were generally not indexed hierarchically enough to allow an appropriate search using index terms. In addition, there was some concern that "cognitive disorders" of the kind thought to occur after traumatic brain injury had also been given various category labels. After additional consultation with Robert Mormon, Director of the Medical Library at Walter Reed Army Medical Center, the final search was ultimately done using a search string to identify closed head injury, in conjunction with a variety of cognitive disorders. The search for pharmacologic treatments was done manually, using the titles of the retrieved articles. The exact search string that was used for MEDLINE and PsychLit through January 2002, was the following:

> (Craniocerebral trauma [mh] OR brain injuries [mh] OR head injuries, closed [mh] OR brain damage, chronic [mh]) AND (Delirium, Dementia, Amnestic, Cognitive Disorders [mh] OR cognition [mh] OR cognitive symptoms [mh] OR memory [mh] OR memory disorders [mh] OR attention [mh] OR arousal [mh] OR neuropsychological tests [mh] OR activities of daily living [mh] OR affective symptoms [mh] OR laughter [mh] OR akathisia, drug-induced [mh] OR motor activity [mh] OR dysarthria [mh] OR akinetic mutism [mh] OR delirium [mh] OR hallucinations [mh] OR neurologic manifestations [mh] OR behavioral symptoms [mh])

This comprehensive process identified 61 papers that were reviewed and entered into the evidence tables for the Cognitive Disorders working group.

III. Aggression

At the initial meeting of the Aggression working group, the primary focus question for the group was determined to be "What is the evidence to direct pharmacologic management of aggressive disorders following traumatic brain injury?" The group decided to defer an investigation of treatment for agitation of individuals in an acute confusional state and to focus the current investigation on those individuals with TBI seen in the post-acute stage, such as in a rehabilitation unit or an outpatient setting. Members discussed topic areas and identified search terms for the literature search for articles on aggression. Literature from institutionalized populations (e.g., prison populations) was not reviewed as it was deemed difficult to generalize to the larger population of patients with brain injury. The methodology chosen was based on the Institute of Medicine (IOM) Committee to Advise the Public Health Service on Clinical Practice Guidelines (1990). The search string used in the Medline search engine included the following:

> (craniocerebral trauma OR head injury OR brain injury) AND (aggression OR irritability OR violence) AND (drug therapy OR beta blockers OR anticonvulsants OR propranolol OR valproate OR lithium OR benzodiazepines OR neuroleptics OR antidepressants)

Later searches were completed for penetrating brain injury, as well as individual anticonvulsants. Titles and abstracts were reviewed for appropriateness. Articles clearly not in the topic area, or reporting preclinical work, were excluded. The aggression subgroup identified a total of 127 articles. The majority of these articles were review papers or not within the topic area and thus were subsequently excluded after bibliography review was conducted. However, 52 remaining articles were considered for evidence.

Search Update

Due to the lengthy review process undertaken in this evidence based report, the initial search will be more than three years old at the time of publication. Although a comprehensive search could not be conducted again for the intervening time period, a focused literature review was performed in October 2004, to identify any new randomized controlled trials. The search term "Brain Injuries" was limited to include only randomized controlled trials on Medline and the resulting references and abstracts were reviewed to determine any relevant publications. Two recent randomized controlled trials were reviewed by group members using the same methodology described above and have been included in this report.

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AFFECTIVE DISORDERS, ANXIETY, AND PSYCHOSIS

I. Recommendations

Standards: There is insufficient evidence to support the development of standards in the treatment of TBI related depression, mania, anxiety and psychosis.

Guidelines: There is insufficient evidence to support the development of guidelines in the treatment of TBI related depression, mania, anxiety and psychosis.

Options:

Depression:

Tricyclic Antidepressants (TCAs)

The use of tricyclic antidepressants is recommended as an option in the treatment of TBI related depression. Specifically, amitriptyline (up to 300 mg/day) and desipramine (150–300 mg/day) have been reported to be effective for the treatment of depression after TBI. However, side effects may limit their utility in this population. Two reports indicate that TCAs may be less effective in patients with TBI than in non-brain injured populations.

Serotonin Reuptake Inhibitors:

The use of sertraline (25–200 mg/day) is recommended as an option in the treatment of depression after TBI based upon an 87% response rate in one class III study ($n = 16$).

Bipolar Disorder/Mania: There is insufficient evidence to support or refute the use of commonly used medications including lithium, anticonvulsants, and antipsychotics in the management of TBI-related bipolar disorder or mania.

Anxiety: There is insufficient evidence to support or refute the use of commonly used medications including TCAs, benzodiazepines, and SRIs in the treatment of anxiety after TBI.

Psychosis:

Atypical Antipsychotics:

The use of olanzapine (5–20 mg/day) is recommended at the level of an option for the treatment of psychotic symptoms after TBI based on two case reports.

Others: There is insufficient evidence to support or refute the use of other commonly used medications for psychosis. One of two available reports suggests that the use of clozapine was associated with significant sedation, weight gain and seizures, which have also been noted in individuals without TBI.

There is insufficient evidence in TBI populations to support or refute the use of other commonly used medications for affective disorders, anxiety and psychosis. However, evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.

II. Search Results

The review of 43 papers resulted in two class II studies and 12 class III studies that could be considered for evidence in the treatment of psychiatric sequelae after TBI. Although by research design, other studies seemed to qualify for class I, II or III evidence (ex. in three randomized controlled trials by Adeloye,[1] Kitamura,[2] and Wroblewski et al.,[3] significant methodological flaws seriously weakened the ability to generalize the findings and thus limited the conclusions that can be drawn to that of treatment options at best (see Table 2 for summary).

A. Depression

Class II. Two class II studies addressed the treatment of depression. In a cohort study of 13 patients with mild

Table 2. Affective Disorders, Anxiety, and Psychosis Evidence

Article	*Description of study*	*Data class*	*Conclusion*
I. Major depression			
Dinan, 1992[4]	Cohort study of amitriptyline (up to 250 mg): 13 MTBI patients with depression matched with 13 depressed patients without TBI	II	Only 4 MTBI patients showed marked improvement on CGI (vs. 11 of depressed patients without TBI). Depression following MTBI is relatively resistant to treatment with tricyclic antidepressants—however, amitriptyline was effective in some TBI patients.
Saran, 1985[5]	Open label cohort study of amitriptyline (200–300 mg per day) without placebo condition. 21 depressed patients: 10 with historyof MTBI.	II	After four weeks of treatment, the mean Hamilton score for the MTBI group improved some but was still in the clinically depressed range, whereas the non-injured group mean score was in the non-depressed range ($p < 0.001$). Depression following MTBI is relatively resistant to treatment with tricyclic antidepressants.
Wroblewski, 1996[3]	Randomized, placebo-controlled prospective crossover study of desipramine (150–300 mg/day): 10 individuals with severe TBI and depression	III	Of the 7 patients who completed the study, 6 improved on desipramine treatment. Significant methodological flaws and small sample size limited the strength of the findings.
Fann, 2000[6]	Nonrandomized, single-blind, placebo run-in trial of sertraline (25–200 mg/day) for the treatment of depression in 16 outpatients with mild TBI	III	Following eight weeks of treatment, 87% of patients were classified by investigators as responders and 67% of patients as in remission based on their improvement in scores on the Hamilton Depression Scale
Baker-Price, 1996[7]	Case series: use of weak pulsed magnetic fields in 4 patients with frequent or persistent depression after TBI	III	After 5 sessions of therapy conducted over 5 weeks, patients showed significant improvement in scores on the Beck Depression Inventory ($p < 0.04$) and a decrease in the magnitude of phobias ($p < 0.01$). Lack of a control group or condition and small sample size limit the strength of the study findings.
Newburn, 1999[8]	Retrospective case series of moclobemide (450–600 mg/day): 26 patients with TBI and a diagnosis of depression	III	23 patients were considered responders based on improvement in scores on the Hamilton Depression Scale. This medication is not FDA approved for use in the United States.
Perino, 2001[9]	Open trial of citalopram (20 mg/day) and carbamazepine (600 mg/day): 20 patients with severe TBI and a diagnosis of depression	III	Patients showed a significant improvement in BPRS ($p < 0.05$) and Clinical Global Improvement Scores ($p < 0.05$). No specific depression rating scale was used. Since combination therapy was used, it is not possible to determine whether one or the other drug was primarily responsible for the improvement in rating scores.
II. Bipolar disorders/mania			
Bakchine, 1989[10]	Case study of clonidine (150–600 micrograms [mcg]/day) and other agents for a patient with severe TBI and mania	III	Treatment with clonidine resulted in 37% symptom reduction, symptoms recurred during a placebo trial. Levodopa-benserazide resulted in 15% increase in manicsymptoms. Patient was given clonidine again (300 mcg/day) and had a 55% drop in symptoms from baseline and no longer met criteria for diagnosis of mania. Dosage maintained at 150 mcg/day.
Clark, 1987[11]	Case series of mania in TBI: 1 patient treated with thioridazine (50 mg/day) and amitriptyline (100 mg/day), 1 patient treated with ECT	III	Case 1 was successfully managed on of amitriptyline and thioridazine for manic episodes and depression. Case II, patient not compliant with lithium therapy and was treated with 4 sessions of ECT. When ECT was discontinued, manic symptoms recurred. 2 more ECT sessions again reduced symptoms and patient could then be maintained on lithium.

Table 2. Affective Disorders, Anxiety, and Psychosis Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Hale, 1982[12]	Open label trial of lithium (900 mg/day) in two patients with moderate to severe TBI and described manic symptoms	III	Both patients experienced a marked improvement of manic symptoms in the trial. Findings are limited by the lack of formal diagnostic criteria, standardized outcome measures and placebo condition, as well as the small sample size. More supporting reports are needed.
Pope, 1988[13]	Open label trial of valproate (max dose 750–100 mg/day): 2 patients with bipolar syndromes after mild to moderate TBI	III	Both patients failed to respond to standard treatments including lithium and neuroleptics, but bipolar illness remitted after valproate was added. The use of multiple medications, small sample size and use of poorly described, non-standardized outcome measures limit the results.
III. Anxiety disorders			
Khouzam, 1998[14]	Retrospective study of venlafaxine (150 mg/day) in the treatment of a patient with compulsions after TBI	III	Venlafaxine resulted in a decrease in compulsive symptoms (Y-BOCS score decreased from 35 to 3), reportedly stable over 4 months. Limitations include lack of a control condition or withdrawal from medication, the limitations of a single case report and the lack of formal diagnostic criteria.
IV. Psychotic disorders			
Butler, 2000[15]	Case report: Olanzapine (5 mg/day) for Cotard's syndrome and Capgras delusion following severe TBI	III	After 10 days of treatment with olanzapine, the individual's mood stabilized, and there was a complete resolution of dysphoria, restless apprehension, and delusional ideation.
Umansky, 2000[16]	Case report: Olanzapine (20 mg/day) for psychosis following second severe TBI	III	After 6 months of treatment with olanzapine, the individual no longer heard persecutory voices, had no delusional symptoms or rage outbursts and exhibited improvements in mood, behavior and follow-up compliance.

TBI (MTBI) matched with 13 depressed patients without brain injury, Dinan and Mobayed[4] studied the effectiveness of amitriptyline in the treatment of depression. Participants were responders to a questionnaire sent to individuals seen in an emergency department who met entry criteria following a TBI. Individuals who met cut-off scores for depression were then invited for full assessment. Patients with depression and no history of TBI were drawn from outpatient referrals. Patients received a starting dose of 100 mg of amitriptyline. Dosage was increased by 50 mg per week as tolerated over a 6-week treatment period for a maximum total dosage of 250 mg. Total dosage did not differ significantly between the two groups; the TBI group had a mean daily dose of 158 mg per day. In depressed patients with no history of brain injury, 11 of 13 showed significant improvement on the Clinical Global Impression Scale (CGI) and the Hamilton Rating Scale for Depression (HRSD). Only 4 MTBI patients showed marked improvement on the CGI. The authors concluded that depression following MTBI is relatively resistant to treatment with tricyclic antidepressants. Although the authors stated that the groups differed significantly in the total number of treatment responders (defined as a $\geq$50% drop in symptoms), there was no data presented to support this statement. Other significant limitations included the lack of a placebo condition, and the small sample size. Several MTBI patients did respond to treatment and given the small sample size, the reviewers could not conclude that MTBI patients were resistant to amitriptyline treatment.

Saran[5] compared the response of 21 depressed patients to amitriptyline (200–300 mg per day). Ten of the participants had experienced a MTBI (defined as loss of consciousness less than 20 min), 11 had no history of TBI. This was an open label cohort study without a placebo condition. Response was measured using the Hamilton Rating Scale for Depression. At the end of 4 weeks of treatment although the mean Hamilton score for the MTBI group improved some, it was still within the clinically depressed range, whereas the non-injured group

mean score was in the non-depressed range. Analysis of covariance using baseline Hamilton score as the covariate showed a significant between group difference ($p < 0.001$).

Class III. Wroblewski and colleagues[3] studied the efficacy of desipramine in the treatment of depression in individuals after TBI. This study was a randomized, placebo-controlled prospective study, in which 10 individuals with severe TBI and depression were given placebo and desipramine in a crossover fashion. All subjects were diagnosed using DSM III-R criteria. Of the seven patients who could be evaluated based on the DSM-III-R criteria (two dropped out due to adverse events: mania and seizures; one refused to be evaluated), six improved on desipramine treatment. Again there were a number of methodological concerns including small sample size, use of other psychotropic treatments, a short placebo lead in period, use of unspecified exclusion criteria, the failure of all subjects to meet DSM-III-R MDD criteria, a relatively mild level of depression severity, and a lack of clarity of who was blind to active treatment after the first month. These concerns limited the strength of evidence from this report and those of Dinan and Mobayed[4] and Saran[5] to the level of an option for tricyclic antidepressants in the treatment of depression after TBI.

Sertraline has also been studied in a series of 16 outpatients with mild TBI and a DSM-III-R diagnosis of depression.[6] Following 8 weeks of treatment, 87% of patients were classified by investigators as responders and 67% of patients as in remission based on their improvement in scores on the Hamilton Depression Scale. The patients in this study were not randomized to treatment condition, there was no control group used, and the investigator was not blind to the treatment given. This well designed class III study supports the recommendation of sertraline for the treatment of depression after TBI at the option level.

A study by Baker-Price and Persinger[7] examined the use of weak pulsed magnetic fields in 4 patients with frequent or persistent depression after TBI as diagnosed by their physician. The patients were within 6 years of injury and refractory to treatment with antidepressants. Severity of the patients' injuries could not be determined from the report. After 5 sessions of therapy conducted over 5 weeks, patients showed significant improvement in scores on the Beck Depression Inventory and a decrease in the magnitude of phobias. Lack of a control group or condition and small sample size limit the strength of the study findings. More supporting reports are needed to support a recommendation for the use of weak pulsed magnetic fields in the treatment of depression after TBI.

Newburn and colleagues[8] reported a significant improvement in scores on the Hamilton Depression Scale in 23 of a series of 26 patients with TBI and a DSM-III diagnosis of depression treated with moclobemide. Severity of the patients' injuries could not be determined from the report and the study was an unblinded retrospective analysis. Although this agent appears to show promise in the treatment of post-TBI depression, we are unable to recommend medications not FDA approved for use in the United States.

Twenty patients with severe TBI and a DSM-IV diagnosis of depression were given an open trial of citalopram and carbamazepine.[9] Patients showed a significant improvement in BPRS and Clinical Global Impressions Scores. However, no specific depression rating scale was used. As the study used a combination of citalopram and carbamazepine, it is not possible to determine whether one or the other drug was primarily responsible for the improvement in rating scores or whether it was indeed the combination therapy that was effective. Thus a recommendation for either citalopram or carbamazepine could not be supported.

B. Mania/Bipolar Disorders

Class III. Bakchine and colleagues[10] treated a patient with severe TBI and a DSM-III-R diagnosis of organic affective disorder, manic type, with several drugs and placebo. The individual experienced more than a 37% reduction in symptoms measured with the Manic Rating Scale following 8 days of treatment with clonidine (600 micrograms/day). Symptoms recurred during a placebo trial. Carbamazepine was also tried (600–1200 mg/day), but had no effect on manic symptoms. A trial of levodopa-benserazide (375 mg/day) resulted in a 15% increase in manic symptoms and this treatment was discontinued after 5 days. The patient was then given clonidine again (300 micrograms/day) and experienced a 55% drop in symptoms from baseline and the patient no longer met criteria for diagnosis of mania. Symptom improvement continued at a slower rate when the dosage was maintained at 150 micrograms/day. Twenty-month follow-up found the patient discharged, living alone with little support, and experiencing no manic or depressive symptoms. While replication is needed to support a treatment recommendation as only one individual was studied, this report suggests that clonidine can be used successfully in the treatment of mania following severe TBI.

Clark and Davison[11] described the treatment of two patients with bipolar disorder after TBI. Case I was a 70-year-old man treated with thioridazine (100 mg/day) for manic symptoms following TBI. Two months later, he developed depressive symptoms and was successfully

treated with 100 mg/day of amitriptyline and reduction of thioridazine to 50 mg/day. He was discharged to home and maintained on that regimen without symptom recurrence. Case II was a 60-year-old man with manic behavior including physical and verbal aggression after TBI. Tranquilizers were ineffective at controlling his behavior and he was not compliant with lithium therapy. After two sessions of bilateral ECT, the authors report that he was less irritable and more cooperative with medical treatment. After two more sessions, his mood was only mildly elevated and he was experiencing normal sleeping and eating patterns. When ECT was discontinued, the manic symptoms recurred. Two more treatments again resulted in significant symptom improvement and at that point the patient could be maintained on lithium therapy. The findings of this case series are tempered by several weaknesses such as the small sample size and lack of formal diagnostic and response criteria and cannot support a treatment recommendation.

Hale and Donaldson[12] described an open-label trial of lithium (900 mg/day) in two patients with moderate to severe TBI and described manic symptoms. While both patients experienced a significant improvement of manic symptoms in the trial, these findings are limited by the lack of formal diagnostic criteria, standardized outcome measures and placebo condition, as well as the small sample size. More supporting reports are needed to support a recommendation for the use of lithium in the treatment of mania after TBI.

Pope and colleagues[13] conducted an open-label trial of valproate for bipolar syndromes after TBI. Two patients with mild to moderate TBI had sufficient clinical data presented to be considered for evidence. Both patients failed to respond to standard treatments including lithium and neuroleptics, but bipolar illness remitted after valproate (maximum dose 750–100 mg/day) was added to the regimen. However, the use of multiple medications, small sample size and use of poorly described, non-standardized outcome measures limit the ability to generalize the results. Again, more evidence is needed to support the use of valproate for bipolar syndromes after TBI.

C. Anxiety Disorders

Class III. There were no class I or II studies found which addressed the treatment of anxiety disorders. Although some class III studies addressed this patient population, the degree of methodological flaws in these studies rendered all but one unusable.

Only one case report could be considered as class III evidence. The report was a retrospective study of venlafaxine in the treatment of compulsions in an individual with TBI of unknown severity.[14] Treatment with venlafaxine (150 mg/day) resulted in a decrease in compulsive symptoms (Y-BOCS score decreased from 35 to 3), which was reportedly stable over 4 months. The dramatic symptom improvement reported must be tempered by the lack of a control condition or withdrawal from medication, the limitations of a single case report and the lack of formal diagnostic criteria.

D. Psychotic Disorders

Class III. Only two articles were rated as class III in the area of pharmacological treatment of psychotic disorders after TBI. Butler[15] described a 17-year-old man with Cotard's syndrome and Capgras delusion following severe TBI. After 10 days of treatment with olanzapine (5 mg/day), the individual's mood stabilized, and there was a complete resolution of dysphoria, restless apprehension, and delusional ideation. The second class III study was also a case report of olanzapine. This report[16] details the case of an individual with psychosis after experiencing a second severe TBI. Olanzapine (10 mg/day) was added to his valproic acid treatment (600 mg/day). After two months, some improvement was noted and the olanzapine dosage was increased to 20 mg/day. After 6 months of treatment at this dose, the individual no longer heard persecutory voices, had no delusional symptoms or rage outbursts and exhibited improvements in mood, behavior and follow-up compliance. These reports are limited by small sample size, lack of standardized diagnostic and outcome measures and lack of a placebo or other control condition. However, evidence supports the recommendation of olanzapine as an option for the treatment of psychosis after TBI.

E. Other Reports

A large number of other case series and case reports address the treatment of depression, anxiety, mania or psychosis after TBI. However, a variety of methodological problems limited the conclusions that could be drawn from many of these reports. These methodological issues took several forms including samples of mixed populations (e.g., stroke, penetrating brain injury, TBI, epilepsy),[17–19] more than one psychiatric diagnosis,[17,20] absence of clear diagnostic criteria and inadequate information given to substantiate the authors diagnosis,[1,17,19,21–26] absence of validated or clear outcome measures and inadequate information given to substantiate authors' claims of improvement,[1,19–30] use of more than one pharmacologic intervention at a time making it difficult to attribute the improvement to the putative agent,[21,27,28,30] absence of placebo condition and/or crossover design,[19,21–30] and poorly documented link between remote TBI and current symptoms.[24] Several class

III studies have addressed the use of selective serotonin re-uptake inhibitors in this population, but again basic methodological flaws, and small numbers make it difficult to draw conclusions from even the better class III studies.

III. Consideration of Potential Adverse Side Effects

As noted, one of the common tenets of clinical lore holds that individuals with TBI may be more sensitive to the side effects of psychotropic medications and other pharmacologic interventions. Thus we felt it important to review reports of potential toxicity associated with pharmacologic interventions. While space does not permit a comprehensive review of these reports, the following provides a summary of agents and their potential side effects in the TBI population as reported in the literature: seizures with tricyclic antidepressants[31]; weight gain, drooling and seizures with clozapine[32]; mania with desipramine[33]; dysarthria and speech blocking after fluoxetine treatment[34]; severe akathisia with both sertraline and paroxetine[35]; and increased cognitive impairment with lithium (with serum lithium levels at 1.0 meq/L that resolved when reduced to 0.5 meq/L).[36]

The overall impression from reading the literature is that the full range of side effects associated with the use of psychotropic medications seen in the non-brain injured population can be seen in individuals with TBI. It is not possible to conclude from this literature that individuals with TBI are more sensitive to these side effects, nor is it apparent that novel side effects occur in this group.

IV. Conclusions

There is limited evidence in the published literature to support or refute the use of psychotropic medications commonly used in the general population for individuals with traumatic brain injury. There is insufficient evidence to support any standards or guidelines for the treatment of affective disorders, mania, or psychosis in this population. However, options are recommended for the treatment of major depression with amitriptyline, desipramine and sertraline, as well as olanzapine for the treatment of psychosis. Clearly, more well designed and executed randomized controlled trials are needed to examine the effectiveness of pharmacotherapy for these disorders in individuals with TBI.

V. Recommendations for Future Research

Even though mood and anxiety disorders following TBI may be etiologically distinct and have phenomenological differences from idiopathic cases, several critical questions remain regarding future directions for treatment: (1) Do TBI patients with mood, anxiety, or psychotic disorders respond to standard treatments? (2) Are certain symptoms more or less responsive in TBI patients than in idiopathic cases? (3) Does treating psychiatric syndromes improve functional outcome in TBI patients? (4) Are certain pharmacologic therapies more effective than others? (5) Are side effects more burdensome in TBI patients than in idiopathic cases? (6) Does TBI severity influence treatment outcome? (7) Does the presence of multiple psychiatric syndromes affect treatment response?

As the etiology of TBI-associated mental disorders remains unknown, the most easily answered questions can be tested first, especially regarding the efficacy of existing standard treatments for TBI patients in randomized-controlled clinical trials. Without the ability to discern etiology, standard syndromal criteria, such as those elaborated in the DSM-IV, would be a reasonable starting point for study inclusion. Other inclusion criteria might include patients with similar level of TBI severity and cognitive capacity, absence of current substance abuse, absence of current epilepsy, absence of prior or comorbid psychiatric disorder, and development of symptoms within a circumscribed time period of the TBI (e.g., 2 years). In the absence of validated rating scales for TBI patients with mood or anxiety disorders, standard symptom rating instruments (i.e., Hamilton Anxiety and Hamilton Depression Rating Scales, MADRAS, CGI) in combination with other symptom check-lists (SCL-90) and validated functional rating instruments (i.e., SF-36) would be reasonable outcome measures.

Which treatments to study remain at issue. Effective standard treatments for idiopathic mood or anxiety disorders, especially those with a favorable safety profile would be reasonable first candidates. The largest number of previously studied patients took tricyclic antidepressants, though the benefits of the tricyclic antidepressants are mixed, one study suggesting that mild TBI patients are minimally responsive to amitriptyline, but another report suggesting that patients with severe TBI may improve with desipramine (Wroblewski, 1996), even though toxicity may be problematic. Hence, the tricyclics are not the likeliest first choice for controlled investigation because of their questionable benefit and propensity for significant toxicity. Similarly, the propensity for toxicity makes the MAOI antidepressants unlikely initial choices for controlled study. Although electroconvulsive therapy is often helpful in severe cases of mania or depression, and there is anecdotal evidence for its benefit in TBI patients, this treatment should likely be reserved for refractory cases because of its propensity for cognitive toxicity.

The serotonin reuptake inhibitor (SRI) antidepressants have become the consensus first-line treatments for idio-

pathic mood and anxiety disorders because of their broad-spectrum effectiveness. These agents would be the natural first-line choices for study in TBI patients. Any of the agents would be reasonable candidates, though the sedation of fluvoxamine would render it less desirable than other SRIs. The preponderance of evidence with fluoxetine and sertraline support their use in depression. In anxiety disorders, any of the SRIs would be potentially useful for study, though fluoxetine may be the least desirable for panic disorder because of its propensity exacerbate panic at treatment onset.

Similarly, for mania following TBI, standard treatments, such as valproic acid or lithium, should be examined first. Following that, atypical antipsychotics in combination with or separate from standard mood stabilizers would be reasonable choices. Persisting psychotic symptoms associated with manic syndromes are relatively uncommon following TBI, though they too should be studied. Treatment with atypical antipsychotics should be examined first because patients with neurological pathology are prone to develop extrapyramidal symptoms.

Compared with mood and anxiety disorders, psychotic disorders uncommonly follow TBI and there is little information to guide treatment of post-TBI psychotic syndromes. Future studies could examine the treatment of psychosis in several categories: (1) with or without associated significant mood symptoms; (2) with or without concomitant seizures; (3) with or without significant cognitive impairment. Ideally, patients for study would include those whose psychosis developed within a reasonable time period from the TBI (i.e., 2 years) and were not associated with substance abuse.

Few patients would likely experience all the DSM-IV signs and symptoms of schizophrenia, though patients reasonable for study would include those with consistent and bothersome psychotic signs or symptoms (i.e., delusions or hallucinations). Standard rating scale instruments such as the BPRS or PANSS should be employed. As the older antipsychotics are more prone to induce extrapyramidal effects in patients with brain injury, the newer antipsychotics (i.e., risperidone, olanzapine, quetiapine or ziprasidone) would be reasonable choices for study.

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COGNITIVE DISORDERS

I. Recommendations

Standards. There are insufficient data to support a treatment effect for any of the cognitive functions considered.

GUIDELINES

A. General Cognitive Functions. There are insufficient data to support a treatment effect for this function. However, phenytoin should not be given in severe TBI unless medically indicated, as there is evidence that it can produce an impairment in cognitive functions in severe TBI at 1 month post-event, although not at 12 months. Where ongoing anticonvulsant treatment is required, valproate or carbamazepine appear to be preferable to phenytoin in terms of cognitive effects.

B. Deficits in Attention and Speed of Processing

Stimulants: Methylphenidate (0.25–0.30 mg/kg bid) is recommended to enhance attentional function. The evidence is strongest for an effect on speed of cognitive processing and sustained attention/vigilance. Methylphenidate (0.25–0.30 mg/kg bid) is also recommended to enhance the speed of cognitive processing, although only one study provides evidence to support a change in speed in a naturalistic task.

Cholinesterase Inhibitors: Donepezil (5–10 mg/day) is recommended to enhance aspects of attention for patients with moderate to severe TBI in subacute and chronic periods of recovery.

C. Deficits in Memory

Cholinesterase Inhibitors: Donepezil (5–10 mg/day) is recommended to enhance aspects of memory function for patients with moderate to severe TBI in subacute and chronic periods of recovery.

D. Deficits in Executive Functions

Dopamine Enhancers: Bromocriptine in a dose of 2.5 mg is recommendation for use in enhancing aspects of executive functioning (e.g., divided attention/central executive functions) in patients with severe TBI.

OPTIONS

A. General Cognitive Functions

Stimulants: Methylphenidate is recommended at the option level for general cognitive functioning in moderate to severe TBI.

Dopamine Enhancers: Amantadine may be considered for general cognitive functioning in moderate to severe TBI.

B. Deficits in Attention and Speed of Processing

Stimulants: Dextroamphetamine may be considered for use in enhancing attentional function in patients with TBI. In particular, dextroamphetamine may reduce variability in performance in tasks of attention and working memory but this phenomenon was reported in only one study.

Dopamine Enhancers: Amantadine may be considered to improve attention and concentration in moderate to severe TBI.

Cholinesterase Inhibitors: Physostigmine may be considered for use in enhancing aspects of attentional function in patients with moderate-to-severe TBI in the subacute to chronic phase of recovery.

C. Deficits in Memory

Stimulants: Methylphenidate in a dose of 0.30 mg/kg bid may be considered as an option to enhance learning and memory.

Other Agents: CDP choline (cytidine diphospheryl choline, 1 gram) may be considered for use in enhancing aspects of memory function in patients with mild to moderate TBI in the subacute phase of recovery.

There is insufficient evidence in TBI populations to support or refute the use of other commonly used medications for cognitive disorders. However, evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.

II. Search Results

Of a total of 61 papers meeting the cognitive disorders subgroup inclusion criteria, only seven were deemed class I evidence, six qualified as class II evidence, and 22 were class III; the remainder (27) were unusable. Two additional articles were identified in the updated search of clinical trials conducted in the fall of 2004 and were also rated. Evidence is presented in Table 3 divided by cognitive functional category and by drug class within categories.

A. General Cognitive Functions

These functions include level of consciousness, attention, memory, and executive-type functions. This category was used when either (a) studies demonstrated an effect on two or more of these functions or (b) when the tasks reported did not allow a more specific assignment of effect(s).

Table 3. Cognitive Disorders Evidence

Article	*Description of study*	*Data class*	*Conclusion*
I. General cognitive function			
Dikmen, 1991[1]	Double-blind, randomized, placebo-controlled study of phenytoin; 244 adults with a moderate to severe brain injury and post-traumatic epilepsy.	I	Within 1 month of injury, phenytoin produced significant impairment in cognitive functions ($p < 0.05$). At 12 months post-injury, there was no difference between the medication and placebo groups in general cognitive functioning.
Dikmen, 2000[2]	Randomized, double-blind parallel group clinical trial compared the seizure prevention and neuropsychological effects of VPA to phenytoin in 279 patients with TBI.	I	No significant effect of valproate acid (positive or negative) on neuropsychological function at 1, 6, or 12 months.
Azouvi, 1999[3]	Open label trial of carbamazepine (400–800 mg/day) on agitation and aggressive behavior in 10 patients with severe TBI	III	No global cognitive change found on Mini Mental Status Examination scores.
Plenger, 1996[4]	Double-blind placebo controlled, randomized trial of methylphenidate (0.6 mg/kg per day) in 23 patients with complicated mild to moderately severe brain injury.	II	At 1 month, improvement was noted with methylphenidate on functional outcome on the DRS ($p < 0.02$). At 90 days, there was no significant difference between groups.
Kaelin, 1996[5]	Cohort study of methylphenidate (30 mg/day) in 10 patients with mixed severity TBI performing two standard deviations below the mean on neuropsychological measures.	III	Trend for improvement on DRS scores ($p < 0.06$).

(*continued*)

Table 3. Cognitive Disorders Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Kraus, 1997[6]	Case Series of amantadine (up to 400 mg/day) in 5 patients with severe TBI and cognitive or behavioral deficits.	III	3/5 TBI patients showed improvement (2 STD) on at least one neuropsychological test. Patients showed improvement on executive domains including tests of verbal fluency initiation and sequencing, as well as overall improved functioning based on caregiver ratings.
Kraus, 1997[7]	Case report of amantadine for persistent frontal lobe dysfunction after severe TBI.	III	Improvement in global functioning, divided attention and constructional praxis. Further improvement was observed with the addition of L-dopa/carbidopa.
Schneider, 1999[8]	Double blind placebo controlled crossover study of amantadine (100–300 mg/day) in 10 patients with moderate to severe TBI and measured deficits in attention/concentration.	III	Although patients improved over time, they showed no positive effects from treatment with amantadine over placebo.
Chapman, 1999[9]	Randomized, double-blind, placebo controlled study of homeopathy for patients with mild TBI.	I	No effect on measured cognitive functioning. However, there was a significant effect ($p < 0.01$) on a self-report measure.
McLean, 1991[10]	Double-blind placebo controlled crossover trial of pramiracetam (1200 mg/day) on memory and other cognitive problems in 2 TBI patients.	III	Patients had improvement in verbal memory, but no effect on attention or speed of information processing
II. Deficits in attention			
Whyte, 1997[11]	Randomized, placebo-controlled, repeated crossover study of methylphenidate (0.5 mg/kg per day) for attentional problems in 19 patients with TBI and.	I	Significant drug by performance variable interaction ($p < 0.01$). Specific improvement noted on speed of performance and arousal. Other attentional components (e.g., distractibility and vigilance) and motor speed were not affected by MP.
Whyte, 2004[12]	Randomized, placebo-controlled, repeated crossover study of methylphenidate (0.6 mg/kg per day) for attention complaints in 34 patients with moderate to severe TBI.	I	Patients showed significant improvement on speed of information processing ($p < 0.01$), attentiveness during work tasks ($p = 0.01$) and caregiver ratings of attention ($p = 0.01$).
Plenger, 1996[4]	Double-blind placebo controlled, randomized trial of methylphenidate (0.6 mg/kg per day) in 23 patients with moderate to moderately severe brain injury.	II	At 1 month, improvement was noted on tests of attention and motor performance ($p < 0.05$). At 90 days, there was no significant difference between groups. Possible enhanced rate of recovery for the drug group in the subacute recovery period.
Speech, 1993[13]	Double-blind placebo controlled, randomized crossover trial of methylphenidate (0.6 mg/kg per day) in 12 patients with moderate to severe TBI.	II	No significant effect was found on attentional measures.
Gualtieri, 1988[14]	Double-blind placebo controlled, randomized crossover study of methylphenidate (0.15 to 0.3 mg/kg bid) in 15 patients with severe TBI and mild to moderate deficits	II	Trend for significance in 10 responders for attention and memory.
Kaelin, 1996[5]	Cohort study of methylphenidate (30 mg/day) in 10 patients with mixed severity TBI performing two standard deviations below the mean on neuropsychological measures.	III	Patients had significant improvement on digit span, mental control and symbol search ($p < 0.05$).

Table 3. Cognitive Disorders Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Hornstein, 1996[15]	Retrospective chart review of patients with severe TBI treated with dextroamphetamine (5–30 mg/day) for severe attentional or initiation problems interfering with rehabilitation.	III	Ten of 22 TBI patients experienced a positive effect on attention as indicated by their ability to continue in rehabilitation.
Bleiberg, 1993[16]	Double-blind, placebo crossover case study of lorazepam (0.5 mg) and dextroamphetamine sulfate (5 mg) in a patient with TBI and complaints of concentration difficulties.	III	Performance on a computerized battery of attention and working memory tasks was less variable after administration of dextroamphetamine. Lorazepam caused more variable performance on one of the subtests. Generalizability of this finding is limited because this is a single case and the measures are experimental.
Zhang, 2004[17]	Double-blind, placebo-controlled crossover design of donepezil (5–10 mg/day) in 18 patients with moderate to severe TBI with attention and/or memory impairment.	I	The results demonstrated statistically significant improvement in attention and processes with donepezil. Moreover, improved test scores were sustained in Group A in the placebo phase.
Cardenas, 1994[18]	Double-blind, placebo-controlled crossover design of scopolamine (5 μg/h) and physostigmine (2–4 mg TID) in 36 patients with severe TBI and significant memory impairment on WMS.	III	Mean digit symbol scores improved with oral physostigmine in the responders but not in the non-responders. Possible practice effects and complex study design are the primary limitations.
Levin, 1986[19]	Double-blind, placebo-controlled crossover study of oral physostigmine (3.0 or 4.5 mg/day) and lecithin (16 g/day) in 16 patients with moderate to severe head injury and residual memory deficit measured by the Benton Visual Retention Test	I	Demonstrated a trend toward significance ($p = 0.07$) of the effect of oral physostigmine in combination with lecithin on sustained attention (as measured by the Continuous Performance Test) when the oral physostigmine was administered before the placebo.
Kraus, 1997[6]	Case series of amantadine (up to 400 mg/day) in 5 patients with severe TBI and cognitive or behavioral deficits.	III	Statistically significant improvement on Trials A.
Kraus, 1997[7]	Case report of amantadine for persistent frontal lobe dysfunction after severe TBI.	III	Improvement for global functioning, divided attention and constructional praxis was noted. Further improvement was observed with the addition of L-dopa/carbidopa (75/300 mg/day).
Schneider, 1999[8]	Double blind placebo controlled crossover study of amantadine (100–300 mg/day) in 10 patients with moderate to severe TBI and measured deficits in attention/concentration.	III	Although patients improved over time, they showed no positive effects from treatment with amantadine over placebo.
III. Deficits in memory			
Zhang, 2004[17]	Double-blind placebo-controlled crossover design of donepezil (5–10 mg/day) in 18 patients with moderate to severe TBI with attention and/or memory impairment.	I	The results demonstrated improvement in memory processes with donepezil. Moreover, improved test scores were sustained in Group A in the placebo phase.
Taverni, 1998[20]	Open-label case series ($n = 2$, only 1 with objective data) of donepezil at least one year post severe TBI with long term memory dysfunction.	II	Patients showed improvement in memory. One patient had measured improvement. In the other case the staff noted improvement.

(*continued*)

Table 3. Cognitive Disorders Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Masanic, 2001[21]	Open-label case series of donepezil (5–10 mg/day) for 4 patients at least 2 years post TBI	III	Trend for improvement in memory and behavior (Rey Auditory Verbal Learning Test, Complex Figure Test, Rivermead Behavioural Memory Test, Neuropsychiatric Inventory). Treatment seemed to specifically impact new learning and recall.
Cardenas, 1994[18]	Double-blind placebo-controlled cross-over design of scopolamine (5 μg/h) and oral physostigmine (2–4 mg TID) in 36 patients with severe TBI and significant memory impairment as measured on WMS.	II	16 subjects showed improvement in memory test performance (storage and recall of information). Possible practice effects and complex study design are the primary limitations.
Levin, 1986[19]	Double-blind placebo-controlled crossover study of oral physostigmine (3.0 or 4.5 mg/day) and lecithin (16 g/day) in 16 patients with moderate to severe head injury and residual memory deficit measured by the Benton Visual Retention Test	II	Improvement was only seen on sustained attention (see table above), not memory measures.
Gualtieri, 1988[14]	Double-blind placebo controlled randomized crossover study of methylphenidate (0.15–0.3 mg/kg bid) in 15 patients with severe TBI and mild to moderate deficits	II	Improved memory and attention test scores in 10 MPH responders.
Speech, 1993[13]	Double blind placebo controlled randomized crossover trial of methylphenidate (0.6 mg/kg per day) in 12 patients with moderate to severe TBI.	II	Study failed to show a significant effect of the study drug on memory measures. However, statistical power was low for this study.
Mooney, 1993[22]	Randomized placebo controlled single blind study of methylphenidate (30 mg/day) in 38 patients with moderate to severe TBI.	III	No significant effects were noted on memory measures in patients receiving methylphenidate.
Tiberti, 1998[23]	Randomized double-blind, placebo-controlled study of methylphenidate (10–40 mg) in 10 patients with TBI and amnesia.	III	No significant effects were noted on memory measures.
Levin, 1991[24]	Double-blind, placebo-controlled study of CDP choline (1 g) in 14 patients with mild-to-moderate TBI in the subacute level of recovery after post traumatic amnesia (PTA) cleared.	II	Results showed improvement in verbal and visual-spatial memory, although the only significant finding was for spatial recognition memory in which the CDP-choline group improved by over 100% versus 29% in the placebo group ($p < 0.02$).
Fewtrell, 1982[25]	Double-blind crossover study of vasopressin (16 IU/day) conducted in 6 patients with severe TBI.	III	Patients had no significant improvement on verbal or visual memory.
Eames, 1999	Cohort study of vasopressin (8 IU/day) in 26 patients with severe TBI.	III	Patients had improved verbal and visual memory.
IV. Deficits in executive functions			
McDowell, 1998[26]	Double-blind, placebo-controlled crossover trial of bromocriptine for patients with severe TBI.	I	Treatment resulted in significant improvement on executive function tasks thought to tap prefrontal functioning ($p < 0.05$). No improvement was seen for measures of working memory that did not involve executive control processes.

Anticonvulsants. **Phenytoin:** A class I study by Dikmen and colleagues[1] showed that phenytoin produced significant impairment in cognitive functions acutely (1 month post-injury) in patients with severe TBI. This study focused on patients with post-traumatic epilepsy and examined cognitive side effects of phenytoin in this population. At 12 months post-injury, there was no difference between the medication and placebo groups in general cognitive functioning. **Valproate:** One class I study of patients with post-traumatic epilepsy by Dikmen et al.[2] showed no positive or negative cognitive side effects of valproate. **Carbamazepine:** A class III open-label study examined the effect of carbamazepine (400–800 mg/day) on agitation and aggressive behavior in 10 patients with severe TBI.[3] There was no global cognitive change noted on Mini Mental Status Examination scores. Therefore, the use of valproate or carbamazepine may be preferable to phenytoin in patients experiencing cognitive impairment after TBI. This recommendation is supported at the guideline level.

Stimulants. **Methylphenidate (MP):** One small randomized controlled study (class II)[4] and one small class III study[5] reported greater early recovery with methylphenidate treatment, as measured by the Disability Rating Scale. The Plenger study was a parallel group study, but the treatment group had significantly higher GCS scores at treatment onset than the placebo group. The Kaelin study was an AABA design, where the pace of recovery was slightly greater during the treatment interval that during the interval between the initial baselines. The results of these studies support recommendation of methylphenidate as an option for the treatment of general cognitive deficits after TBI.

Dopamine Enhancers. **Amantadine:** Three class III reports examine the use of amantadine for general neurocognitive function in moderate to severe TBI with two of the three reports demonstrating improvement on testing. One six-case and one single-case study by Kraus and Maki[6,7] (class III) revealed evidence for improvement in cognitive function using amantadine (200–400 mg/day). In the single case study further improvement was observed with the addition of L-dopa/carbidopa (75/300 mg/day). In the case series, 3/5 TBI patients showed improvement (2 STD) on at least one neuropsychological test. Patients showed improvement on executive domains including tests of verbal fluency initiation and sequencing, as well as overall improved functioning based on caregiver ratings. One class III study by Schneider et al.[8] reported no positive effects of amantadine (100–300 mg/day) in seven TBI subjects. Overall, these findings support the recommendation of amantadine at the option level for the treatment of attentional function after TBI.

Other agents. **Homeopathy:** A single class II study by Chapman et al.[9] compared a menu of 18 possible homeopathic medications that were individually matched to the clients' pattern of symptoms vs. placebo treatment. Three to seven total doses were given. No significant differences were noted in subsections of the Woodcock-Johnson tests of Cognitive Abilities–revised. However, self-reports on a variety of functional tasks tapping a range of cognitive capacities, and self-reports of symptoms, many of which concerned cognitive difficulties (e.g., short-term memory problems), though measured on unvalidated scales, showed significantly greater improvement on the active treatment than on placebo. While patients' subjective improvement is noteworthy, as no measurable improvement was found on formal cognitive testing, these results do not support a treatment recommendation. **Pramiracetam:** A class III study examined the effects of pramiracetam (1200 mg/day) on memory and other cognitive problems in 2 patients with TBI.[10] The study found improvement in verbal memory, but no effect on attention or speed of information processing. More well-designed and conducted studies are needed to support a recommendation for pramiracetam for cognitive deficits after TBI.

B. Deficits in Attention and Speed of Processing

The assessment of drug benefits on attention is complicated by a lack of agreement about the relevant subdivisions within the broad domain of arousal/attention. Even within a given subdomain (e.g., distraction) there is disagreement about the optimal measures to use for detection of drug benefits. Thus, some of the discrepancies in results may be due to differences in the choice of measures to assess drug effects. In addition, most of the measures of drug benefit with respect to attention focus at the impairment level, making it difficult to assess the real-world impact of any improvements noted.

Stimulants. **Methylphenidate (MP):** One class I study[11] and one class II study[4] found beneficial effects of MP on sustained attention/vigilance while a different class II study,[13] using a similar dose and methodology, found no significant benefit. Another class II study[14] did find improvement in a post hoc analysis in 10 of 15 patients, i.e., medication responders. The available evidence regarding the impact of methylphenidate on distractibility is mixed. The class I study by Whyte and colleagues[11] failed to find a significant reduction in distractibility in a laboratory task, but the effect size was medium and the

study was small. This study also assessed distractibility in a naturalistic environment and found an effect size of zero. In their more recent class I study,[12] however, MP was associated with less off-task behavior during individual work time. The class II study[13] using the Gordon Diagnostic System, similarly found no improvement in distraction. There is evidence for an effect on speed of processing. The two class I studies[11,12] found improvements in processing speed during MP treatment. Only one class II study[13] that looked specifically at processing speed, failed to find a positive effect. Another class III study[5] found a positive effect on speed in only one of two speed-related subtests. The collective evidence supports guidelines for MP in the treatment of both attentional function and speed of cognitive processing. **Dextroamphetamine:** Two class III studies support the use of dextroamphetamine for attention in patients with TBI. Hornstein and colleagues performed a retrospective chart review of patients with severe TBI treated with dextroamphetamine (5–30 mg/day) for severe attentional or initiation problems interfering with rehabilitation.[15] Ten of 22 TBI patients experienced a positive effect on attention as indicated by their ability to continue in rehabilitation. However, no formal cognitive testing was conducted. A single case, double-blind, crossover study by Bleiberg et al.[16] used a computerized battery of tasks of attention and working memory. The effect of dextroamphetamine (5 mg) was determined by comparing performance on subtests of the battery to performance following administration of lorazepam (0.5 mg) or placebo given randomly on consecutive days. Performance was less variable on three of the five subtests after administration of dextroamphetamine. Lorazepam caused more variable performance on one of the subtests. There were no reported side effects of dextroamphetamine. Although the effect in this study was significant, the generalizability of this finding is limited because this is a single case and the measures are experimental. Dextroamphetamine is recommended as an option for the treatment of attentional function after TBI.

Cholinesterase inhibitors. **Donepezil:** One small class I study,[17] a double-blind, placebo-controlled two-group cross-over design ($n = 18$) used moderate to severe TBI patients 2–24 months post-injury with attention and/or memory impairment. Immediate verbal memory was assessed with the Wechsler Memory Scale Third Edition (WMS-III) Auditory Immediate Index, including immediate recall of stories and pairs of associated words. Immediate visual memory was assessed with the WMS-III Visual Immediate Index including recall of faces and details of a complex picture. The Paced Auditory Serial Addition Test (PASAT) was also administered and this test involves working memory and attentional processes. Patients in Group A received donepezil first while patients in Group B received placebo first. The results demonstrated improvement in both attention and memory processes with donepezil. Moreover, improved test scores were sustained in Group A in the placebo phase. Donepezil is recommended as a guideline for the treatment of attentional function after TBI. **Physostigmine:** Two studies suppor the recommendation for physostigmine at the option level. Cardenas et al.[18] reported improved scores on one measure tapping attentional processes in patients who were felt to be medication responders in terms of memory functioning. However, this was a complex study design, results were difficult to tease out, and data and statistical analyses were not reported. The other study[19] was a double-blind placebo-controlled study of oral physostigmine in combination with lecithin in a small group of patients. While multiple measures of attention and memory were used, there was a statistical trend for patients on physostigmine to show improvement on just one test of sustained attention. These studies support the recommendation of physostigmine at the option level for the treatment of attentional function after TBI. Physostigmine is rarely used in clinical practice for enhancing cognitive functioning but donepezil and other recently developed cholinesterase inhibiting medications are commonly used for memory, attention, and behavioral dysfunction for patients with dementia. No other studies were available using these medications in TBI.

Dopamine enhancers. **Amantadine:** Three class III reports examine the use of amantadine for attention/concentration in moderate to severe TBI with two of the three reports demonstrating improvement on testing. One six-case and one single-case study[6,7] (class III) revealed evidence for improvement in sustained attention, initiation, and mental flexibility using amantadine (200–400 mg/day). In the single case study further improvement in these cognitive domains as well as constructional praxis was observed with the addition of L-dopa/carbidopa (30/300 mg/day). One class III study by Schneider et al.[8] reported no positive effects for the use of amantadine (100–300 mg/day) in seven TBI subjects. Overall, these findings studies support the recommendation of amantadine at the option level for the treatment of attentional function after TBI.

C. Deficits in Memory

Cholinesterase inhibitors. **Donepezil:** One small class I study,[17] described in detail above (Deficits in Attention and Speed of Processing) examined the use of donepezil for memory deficits. The results demonstrated improve-

ment in both memory and attention scores with donepezil. Moreover, improved test scores were sustained in Group A in the placebo phase. Two class III studies[20,21] consisted of open-label donepezil case series at least one year post severe TBI. Masanic et al.[21] had four subjects, and Taverni et al.[20] had one out of two subjects with objective data. Both studies suggested improvement in verbal and visual-spatial memory with donepezil. These studies support the recommendation of donepezil for the treatment of memory deficits after TBI at the guideline level. **Physostigmine:** Two class-II studies support this recommendation at the option level. One study[18] was a double blind, placebo-controlled cross-over design of 36 patients (ages 19–51) with severe TBI, at least three months post-injury with significant, on-going memory impairment. Patients received oral physostigmine, transdermal scopolamine, or placebo in different sequences in four treatment conditions. Scopolamine was evaluated because of its potential detrimental affects on memory, as a possible predictor of responsiveness to ACh inhibitors. Findings demonstrated improvement (50% or greater increase) in verbal long-term storage and retrieval for 44% of patients. Limitations to the interpretation of this study include potential practice effects for the neuropsychological measures and the lack of data and statistical analyses available for some measures. The other study[19] was a double-blind placebo-controlled study of oral physostigmine in combination with lecithin in a small group of patients. While multiple measures of attention and memory were used, there was a statistical trend for patients on physostigmine to show improvement on just one test of sustained attention. As mentioned above in attentional processes, physostigmine is rarely used in clinical practice for enhancing cognitive functioning, but donepezil and other recently developed medications in this class are commonly used for memory, attention, and behavioral dysfunction for patients with dementia. No other studies were available using other cholinesterase inhibitors in patients with TBI.

Stimulants. **Methylphenidate (MP):** One class II study[14] found improved verbal learning and memory on MP. One class II study[13] failed to show a significant effect of the study drug, however, statistical power was low for this study. Two class III studies[22,23] also showed no significant effect of the study drug.

Other agents. **CDP Choline:** One class II study[24] supported the use of CDP choline at the option level. The study was a double blind, placebo-controlled study of 14 patients with mild-to-moderate TBI in the subacute level of recovery after post traumatic amnesia (PTA) cleared. Results showed improvement in verbal and visual-spatial memory, although the only significant finding was for spatial recognition memory. Although this study was designed as a randomized controlled trial, the small number of subjects and the multiple statistical comparisons limit the strength of this recommendation to the option level.

Vasopressin. Two class III studies examined the use of vasopressin to improve learning and memory after TBI. No effect on visual or verbal memory in a double blind crossover study of vasopressin (16 IU/day) conducted in 6 patients with severe TBI.[25] Another class III study of vasopressin (8 IU/day) in 26 patients with severe TBI found improved verbal and non-verbal memory.[27] However, this study had no control condition and patients were actively undergoing rehabilitation concurrent with the study. There is not enough evidence at this time to support a recommendation for vasopressin in the treatment of memory deficits after TBI.

D. Deficits in Executive Functions.

Dopamine enhancers. **Bromocriptine:** One class I study[26] found improvement on measures of executive functioning (e.g., tasks involving initiation, mental flexibility) in 24 severe TBI patients. Specifically, this study used a double blind, placebo-controlled crossover trial, counterbalanced for order. Improvement on executive function tasks thought to tap prefrontal functioning (Dual Task: counting, Dual Task: digit span, Trail Making Test, was observed with the with administration of bromocriptine; significant drug by test interaction; positive effect for Dual Task-counting p.028; Dual Task-Digit span, p.016; Trail Making Test, Stroop Test, Wisconsin Card Sorting Test, Controlled Oral Word Association Test). No improvement was seen, however, for measures of working memory that did not involve executive control processes.

III. Consideration of Potential Adverse Side Effects

The following section provides a summary of the potential side effects from the above listed medications in TBI patients as reported in the literature:

Amantadine: In one study,[8] one subject experienced a side effect of light-headedness that resolved with decreased dosage.

Homeopathy: Side effects, including nausea, vomiting, dizziness, fever, depression, and temporary increases in cognitive complaints, were seen in 10% of the treatment group but none of those on placebo in the Chapman et al.[9] study.

Stimulants: In terms of side effects with methylphenidate (MP), studies that reported side effects found no significant differences between drug and placebo. However, the Kaelin et al study[5] did drop one of 11 study subjects due to drug-related tachycardia, suggesting, as expected, that this is a potential side effect of treatment with MP. In the class I study by Whyte and colleagues,[28] reduced appetite was the only subjective side effect of methylphenidate that approached statistical significance. There was a small but significant increase in pulse and blood pressure on active drug, which, in a few subjects, was clinically significant.

Cholinesterase inhibitors: Side effects for this general class of medication included nausea, vomiting, diarrhea, and insomnia in a small number of patients.

Dopamine agonists: Common side effects for this general class of medication include nausea, dizziness, and insomnia.

Anticonvulsants: As noted earlier, a class I study by Dikmen and colleagues[1] reported that phenytoin produces significant impairment in cognitive functions in patients acutely (one month post injury) with severe TBI.

CDP choline: Gastrointestinal distress was reported as a side effect for CDP choline.[24]

IV. Conclusions

While many studies have been conducted to examine the effects of pharmacotherapy on cognitive disorders following TBI, the majority of the available evidence was limited by the design of the study or its execution. There is insufficient evidence to support the development of any standards for the treatment of cognitive disorders after TBI. Evidence does support guidelines for the use of methylphenidate and donepezil for deficits of attention and speed of processing, the use of donepezil for memory deficits, and bromocriptine for deficits in executive functioning after TBI. At the option level, methylphenidate and amantadine are recommended for deficits of general cognitive function; dextroamphetamine, amantadine and physostigmine are recommended for deficits of attention and speed of processing; methylphenidate and CDP choline are recommended for memory deficits. More well-designed and executed randomized controlled trials are needed to develop treatment standards for cognitive disorders in individuals with TBI.

V. Recommendations for Future Research

In order to achieve the level of rigor required to develop treatment standards for cognitive disorders after TBI, large randomized controlled studies (parallel and cross-over designs) are needed. Moreover, given the remaining controversy about the definitions and appropriate measures of various cognitive domains, investigators should typically use several measures of a cognitive domain in a given study, at least in early phases of research. To enhance comparability across studies, efforts to develop consensus measures for treatment studies in specific domains should be encouraged by professional organizations and by federal research funding agencies. In some cases, research support to develop optimal outcome measures in a given domain will be required.

With respect to specific drugs to study, the current guideline and option level drugs (e.g., methylphenidate, amantadine) need to be examined with more methodologically rigorous studies so that they may be able to reach the standard level. Methylphenidate has the most evidence with respect to the treatment of attentional disturbances after TBI warranting a guideline recommendation. Clearly, however, large scale randomized control trials are needed to see if it can reach the standard level. Other psychostimulants such as dextroamphetamine and the new atomoxetine also need further study. Amantadine has limited evidence regarding the treatment of attentional problems and general cognitive functioning and further study is needed to see if it remains a viable option in the future.

Cholinesterase inhibitors first found to be useful in the treatment of dementia such as donepezil and physostigmine have some evidence to suggest usefulness in the treatment of memory and attention deficits after TBI but again larger scale randomized control trials are needed. Other cholinesterase inhibitors (e.g., rivastigmine, galantamine), as well as other medication classes found useful in the treatment of cognitive dysfunction in the dementias (e.g., memantine) should also be examined to see if there is utility in the TBI population. CDP choline and methylphenidate also have limited evidence for memory disorders and need further study.

Bromocriptine is the only medication found to have any evidence in the treatment of executive dysfunction (initiation, mental flexibility). Executive dysfunction can have significant morbidity with respect to social and vocational functioning and well-controlled studies examining possible pharmacologic intervention are much needed.

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AGGRESSION

I. Recommendations

STANDARDS. There is insufficient evidence to support the development of standards in the treatment of aggression after TBI.

GUIDELINES

Beta blockers: Beta blockers are recommended as a guideline for the treatment of aggression after TBI. Studies reported the efficacy of both propranolol (maximum dose 420–520 mg/day) and pindolol (maximum dose 40–100 mg/day) in the treatment of aggression in this population.

OPTIONS

Methylphenidate: Methylphenidate (dose) is recommended as an option for the treatment of aggression. Although evidence was mixed, the study with the greatest number of participants showed a positive effect. There is clear evidence that methylphenidate may be safely used without concern of adverse effects on cognition. However, it should be noted that one case report reported increased agitation with methylphenidate.

Cranial Electrical Stimulation (CES): CES is recommended at the option level for the treatment of aggression following TBI. Although the supporting class II study was well constructed, there were no additional supporting studies to support the recommendation of CES at the guideline level.

Homeopathy: Homeopathic therapy is recommended at the option level for the treatment of self-reported irritability and anger following mild TBI. This recommendation is based on a single randomized controlled trial. Although were no other studies to offer supporting evidence, the strength of the design of this single study merits its consideration at the option level.

Serotonin Reuptake Inhibitors: SSRIs are recommended at the option level for the treatment of aggression following TBI. Specifically, sertraline (25–200 mg/day) and paroxetine (20 mg/day) have been reported to be effective for the treatment of aggression in this population.

Valproate: The use of valproate (750–2250 mg/day to reach therapeutic serum level) is recommended at the option level based on two case reports and one case series describing marked improvement in aggressive or assaultive behavior.

Lithium: The use of lithium is recommended at the option level for the treatment of aggression after TBI. Behavioral response was achieved at therapeutic levels ranging from 0.4 to 1.4 mEq/L. Although the majority of patients reported showed a positive response to treatment with lithium, it should be noted that one patient showed no response and two patients experienced increased irritability/agitation. Neurotoxicity and increased EEG spiking have also been reported. Thus, lithium should be used only with careful monitoring of cognitive status.

Tricyclic Antidepressants: The use of the tricyclic antidepressants is recommended as an option for the treatment of aggression after TBI. Specifically, amitriptyline and desipramine (both up to 150 mg/day) have been reported to be effective for the treatment of aggression in this population.

Buspirone: The use of buspirone (10–60 mg/day) is recommended as an option for the treatment of aggression after TBI. There are several case series and case reports of the use of buspirone as single agent therapy and as a component of a multi-drug regimen. The majority of patients reported showed good response to treatment. However, it should be noted that several patients had to be discontinued secondary to side effects.

There is insufficient evidence in TBI populations to support or refute the use of other commonly used medications for aggression. However, evidence of efficacy in other patient populations is also a useful source of treatment options in TBI in many cases.

II. Search Results

The review of 52 papers resulted in 33 studies that could be considered for evidence in the treatment of aggression after TBI. Nine articles were determined to have the potential for class I or II evidence (i.e., a randomized controlled trial or a study that utilized a comparison group). No studies were ultimately classified as class I evidence due to study design flaws. Six studies were classified as class II evidence. Three of the initial nine were classified as class III because though unusable as randomized trials, they could be considered as case series. Other potential class I or II articles were often considered unusable because the treatment group was not limited to individuals with traumatic brain injuries, and those TBI patients could not be analyzed separately from available data. Evidence is provided in Table 4 by drug category for the treatment of aggression after TBI.

Beta Blockers

Studies have been conducted over the past 20 years regarding the use of beta blockers in the treatment of aggression after a number of neurological disorders, including traumatic brain injury. While several of the articles reviewed were class I by design, significant flaws limited their contributions to evidence to class II at best.

Class II. Brooke[1] performed a randomized placebo-controlled 7-week clinical trial of propranolol in 21 individuals with severe TBI and agitation (episodic motor or verbal behavior that interfered with patient care, therapy, or safety) rated on the Overt Aggression Scale (OAS). Propranolol LA ($n = 11$) or placebo ($n = 10$) was given after one-week baseline measurement, beginning with 60 mg/day, and increased by 60 mg/day every third day to a maximum of 420 mg unless agitation ceased or side effects occurred. After three weeks the study drug was tapered over the course of two weeks. Patients experienced a significant reduction in intensity of the most severe episode per week, but no significant change in frequency of episodes. Limitations of the study include loss of subjects to follow-up and small sample size.

Table 4. Aggression Evidence

Article	*Description of study*	*Data class*	*Conclusion*
Beta blockers			
Brooke, 1992[1]	Randomized placebo controlled trial of propranolol (up to 420 mg/day) in 21 individuals with severe TBI and agitation rated on the OAS	II	Patients experienced a significant reduction in intensity of the most severe episode per week ($p < 0.05$), but no significant change in frequency of episodes.
Greendyke, 1986[2]	Double blind, placebo controlled crossover study of propranolol (520 mg/day) for violent behavior in a mixed population (4/9 patients had TBI).	III	There were significantly fewer assaults and attempted assaults during propranolol treatment ($p < 0.05$). Although the specific efficacy in TBI patients alone in this sample is difficult to determine, the significant overall group response warrants consideration.
Greendyke, 1986[3]	Double blind, placebo controlled crossover study of pindolol (60–100 mg/day) for violent behavior in a mixed population (5/11 patients had TBI).	III	Statistically significant improvement in number of assaultive episodes, and other aggression ratings ($p < 0.05$). The need for supplemental medication was reduced significantly. Optimal response was at 40–60 mg/day.
Greendyke, 1989[4]	Double blind, placebo controlled crossover study of pindolol (20 mg) for violent behavior in a mixed population (3/13 patients had TBI).	III	There was a trend toward decreased aggressive behavior for the group as a whole, but this did not reach statistical significance. For the three individuals with TBI, clinical improvement was rated as "marked," "moderate," and "none."
Elliot, 1977[5]	Case series of propranolol (40–120 mg/day) in 5 patients for belligerent behavior (4 with CHI and 1 with PHI).	III	Propranolol controlled belligerent behavior without inducing general sedation. 2 patients experienced bradycardia, hypotension and lightheadedness.
Mansheim, 1981[6]	Case study of propranolol (20 mg TID), A-B-A design, for treatment of violent outbursts and suicide attempts 5 years post TBI.	III	Number of outbursts decreased from 2.5 to 1 per month and no suicidality on 3-month trial of propranolol 20 mg TID; behavior recurred when withdrawn for 2 weeks, and improved when reinstated
Yudofsky, 1981[7]	Case report of propranolol (320 mg/day) for violent episodes 4–10 times daily after severe TBI.	III	Propranolol 320 mg/day (and chlorpromazine 400 mg/day) improved behavior, and patient could be managed at home.
Ratey, 1983[8]	Case report of propranolol (300 mg/day) in patient with severe TBI, psychotic depression, suicide attempts and periodic assaultive episodes and no response to ntidepressants or aantipsychotics	III	Propranolol given for tremor caused dramatic improvement in behavior. When dose reduced due to bradycardia, episodes recurred.
Mattes, 1985[9]	Case report of metoprolol (100 mg BID) for aggressive outbursts after penetrating TBI.	III	Substantial decrease of outbursts when metoprolol was added to carbamazepine 800 mg/d.
Methylphenidate			
Mooney, 1993[10]	Randomized single-blind placebo-controlled 6-week trial of methylphenidate (30 mg/day) of 38 men with moderate to severe TBI.	II	Scores on measures of anger—KAS Belligerance, State-Trait Anger Scale (State), and POMS anger/hostility factor significantly improved ($p < 0.01$). However, because study entry was not based on relevant anger symptoms, one cannot determine whether anger is a significant clinical problem for this group of individuals.

(*continued*)

Table 4. Aggression Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Speech, 1993[11]	Randomized double-blind, placebo-controlled crossover study of methylphenidate (0.3 mg/kg BID) in 12 patients with moderate to severe TBI and cognitive impairment.	II	While this study was not designed to treat aggression, the belligerence variable on Katz scale showed no significant adverse reaction of methylphenidate.
Cranial electrical stimulation			
Smith, 1994[12]	CES (1.5 mA output, alternating current, pulsing 100 times/sec) was administered to 10 chronic severe TBI patients	II	Patients had statistically significant decreases in Tension/Anxiety and Anger/Hostility, as well as all other subscores on the POMS.
Homeopathy			
Chapman 1999[13]	Randomized controlled trial of homeopathy in 61 outpatients with mild TBI.	II	Treated group had a decrease in 2 of 3 items relating to irritability and aggression on a 34-item scale. Analysis was conducted on the symptom scale as a whole, though scores for individual items were also presented. However, because study entry was not based on relevant anger symptoms, patients had a questionable level of irritable and aggressive symptoms at study entry.
Serotonin reuptake inhibitors			
Fann, 2000[14]	Single-blind study of sertraline (25–150 mg) in 16 mild TBI patients with major depression.	III	During the 8-week study, scores on the Brief Anger and Aggression Questionnaire dropped significantly ($p < 0.05$). Scores of irritability and loss of temper on the Head Injury Symptom Checklist also improved during treatment.
Kant, 1998[15]	Open-label 8-week trial of sertraline (50–200 mg) in 13 mixed severity TBI patients with complaints of irritability and/or aggression.	III	Significant changes in aggression and irritability scores on the OAS-M were seen at both week 4 and 8, compared with baseline ($p < 0.01$).
Kim, 2001[16]	Case series of 3 older adults with TBI and aggressive behaviors treated with sertraline (100–150 mg/day) or paroxetine (20 mg/day).	III	All 3 patients were said to have experienced improved mood and a prompt decrease in aggression
Valproate			
Wroblewski 1997[17]	Case series of 4 patients with TBI and aggressive behaviors treated with valproate (750–2250/day).	III	Patients were reported to show improvement in all behaviors in a dose dependent manner.
Horne, 1995[18]	Case study of divalproex (serum level 50 micrograms/ml) for severe agitation after TBI	III	Irritability improved and patient could be discharged to a residential home.
Geracioti, 1994[19]	Case study of valproate (750–1000 mg/day) for episodic explosiveness after TBI.	III	Dramatic report of reduction of symptoms
Lithium			
Glenn, 1989[20]	Case series of lithium for aggression following TBI. Mixed population, 3/10 patients had TBI (therapeutic levels ranged from 0.7 to 1.4 mEq/L).	III	Five patients were reported to have had a "dramatic response" to treatment.
Bellus, 1996[21]	Case report of lithium (900 mg/day) for severe behavior problems after TBI (therapeutic levels ranged from 0.48 to 0.78 mEq/L).	III	Patient experienced decreased numbers of seclusions, and aggressive and self destructive behaviors

Table 4. Aggression Evidence (Cont'd)

Article	*Description of study*	*Data class*	*Conclusion*
Haas, 1985[22]	Case report of lithium for irritability and aggression after TBI (therapeutic levels ranged from 0.4 to 0.8 mEq/L).	III	Lithium was calming, but patient remained calm after placebo was given.
Schiff, 1982[23]	Case report of lithium added to phenytoin and carbamazepine aggression after TBI.	III	Report described a paradoxical increase of aggressivity and EEG spiking when lithium was added to regimen.
Tricyclic antidepressants			
Jackson, 1989[24]	Open randomized trial of amitriptyline ($n = 5$) and desipramine ($n = 10$) (both up to 150 mg/day) on agitated behavior in patients with severe agitation 2–10 months post-TBI.	III	67% responded with >50% decrease in number of agitated episodes over 7 days.
Jackson, 1985[25]	Case report: amitriptyline (50 mg/day) for aggressive behaviors.	III	Improvement was seen in aggressive behaviors after 2 weeks.
Buspirone			
Gualtieri 1991[26]	Retrospective case series of thirteen TBI patients treated with buspirone (10–45 mg/day) for agitated behaviors.	III	Buspirone therapy resulted in an average decline of the Neurobehavioral Rating Scale from 42 to 22. Patients with a positive response to buspirone therapy had mild TBI with no severe motor or cognitive deficits. However, 6 patients discontinued due to side effects.
Stanlislav, 1994[27]	Retrospective chart review series of 8 patients with TBI in a rehabilitation facility treated with buspirone (10–20 mg) for more than 3 months.	III	Six patients improved, one had equivocal results, and one was clearly worse. Four of eight patients had at least a 50% reduction in behavioral target symptoms. Improved subjects had higher doses than non-responders.
Holzer, 1998[28]	Case report of buspirone (60 mg/day) for assaultive behavior after severe TBI	III	All behaviors were reported to improve with treatment.
Ratey, 1992[29]	Case report of buspirone (10 mg/day) for violent outbursts after severe TBI	III	Adding buspirone to existing regiment of lithium, Carbamazepine, and nadolol significantly decreased masturbatory behavior. The patient no longer required restraints, and was discharged to the community
Carbamazepine			
Azouvi, 1999[30]	Open trial of carbamazepine (400–800 mg/day) in 10 patients with aggressive behavior following severe TBI.	III	Group had significant improvement on measures of agitation and disinhibited behavior after treatment ($p < 0.05$). Analysis of individual response showed that five patients had marked improvement, three had moderate improvement, and two had no improvement at all.
Estrogen			
Arnold, 1993[31]	Case report of estrogen (1.25 mg/day) for refractory aggression after TBI in a male patient.	III	Patient experienced a "dramatic response" with sustained improvement after 4 months.
Amantadine			
Chandler, 1988[32]	Case series of amantadine (up to 400 mg/day) for refractory aggressive behavior after TBI ($n = 2$).	III	Patients experienced a decrease in the frequency of aggressive behaviors.
Pyritinol			
Kitamura, 1981[33]	Placebo-controlled cohort study of pyritinol (600 mg/day) in 270 patients with head injury or sequelae following neurosurgery.	II	Patients treated with pyritinol reported improvements in several symptoms including irritabiity on a global self-rating scale. Limitations include mixed patient population, lack of detail in reported study design and lack of statistical rigor.

Class III. Three studies conducted by Greendyke and colleagues were class I in design, but were downgraded by reviewers to class III evidence due to significant flaws.

Greendyke[2] conducted a double-blind, placebo-controlled crossover study of propranolol for violent behavior in a mixed VA hospital inpatient psychiatric population. Of the 9 individuals in the study, four had traumatic brain injury. Subjects had "lack of impulse control and a high frequency of violent behavior." Patients were randomly assigned to receive propranolol LA (starting at 80 mg/day with increases of 80 mg every 3–4 days to a total of 520 mg) or placebo for 11 weeks. After this time, drug was tapered over 3 weeks and crossover to the other study agent. There were significantly fewer assaults and attempted assaults during propranolol treatment. Seven patients had episodes of hypotension or bradycardia, which was not clinically evident. Although the specific efficacy in TBI patients alone in this sample is difficult to determine, the significant overall group response warrants consideration as class III evidence.

Later, Greendyke and Kanter[3] conducted a double-blind, placebo controlled crossover study of pindolol for violent behavior in a mixed VA hospital inpatient psychiatric population. Five of the 11 individuals in the study had traumatic brain injury. Subjects were "pathologically impulsive, assaultive, openly hostile, and generally uncooperative. All were severely demented." Patients were randomly assigned to receive pindolol (starting at 10 mg/day with increases of 10 mg/day every 3–4 days up to a total daily dose of 60 mg) or placebo for 10 days. Further dose increases were permitted up to 100 mg/day. After this time, drug was tapered and patient crossover to the other study drug. It was not clear how long treatment was for each phase of the study. All regular treatment with psychotropic medications was discontinued 2 weeks before initiation of the study.

There was a statistically significant improvement in number of assaultive episodes, and ratings of hostility, uncommunicativeness, uncooperativeness, and repetitive behaviors. The need for supplemental medication was reduced significantly. Optimal response was 40–60 mg/day. On higher dosages, some patients appeared to be over stimulated. While individual response of the five patients with TBI was not given, the significant overall group response warrants consideration as class III evidence.

Also, Greendyke[4] conducted a double-blind, placebo-controlled crossover study of pindolol for violent behavior in a mixed VA hospital inpatient psychiatric population. Three of the 13 individuals in the study had traumatic brain injury. Subjects had behavioral or management problems. The OAS was used to monitor physical and aggressive acts. Individuals received either pindolol 20 mg bid or placebo. At the end of 10 weeks, there was a six-day crossover period. There was a trend toward decreased aggressive behavior for the group as a whole, but this did not reach statistical significance. For the three individuals with TBI, clinical improvement was rated as "marked," for a 38-year-old man (also on thioridazine 200 mg and imipramine 75 mg), "moderate," for a 53-year-old man (also on thioridazine 150 mg and imipramine 100 mg), and "none" for a 72-year-old man who had an old CVA (no other medications). Overlap with patients enrolled in Greendyke's other two studies is possible, but not reported.

Supporting case reports and case series for propranolol included Elliott[5] (seven patients), Mansheim[6] (one patient), Yudofsky et al.[7] (one patient), and Ratey[8] (one patient). There was one case report of successful treatment with metoprolol[9] (one patient). Three case reports primarily focused on other drug treatments noted a lack of response to beta blockers: Haas and Cope[22] (one patient), Arnold[31] (one patient), and Holzer[28] (one patient). However, the preponderance of evidence supports a guideline for the use of beta blockers in the treatment of aggression after TBI.

Methylphenidate

Class II. Mooney[10] conducted a randomized single-blind placebo-controlled 6-week trial of methylphenidate in 38 men who had sustained TBI. All patients experienced a TBI with LOC of 6 h or greater, or PTA of 24 h or longer. Subjects were randomly assigned to receive either methylphenidate or placebo (single blind). Medication was gradually increased over the first 4 weeks of the study, and remained at the final dosage (methylphenidate 30 mg/day) for the final two weeks. Scores on measures of anger-KAS, State-Trait Anger Scale, and POMS anger/hostility factor significantly improved. Several weaknesses temper the results of this trial. The authors did not provide data on each treatment group with reference to confounders and or any details on randomization methods. There was no a priori definition of a responder. Thus, it is not clear what the clinical meaning is for these changes in rating scale scores. Because study entry was not based on relevant anger symptoms, one cannot determine whether anger is a significant clinical problem for this group of individuals. Individuals who had greater pretreatment anger appeared to have greater improvement. Therefore, one explanation of the results is regression of these anger scores toward the mean. Due to these significant flaws, this class I design study was downgraded to class II evidence. It is important to note that patients did not exhibit increased aggression on methylphenidate.

Speech[11] conducted a randomized double-blind, placebo-controlled crossover design study in 12 patients with closed TBI with cognitive impairment. Patients were 14–108 months post-injury. They were required to have LOC or PTA of at least 1 day (average 14.4 days). Patients received either 0.3 mg/kg methylphenidate BID for 1 week, followed by 1 week of placebo, or the opposite regimen. Behavior was assessed with the Katz Adjustment Scale, as well as several cognitive tasks. While this study was not designed to treat aggression, the belligerence variable on Katz scale showed no significant adverse reaction of methylphenidate.

Class III. One case report of lithium for irritability and aggression after TBI noted increased agitation when the patient was treated with methylphenidate.[22] However, the majority of the evidence supports an option for the use of methylphenidate in the treatment of aggression after TBI.

Cranial Electrical Stimulation

Class II. Smith and colleagues[12] administered cranial electrotherapy stimulation (CES) to 10 of 21 chronic severe TBI patients in a sheltered living facility. CES was delivered with a maximum of 1.5 mA output, alternating current, pulsing 100 times per second. CES or sham treatment was delivered for 45 min, 4 consecutive days/week for 3 weeks. The POMS was administered at baseline and after the 12 sessions to CES ($n = 10$), sham controls ($n = 5$) and ordinary controls ($n = 6$) with no access to the device administering sham or active intervention. Forty-three percent of patients had received chemical dependency treatment prior to their injury and 86% of patients had a seizure disorder; all patients were on 3–5 medications. Although details of the sham treatment were provided, the reviewers were not clear how patients could be unaware of receiving above threshold current to their scalp. Still, the report was suggestive for the statistically significant decreases in Tension/Anxiety and Anger/Hostility, as well as all other subscores on the POMS. Although this study was well constructed, there were no additional supporting studies to support a higher recommendation. Therefore, CES is recommended as an option for the treatment of aggression after TBI.

Homeopathy

Class II. Homeopathy uses minute amounts of substances derived from plant, animal, or mineral sources, which are produced by serially agitated dilution (SAD) with water or pharmaceutical alcohol. Chapman et al.[13] studied outpatient volunteers with mild TBI who were followed for 4 months in a RCT study and rated on a new measure of post concussive symptoms. Fifty subjects of the 61 originally randomized were available for analysis (27 in active treatment and 23 in placebo). The persistence of post concussive symptoms is implied in the methodology. The treated group reported a decrease in two of three items relating to irritability and aggression on a 34-item scale. Statistical analysis was conducted on the symptom scale as a whole, though scores for individual items were also presented. Weaknesses of the study include a loss to follow-up of 18% of patients and questionable level of irritable and aggressive symptoms at study entry. This study supports the recommendation of homeopathy as an option for the treatment of aggression after TBI.

Serotonin Reuptake Inhibitors

Class III. Three open case series examined sertraline in the treatment of post-TBI aggression. Fann et al.[14] conducted a trial of sertraline in 16 patients with mild TBI who met criteria for major depression (DSM-III-R) and had at least 18 on the HAM-D. During this 8-week single blind study of sertraline, scores on the Brief Anger and Aggression Questionnaire dropped significantly (from 9.3 at baseline to 6.5 post-treatment), as did the HAM-D scores. Scores of irritability and loss of temper on the Head Injury Symptom Checklist also improved during treatment. The final dose of sertraline ranged from 25 to 150 mg. Limitations of this study include the lack of ability to control for natural improvement, and regression to the mean. Although the clinical significance of the statistical improvement of the aggression scale improvement is not clear, the PCS scale clearly showed patients reporting improvement in irritability and anger outbursts compared with baseline levels.

Kant et al.[15] reported an 8-week open label trial of sertraline in 13 patients with mixed severity TBI presenting to a neuropsychiatry clinic with complaints of irritability and/or aggression. Dosage ranged from 50 to 200 mg. Ten patients completed the trial. Significant changes in aggression and irritability scores on the OAS-M were seen at both week 4 and 8, compared with baseline. This study was limited by lack of a control group or blind ratings.

Kim et al.[16] reported three older adults (45 +years) who had sustained TBI in their 20's. Each had a remote or recent history of alcohol abuse and decreased cognitive abilities. Each received sertraline for aggressive behaviors and was described to experience improved mood and a prompt decrease in aggression.

These studies support the recommendation of serotonin reuptake inhibitors at the option level for the treatment of aggression after TBI.

Valproate

Class III. Two case reports and one case series support the recommendation of valproate as an option for this indication. Wroblewski[34] reported a series of four patients who showed improvement in all behaviors in a dose-dependent manner. Horne[18] described one patient whose irritability improved and could be discharged to a residential home. Geracioti[19] also reported dramatic symptom reduction in one patient.

Lithium

Class III. There have been several case series/case reports on the use of lithium. Supporting reports include Glenn et al.[20] (mixed population, 10 patients, five patients had a "dramatic response," three of these individuals had a traumatic brain injury); Bellus et al.[21] (one case); and Haas[22] (one case). The dramatic improvement in aggressive episodes described by all of these reports supports a recommendation at the option level. It should be noted, however, that one case report described a paradoxical increase of aggressivity and EEG spiking on lithium when added to phenytoin and carbamazepine.[23] Thus, while lithium is recommended at the option level, cognitive status should be carefully monitored.

Tricyclic Antidepressants (Amitriptyline and Desipramine)

Class III. Jackson et al.[24] investigated the effect of TCAs on agitated behavior and cortisol secretion and suppression in a study of 35 patients with severe TBI undergoing rehabilitation. Patients exhibiting severe persistent agitation at 2–10 months post-TBI ($n = 15$) were openly randomized to amitriptyline ($n = 5$) or desipramine ($n = 10$). Doses were less than 150 mg total per day. Sixty seven percent responded with $>50\%$ decrease in number of agitated episodes over 7 days by prospective nursing records. TCA non-responders had a shorter duration of coma (4.8 vs. 9.6 days), a longer duration from injury to rehabilitation admission (104 vs. 50 days) and a lower percentage of PTA clearing at 81 days (40% vs. 80%) compared to TCA responders. Of the TCA responders, seven were receiving phenytoin and three were receiving phenobarbitol. Of the TCA non-responders, five were receiving phenytoin and none were receiving phenobarbitol. There was essentially no association identified between cortisol dynamics and response to TCAs. Jackson et al[25] also reported a single case treated with amitriptyline (50 mg QHS) with improvement seen in aggressive behaviors after 2 weeks. These studies support the recommendation of tricyclic antidepressants at the option level for the treatment of aggression following TBI.

Buspirone

Class III. Two case reports and two case series examined the use of buspirone for post-TBI aggression. Gualtieri[26] reported a retrospective case series of 13 TBI patients treated with buspirone for agitated behaviors. Six patients had therapy discontinued for side effects, including headache (2), lightheadedness (2), rash (1), or non-response (1). Patients with a positive response to buspirone therapy had mild TBI with no severe motor or cognitive deficits. Three of the responders had dysphoria and restlessness consistent with post traumatic akathisia and four had agitation, irritability or angry outbursts, all with temporal lobe lesions. Buspirone (10–45 mg/day) therapy resulted in an average decline of the Neurobehavioral Rating Scale from 42 to 22.

Stanislav[27] described a series of nine patients with TBI in a rehabilitation facility. Retrospective pharmacy and chart review over a 3-year period was undertaken to identify individuals receiving buspirone therapy. Outcome was documented by quantified and qualified aggressive events by behavioral therapists. Of the patients with greater than three months of buspirone therapy (10–20 mg tid), eight had TBI. Of these, six improved, one had equivocal results and one was clearly worse. Four of eight patients had at least a 50% reduction in behavioral target symptoms. Improved subjects had higher doses than non-responders. Of the four patients receiving buspirone on admission, one had TBI. This patient failed a 6-week trial of buspirone in combination with carbamazepine and haloperidol resulting in its discontinuation.

Supporting case reports of buspirone in the treatment of aggression after TBI include Holzer[28] and Ratey et al.[29] These class III reports support the recommendation of buspirone as an option in the treatment of aggression after TBI.

Carbamazepine

Class III. Azouvi et al.[30] reported on a therapeutic trial of carbamazepine in 10 patients with aggressive behavior following severe TBI. The group showed significant improvement on measures of agitation and disinhibited behavior after treatment. Analysis of individual response showed that five patients had marked improvement, three had moderate improvement, and two had no improvement at all. While quantitative measures of therapeutic response were utilized, the open-label design, absence of controls, and variation in concomitant pharmacologic therapies limit the conclusions that can be drawn from this trial. Indeed, the authors concluded that it "might help," but that significant inter-individual variability existed. Although carbamazepine seems to be effective for some patients experiencing aggression after TBI, the re-

ported literature did not support a recommendation at this time.

Estrogen

Class III. Arnold[31] published a case report on a male patient with refractory aggression post-TBI who significantly improved with estrogen therapy. More supporting cases are needed to support a recommendation for estrogen therapy in the treatment of aggression after TBI.

Amantadine

Class III. Chandler and colleagues[32] reported on two patients with refractory aggressive behavior tried on amantadine (up to 400 mg/day) who experienced a decrease in the frequency of aggressive behaviors. More supporting cases are needed to support a recommendation for the use of amantadine in the treatment of aggression after TBI.

Pyritinol

Class II. One placebo-controlled cohort study examined the use of pyritinol in 270 patients with head injury or sequelae following neurosurgery.[33] Patients treated with pyritinol reported significant improvements in several symptoms including irritability on a global self-rating scale. Limitations of this study included the mixed patient population, lack of detail in reported study design and lack of statistical rigor. Although this agent may show promise in the treatment of post-TBI aggression, we are unable to recommend medications not FDA approved for use in the United States.

III. Consideration of Potential Adverse Side Effects

Not all of the studies and case reports reported adverse events. For many of these medications, which have been studied for other neurobehavioral problems after TBI, side effects have been reported. The reader is referred to those studies noted above. Specifically in the studies of aggression, valproate, carbamazepine, amantadine, and SSRI's did not list specific adverse reactions. We assume that the side effect profile for these medications will be similar to those experienced by other patient populations. Specific data was available for several medications:

Beta blockers. The major side effects of beta-blockers when used to treat aggression are a lowering of blood pressure and pulse rate. Because peripheral beta receptors are fully blocked in doses of 300–400 mg/day, further decreases in these vital signs usually do not occur even when doses are increased to much higher levels. Despite reports of depression with the use of beta-blockers, controlled trials indicate that it is a rare occurrence.[35,36]

Methylphenidate. Of most importance was that there was no increase in aggression or irritability.[10,11,22]

Homeopathy. As noted in the cognitive section, side effects occurred, including nausea, vomiting, dizziness, fever, depression, and temporary increases in cognitive complaints, were seen in 10% of the treatment group but none of those on placebo in the Chapman et al.[13] study.

Lithium. Neurotoxicity[20] and increased EEG spiking[23] have been reported. Thus, lithium should be used with careful monitoring of cognitive status.

Buspirone. Reported side effects in one study included headache, lightheadedness, or rash.[26] Three of the responders had dysphoria and restlessness consistent with post-traumatic akathisia, and four had agitation, irritability, or angry outbursts

IV. Conclusions

Although many publications examine the use of pharmacotherapy for the treatment of aggression after TBI, the majority of studies suffer significant methodological flaws. To date, there is insufficient evidence to support the development of any standards for the treatment of aggression following TBI. Evidence does support guidelines for the use of the beta blockers propranolol and pindolol for treating aggression in TBI patients. At the option level, methylphenidate, cranial electrical stimulation, homeopathy, serotonin reuptake inhibitors, valproate, lithium, tricyclic antidepressants, and buspirone are recommended for the treatment of aggression following TBI. More well-designed and executed randomized controlled trials are needed to develop treatment standards for aggression in individuals with TBI.

V. Recommendations for Future Research

Primary recommendations for future research on pharmacologic treatment of aggressive behavior include the use and development of defined measures of aggression, consistent assessment of aggression severity, reports focused specifically on TBI rather than mixed patient populations, inclusion of data on comorbid disorders (especially depression), and the use of placebo-controlled designs.

Due to the paucity of current studies, there are a number of medications that can be studied. It will be important to pursue research on medications that appear promising regardless of the level of industry support for individual agents.

Standardized measures of aggression should be utilized. This report was limited by the non-standardized descriptions of aggression provided in the current literature. Although theoretical discussions of aggression and irritability define concepts in discrete terms, we found that these treatment reports commonly did not define the behaviors in these terms. There are spontaneous day-to-day and week-to-week fluctuations in aggression that cannot be validly interpreted without prospective documentation. In addition, aggression like certain mood disorders may have cyclic exacerbations. The use of an objective measurement scale such as the Overt Aggression Scale (OAS),[37–39] the Overt Agitation and Severity Scale,[40] or the Agitated Behavior Scale[41] would greatly strengthen the findings of future studies of aggression after TBI. Future studies also need to focus specifically on patients with TBI. Several studies we reviewed included patients with varied neuropsychiatric disorders. In order to eliminate the possibility of differential response by diagnosis, studies should be conducted exclusively with patients with TBI. Studies should include measures of co-existing psychiatric disorders, such as depression, psychosis, anxiety, to explore whether these may predict efficacy. There is some suggestion that the presence of depression correlates with aggressive behavior after TBI.[42]

Study design must consider the expected change with medication so that sufficient numbers of patients are included. We believe that adequate statistical power can only be obtained through the use of multi-center studies. Due to the spontaneous fluctuations in the number of aggressive episodes, and the natural tendency for regression to the mean (where patients are entered at the most severe levels of aggression and naturally exhibit fewer episodes with time), a placebo control arm must be included.

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