

Pharmacological management of neurobehavioral disorders following traumatic brain injury—A state-of-the-art review

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Abstract—Pharmacological management of neurobehavioral disorders following traumatic brain injury (TBI) is common practice. However, the evidence available to guide this practice remains sparse. This review summarizes, in brief, the state of knowledge, organized via a time continuum from injury as well as by symptom complex. The areas of neuroprotection, hypoarousal, attention and memory deficits, aggression, agitation, depression, and mania are reviewed. The literature was searched with PubMed on the terms “traumatic brain injury” or “brain injury” with “pharmacology” (and the symptoms according to which this review is arranged). Additional searches were conducted with the specific symptoms as search terms, crossed with the therapeutic agents or drug classes discussed. Where a paucity of prospective data exists, case reports and retrospective studies are included. Studies to date have yielded minimal positive evidence for enhancing function, memory, and behavior after TBI. No single agent likely will become sentinel in the recovery process, and combination therapy in the acute and post-acute settings are required. A need exists to further define the role of psychopharmacology in postacute TBI medicine and the specific characteristics of subpopulations who might benefit.

Key words: aggression, agitation, arousal, attention, depression, mania, memory, neuroprotection, pharmacology, psychosis, traumatic brain injury.

INTRODUCTION

More than 5.3 million people, or approximately 2 percent of the U.S. population, are living with disabilities

resulting from traumatic brain injury (TBI). TBI also accounts for a large proportion of casualties among surviving soldiers of the conflicts in Iraq and Afghanistan, with 22 percent of wounded soldiers having sustained injuries to the head, face, or neck [1]. The neurobehavioral sequelae of TBI are the most debilitating problems to survivors in their attempts to reestablish family and work relationships [2].

Abbreviations: ADHD = attention deficit hyperactivity disorder, BID = bis in die (twice a day), CSF 5-HIAA = cerebrospinal fluid 5-hydroxyindoleacetic acid, DRS = Disability Rating Scale, DSM = Diagnostic and Statistical Manual of Mental Disorders, FIM = Functional Independence Measure, GABA = gamma-aminobutyric acid, GCS = Glasgow Coma Scale, GOAT = Galveston Orientation and Amnesia Test, GOS = Glasgow Outcome Scale, ICP = intracranial pressure, ICU = intensive care unit, IM = intramuscular, MCS = minimally conscious state, MMSE = Mini-Mental State Examination, NMDA = N-methyl-D-aspartic acid, PTA = posttraumatic amnesia, PVS = persistent vegetative state, RLAS = Rancho Los Amigos Scale, SPECT = single-photon emission computed tomography, SSRI = selective serotonin reuptake inhibitor, TBI = traumatic brain injury, TID = ter in die (three times a day), VS = vegetative state, WMS = Wechsler Memory Scale, WNSSP = Western NeuroSensory Stimulation Profile.

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While pharmacological management of the diverse set of neuropsychiatric disorders following TBI is common practice, the evidence available to guide pharmacological interventions is inadequate. Pharmacological therapy to this heterogeneous disorder should be guided by pathophysiology, mechanism, and site of injury.

This review summarizes in brief the state of knowledge of pharmacological interventions for TBI. Nonpharmacological interventions such as cognitive rehabilitation, psychotherapy, and behavioral modification techniques are complementary and vital to the management of neuropsychiatric sequelae of TBI but are outside the scope of this review. This review is organized via a time continuum from injury as well as by symptom complex. The data presented here are limited by prior paradigms, the limitations of metrics used in individual studies, and the extent of resources available to evaluate this important issue. Still, opportunities exist to enhance the lives of those with TBI.

This narrative review focuses on psychopharmacology in the postacute period. Some comments on acute neuroprotection have been included. We conducted our literature search using PubMed (through June 2008). For review of therapeutic agents in the postacute period, we crossed the search terms “traumatic brain injury” or “brain injury” with “pharmacology” and the symptoms according to which this review is arranged. We conducted additional searches using the specific symptoms as search terms, crossed with the therapeutic agents or drug classes discussed. Additional terms used for disorders of consciousness were “vegetative,” “conscious state,” “arousal,” “coma,” and “awareness.” Our discussion of neuroprotective agents is limited to those presented in this article. Search terms for this section were “neuroprotection” and “hypothermia,” “progesterone,” “citicoline,” and “N-methyl-D-aspartic acid (NMDA) antagonists.” English-language articles were identified. Bibliographies of resultant articles were also searched to identify additional pertinent studies. Where we found a paucity of prospective data, case reports and retrospective studies are included.

ACUTE PHASE

Neuroprotection

For more than two decades, researchers have been interested in the role that various pharmacological agents may have in neuroprotection and neurofacilitation. Clinical

trials targeted at specific pathways have almost uniformly been disappointing, and no clear neuroprotection strategy yet exists. Based on pathophysiological extrapolations and promising results in animal studies, multiple agents have been tested as possible neuroprotective agents in TBI. Methylprednisolone, nimodipine, magnesium, and tirilazad have thus far yielded negative results in humans and will not be further discussed in this review. Still, other agents are presently under investigation, including hypothermia, progesterone, and citicoline.

Trials with hypothermia in TBI have met with mixed results. Hypothermia has been trialed in other ischemic injuries, including postanoxic brain injury, stroke, and cardiopulmonary arrest. Its neuroprotective effect is attributable to a reduction of brain metabolic rate, cerebral blood flow, edema, calcium antagonism, and blockade of excitotoxic mechanisms, among other factors. Preliminary positive findings were followed by a large multicenter randomized trial in 392 adults with severe TBI; hypothermia conferred no survival or functional benefit [3] despite being effective in lowering intracranial pressure (ICP). Benefits were seen only in a subgroup who already had hypothermia on admission and who were not rewarmed. Higher complication rates of hypotension and bradycardia were observed in the hypothermia group. Criticisms of this study include the relatively late initiation of hypothermia and large intercenter variance in outcomes (large centers familiar with cooling procedures had better outcomes) [4]. Another recent multicenter, international randomized trial involving 225 children with severe TBI also found hypothermia to have no survival or functional benefit [5]. Older children and those with normal ICPs had a higher risk of unfavorable outcome, and a trend toward increased mortality was observed in the hypothermia group. Recent meta-analyses of hypothermia in the early management of TBI [3,6–11] were limited by the heterogeneity of the studied population (with and without intracranial hypertension), the variety of hypothermic protocols used, and uncontrolled confounding cointerventions. In summary, no distinct improvement in mortality and neurological outcome has been shown. Subgroup analyses suggest that continuation of cooling for 48 hours or more and slow rewarming for at least 24 hours may yield better results. Higher rates of complications of pneumonia and hypotension were noted with hypothermia. Current evidence is insufficient to support the use of hypothermia for neuroprotection in TBI. The Brain Trauma Foundation/American Association of Neurological Surgeons guidelines task force has issued a Level III

recommendation for optional and cautious use of hypothermia for adults with TBI. More studies are required to determine whether earlier initiation, a longer duration of cooling, and more aggressive prevention and treatment of complications will improve the efficacy of this treatment modality. Hypothermia is being evaluated in ongoing clinical trials targeted at a subpopulation of those with severe injury.

Progesterone acts by down-regulating inflammation and excitotoxic cell death, reducing cerebral edema, and preventing neuronal loss. In animal TBI models, progesterone reduced the incidence of cerebral edema and lesion volume if given within the first 2 hours of TBI [12]. A recent phase II, randomized placebo-controlled trial with 100 subjects with moderate to severe TBI demonstrated a trend toward lower mortality rates in subjects given 3 days of intravenous progesterone. ICPs did not differ in the two groups [13]. Functional outcomes in the severely injured subgroup treated with progesterone were worse at 30 days, possibly reflecting improved survival in this group. Moderate TBI survivors on progesterone had better disability ratings. In another randomized placebo-controlled trial, a 5-day course of intramuscular progesterone, initiated within 8 hours of severe TBI, produced modest improvement in mortality and functional scores at 3- and 6-month follow-ups [14].

Citicoline is an intermediate in phosphatidylcholine synthesis, essential for membrane integrity and repair. Administration of citicoline decreased cognitive impairment, cerebral edema, neuronal loss, and cortical contusion and improved neurological recovery in adult rat models of TBI [15–16]. The proposed mechanism of neuroprotection is through the prevention of glutamate-mediated excitotoxic cell death by the prevention of the oxidative damage that results from the activation of the enzyme PLA2. In stroke, citicoline has shown some positive results in randomized double-blind trials [17]. A meta-analysis of pooled data of patients with moderate to severe strokes showed citicoline to be beneficial if initiated within 24 hours of symptom onset [18]. Citicoline is presently being evaluated as a neuroprotection and neurofacilitatory agent for those with severe, moderate, and complicated mild TBI.* Glutamate-mediated excitotoxicity has been targeted as a site for neuroprotection through NMDA receptor antagonism. Clinical trials with NMDA receptor antago-

nists have yet to demonstrate clear efficacy. A trend toward mortality benefit was found in a clinical trial with traxoprodil, a selective NMDA antagonist [19]. Dexanabinol, a cannabinoid with weak noncompetitive NMDA antagonist action, was found to be an ineffective neuroprotective agent in a phase III trial [20]. Other clinical trials with NMDA antagonists (aptiganel [21], eliprodil, selfotel [22]) have yielded negative or inadequate results [23].

Summary

Clear data are limited and no strong evidence exists to support any singular acute therapeutic intervention. While some agents have shown promise in the arena of neuroprotection, these await validation in large clinical trials with measures targeted toward functional change. Present thinking has begun to consider combination therapies at both the acute stage and in a time-based series of treatments.

POSTACUTE PHASE

Disorders of Consciousness and Arousal

Impaired consciousness and arousal remains a sentinel issue in the recovery of those with severe injury. We focus this review on emergence from the defined states of coma, vegetative state (VS) and minimally conscious state (MCS), following moderate to severe brain injury (**Table 1**). While definitions of disorders of consciousness and important measures have been established, no single medication has been well defined to clearly improve the arousal and recovery process.

Arousal is mediated by a complex network comprising the cholinergic reticulothalamic projections; glutaminergic thalamocortical projections; and the reticulocortical projections, a network of dopaminergic, noradrenergic, serotonergic, and cholinergic projections. Mechanical injury to white matter connections of this network through diffuse axonal injury may impair cognition and consciousness to varying degrees.

Clearly, consideration of the differential causes of impaired consciousness before initiation of pharmacological treatment is of paramount importance. These causes will not be covered in this review.

Agents targeting each of the above neurotransmitter pathways have been explored to augment arousal, particularly dopaminergic agents. However, the body of evidence to date is insufficient to clearly guide clinical practice.

*Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Study of citicoline for the treatment of traumatic injury (CORBIT); 2007. ClinicalTrials.gov Identifier: NCT00545662; <http://clinicaltrials.gov/ct2/results?term=NCT00545662>.

Table 1.
Pharmacological agents for treatment of disorders of consciousness.

Agent	No./Population	Study Design	Results
Neurostimulants			
Methylphenidate [1]	<i>n</i> = 22:MCS or VS (17 traumatic).	Meta-analysis of single-subject crossover studies.	Methylphenidate 7.5–25 mg/d produced no significant difference in responsiveness or accuracy in command-following.
Methylphenidate [2]	<i>n</i> = 80:ICU patients with moderate to severe TBI.	Randomized placebo-controlled.	Methylphenidate (0.3 mg/kg/dose twice daily to maximum of 20 mg/dose) resulted in 23% decrease in ICU and hospital length of stay in patients with severe TBI (<i>p</i> = 0.06 for ICU and <i>p</i> = 0.029 for hospital stay time).
Dopaminergic Agents			
Amantadine [3]	<i>n</i> = 1:MCS.	ABAB.	Dose-dependent emergence from MCS was observed with amantadine (100–400 mg/d).
Amantadine [4]	<i>n</i> = 30.	Case series.	Improved arousal, decreased fatigue, decreased distractibility, and decreased assaultiveness.
Amantadine [5]	<i>n</i> = 35:Severe TBI, 4 days to 6 weeks postinjury.	Randomized, double-blind, placebo-controlled crossover.	Trend toward improved functional measures (MMSE, GOS and DRS), regardless of when amantadine therapy (200 mg/d for 6 weeks) was initiated during recovery period.
Amantadine [6]	<i>n</i> = 123:Patients with severe TBI who remained in coma for >1 week despite being medically stable.	Retrospective cohort.	28 of 123 subjects received amantadine 100–200 mg twice daily. No significant difference in rate of emergence from coma with and without amantadine.
Various dopamine agonists [7]	<i>n</i> = 10:Children and adolescents in MCS/VS in subacute rehabilitation.	Retrospective chart review.	Rate of improvement of WNSSP was significantly better with dopamine agonist treatment (amantadine, methylphenidate, pramipexole, bromocriptine, or levodopa) than without.
Amantadine [8]	<i>n</i> = 12:Heterogeneous brain injury treated with amantadine for cognitive deficits.	Retrospective chart review.	8 of 9 low arousal subjects had increased level of responsiveness with amantadine 100–200 mg twice daily.
Pramipexole [9]	<i>n</i> = 10:Children and adolescents in MCS or VS at least 1 month postinjury.	Randomized double-blind trial.	No difference in efficacy between amantadine (up to 100 mg twice daily) and pramipexole (dosed according to age, up to 0.25 mg twice daily) for 8 weeks. Higher rate of change of Coma/Near Coma scale of WNSSP while on medication.
Bromocriptine [10]	<i>n</i> = 5:VS.	Retrospective chart review.	Greater than normally reported rate of transition from VS to MCS on bromocriptine (2.5 mg twice daily).
Levodopa [11]	1 PVS patient.	Case report.	Became responsive and conversant within days of initiation of levodopa/carbidopa therapy (100/10 mg twice daily).
Levodopa [12]	<i>n</i> = 8:VS >1 month postinjury (2 patients >9 months postinjury).	Prospective series.	All followed commands within 2 weeks of initiation of carbidopa/levodopa (25/250 mg 1/4 tab 5 times a day to 1 tab TID). 7 had reciprocal interaction in a mean time of 31 days (including the 2 patients >9 months postinjury). 1 remained in MCS.
Antidepressants			
Sertraline [13]	<i>n</i> = 11:Within 2 weeks of severe TBI.	Randomized prospective placebo-controlled trial.	No significant difference in rate of cognitive recovery measured by O-log, GOAT, and ABS with sertraline 100 mg/d for 2 weeks.

Table 1. (Continued)

Pharmacological agents for treatment of disorders of consciousness.

Agent	No./Population	Study Design	Results
Amitriptyline, desipramine [14]	<i>n</i> = 3:5–19 months post-severe injury.	Case series.	Amitriptyline 50 mg/d was initiated for treatment of complex regional pain syndrome; desipramine 50 mg/d and 75 mg/d. Significant improvement in arousal and initiation, which was reversed in 2 subjects on drug withdrawal.
Modafinil			
Modafinil [15]	<i>n</i> = 10:Closed head injury.	Open-label case series.	Modafinil 100–400 mg/d decreased daytime sleepiness.
Modafinil [16]	<i>n</i> = 51:Chronic TBI without neurological deficits.	Randomized, blinded, placebo-controlled crossover.	No significant differences in measures of fatigue and daytime sleepiness with modafinil 400 mg/d for 4 weeks.
Zolpidem			
Zolpidem [17]	<i>n</i> = 1:PVS 3 years post-TBI.	Case report.	Zolpidem 10 mg/d was administered initially to treat restlessness. Verbal responsiveness improved 15 min after first administration. Increased blood flow seen through areas of hypoactivity on brain SPECT.
Zolpidem [18]	<i>n</i> = 3:PVS at least 3 years post-TBI (2) or anoxic injury (1).	Case reports.	GCS score improved from 6–9 to 10–15. RLAS score improved from I–II to V–VII with zolpidem 10 mg/d.
Zolpidem [19]	<i>n</i> = 1:MCS, 4 years post-TBI.	Assessor blinded single-case.	Zolpidem 10 mg/d for 1 week resulted in no benefit in tests of following instructions of increasing complexity, compared with placebo.
Naltrexone			
Naltrexone [20]	<i>n</i> = 1:RLAS Level II, 14 weeks post-TBI.	Case report.	Naltrexone 50 mg/d increased to 100 mg/d after 1 week. FIM score improved 16 points in 6 weeks, compared with 5 points in preceding 12 weeks before medication. Improved accuracy in answering of nonverbal questions, initiation, and attention.
Naltrexone [21]	<i>n</i> = 1:Severe abulia and akinesia following TBI.	Case report.	Improved FIM scores with naltrexone after unsuccessful trials of other pharmacotherapy.

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Table 1. (Continued)

Pharmacological agents for treatment of disorders of consciousness.

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ABS = Agitated Behavior Scale, DRS = Disability Rating Scale, FIM = Functional Independence Measure, GOAT = Galveston Orientation and Amnesia Test, GCS = Glasgow Coma Scale, GOS = Glasgow Outcome Scale, ICU = intensive care unit, MCS = minimally conscious state, MMSE = Mini-Mental State Examination, O-log = orientation log, PVS = persistent vegetative state, RLAS = Rancho Los Amigos Scale, SPECT = single-photon emission computed tomography, TBI = traumatic brain injury, TID = ter in die (three times a day), VS = vegetative state, WNSSP = Western NeuroSensory Stimulation Profile.

Neurostimulants

Amphetamines and methylphenidate increase dopamine and norepinephrine availability by increasing their release, blocking reuptake, and inhibiting monoamine oxidase, resulting in increased activity in the striatum and large areas of the cerebral cortex in animal models, particularly in dopamine-rich areas of the caudate nucleus and mediofrontal cortex.

Few studies and no conclusive evidence support the use of neurostimulants to enhance emergence from states of impaired consciousness. A recent meta-analysis of 22 (17 TBI) single-subject repeated crossover trials found no clinically meaningful effect of methylphenidate on responsiveness or command-following in patients with altered consciousness [24]. Another randomized, placebo-controlled study suggests that early use of methylphenidate in the intensive care unit (ICU) is associated with

shorter hospital stays, with a trend toward shorter ICU stays following severe injury [25].

Dopaminergic Agents

Amantadine is an anti-parkinsonian, antiviral agent that increases pre- and postsynaptic dopamine availability in the striatum. It is also a weak NMDA receptor antagonist. A small body of evidence supports the use of amantadine in impaired consciousness due to TBI.

A double-blind, placebo-controlled, crossover study demonstrated a trend toward treatment benefit with a 6-week course of amantadine in the acute phase of severe TBI using outcome measures of Mini-Mental State Examination (MMSE), Glasgow Outcome Scale (GOS), and Disability Rating Scale (DRS) [26]. The strength of the study was limited by baseline differences in DRS between the treatment and control groups and by spontaneous recovery

in the acute phase, which poses difficulty in a crossover design. The sample size did not allow for comparison between starting amantadine earlier or later. Zafonte et al. reported a dose-dependent effect of amantadine on emergence from MCS, which was reversible upon withdrawal and reinitiation of the drug [27]. Gualtieri et al. reported benefits in arousal, fatigue, distractibility, and assaultiveness in 30 patients with TBI with amantadine treatment [28].

Negative studies include a retrospective cohort study of 123 medically stable subjects with severe TBI in coma for more than 1 week, 28 of whom had received 100 to 200 mg of amantadine twice daily [29]. No difference was found in the rate of coma emergence between those who had received amantadine and those who had not.

In the pediatric population, a randomized, double-blind study found that both amantadine and pramipexole, another dopamine agonist, were associated with improved responses in patients in low-response states following TBI [30]. Significant improvement was found on the Coma/Near Coma Scale, Western NeuroSensory Stimulation Profile (WNSSP), and DRS in 10 children and adolescents in low-response states while on amantadine or pramipexole compared with off medication. No difference was found between the two treatment groups.

Other dopamine-enhancing agents that have been examined less extensively include bromocriptine, a predominantly postsynaptic D₂ dopamine receptor agonist, which has been associated with a greater rate of transition from persistent VS (PVS) to MCS in a retrospective chart review [31]. Case reports on levodopa include the remarkable recovery of a 24-year-old man in a VS 6 months postinjury who became conversant within days of levodopa initiation [32]. Matsuda et al. reviewed five case reports of patients with chronic TBI in PVS and MCS who became more responsive with levodopa, initiated for the treatment of rigidity [33]. Krimchansky et al. described the clinical pattern of recovery of consciousness in eight patients in VS who were treated with incremental doses of levodopa [34]. All patients could follow commands within 2 weeks of initiating medication: seven achieved ability for reciprocal interaction, including two who were more than 9 months postinjury.

A retrospective review of 10 children and adolescents in VS or MCS who were on various dopamine-enhancing medications (amantadine, methylphenidate, pramipexole, bromocriptine, levodopa) showed significant improvement in responses to structured stimuli in a double-baseline

serial measure ABA design [35]. Seven of the ten subjects had sustained a TBI.

Antidepressants

Serotonergic interactions following TBI are a matter of some controversy. Acute injury appears to be associated with an increase in hemispheric serotonin levels, decreased cerebral glucose utilization, and excitotoxicity. In the chronic phase, however, a down-regulation of the serotonin system occurs. Nonetheless, sertraline, a selective serotonin reuptake inhibitor (SSRI) did not improve arousal in a small, randomized, prospective, placebo-controlled trial of 11 subjects with severe TBI [35].

Amitriptyline and desipramine are tricyclic antidepressants that are postulated to exert their action by blocking reuptake of serotonin and norepinephrine. Reinhard et al. reported three patients with severe injury who demonstrated significant improvement in arousal and initiation following administration of amitriptyline or desipramine [36]. Two of these experienced deterioration of symptoms when the medications were discontinued and improvement again when reinitiated. The third patient began verbalizing after being mute for more than a year following TBI.

Modafinil

Modafinil is a wakefulness-promoting agent approved for treatment of excessive daytime sleepiness associated with narcolepsy. Its mechanism of action is unclear. Modafinil has little effect on the catecholamine, serotonin, histamine, adenosine, and monamine oxidase B systems. Evidence exists to show that it causes inhibition of the posterior hypothalamus and medial preoptic area and also an increase in the level of glutamate in these regions. Animal models have demonstrated increased activation in the anterior hypothalamus, hippocampus, and amygdala. In the narcolepsy population, modafinil resulted in improved energy level, overall social functioning, improved psychological well-being, and increased productivity, attention, and self-esteem when compared with controls. In sleep-deprived military personnel, modafinil improved performance in cognitive tasks [37]. In one open-label series of 10 patients with closed head injury not otherwise characterized, modafinil was reported to decrease daytime sleepiness [38]. However, a recent, randomized, placebo-controlled crossover study of subjects with chronic TBI with disabling fatigue and/or excessive daytime sleepiness showed no significant difference in measures of fatigue and daytime sleepiness between treatment and control groups [39]. A substantial

placebo effect in fatigue symptoms was noted. No studies to date have investigated the use of modafinil to improve emergence from impaired conscious states following severe TBI.

Zolpidem

Zolpidem belongs to the drug class imidazopiridines. It acts as an agonist on the 1 subtype of gamma-aminobutyric acid (GABA)-A receptors, while benzodiazepines act on all GABA-A receptor subtypes. A number of case reports exist on the use of zolpidem as an “awakening” agent in patients in PVS or MCS. The postulated mechanism of action is through reversing GABA-mediated diaschisis in the brain. Single-photon emission computed tomography (SPECT) studies have shown improved blood flow in areas of hypoperfusion after zolpidem administration [40–41].

Clauss et al. reported on the dramatic effect of zolpidem in 4 patients in PVS 3 to 5 years following traumatic or anoxic brain injury [40–42]. Patients were reported to be able to answer questions appropriately, converse on the telephone, self-feed, comment on rugby, and catch a baseball shortly after single doses of zolpidem. Improvement was noted in the Glasgow Coma Scale (GCS) (from 5–9 to 10–15) and the Rancho Los Amigos Scale (RLAS) (from I–II to V–VII). The conscious states in these subjects returned 2 to 4 hours after drug administration but improved again with zolpidem readministration. Similar transient effects have been reported in MCS due to anoxic brain injury [43–44]. However, in an assessor-blinded, single case study of a man in MCS 4 years following TBI, zolpidem did not improve ability to follow instructions, and in fact, resulted in slight worsening in performance at some tasks. Assessments in this study were performed daily for 1 week while on zolpidem and for another week off zolpidem [45]. Clearly, more controlled studies are required to determine the role of zolpidem in disorders of consciousness following TBI.

Naltrexone

Naltrexone is a competitive pure opioid antagonist. It is commonly used as an opioid antidote and for the treatment of alcohol dependence. Endogenous opioids have been implicated in pathophysiological processes contributing to neuronal damage following brain injury, through impairing NMDA-mediated cerebrovasodilation in the pial arteries [46]. Selective activation of kappa receptors has been shown to exacerbate, while selective blockade of kappa receptors provided protection, in animal models of TBI [47–49].

Immunoreactivity to dynorphin, an endogenous opioid, is also increased in regions of histopathologic damage, and decreased blood flow in rat brain following fluid-percussion TBI [48]. However, other studies suggest the protective effect of μ -selective agonists and the deleterious effect of μ -selective antagonists in rat models of TBI [50–51]. Clinical data are currently limited to case reports, in which naltrexone resulted in overall improvement in functional status in patients with TBI in low arousal states and in cases of abulia and akinesia [52–53]. Naltrexone is also reported to improve symptoms of postconcussion syndrome [54].

Summary

At this time, insufficient evidence exists to support the use of any one agent for the augmentation of arousal following severe TBI. Limited data to date suggest a tenable role for dopaminergic agents, particularly amantadine, as “awakening” agents following TBI. A more complex understanding of the factors leading to emergence from low-response states will likely yield the most efficacious results in particular patients.

Attention

The lack of consensus regarding the subdivisions within the broad domain of attention makes direct comparison of studies challenging. The constructs of attention most commonly explored include vigilance/sustained attention, processing speed, and distractibility (**Table 2**). Studies are also limited by small sample sizes, divergent sample characteristics, experimental rigor, and outcome measures. Some studies of cognitive impairment employ neuropsychological instruments that combine tests of memory and attention. They will be repeated in both sections of this review where relevant.

Neurostimulants

Despite limitations, reasonable strength of evidence exists to support the use of methylphenidate in various aspects of attention, particularly processing speed and sustained attention/vigilance, in the acute and subacute phases of recovery.

A number of randomized controlled trials have shown positive effects of methylphenidate on attention. An early double-blind, crossover study conducted by Gualtieri and Evans reported subjective improvement in mood, work performance, and alertness in 14 of 15 subjects with chronic TBI with subjective attentional and memory difficulties treated with methylphenidate [55]. Objective measures of

Table 2.
Pharmacological agents for treatment of attentional and memory disorders.

Agent	No./Population	Study Design	Results
Neurostimulants			
Methylphenidate [1]	<i>n</i> = 15:Chronic phase, high functioning, but with subjective persistent attentional or memory deficits.	Double-blind, placebo-controlled crossover.	Subjective improvement in mood, work performance, and alertness in 14 subjects. 10 had objective measures (nonverbal fluency and selective attention) trend toward significance. Methylphenidate dosed at 0.15–0.30 mg/kg twice daily.
Methylphenidate [2]	<i>n</i> = 23:Subacute phase, complicated mild to moderately severe TBI.	Randomized, double-blind, placebo-controlled.	Methylphenidate 0.3 mg/kg twice daily for 30 days improved DRS, attention (concentration, vigilance), and motor memory at 30 day follow-up. Declarative memory domains of testing were not significantly different. No significant difference at 90 day follow-up. High attrition rate for follow-up.
Methylphenidate [3]	<i>n</i> = 11:Subacute phase, multiple causes of brain injury. 7 with TBI including penetrating injury.	Prospective cohort AABA multiple baseline.	Incremental dose up to 15 mg BID resulted in significant improvement in Digit Span, Mental Control, and Symbol Search scores after 1 week on methylphenidate and persisted 1 week after discontinuation.
Methylphenidate [4]	<i>n</i> = 19:Subacute to chronic phase. TBI of variable severity, recommended by attending physician for methylphenidate therapy for attention issues.	Randomized, double-blind, placebo-controlled repeated crossover.	Significant benefit in tasks related to arousal and mental processing speed with methylphenidate 0.25 mg/kg BID. No effect on motor speed, distractibility, and most aspects of vigilance.
Methylphenidate [5]	<i>n</i> = 34:Adults with moderate to severe TBI and attention complaints, subacute phase.	Double-blind, placebo-controlled repeated crossover.	Significant positive effect on processing speed, caregiver ratings of attention, and attentiveness during work tasks with methylphenidate 0.3 mg/kg BID for 6 weeks. Effect sizes were small to medium. No significant improvement on tasks of divided attention, sustained attention, or distractibility. Small effect size.
Methylphenidate [6]	<i>n</i> = 12:Chronic phase, severe injury.	Double-blind, placebo-controlled randomized crossover.	No significant difference in memory scanning tasks and distractibility tasks with methylphenidate 0.3 mg/kg BID. Digit symbol and complex reaction time tasks trended toward significance.
Methylphenidate [7]	<i>n</i> = 10:Pediatric subacute to chronic mild to severe injury.	Double-blind, placebo-controlled crossover.	No effect on behavior, attention, memory, or processing speed with methylphenidate for 4 days. Dose: <20 kg/5 mg BID; 21/29 kg/7.5 mg BID; >30 kg/10 mg BID.
Dextroamphetamine [8]	<i>n</i> = 1:5 years after mild TBI, with concentration difficulties.	Double-blind, placebo crossover single-subject.	Dextroamphetamine 5 mg compared with lorazepam 0.5 mg and placebo. Performance on tasks of attention and working memory on placebo became more variable over time, whereas cognitive efficiency and performance variability improved over time on dextroamphetamine.
Dextroamphetamine [9]	<i>n</i> = 22:Severe TBI.	Retrospective chart review.	10 of 22 experienced positive effect on attention and participation in rehabilitation on dextroamphetamine 5–30 mg/d.
Dopaminergic Agents			
Bromocriptine [10]	<i>n</i> = 12:Moderate to severe, at least 3 months after injury.	Randomized, double-blind, placebo-controlled crossover trial.	No significant difference in measures of attention with 8 weeks of bromocriptine 5 mg BID. Trend toward worse performance in treatment group.
Amantadine [11]	<i>n</i> = 7:Frontal lobe syndrome (6 from TBI).	Case series.	Improved attention, among other neuropsychological measures, with amantadine 400 mg/d.

Table 2. (Continued)

Pharmacological agents for treatment of attentional and memory disorders.

Agent	No./Population	Study Design	Results
Amantadine [12]	<i>n</i> = 10:Acute phase, moderate to severe injury.	Double-blind placebo-controlled crossover.	No significant difference in attention on amantadine 100–300 mg/d compared with placebo.
Bromocriptine [13]	<i>n</i> = 1:63-year-old severe TBI with parkinsonism, postacute phase.	Case report.	Dose-related improvement in motor tasks and measures of memory, visuospatial attention, and processing speed with bromocriptine (incremental dose to 35 mg/d). Levodopa did not achieve same response.
Cholinesterase Inhibitors			
Physostigmine [14]	<i>n</i> = 16:Moderate to severe TBI Inpatients with memory deficits.	Double-blind, placebo-controlled.	Combined physostigmine 3.0 or 4.5 mg/d and lecithin 16 g/d, vs lecithin alone. Trend toward significant difference in sustained attention on continuous performance test with physostigmine first in crossover design.
Physostigmine [15]	<i>n</i> = 36:Severe TBI with memory impairment.	Double-blind, placebo-controlled crossover.	Physostigmine 2–4 mg TID, vs placebo, vs scopolamine 5 mcg/h. 44% responded to physostigmine. Significant improvement in mean digit symbol in responders to physostigmine.
Donepezil [16]	<i>n</i> = 10:Subjects with TBI with chronic cognitive impairment.	Case series.	Donepezil 5 mg/d for 1 month, increasing to 10 mg/d. 8 subjects reported subjective improvement in at least 1 cognitive domain. Improved speed of processing, learning, verbal memory, and divided attention (Stroop, color naming, Rey Auditory Verbal Naming Test).
Donepezil [17]	<i>n</i> = 18:Postacute phase, all severities.	Randomized, placebo-controlled, double-blind crossover trial.	Significant improvement in measures of sustained attention and short-term memory found with 10 weeks of donepezil 10 mg/d (PASAT and WMS). Benefits were sustained in the placebo phase of Group A.
Rivastigmine [18]	<i>n</i> = 157:Postacute phase, all severities.	Multicenter randomized double-blind, placebo-controlled trial.	No significant treatment benefit in primary outcome measures of attention and verbal memory found with rivastigmine 3–6 mg/d for 12 weeks. Post hoc analysis showed significant benefit in verbal memory for more severely impaired subjects. Placebo group had greater-than-expected improvement.
Various central cholinesterase inhibitors [19]	<i>n</i> = 111:Chronic, all severities, having any of target symptoms of fatigue, poor memory, attention or initiation.	Open-label trial.	Donepezil (7.2 ± 0.9 daily), Galantamine (5.0 ± 1.1 BID), rivastigmine (2.3 ± 0.4 BID). Subjective positive response in 41% on donepezil, 60% on galantamine, 59% on rivastigmine. Most reported benefit in area of vigilance.
Donepezil [20]	<i>n</i> = 3:Adolescents with severe TBI.	ABA.	Donepezil 5–10 mg/d resulted in improvement in tests of memory in all subjects (Total Recall, Long-Term Storage, Consistency of Long-Term Retrieval, Delayed Recall).
Donepezil [21]	<i>n</i> = 4:Chronic severe TBI.	Open-label trial.	Donepezil 5 mg/d for 8 weeks, then 10 mg/d for 4 weeks resulted in trend toward better performance on tests of verbal and visuospatial memory (Rivermead Behavioral Memory Test and Neuropsychiatric Inventory subscales).

Table 2. (Continued)

Pharmacological agents for treatment of attentional and memory disorders.

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BID = bis in die (twice a day), DRS = Disability Rating Scale, PASAT = Paced Auditory Serial Addition Task, TBI = traumatic brain injury, TID = ter in die (three times a day), WMS = Weschler Memory Scale.

attention in 10 subjects trended toward significance. Other randomized double-blind trials reported improvement in tests of concentration, vigilance, and motor memory [56], improved arousal and processing speeds and DRS measures [57–59]; and better caregiver ratings of attention, and attentiveness during work tasks [59] with methylphenidate treatment in “complicated mild” to moderate and subjects with severe TBI [56–59]. Less deterioration in response rate to repeated performance was also found in one study [58], although speed and accuracy of performance was not affected. Another study reported no significant improvement in tasks of divided attention, sustained attention, or distractibility [59]. Effects in these studies were sustained in the short to medium term [47–48]. One prospective AABA multiple baseline measure study also demonstrated significant improvement in attention span and memory with methylphenidate in the subacute phase of recovery from various causes of acquired brain injury [57].

Studies have shown no treatment benefit with methylphenidate in adults [60] and children [61]. Apart from small sample sizes, that the population studied were mostly in the chronic phase of recovery may be significant.

Dextroamphetamine has also been evaluated in the treatment of attentional issues following TBI. Bleiberg et al. found improved processing efficiency on tasks of attention and working memory with dextroamphetamine, compared to lorazepam or placebo, in a case of mild TBI 5 years postinjury [62]. Performance on placebo became more variable over time, while cognitive efficiency and performance variability improved over time in the dextroamphetamine condition. A retrospective chart review of patients with severe TBI treated with 5 to 30 mg/d of dextroamphetamine for severe attentional or initiation problems found a positive effect on attention and participation at rehabilitation in 10 of 22 subjects [63]. No neuropsychological measures were conducted.

Some reluctance exists among clinicians to use methylphenidate in brain-injured patients because of its potential for lowering seizure threshold. A retrospective study of seizure frequency before and after methylphenidate initiation in 30 consecutive patients with active seizure disorders with brain injury showed a trend toward less frequent seizures while on methylphenidate [64]. Four patients had greater seizure frequency while on methylphenidate, three of whom received concomitant tricyclic antidepressants. Small open-label trials of methylphenidate in adult patients with epilepsy concomitant attention deficit hyperactivity disorder (ADHD) have not demonstrated increased seizure

activity [65–66]. In the pediatric ADHD population, no controlled studies have shown convincing evidence of increased development or increased frequency of seizures in children with concomitant active seizure or those with electroencephalographic abnormalities [66–67]. Children with well-controlled epilepsy have been treated safely with methylphenidate [68].

With regard to the adverse effects of methylphenidate on blood pressure and heart rate, one randomized placebo-controlled crossover study found modest increases in mean pulse rate and blood pressure with methylphenidate therapy, 0.3 mg/kg/dose twice daily. (mean pulse increase 7 bpm, average increase in mean arterial pressure 2.5 mmHg [$p = 0.046$], average systolic pressure rise 3.67 [$p = 0.024$]) [69]. No correlation existed between baseline blood pressure and pulse rate on their subsequent increase with treatment. The authors concluded that pretreatment hypertension was not an indication for withholding methylphenidate. Nevertheless, monitoring of vital signs is important upon initiation of methylphenidate therapy.

Atomoxetine

Atomoxetine is a selective nonstimulant norepinephrine reuptake inhibitor licensed for the treatment of ADHD in children and adults. It is currently being evaluated for use in hypoarousal, initiation, and attentional problems following TBI [70]. Its primary location of action is at the locus ceruleus and the prefrontal cortex. In a recent study conducted on a rat model of TBI, low-dose atomoxetine administered early after experimental TBI resulted in improved cognitive ability measured by performance on the Morris water maze. No benefit was found with delayed initiation of atomoxetine (11 days postinjury). High-dose atomoxetine was associated with increased agitation [71]. No efficacy study has yet been reported in human subjects with TBI.

Dopaminergic Agents

In a recent crossover trial, no treatment benefit on attentional tasks was seen with a 4-week trial of bromocriptine 5 mg twice daily in 12 subacute to subjects with chronic TBI [72].

Few controlled trials have investigated the effect of amantadine on attention deficit post-TBI. Improved attention was reported, among other benefits, with amantadine in a series of seven subjects with frontal lobe syndrome, six of whom had sustained a TBI [73]. No effect on attention was reported in another double-blind, crossover study with

10 subjects with acute TBI [74]. One case reports a 63-year-old patient with severe TBI associated with parkinsonism in the postacute phase of recovery who improved on motor tasks and measures of memory, visuospatial attention, and processing speed with bromocriptine [75]. Levodopa did not achieve the same response in this subject.

Cholinesterase Inhibitors

Cholinergic pathways are intimately associated with cognitive function, particularly memory. Chronic deficits in cholinergic function have been demonstrated following TBI [76]. Cholinergic augmentation with cholinesterase inhibitors has shown benefit in the treatment of Alzheimer disease. Studies of cholinesterase inhibitors effect on memory and sustained attention in TBI have yielded generally positive results (see next section on “Memory”).

Physostigmine is a reversible cholinesterase inhibitor used to reverse the central effects of anticholinergic overdose. Although some have reported positive results in cognitive impairment following brain injury, physostigmine's utility is limited by its short duration of action and adverse effect profile. One study comparing physostigmine/lecithin to lecithin alone in 16 subjects with moderate to severe TBI with memory deficits found no difference in measures of attention and memory between the two treatment groups, apart from improved sustained attention on the continuous performance test when physostigmine was initiated first in the crossover design [77]. A double-blind, placebo-controlled study comparing the effect of physostigmine, placebo, and scopolamine on attention and memory in 36 subjects found improvement in scores on one measure of attentional processes in the physostigmine group [78].

Donepezil has demonstrated benefit for cognitive deficits, including attention deficits following TBI. One randomized crossover trial demonstrated attention and memory benefits with donepezil therapy, which were sustained after the washout period [79]. Another case series reported subjective improvement and improvement in processing speed, verbal memory, and divided attention in 8 of 10 subjects treated with donepezil [80].

Silver et al. failed to show a treatment benefit for measures of attention with rivastigmine in a relatively large multicenter, randomized double-blind placebo-controlled trial [81]. This trial was conducted in the postacute rehabilitation period, with better than expected improvements in the placebo group.

An uncontrolled open-label study of chronic survivors of TBI of all severities reported a 55 percent subjective positive response rate to medication in 111 patients being treated by one physician. The patients had symptoms of fatigue, poor memory, attention, or initiation and were treated with donepezil, rivastigmine, or galantamine [82]. The most frequently reported benefit was in the area of vigilance.

Antiepileptic Agents

Phenytoin produced significant cognitive impairment acutely in patients 1 month post-severe TBI in a double-blind, randomized placebo-controlled study [83]. Studies using valproate and carbamazepine as antiepileptic agents post-TBI have shown no positive or negative cognitive effects [84–86].

Newer anticonvulsant agents such as topiramate, lamotrigine, gabapentin, and pregabalin have less well-defined adverse effect profiles. No studies specifically address the cognitive effects of topiramate in the population with TBI; however, topiramate is known to cause impairment of language, attention, memory, and executive function in patients with epilepsy and intellectual impairment [87]. In a study of chronic administration of low-dose topiramate for epilepsy, 44 percent of 47 patients demonstrated cognitive deficits [88]. Behavioral difficulties such as psychomotor agitation, aggressiveness, and psychoses have also been reported after topiramate therapy [89]. Gabapentin has been reported to cause heightened anxiety and psychomotor agitation in two cases [90].

Summary

Methylphenidate is strongly suggested to be helpful to ameliorate attention, particularly in the domains of processing speed, concentration, and vigilance. Although compelling evidence for the use of cholinesterase inhibitors in this context is lacking, preliminary evidence for their role in improving attention encourages further investigation. Distinct conclusions await further clinical trials.

Memory

Memory disturbance remains a sentinel concern of patients with severe TBI and their families. Small trials of pharmacological strategies have yielded mixed results. Attempts have been made to enhance memory function employing the cholinergic and adrenergic systems.

Neurostimulants

The evidence for the role of neurostimulants in enhancing memory is not strong. A double-blind placebo-controlled study with 18 subjects with TBI showed improved response accuracy in measures of working memory and visuospatial attention with a single dose of methylphenidate [91]. Other randomized studies demonstrated improvement in tests of verbal learning and memory [55] and improvement in anger, which was accompanied by improved memory in the treatment response group [92].

Studies that show methylphenidate to have no effect on memory include the randomized trials discussed in the previous section [56,60–61].

Cholinesterase Inhibitors

Cholinergic augmentation with cholinesterase inhibitors has been shown to enhance psychometric measures of various aspects of memory in the population with TBI. One randomized, placebo-controlled, double-blind crossover trial demonstrated significant improvement in short-term memory and sustained attention with a 10-week regime of donepezil [79].

A number of case series report positive effects of donepezil on learning and memory in chronic severe TBI [80,93–94]. However, a multicenter, randomized, double-blind placebo-controlled study found no significant effect on memory with rivastigmine [81]. Post hoc analysis did find significant benefit in verbal memory in the more severely impaired subjects. The placebo group had greater-than-expected improvement.

Physostigmine was shown in a placebo-controlled study, to improve verbal long-term storage and retrieval in 4 percent of 36 subjects with TBI with severe memory impairment [78]. Another study combining physostigmine with lecithin did not show an improvement with measures of memory [77].

Summary

Further investigation into the role of cholinergic augmentation with cholinesterase inhibitors for those with impaired memory following TBI is warranted. Use of neurostimulants for this purpose has met with mixed results. No clear conclusion regarding agents to improve memory can be made at this time.

Other Cognitive Domains

Pharmacological augmentation of other cognitive domains, such as executive function, has been attempted.

Kraus and Mak reported decreased impulsivity and perseveration, and improved executive function with amantadine in a 50-year-old woman with frontal dysfunction 5 years post-TBI [95]. Addition of levodopa further improved constructional praxis, divided auditory attention, and cognitive flexibility.

Positron emission tomography imaging studies of glucose metabolism and dopamine D₂ receptor function following amantadine administration showed increase in left prefrontal and medial temporal resting glucose metabolism, which correlated strongly with improvement in measures of prefrontal executive function [96]. Memory and attention did not improve significantly in this study. Striatal D₂ receptor availability demonstrated a nonsignificant increase.

Bromocriptine has also been shown to enhance aspects of executive functioning in patients with severe TBI. A double-blind, placebo-controlled crossover study with 24 subjects with severe TBI showed improvement in tasks thought to engage executive processes (dual task, trail making test, Stroop Test, verbal fluency, and Wisconsin Card Sorting Test) [97].

No conclusions can be drawn from the current evidence on the efficacy of any agent in improving executive function post-TBI.

Neurobehavioral Issues

Patients with TBI are prone to psychiatric sequelae. Depression after TBI develops in 15.3 to 60.0 percent of individuals [98]. Anxiety is frequently associated with depression. Although relatively uncommon, psychosis occurs more frequently in individuals with TBI and causes significant functional disability.

Depression

Multiple factors contribute to symptoms of depression, including sleep disturbance, fatigue, apathy, and limited coping strategies. Physiological changes, such as disruption of biogenic amine-containing neurons in the basal ganglia or frontal-subcortical white matter, may also contribute.

SSRIs

Of the SSRIs, sertraline has the most dopaminergic activity, which may confer additional theoretical cognitive benefits in the population with TBI. Fann et al. reported an 87 percent response rate in an 8-week, single-blind placebo run-in trial of sertraline 25 to 200 mg/d in 15 subjects with major depression 3 to 24 months follow-

ing mild TBI [99]. They further reported improved psychomotor speed, recent verbal and visual memory, and cognitive efficiency with sertraline treatment, associated with significant improvement in depression scores [100].

Fluoxetine was also been reported to improve mood, attention, processing speed, and working memory in five patients with TBI, with no to moderate depression, in an 8-month, open-label study using fluoxetine 20 to 60 mg/d [101].

Less evidence is available for newer SSRIs. Perino et al. conducted an open trial of 12 weeks of citalopram 20 mg/d combined with carbamazepine 600 mg/d. Significant improvement was found in Brief Psychiatric Rating Scale scores and Clinical Global Impressions scores; however, no specific depression rating scale was used [102]. Results of a recently concluded, randomized, double-blind placebo-controlled trial of venlafaxine in posttraumatic depression have yet to be published.

Tricyclic Antidepressants

Tricyclic antidepressants has been less commonly used since the advent of SSRIs. In the population with TBI, their use is also limited by concerns of higher rates of seizures.

Wroblewski et al. examined 10 subjects with severe TBI with long-standing depression in a randomized, placebo lead-in study with desipramine [103]. Two patients dropped out because of adverse events and one refused evaluation. Six of the seven subjects who completed the study had resolution of depression.

Amitriptyline may be less effective in the treatment of depression post-TBI compared with noninjured subjects. In a crossover study of phenelzine and amitriptyline, Saran found that of 21 depressed subjects, 10 of whom had minor TBI, clinical improvement was noted in the noninjured control subjects, while the improvement in the subjects with minor TBI was not significant [104]. Similarly, in a cohort study with matched subjects, Dinan and Mobayed reported more response to amitriptyline in the noninjured depressed group compared with the mild group [105].

Summary

A small body of evidence suggests that sertraline is effective for the treatment of depression in the subacute/chronic phases of recovery. No clear evidence for the treatment of depression exists while we await the results of larger planned trials.

Agitation, Irritability, Aggression

Agitation, irritability, and aggression are major behavioral problems impacting those with TBI (**Table 3**). Typical and atypical neuroleptic agents are commonly used; however, little evidence supports their long-term use.

Beta-Blockers

Beta-blockers were shown to decrease the intensity of agitated episodes and the frequency of assault attempts in four randomized controlled trials with subjects with TBI identified in a recent Cochrane review [106–110]. All trials were small in sample size (up to 21 subjects). Overt aggression scale scores, the need for restraints, and the number of assault attempts were followed. The doses of beta-blockers tend to be high (propranolol up to 520 mg/d, pindolol up to 100 mg/d). The effects of high doses of beta blockers on hypotension and bradycardia may limit their use.

Neuroleptics

Neuroleptics are commonly used to control acute episodes of aggression and agitation. Unfortunately, their sedative properties are sometimes employed to control problematic behavior.

The use of dopamine-blocking typical antipsychotic agents raises concerns in the population with TBI, because they are associated with poorer outcomes in animal and human studies. Haloperidol administration has been shown to prolong the duration of posttraumatic amnesia, although eventual outcome was unchanged [111]. Cognitive improvement was also reported when typical antipsychotics were discontinued [112]. In rat models, haloperidol had detrimental effects on motor function persisting long after the drugs were metabolized [98]. In primates and cats, it blocked amphetamine-promoted motor recovery [114].

Haloperidol, a prototype of butyrophenones, is a high-affinity D₂ postsynaptic receptor blocker. Its effect on dopamine receptors in the mesocortical and nigrostriatal pathways is thought to be the cause of cognitive and extrapyramidal adverse effects. Alpha-adrenergic receptor activity has also been implicated to impair motor recovery post-TBI in animal models.

Atypical antipsychotics are preferred over typical antipsychotics for their reduced incidence of extrapyramidal side effects, because they exert their effect at other receptor sites besides D₂, including serotonergic 5HT_{2A}, 5HT_{2C}, dopaminergic D₁, D₄, histamine, alpha-1 adrenergic, and muscarinic receptors. However, the effect of

atypical antipsychotics on cognition is not well established in the population with TBI. In rat models, multiple administration of olanzapine did not impair cognitive function, as did haloperidol [115]. Another rat study showed deterioration of motor and cognitive performance after multiple administrations of both haloperidol and high-dose risperidone [116]. The effect persisted after a

Table 3.

Pharmacological agents for treatment of agitation and aggression.

Agent	No./Population	Study Design	Results
Beta-Blockers			
Propranolol [1]	<i>n</i> = 21:Severe injury, agitation.	Randomized double-blind, placebo-controlled trial.	Intensity of agitated episodes decreased with propranolol 420 mg/day for 8 weeks. Frequency of episodes unchanged (Overt Aggression Scale scores and need for restraints were followed).
Propranolol [2]	<i>n</i> = 9:4 subjects had TBI.	Randomized double-blind, placebo-controlled crossover.	Decreased number of attempted assaults with propranolol 520 mg/d for 11 weeks.
Pindolol [3]	<i>n</i> = 11:5 subjects had TBI.	Randomized double-blind, placebo-controlled crossover.	Significantly fewer number of assaults. Need for supplemental medications reduced with pindolol 100 mg/d. (Optimal response at 40–60 mg/d.)
Neuroleptics			
Droperidol, haloperidol [4]	<i>n</i> = 27.	2-month prospective monitoring of episodic agitation and treatment with 1 of 4 agents.	Time to achieve calming was shortest with IM droperidol (1.25–10 mg) compared with IM haloperidol (2–10 mg), lorazepam (1–5 mg), or diphenhydramine (25–75 mg).
Haloperidol [5]	<i>n</i> = 26:Severe injury with agitation, 11 requiring haloperidol intervention.	Retrospective chart review.	No difference in rehabilitation outcome. Prolonged PTA duration in those treated with haloperidol.
Methotrimeprazine [6]	<i>n</i> = 120.	Retrospective chart review.	Agitation was controlled in most cases treated with methotrimeprazine (2–50 mg up to 4 times a day).
Clozapine [7]	<i>n</i> = 9:7 aggressive TBI, psychotic symptoms, or rage outbursts.	Case series.	Marked decrease in aggression in 2 subjects, less bizarre behavior in 1, mild improvement in agitation and hallucination in 3, indeterminate response in 3. Seizures in 2. Clozapine dose 300–750 mg/d.
Quetiapine [8]	<i>n</i> = 7:At least 3 months postinjury.	Pilot open-label flexible dose.	84.5% reduction in Overt Aggression Scale–Modified and Clinical Global Impression from 4.14 to 2.29. Sedation reported in 3 patients. Quetiapine dose 25–300 mg/d for 6 weeks.
Ziprasidone [9]	<i>n</i> = 5:Severe injury with posttraumatic amnesia and agitation.	Case series.	Agitated Behavior Scale decreased from 27.2 to 18.0 with ziprasidone 40–80 mg/d for 2 weeks.
Valproate [10]	<i>n</i> = 29:Subacute injury, received divalproex for agitation symptoms.	Retrospective chart review.	Subjective improvement in agitation in 26 patients within 7 days of initiating divalproex 1,250 mg/d.

washout period. Performance was not affected by a single dose of risperidone or haloperidol in this study.

Of the typical antipsychotic agents, one study showed droperidol achieved a calming effect faster than haloperidol or lorazepam [117]. Methotrimeprazine has also been shown to effectively control acute episodes of agitation

Table 3. (Continued)

Pharmacological agents for treatment of agitation and aggression.

Agent	No./Population	Study Design	Results
Valproate [11]	<i>n</i> = 5.	Case series.	Improvement in destructive and aggressive behaviors in dose-dependent manner (750–2,250 mg/d).
Carbamazepine [12]	<i>n</i> = 10: Agitation and anger outbursts, various stages after severe injury.	Prospective open trial.	Agitation and social disinhibition improved with no significant change in cognitive function. Carbamazepine 400–800 mg/d for 8 weeks.
Lamotrigine [13]	<i>n</i> = 1: 40-year-old, severe chronic TBI.	Case report.	Decreased need for intermittent short-acting benzodiazepine to control outbursts, improved participation at therapy and activities of self-care with lamotrigine 50 mg/d.
Antidepressants			
Amitriptyline [14]	<i>n</i> = 20: Inpatient recent severe injury.	Retrospective review.	Decrease in agitation within 7 days of initiation of amitriptyline in 12 of 17 patients with PTA. No benefit in 2 of 3 patients with PTA. No effect on cognitive recovery.
Tricyclic antidepressants [15]	<i>n</i> = 68: Severe injury at high risk of seizures.	Retrospective review.	14 developed seizures caused by tricyclic antidepressants (19%) (amitriptyline, desipramine, doxepin, imipramine given for at least 3 weeks).
Sertraline [16]	<i>n</i> = 11: Within 2 weeks of severe TBI.	Randomized, double-blind, placebo-controlled crossover.	No significant change in measures of orientation and agitated behavior with sertraline 100 mg/d for 2 weeks.
Sertraline [17]	<i>n</i> = 13: Mixed severity, with irritability and/or aggression.	Open-label trial.	Significant improvement in Overt Aggression Scale without significant effect on depression with sertraline 50–200 mg/d for 8 weeks.
Buspirone [18]	<i>n</i> = 10.	Retrospective chart review.	9 of 10 had improved behavior and aggression on buspirone 10–20 mg/d.
Buspirone [19]	<i>n</i> = 3.	Case series.	Agitation resolved.
Neurostimulants			
Methylphenidate [20]	<i>n</i> = 38: Severe injury >2 years after injury.	Randomized, single-blind, placebo-controlled trial.	Measures of anger were significantly reduced after methylphenidate 30 mg/d for 6 weeks. Improvement in memory was also seen in treatment response group.
Amantadine [21]	<i>n</i> = 12: Heterogeneous brain injury treated with amantadine for cognitive deficits.	Retrospective analysis.	2 subjects in whom amantadine was initiated for treatment of agitation showed reduction in agitation, improvement in attention and concentration, and participation at therapy.
Amantadine [22]	<i>n</i> = 2: Difficult-to-treat destructive behavior following TBI.	Case reports.	Decreased frequency of agitation and aggression with amantadine (up to 400 mg/d).
Lithium			
Lithium [23]	<i>n</i> = 10: Severe, unremitting aggression.	Case series.	5 had dramatic response with lithium (therapeutic levels 0.7–1.4 mEq/L). 3 had neurotoxic side effects.
Lithium [24]	<i>n</i> = 2: Chronic injury.	Case reports.	Decrease in frequency of aggressive outbursts and need for neuroleptics with lithium (900 mg/d).

Table 3. (Continued)

Pharmacological agents for treatment of agitation and aggression.

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IM = intramuscular, PTA = posttraumatic amnesia, TBI = traumatic brain injury.

[118]. Loxapine is a typical dibenzoxasapine antipsychotic with high affinity for binding to serotonin 5HT₂ receptors, making it less likely to cause extrapyramidal side effects. Loxapine has been reported to effectively treat agitated behavior, when a treatment combination with olanzapine, sertraline, propranolol, and diazepam had failed [119]. Used intravenously for sedation, loxapine was found to decrease brain electrical activity, without any significant effect on cerebral blood flow velocity and ICP [120].

Studies of atypical agents are limited in number and size. Clozapine is not frequently used because of its unfavorable side effect profile. One series found it effectively controlled agitation in three of nine patients, but resulted in seizures in two patients [121]. Quetiapine was found to reduce irritability and aggression in seven subjects in a 6-week open-label, flexible-dose study [122]. Of the newer agents, ziprasidone has demonstrated efficacy in controlling agitation during the period of posttraumatic amnesia (PTA) in a series of five patients with severe TBI [123]. Aripiprazole is a partial dopamine agonist at the D₂ and D₃ receptors, making it theoretically a superior agent for the treatment of various TBI-related sequelae. No studies of aripiprazole in subjects with TBI exist at this time.

Antiepileptic Agents

Carbamazepine and valproate are the anticonvulsant agents most frequently used as mood stabilizers to treat agitated behavior. The antimanic properties of valproate were quickly recognized following its introduction as an anticonvulsant, and it became a prophylactic agent for bipolar disorders. Its mode of action is believed to be through inhibition of GABA.

Concerns exist that carbamazepine, like phenytoin, may impair cognitive function and delay recovery following brain injury. Valproate may have fewer cognitive adverse effects in this regard. In a randomized, double-blind placebo-controlled study comparing continuation of seizure prophylaxis and placebo, continuation of phenytoin and carbamazepine was found to negatively impact cognitive performance, particularly motor and speed tasks, when compared with switching to placebo [124]. In another randomized, double-masked parallel-group clinical trial comparing 279 subjects with TBI who received valproate, phenytoin, or placebo within 24 hours of injury for seizure prophylaxis, valproate treatment did not have positive or negative neuropsychological effects at 1 or 6 months [125].

For treatment of agitation and aggression, both agents have proven efficacy. Divalproex was found to improve

agitation in 26 of 29 treated patients within 7 days of a typical 1,250 mg/d dose in a retrospective chart review [126]. Valproic acid was reported to effectively control aggression in five patients in whom other pharmacological interventions had not been effective [127]. Azouvi et al. described a series of 10 patients who were treated prospectively with carbamazepine 400 to 800 mg/d for 8 weeks for agitation and anger outbursts at variable intervals post-TBI [86]. Agitation and social functioning improved with no significant change in cognitive function. Another series describes seven patients in whom carbamazepine brought about a decrease in combativeness within 4 days of initiation [126].

Novel agents such as lamotrigine have been trialed. One case report noted a decreased need for intermittent short-acting benzodiazepine to control outbursts and improved participation at therapy and activities of self-care with lamotrigine in a patient with chronic TBI with aggression and agitation [128].

Antidepressants

Use of serotonergic agents to treat agitation is supported by biochemical studies in animals and humans. Serotonin levels were found to correlate negatively with aggression. Low cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) correlated with increased aggression and risk-taking behavior in free ranging monkeys [129] and impulsive aggression, suicidal behavior, and antisocial aggression in humans [130]. However, at the current time, insufficient clinical data exist to support the use of SSRIs for this purpose.

In one study, sertraline 25 to 50 mg twice daily for 2 weeks was found to have no effect on measures of orientation and agitated behavior in a randomized, double-blind, placebo-controlled crossover trial of 11 patients within 2 weeks of severe TBI [131]. However, Kant et al. found significant improvement in measures of aggression without significant effect on depression in a series of 13 patients with TBI treated with sertraline 50 to 200 mg/d [132].

Tricyclic antidepressants are not commonly used for the treatment of agitation. Nevertheless, one retrospective review comparing 20 patients who were treated with amitriptyline for agitation to nonagitated patients found that 12 of 17 patients with PTA on amitriptyline had a dramatic decrease in agitation within 7 days of initiating amitriptyline. Two of the three patients who were out of PTA did not respond to amitriptyline [133]. No impedance on cognitive recovery was noted. One review of patients with TBI

on various tricyclic antidepressants revealed an increase in seizure rate of 19 percent [134].

Buspironone is a serotonergic and weak dopaminergic agent and has demonstrated efficacy in improving behavior and aggression in a number of case series and retrospective chart reviews [135–136].

Neurostimulants and Amantadine

Methylphenidate 30 mg daily for 6 weeks was shown to reduce measures of anger significantly in a randomized, single-blind placebo-controlled trial of 38 patients with severe TBI more than 2 years after injury [92]. Improvement in memory was also noted.

Several randomized, placebo-controlled trials examining the effect of amantadine on agitation have yielded inconclusive results [74]. In one retrospective analysis of 12 subjects treated with amantadine for cognitive deficits [137], 2 subjects in whom amantadine was initiated for the treatment of agitation showed reduction in agitation and improvement in attention, concentration, and participation at therapy. Other case reports of difficult-to-treat destructive behavior following TBI that responded to amantadine therapy exist [138].

Lithium

Lithium is used in the management of mania, bipolar disease, and aggression associated with personality disorders [139] and intellectual disabilities [140]. Its primary action is to alter sodium transport and increase intracellular metabolism of catecholamines. Case reports and case series have documented its utility in agitation following TBI. Doses range from 600 to 1,200 mg/d, with serum levels ranging between 0.44 to 1.4 mL/L [141].

Glenn et al. reported a series of 10 TBI patients with severe, unremitting aggression [142]. Five had dramatic response with lithium, while three had neurotoxic side effects. Another report of two patients with chronic TBI treated with lithium found a decrease in the frequency of aggressive outbursts and need for neuroleptics [143].

Summary

Beta-blockers have demonstrated efficacy in a number of small randomized controlled trials. However, some populations may not tolerate the doses of beta-blockers required for effective amelioration of agitation. Although effective, antipsychotics, particularly those with strong dopamine blockade, are limited by the adverse cognitive impact demonstrated in animal, and a small number of

human, subjects. Further studies are warranted to determine if atypical antipsychotic agents have a more benign profile. Antiepileptic agents such as valproate and carbamazepine are promising. Limited data also suggest the benefit of lithium and possibly amantadine. The roles of these agents need to be further clarified in controlled studies.

Mania and Psychoses

Posttraumatic mania has been reported to occur in 9 percent of patients with TBI [144]. Although mood stabilizers are commonly used to treat primary manic disorders, possible pathological differences may result in different responses to therapy in posttraumatic mania. Literature in the population with TBI to date consists of case reports and uncontrolled studies.

Lithium has been reported to benefit patients with mania following moderate to severe TBI in case reports [145]. Valproate has also been used successfully to treat bipolar symptoms in cases for which treatment with lithium and neuroleptics had failed [146–148]. Symptoms recurred on drug withdrawal. No standardized outcome measures were reported. In one report, the patient had failed multiple combinations of treatment with lithium, carbamazepine, and antipsychotic agents but responded to valproate in combination with lithium and levomepromazine, which were later withdrawn [148].

Carbamazepine has been reported to be effective in combination with lithium for the treatment of rapid-cycling bipolar symptoms [149]. A recent retrospective review of 18 subjects treated with carbamazepine or valproate for affective lability and/or anxiety post-TBI, who also had alcohol dependence, showed an improvement in reported affect and a high rate of abstinence from alcohol at 6 weeks [150]. Clonidine has met with success in a case of carbamazepine failure [151]. Withdrawal of clonidine in this case caused symptom recurrence, and levodopa caused further worsening of symptoms.

Atypical antipsychotics have been used successfully in acute episodes of idiopathic mania. Quetiapine has been reported to successfully treat cases of posttraumatic mania alone or in combination with valproate or citalopram [146,152]. Venlafaxine has also been trialed successfully in a patient with compulsions after TBI [153].

Psychosis following TBI is reported to occur in 0.7 to 8.9 percent of survivors [154]. Delayed onset is possible. Temporal or frontal lobe abnormalities are seen in the majority of subjects with psychotic disorders following TBI, not unlike in schizophrenia.

Two case reports describe the use of olanzapine in patients with psychotic symptoms post-TBI. Butler described a patient who had Cotard and Capgras delusions following severe TBI [155]. The patient had a complete resolution of dysphoria, apprehension, and delusional ideation after 10 days of olanzapine therapy. Umansky and Geller reported a case of psychosis following a second severe TBI [156]. After 6 months of treatment with olanzapine, persecutory auditory hallucinations and delusions ceased.

More studies are required to delineate the role and adverse effect profile of mood-stabilizing antiepileptic agents and atypical antipsychotic agents in the treatment of post-TBI mania and psychosis.

NEW FRONTIERS

A need exists to clarify and further understand the role of psychopharmacology in postacute TBI medicine, as well as to further define the risks it presents. In addition, no single agent will likely become sentinel in the recovery process. More likely is the need to look at combinations of pharmacotherapeutic agents in both the acute and postacute settings. Such combination therapy may be necessary as a series of interventions in the acute or postacute setting, as well as a longitudinal set of therapies administered over time. In addition, we must clarify the specific characteristics of those who might benefit (i.e., sex, genotype, and injury pattern), as well as refine the timing of coercive interventions (i.e., therapy based in dose and intensity) [157].

To make inroads, we need to refine postacute models and understand the recovery process in a better way as well as develop postacute biomarkers of recovery, be these serum, imaging, or electropsychological in origin, since almost every challenging disease process becomes somewhat easier to design interventions for when there exists a meaningful biomarker. The future of pharmacotherapy in this population is likely bright, and small benefits can mean substantial real-world gains for these patients. It is our long-term responsibility to help refine these metrics in a better way.

CONCLUSIONS

The body of evidence for pharmacological intervention of neurobehavioral sequelae of TBI is expanding. Limited evidence is emerging of the role of neurostimulants to improve certain aspects of attention, dopaminergic agents to augment arousal in impaired conscious states, SSRIs for the treatment of depression, and beta-blockers for the control of agitated behavior. While studies to date have yielded minimal positive evidence for enhancing function, memory, and behavior after TBI, much opportunity exists. Like other clinical care domains, refining population-based differences, understanding biological and clinical targets, and limiting expectations to practical levels of improvement may yield more robust findings.

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