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Review

Pharmacotherapy of Traumatic Brain Injury: State of the Science and the Road Forward: Report of the Department of Defense Neurotrauma Pharmacology Workgroup

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Abstract

Despite substantial investments by government, philanthropic, and commercial sources over the past several decades, traumatic brain injury (TBI) remains an unmet medical need and a major source of disability and mortality in both developed and developing societies. The U.S. Department of Defense neurotrauma research portfolio contains more than 500 research projects funded at more than $700 million and is aimed at developing interventions that mitigate the effects of trauma to the nervous system and lead to improved quality of life outcomes. A key area of this portfolio focuses on the need for effective pharmacological approaches for treating patients with TBI and its associated symptoms. The Neurotrauma Pharmacology Workgroup was established by the U.S. Army Medical Research and Materiel Command (USAMRMC) with the overarching goal of providing a strategic research plan for developing pharmacological treatments that improve clinical outcomes after TBI. To inform this plan, the Workgroup (a) assessed the current state of the science and ongoing research and (b) identified research gaps to inform future development of research priorities for the neurotrauma research portfolio. The Workgroup identified the six most critical research priority areas in the field of pharmacological treatment for persons with TBI. The priority areas represent parallel efforts needed to advance clinical care; each requires independent effort and sufficient investment. These priority areas will help the USAMRMC and other funding agencies strategically guide their research portfolios to ensure the development of effective pharmacological approaches for treating patients with TBI.

Key words: animal studies; head trauma; human studies; pharmacology; traumatic brain injury

Introduction

During the Fall of 2012, the Neurotrauma Pharmacology Workgroup developed an approach for strategically reviewing the neurotrauma research portfolio. The approach was designed to identify the capability gaps in pharmacological treatment of patients with traumatic brain injury (TBI) and assist the U.S. Army Medical Research and Materiel Command (USAMRMC) Neurotrauma Steering Committee to direct the advancement of future clinical trials. Specifically, the Workgroup was tasked with ''reviewing the current literature, knowing progress in the ongoing research, and developing a prioritized list of gaps in this area.''

Through the review of the current neurotrauma portfolio, focused reviews of existing literature, and state-of-the-science discussions with Workgroup subject matter experts, members of the Workgroup collaborated to identify research gaps associated with

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targeted pharmacological therapies as well as broader gaps spanning the spectra of TBI severity (mild, moderate, and severe) and stage (acute, subacute, post-acute, and chronic). From the identified gaps, the Workgroup identified the six most critical for advancing the field. Selection of these six gaps was based on the collective expert opinions of the Workgroup members about areas where investment would be most likely to yield rapid results, given the current state of the science and inherent challenges faced by the field.

Each of the six research gaps identified is critical for advancing the field, and efforts to address the gaps should be conducted in parallel to ensure ultimate success in improving clinical care and outcomes for persons with TBI. The gaps are ordered not by importance, but by their alignment to the TBI continuum of care, from pre-clinical through clinical research.

Research Gap 1: Standardized pre-clinical models of TBI designed to optimize translation of pharmacological agents from animal to human research studies

Animal research is a rapid, well-controlled, and cost-effective means to initially assess drug safety and efficacy. Animal models of TBI can be used to evaluate drug pharmacokinetics, pharmacodynamics, toxicity, safety, and efficacy before human clinical trials.[1,2]

Limitations exist in animal models of TBI and their use in pharmacological studies, however. First, because no single animal model accurately mimics all of the features of human TBI, individual investigators have appropriately refined experimental approaches to better fit their specific research goals. The resulting variability in experimental approaches among studies, however, makes comparison of results across laboratories and models difficult, limiting the confidence that results can be translated into successful clinical trials. Advancing pre-clinical research in animal models requires that results are comparable across studies and can translate into human studies. This necessitates standardization of available animal models and introduction of new models when scientifically necessary.

Second, some of the popular current models do not correspond well with the human condition. For example, the most commonly used models that involve a craniotomy and direct injury to the brain, while highly reproducible, have little ecological validity and are not necessarily models of mild injury. Closed head injury models result in greater heterogeneity, which can confound study results, but they may more accurately depict human injury, particularly in the mild end of the spectrum. In addition, most widely used pre-clinical models do not reliably reproduce important mechanisms of human TBI, such as axonal injury.

Third, pre-clinical studies should use the same level of rigor needed for clinical trials. Specifically, assignment of animals to treatment conditions should be randomized, assessments must be conducted by blinded examiners, the primary outcome measure must be pre-determined, and statistical assessment of secondary outcome measures should use appropriate corrections for multiple comparisons. Registration of pre-clinical studies, as is required through ClinicalTrials.gov for clinical trials, would improve the rigor of pre-clinical studies and would further counteract the bias resulting from the failure to publish negative studies.

Fourth, the administration of therapeutic agents in animal models should mimic the timing, delivery route, and dosage feasible in humans, including in the combat theater. For example, administering therapeutic agents before injury would require treating all persons at risk of sustaining a TBI and is generally not feasible in the absence of exceptionally high evidence of safety. Thus, animal studies should generally not involve pre-injury administration of pharmacological agents. When such information is available, doses used in pre-clinical models should not result in blood and tissue levels known to be toxic in humans. Attractive candidate pharmacotherapies should ideally have broad-spectrum action in several pre-clinical models of TBI, across multiple species, and be reproducible by multiple laboratories. There is a paucity of pre-clinical studies of the post-acute and chronic stages of TBI, and pre-clinical studies for which therapy is started days, weeks, or months after injury are needed.

Last, the neurobehavioral outcome measures most widely used in pre-clinical models are not sufficiently sensitive to long-term behavioral and cognitive deficits, and more sensitive rodent behavioral tasks that discriminate injury severity beyond 12 weeks after injury are needed.

Research Gap 2: Early identification of patients with mild TBi (mTBI) who are likely to have long-term complications that interfere with activities of daily living

Pharmacological intervention for patients with mTBI who have long-term complications is a major unmet medical need, with most completed and ongoing clinical trials focused on pharmacological intervention of patients with moderate and severe TBI. According to the Centers for Disease Control and Prevention (CDC), of the 1.7 million persons who sustain a TBI annually in the United States, 75% receive a diagnosis of mTBI.[3] According to statistics collected and analyzed by the Defense Medical Surveillance System and Theater Medical Data Store, of the 262,065 service members who have sustained a TBI from 2000 through the third quarter of 2012, 200,076 (76.4%) had a diagnosis of mTBI.[4]

Historically, within our capabilities to clinically assess improvement, the majority of persons with mTBI appear to recover to their pre-injury state; some, however, may experience long-term complications that may be prevented by early intervention. Early identification of those persons likely to experience long-term complications is essential to maximize benefit and limit risk to study participants enrolled in clinical trials. Strategies to delineate this population from a larger population of persons with mTBI could include enrollment of patients with persistent symptoms 1 to 2 weeks after injury, because recovery is most rapid in the first few days. Such a strategy, however, is not appropriate for drugs targeting mechanisms active in the acute stage after injury.

A more general approach would be to identify prognostic biomarkers (e.g., neuroimaging, biochemical, and objective clinical measures) that signal patients unlikely to fully recover. Prognostic biomarkers are defined by the U.S. Food and Drug Administration (FDA) as indicators that inform the natural history of a disorder in the absence of a therapeutic intervention.[5] The development process for prognostic biomarkers must not only involve validation using standardized clinical outcome measures but should also follow the FDA Guidance for Industry: Qualification Process for Drug Development Tools.[5] This guidance is specific to the qualification process for drug development tools, including biomarkers. Qualification of a biomarker indicates that the results can be relied on for specific interpretation and application in drug development regulatory decisions. Thus, as part of a drug development program for TBI, early adherence to this guidance will enable more rapid and standardized progression of pharmacologic agents through clinical trials.

Research Gap 3: Identification of predictive and pharmacodynamic biomarkers of therapeutic response

Although identifying persons with TBI who are most likely to respond to therapy and evaluating the biologic response to pharmacological intervention are essential for successful clinical trials, the ability to do either is lacking. Predictive and pharmacodynamic biomarkers of therapeutic response are needed to address this challenge. Predictive biomarkers are baseline characteristics that identify persons by their likelihood to respond to a particular pharmacological intervention and may include biochemical markers (e.g., oxidative stress, inflammation, neuronal, and glial integrity), molecular imaging with positron emission tomography (PET), or functional imaging with functional magnetic resonance imaging (fMRI).[5] By identifying patients who are most likely to respond to a particular type of pharmacological intervention, the appropriate population can be selected for enrollment in clinical trials.

Identifying specific predictive biomarkers would decrease the sample size needed to power clinical trials, thus decreasing risk to subjects, time to complete accrual, and cost. Pharmacodynamic biomarkers are dynamic measurements that show a biologic response occurred after pharmacological intervention.[5] Several of the leading treatment candidate compounds have well-understood molecular mechanisms of action that may be assessed for such measurements. Examples may include neuroimaging to measure effects on neuroprotection, neurorecovery, and neuroinflammation, or biochemical biomarkers of oxidative stress, inflammation, and neuronal integrity. Clinical trials would greatly benefit from pharmacodynamic biomarkers, which allow for the measurement of the effect of the drug on the putative mechanism of action, thus providing evidence of engagement of the target by the therapy. Pharmacodynamic biomarkers would also be very useful for dose optimization Phase II studies.

As with prognostic biomarkers, the development of predictive and pharmacodynamic biomarkers should include validation and follow the FDA qualification guidances.[5] In addition, close attention should be paid to pharmacokinetics and absorption, distribution, metabolism, and excretion (ADME) in pre-clinical and clinical studies because these characteristics may change based on injury severity and time since injury.[6]

Research Gap 4: Pharmacological interventions aimed at promoting neurorepair, neuroregeneration, and neuroprotection

Pharmacological interventions targeting repair, regeneration, and protection after TBI are needed. Clinical trials evaluating these interventions must use standardized clinical outcome measures to demonstrate efficacy. In the past, drug development for TBI focused on limiting downstream or secondary brain injury after the initial traumatic event because evidence that the central nervous system could be repaired or regenerated was lacking. Evidence now indicates that the adult brain can be both repaired and regenerated after TBI, and repair and regeneration processes can be activated or enhanced by pharmacological treatment. Brain repair mechanisms that are potential drug targets include angiogenesis, axon guidance and remodeling, remyelination, neurogenesis, and synaptogenesis. Pharmacological therapies may also target regeneration by enhancing the ability of pluripotent cells to differentiate into neurons, glia, and vascular endothelium.[7–9]

Pharmacological interventions supporting regeneration and repair may have a longer therapeutic window than pharmacological interventions designed to limit injury, and they are also potentially effective in the acute, subacute, post-acute, and chronic phases after TBI. Thus, repair and regeneration therapies have the potential advantage of being effective over a prolonged period after TBI.

Research Gap 5: Symptomatic interventions for long-term complications prominent in the chronic period after TBI.

Pharmacological interventions designed to manage the persistent symptoms associated with the chronic stage of TBI (e.g., memory disturbances, depression, headache) are widely used by clinicians. These include pharmacotherapies aimed at modulating the dopaminergic, noradrenergic, serotonergic, glutamatergic, and cholinergic systems. Strong evidence for their efficacy and safety is lacking, however. As a result, the selection of a drug for individual patients, or drug dose and duration, is empirical and highly variable among civilian and military health systems. Clinical trials are needed to assess the efficacy and toxicity of these pharmacological interventions. As part of the evaluation of pharmacological agents targeting symptoms, a corresponding need exists for predictive and pharmacodynamic biomarkers to demonstrate biologic response to therapy akin to that described in Gap 4.

Research Gap 6: Therapeutic interventions that can be used in combination to target multiple parallel mechanisms of injury

To date, no pharmacological agent has received FDA approval for the treatment of patients with TBI. Because TBI damages the brain by multiple mechanisms, combination therapy designed to simultaneously target multiple mechanisms of injury will likely be needed. Clinical trials evaluating these interventions must use standardized clinical outcome measures to demonstrate efficacy. Pharmacotherapy that blocks downstream cellular and molecular mechanisms in the brain combined with pharmacotherapy that targets symptoms resulting from TBI may provide one reasonable strategy. At minimum, drug combinations should be additive, but the most potent drug combinations may be synergistic.[10,11] Thus, drug combinations have the potential of having a larger therapeutic efficacy than that of individual drugs.

Several challenges should be considered. First, although some drug combinations may show additive or synergistic effects, others may prove antagonistic. There has been insufficient pre-clinical research on which drug classes (e.g., anti-inflammatory, anti-oxidant, anti-apoptotic) can be combined to achieve optimal therapeutic potency. Drug combinations need to be tested in animal models that allow the therapeutic efficacy and toxicity of the combination to be compared with that of the individual agents. Potency of drug combinations in pre-clinical studies should be demonstrated using predictive and pharmacodynamic biomarkers that can be replicated in clinical trials. Thus, combinations should ideally be evaluated first in pre-clinical models to evaluate both efficacy and toxicity.

Second, FDA regulations and approval processes should be considered during the development process for combination therapies from the onset of pre-clinical studies. The strategy needed for an FDA new investigational drug application depends on the regulatory status of each of the drugs that comprise the combination therapy. A clinical trial for combination therapy has the additional goal of demonstrating that the drug combination is more efficacious than the individual drugs or placebo. The safety and efficacy of the

combination must be demonstrated even if the safety and efficacy of the individual drugs are known.

Current state of the science of pharmacological treatments for TBI

The Neurotrauma Pharmacology Workgroup examined specific pharmacotherapies for TBI treatment during a closed state-of-the-science meeting session and subsequent Workgroup meetings. Candidate compounds were identified and discussed by members of the Workgroup. Each drug was evaluated on the strength of its pre-clinical and clinical data, biologic mechanism of action, known or suggested biomarkers, and advantages and disadvantages. When applicable, suggestions for moving research on a particular drug forward were made. The Workgroup reconvened via a series of teleconferences in which they further developed the research gaps and priorities and selected drugs to be included in this report.

A review of the available literature was conducted, using PubMed and relevant review articles. In addition, http://www.ClinicalTrials.gov was searched for ongoing and recently completed Phase III trials (Table 1) and Phase II trials (Table 2) of the pharmacological treatment of patients with TBI. Findings from these searches as well as subject matter expert input and discussion during Workgroup meetings were used to refine further the list of candidate compounds. Each candidate compound was reviewed and discussed by the Workgroup in terms of clinical and pre-clinical use and FDA approval, and 12 drug classes or drugs were selected from the list for further review (Table 3).

The selection of these drugs as candidates of interest, although inherently subjective, represents the informed expert opinion of the committee on the current state of the science. Focused literature searches were conducted for each of the 12 compounds to verify, and identify additional, relevant evidence supporting their use for TBI as well as research gaps. Each was discussed with respect to mechanism of action, summary of available pre-clinical evidence in TBI and other related models, and summary of clinical development to date in TBI and other related disorders. There was also evidence-based discussion about the stage of TBI most suitable for clinical development of each drug (e.g., acute versus subacute) and the severity of TBI (e.g., mild versus moderate to severe). Each drug was evaluated on characteristics that supported future investigation (e.g., replicated pre-clinical and clinical data, existing FDA approval, elucidated biological mechanisms of action, valid and reliable biomarker data).

Finally, gaps in knowledge related to each compound were discussed. In addition to the 12 most promising compounds as defined by the Workgroup, 13 additional compounds with less conclusive evidence for use in TBI were considered and briefly reviewed by the committee (Table 4). Drugs classes as well as specific drug candidates are discussed in alphabetical order below.

1. Acetylcholinesterase inhibitors

Mechanism of action. Central acetylcholinesterase inhibitors (AChEI) increase synaptic acetylcholine by inhibiting its breakdown in the synaptic cleft. AChEIs are FDA-approved in the United States for treating patients with mild to moderate Alzheimer disease (AD) and have been used off label for other cognitive disorders, including TBI of all severities. Initial TBI studies reported encouraging findings for the efficacy of the first-generation AChEI, physostigmine.[12,13] With the advent of better-tolerated and safer AChEI over the past decade, an increasing number of clinical trials are using newer AChEIs, including donepezil,[14–35] rivastigmine,[15,29,36–41] and galantamine in trials for chronic TBI. Studies of these compounds for the treatment of patients with TBI suggest they may have potentially beneficial effects—particularly in patients with chronic moderate and severe TBI who have persistent cognitive deficits—by increasing synaptic ACh levels.[14–35]

Summary of pre-clinical evidence. Beneficial effects have been reported in pre-clinical TBI studies with AChEI, including positive effects on acute injury processes with reduced TBI-induced neuronal death, preservation of neurons in the CA1 hippocampal region, reduced blood–brain barrier (BBB) disruption, decreased vasogenic brain edema, and preserved neurologic and motor function.[14,42] A literature search revealed four pre-clinical studies of donepezil, rivastigmine, or physostigmine. Other AChEI studies have been performed in pre-clinical trials for AD. Additional literature searches failed to retrieve studies that compared efficacy or toxicity of different AChEIs as TBI treatment. AChEI

Table 1. Pharmacotherapies with Completed Phase III Trials and Available Results

	Onset of treatment			
TBI Severity	*Acute (<24 hours)*	*Subacute (1 day–7 days)*	*Post-acute (7 days–6 months)*	*Chronic (>6 months)*
Severe	Nimodipine PEG-SOD Tirilazad Selfotel Corticosteroid Traxoprodil Dexanabinol Magnesium Sulfate COBRIT		*Amantadine	
Moderate	Tirilazad Magnesium Sulfate COBRIT			
Mild	COBRIT			

*Denotes positive results.
PEG-SOD, Polyethylene Glycol-Conjugated Superoxide Dismutase; COBRIT, Study of Citicoline for the Treatment of Traumatic Brain Injury.

Table 2. Pharmacotherapies Currently Undergoing Phase II or Phase III Clinical Evaluation for Which Results are Pending

	Time of therapy onset			
TBI Severity	*Acute (<24 hours)*	*Subacute (1 day–7 days)*	*Post-acute (7 days–6 months)*	*Chronic (>6 months)*
Severe	Abeladrug200 Allopregnanolone Divalproex Sodium Erythropoietin Esmolol Glyburide Human Chorionic Gonadotropin Hydrocortisone Ketamine[1] Magnesium Sulfate Minocycline NNZ-2566 Oxycyte Paracetamol Progesterone Propranolol SLV334[2]	Darbepoetin Alfa Dexmedetomidine[3] Human Chorionic Gonadotropin Nerve Growth Factor Levetiracetam[4] Paracetamol Propranolol	Amantadine Androgel Erythropoietin Growth Hormone Huperzine A Methylphenidate	Amantadine Atomoxetine Carbamazepine Growth Hormone Rivastigmine Sildenafil Treximet
Moderate	Allopregnanolone Erythropoietin Glyburide Human Chorionic Gonadotropin Minocycline NNZ-2566 Progesterone Propranolol SLV334[2]	D-cycloserine Human Chorionic Gonadotropin Nerve Growth Factor	Androgel Citalopram Huperzine A Methylphenidate Rozerem	Amantadine Armodafinil[5,6] Atomoxetine Carbamazepine Duloxetine[7] Genotropin Growth Hormone Namenda[8] Rivastigmine Rozerem Somatropin[9] Treximet
Mild	Atorvastatin		Citalopram Methylphenidate Rozerem	Armodafinil[5,6] Amantadine Duloxetine[7] Genotropin Methylphenidate + Galantamine Namenda[8] Pregnenolone Omega-3 FA Rivastigmine Rozerem Sildenafil Somatropin[9] Treximet

[1,3], trial withdrawn (NCT00556387, NCT01007773); [2,4–9], trial terminated (NCT00735085, NCT00566046, NCT00893789 NCT00983437, NCT01223001, NCT00462228, NCT00555009).

studies for TBI have been performed in closed head injury models in rats and mice. These studies showed that drugs acting on acetylcholine were responsible for neuroprotection given that the protective effects of acetylcholine were antagonized by nicotinic and/or muscarinic receptor blockers.

Summary of clinical development. A 2008 review of all donepezil studies for cognitive rehabilitation after TBI found that of 39 potential studies, only 2 were randomized controlled trials (RCTs). The overall lack of methodological quality and small sample sizes prevented formal assessment of the clinical efficacy of donepezil compared with standard treatment for cognitive rehabilitation.[14]

Two completed clinical trials studied rivastigmine in moderate to severe TBI.[38,39] Phase II efficacy and safety evaluation of rivastigmine in adults with moderate to severe TBI and cognitive impairment (NCT00171795) was completed in 2006, and a follow-on extension study evaluating the efficacy and safety of rivastigmine (NCT00219245) was published in 2009. The initial study was a prospective, randomized, double-blind placebo-controlled study sponsored by Novartis. The study did not find significant

TABLE 3. SUMMARY OF THE WORKGROUP'S LEADING DRUG CANDIDATES FOR TRAUMATIC BRAIN INJURY TREATMENT

	State of Development							*Evidence for use in:*								
	FDA Approved	*Preclinical Trials*	*Preclinical Trials in >1 species*	*Independent reproduction*	*Ongoing/ Completed Phase II Trials*	*Ongoing/ Completed Phase III Trials*	*Available Biomarker Data*	*Acute (<24 h)*	*Subacute (1–7 d)*	*Post-Acute (7 d-6 m)*	*Chronic (>6 m)*	*Mild TBI*	*Moderate-Severe TBI*	*Neuroprotection*	*Neuroregeneration*	*Symptomatic Therapy*
Amantadine	✓	✓	✓	✓	✓		✓	4			2		4			4
Cyclosporine A	✓	✓	✓	✓	✓			4			0	0	4	4	0	0
Donepezil	✓	✓	✓	✓	✓						2	2	4	0		2
Erythropoietin	✓	✓	✓	✓	✓	✓	✓	0				0	0	0	0	
FK-506	✓	✓	✓	✓				4	4				4	4		
Glyburide	✓	✓	✓	✓			✓	4				0	0	0	0	4
Growth Hormone	✓	✓		✓			✓			0	4		4	0	4	4
Huperzine A	✓	✓	✓	✓	✓									0		0
Lithium	✓	✓	✓	✓			✓	0			4		0	4	0	0
Methylphenidate	✓	✓	✓	✓	✓			4	4	2	4	2	4	0		4
Minocycline	✓	✓	✓	✓			✓	0			0	0	0	0		
N-Acetyl Cysteine	✓	✓	✓	✓			✓	0					4	4		
Progesterone	✓	✓	✓	✓	✓	✓	✓	4	4				4	4	4	4
Rivastigmine	✓	✓			✓	✓				4	4		4			4
Simvastatin	✓	✓	✓	✓				0			0	0	0	0	0	0

0, preclinical evidence only.
4, preclinical and clinical evidence.
2, clinical evidence only.

Table 4. High-level Summary of Additional Drugs Candidates Considered by the Workgroup

Drug	*Advantages*	*Disadvantages*
Anakinra	Reasonable pre-clinical data Well-tolerated in acute critical illness; two small studies in acquired brain injury show it is well tolerated. FDA-approved	Long-term treatment appears to impair recovery
Calpain inhibitors	Improved functional outcome in two different TBI models. Favorable therapeutic window	Not FDA-approved Unknown mechanism of action
Dexanabinol	Functional outcomes used in human studies	Always used acutely (< 6 h post- injury) Not FDA-approved
Deltibant	Bradykinin antagonists used in non-TBI conditions FDA-approved	Toxicity noted in animal studies
Etanercept	Well studied safety profile	TNF function appears to be important for recovery in TNF knockout mice
Fibroblast growth factor	Functional outcome in addition to histological markers	No replicated pre-clinical data No clinical data
Insulin-like growth factor-1 (IGF-1)	FDA-approved Given both acutely and subacutely in moderate and severe TBI Can track IGF-1 serum levels	Associated with hyperglycemia in humans
Nicotinamide	A commonly consumed nutritional supplement	Pre-clinical studies show marked benefit on histology, but limited evidence for benefit on cognition
Omega-3 fatty acids	Readily available (both by prescription and over-the-counter as dietary supplement) Favorable safety profile Decrease triglycerides and relevant to cardiovascular health Potential for rapid translation to clinical use Significant body of pre-clinical and clinical scientific literature in other disorders May be helpful for comorbid conditions such as depression	Currently no clinical studies with omega-3 fatty acids in TBI Limited pre-clinical data on omega-3 fatty acids in TBI
PEG-SOD	Favorable safety profile demonstrated in severe TBI Targets oxidative stress in the vasculature, which may be important in blast TBI	Drug not available Significant investment required to make drug available Large molecule that does not easily penetrate the BBB
Resveratrol	Some dosing studies in rodents Effective in both perinatal and adult rats	No data on therapeutic window
Selfotel	Phase II study in TBI showed hints of efficacy	Phase III clinical trial in TBI stopped early because of negative results in stroke study Drug no longer available from manufacturer (Pfizer)
Sildenafil	FDA-approved compound with favorable safety profile Clinical trials in stroke and microvascular disease ongoing	Limited pre-clinical development in TBI models

FDA, Food and Drug Administration; TBI, traumatic brain injury; TNF, = tumor necrosis factor; BBB, blood–brain barrier.

differences in primary or secondary variables after 12 weeks on either the Cambridge Neuropsychological Test Automated Battery Rapid Visual Processing (CANTAB RVLP) or the Hopkins Verbal Learning Test (HVLT).[38] The 26-week extension of the initial rivastigmine study demonstrated that rivastigmine was safe in patients with TBI and cognitive impairment up to 38 weeks.[39]

A third clinical trial of rivastigmine, which has not yet started (NCT01670526), will investigate the transdermal rivastigmine patch versus placebo for the treatment of moderate to severe post-traumatic memory impairment in veterans with TBI. This Phase II randomized, multisite, parallel design, placebo-controlled study will use the HVLT-Revised at baseline and after 12 weeks of treatment.

A fourth AChEI trial includes the Cognitive Remediation After Trauma Exposure (CREATE) Trial, which is currently recruiting patients for a randomized, double-blind, controlled 12-week trial of galantamine, methylphenidate, and placebo for the treatment of cognitive symptoms in TBI and/or post-traumatic stress disorder (PTSD). This study is part of the Injury and Traumatic Stress (INTRuST) PTSD-TBI Consortium and is using the Ruff Neurobehavioral Inventory at 12 weeks as the primary end point.

Evidence-based assessment of setting for suitable clinical development. The few pre-clinical data on TBI provide evidence for administration of AChEIs in the full range of mild to

severe TBI during the acute to subacute phases. There is a lack of pre-clinical testing of the efficacy of AChEIs after delayed administration at weeks or months after injury. Clinical studies have targeted this subacute to chronic period with several AChEIs, primarily donepezil, however. Overall, safety and tolerability are well established. Donepezil has the most frequent adverse side effects, but these findings are from clinical studies limited by small sample size and methodology.

Discussion of gaps in knowledge. A large clinical trial of AChEI treatment in mTBI is warranted, given the limited but positive body of pre-clinical studies in models of mild to severe TBI. Chronic studies have suggested benefits with the caveat of methodological limitations. Pre-clinical studies of delayed chronic administration of AChEI after TBI are needed, as are additional studies in mild to severe TBI models.

Huperzine A

Mechanism of action. Huperzine A is a selective and reversible AChEI extracted from a Chinese herb and is used in China for the treatment of AD. It may also have effects on other neurotransmitter systems or molecular pathways and is believed to work as an N-methyl-D-aspartate (NMDA) antagonist with antiseizure properties, a potential added benefit for treatment of penetrating and severe TBI. In the United States, huperzine A is classified as an herbal remedy and is most commonly used for the treatment of memory complaints. The active drug, lycopodiam alkaloid, is believed to be a selective and reversible AChEI. Recent studies have suggested that huperzine A has potential neuroprotective effects through the activation of cholinergic systems and by potentially upregulating β-amyloid precursor protein metabolism.[43] Evidence from one pre-clinical study suggests that huperzine A modulates both non-amyloidogenic and amyloidogenic metabolism of β-amyloid precursor protein in rodents and may reduce oxidative stress by directly acting on mitochondria.[44]

Summary of pre-clinical evidence. A literature search identified three pre-clinical rodent TBI studies on huperzine A and TBI.[44–46] The most recent study used mice to examine the mechanism of action of huperzine through effects on modulation of both amyloidogenic and non-amyloidogenic pathways.[44] Huperzine A provided some attenuation of cognitive deficits in neonatal rats after hypoxia-ischemia.[46] Huperzine A also improved memory in rats with scopolamine-induced deficits.[45] Many pre-clinical and clinical studies have studied huperzine A specifically for dementia disorders—namely AD. These studies may not be applicable to TBI because of different mechanisms of pathology. They do, however, suggest the possibility of an improvement of cognitive symptoms.

Summary of clinical development. Clinical studies with huperzine A and TBI are limited; significantly more studies have been conducted using patients with AD. A Cochrane review of RCTs for efficacy and safety of huperzine A for TBI identified six clinical trials, with a total of 454 patients who met inclusionary criteria of the studies.[47] Some beneficial effects were seen in general cognitive function, global clinical status, behavior disturbance, and functional performance. The methodology of several of these trials was not optimal; only one study had adequate size and quality of the group. A large multicenter, randomized trial is needed to further assess the clinical utility of huperzine A for the treatment of patients with TBI.

One clinical study was an open label study of professional athletes from the National Football League who received a ''formulated enhancement supplement'' that included huperzine A.[48] The study's main outcome assessment of cognitive function was brain SPECT imaging, which was proposed to show cognitive and cerebral blood flow improvements. A large randomized Phase II clinical trial (NCT01676311) will examine the effects of huperzine A versus placebo on learning and memory in patients with moderate to severe TBI. This proposed study will examine biomarkers, neurophysiological markers, and electroencephalography (EEG).

2. Amantadine

Mechanism of action. Amantadine (1-adamantamine hydrochloride) is a tricyclic amine used for the prophylaxis and treatment of influenza A and was serendipitously discovered to have modest efficacy for the treatment of Parkinson disease (PD). The anti-parkinsonian mechanism of action is not fully understood, but research has suggested that amantadine increases extracellular dopamine (DA) concentrations either by blocking DA reuptake or facilitating DA synthesis.[49] Amantadine may also have postsynaptic effects on DA circuits by increasing DA receptor density.[50] Amantadine is also a weak noncompetitive antagonist of NMDA receptors.[51]

Summary of pre-clinical evidence in TBI models. Amantadine has not been extensively studied in pre-clinical models of experimental TBI. One study showed that amantadine treatment, starting 1 day after a closed controlled cortical impact (CCI) model of TBI in rats and continuing for 18 days after injury, resulted in modest improvement in Morris water maze (MWM) latencies.[52] Amantadine had no effect on motor function or survival of hippocampal neurons, however, which dampened the enthusiasm for further pre-clinical studies.

Summary of clinical evidence. Amantadine has evidence for efficacy during the post-acute period in humans with TBI. Two small, randomized trials in patients with traumatic disorders of consciousness demonstrated modest efficacy, although small sample sizes and other methodological limitations reduced their impact.[53,54] A multicenter observational comparative effectiveness study used multiple regression analysis to show that amantadine was associated with improvement in the Disability Rating Scale (DRS) in patients in the vegetative state (VS) or minimally conscious state (MCS) 4 to 16 weeks after injury.[55] These clinical observations, rather than convincing data from animal models, led to a Phase III randomized, placebo-controlled trial that enrolled 184 patients in VS or MCS and treated them for 4 weeks.[56] This recently published study demonstrates that amantadine results in more rapid improvement of DRS compared with placebo ($p = 0.007$), although the rate of change of DRS flattened after the 4-week treatment phase.

This important study represents the first and only evidence to date that pharmacological interventions can affect recovery from TBI. It has also stimulated ongoing research (NCT 00779324) on the use of amantadine for the treatment of post-traumatic irritability in the chronic period after TBI (>6 months after injury). The experience with amantadine justifies further clinical development based on the results of small pilot clinical trials and carefully conducted prospective observational studies.

Evidence-based assessment of setting for clinical development. Sufficient data from Phase III studies in humans in VS

and MCS justifies further Phase III clinical trials. High quality clinical data indicate that patients with severe TBI and profound disorders of consciousness such as VS and MCS should be treated with amantadine for at least 4 weeks. The stage of injury most appropriate for further investigation appears to be the post-acute and chronic stage after TBI, although potential benefits of earlier treatment remain to be investigated.

Discussion of gaps in knowledge. Questions that should be addressed relate to important issues such as duration of therapy, timing of the initiation of therapy, and severity of deficits present in candidates for amantadine therapy. In particular, it is important to know whether starting therapy at an earlier time after the injury confers additional benefits and whether continuing therapy for months or even years post-injury has additional value. Also of great importance is understanding whether amantadine therapy is useful in patients with less severe disabilities after TBI, particularly patients with mTBI and persistent post-concussive symptoms. Identifying pharmacodynamic biomarkers of the amantadine effect would be useful for accelerating such research.

3. Cyclosporine A/FK 506

Mechanism of action. Cyclosporine A (CsA) inhibits opening of the mitochondrial permeability transition pore after TBI, thereby maintaining mitochondrial membrane potential. Many studies in animal models of TBI have suggested that this action of CsA confers benefit by preserving mitochondrial function and reducing reactive oxygen species.[57,58] Inhibition of the protein phosphatase calcineurin via the immunophilin effects of CsA also has beneficial effects on axonal injury and learning and memory.[59–75] Similarly, immunosuppressive effects, also mediated by calcineurin inhibition, may further confer benefit after TBI or mediate potential side effects. The related compound, FK 506, inhibits calcineurin and exhibits immunosuppressive effects but does not inhibit opening of the mitochondrial permeability transition pore.[76]

Summary of pre-clinical evidence. A literature search identified 17 pre-clinical TBI studies on CsA[59–75] and 6 studies on FK 506.[76–81] CsA improved multiple histological outcomes after TBI, including impressive effects on axonal injury and contusion volume. Surprisingly, there were fewer studies on the effects of CsA on functional outcome after TBI: two studies showed benefit on motor outcomes and one on MWM performance. For FK 506, similar histological benefits have been shown on axonal injury, but the extent of studies on other histopathological or behavioral outcomes is more limited. CsA and FK 506, however, have beneficial effects on cerebral microcirculation after TBI and appear to synergize in this regard with mild hypothermia therapy.[75,76]

Not all studies have yielded positive results. For example, neither CsA nor FK 506 have shown any benefit in a model of TBI in developing rats, and FK 506 did not reduce neuroinflammatory markers in injured mouse brain.[67,80] CsA did not improve cognitive outcome in the CCI model in rats.[82] Most of the studies of CsA or FK 506 were performed in rats or mice using either the impact acceleration model or CCI, with a few using fluid percussion model (FPI). A few studies have been conducted in large animals including a pediatric TBI model in piglets.[62]

There have been pre-clinical studies of dose response, route of administration, therapeutic window, and brain tissue levels. The intravenous (IV) route is used clinically. In the swine model, benefit was seen with 20 mg/kg IV of CsA given at 5 min and 12 h after TBI. Therapeutic window studies suggest that initial dosing is better at 15 min rather than 1 h, but efficacy with administration of the first dose up to 8 h after injury is seen in some studies.[72] One concern is that CsA has limited BBB passage. Despite being lipophilic, it has restricted BBB penetration because of P-glycoprotein transporters. Clinical reports suggest some level of BBB passage of CsA and FK 506 with chronic administration given many reports of neurotoxicity with chronic administration, particularly with blood high levels.[83–85]

Summary of clinical development. There have been five reports on Phase II clinical studies of CsA in TBI. In 2006, Empey and colleagues[86] performed a dose escalation study focused on pharmacokinetics and evaluated plasma samples from 30 patients with severe TBI. Doses of 0.625 to 2.5 mg/kg were evaluated. CsA was cleared more rapidly and had a larger distribution volume in patients with TBI than in reported populations. Mazzeo and associates[87] studied immunologic effects of CsA in 59 patients with severe TBI, using a dose of 5 mg/kg in one or two 24-h infusions. Measures of neurologic outcome, cellular immunity, and infection rate did not differ between the CsA and placebo groups. A number of lymphocyte markers were studied. The study was open label and the placebo group had higher Glasgow Coma Scale (GCS) scores, further complicating immunologic comparisons.[87]

A subsequent study examined metabolic and hemodynamic effects of CsA in 50 adults with severe TBI using a dose of 5 mg/kg over 24 h or placebo.[88] Treatment was associated with a higher mean arterial pressure (MAP) and cerebral perfusion pressure (CPP). Cerebral microdialysis monitoring in the CsA group showed higher brain interstitial lactate and glucose levels, while glutamate and lactate/pyruvate ratio were decreased versus placebo. The etiology of the higher lactate levels was not clear, but the direction of the other three parameters was favorable.

Hatton and coworkers[89] studied 40 adults with severe TBI, 32 treated with CsA and 8 with placebo. Four different dosing regimens were used (1.25 to 5.0 mg/kg/d) and no differences in mortality or complications were observed between groups, although a positive effect on 6-month Glasgow Outcome Scale (GOS) score was seen for the CsA- treated patients.[89] Mazzeo and colleagues[90] studied 49 patients with severe TBI, including 36 CsA-treated and 13 placebo-treated. A 5 mg/kg infusion over 12 h was used, and MAP and CPP were significantly increased in the treatment group for 3 days versus placebo. A trend toward increased mortality was observed with treatment (9/36 vs. 2/13), although the sample size of the study was small.[90]

Finally, in transplant patients, chronic encephalopathy and seizures have been reported with CsA and FK 506 treatment.[83–85] Given the complexity of these patients, it is unclear whether toxicity from chronic use of FK 506 or CsA could limit their utility in TBI given that the toxicity is often seen with high plasma levels, is linked to systemic arterial hypertension in some reports, and appears to be partly related to metabolites of these agents.

Evidence-based assessment of setting for suitable clinical development. Both the pre-clinical and clinical studies suggest that the most appropriate avenue for clinical development of CsA or FK 506 is in acute treatment of patients with severe TBI. Limited BBB permeability of CsA could represent a concern for delayed administration or use in mTBI. Chronic neurotoxicity of these agents or their metabolites could also be a potential limitation to prolonged therapy.

Discussion of gaps in knowledge. There has been sufficient pre-clinical and clinical work to support a Phase III clinical trial of acute treatment with CsA and Phase II studies of FK 506 in patients with severe TBI. Additional pre-clinical investigation is needed in models of mTBI, as are studies examining delayed and/or chronic treatment across the injury spectrum. Immunosuppressive effects of these agents could also be limiting in the setting of complex insults such as TBI plus shock or polytrauma.

4. Erythropoietin

Mechanism of action. Erythropoietin (EPO) is a pleiotropic cytokine involved in erythropoiesis and has a number of beneficial effects that could be important in TBI such as attenuation of glutamate and nitric oxide toxicity, antiapoptotic, antioxidant, and anti-inflammatory effects, stimulation of neurogenesis and angiogenesis, and protection of mitochondria.[8–10,91–110] The exact mechanism of benefit is unclear. Although classical EPO receptors are seen in many cell types in the brain, and EPO receptor null mice have a worse outcome than wild type after CCI,[105] EPO receptors do not appear to be required to mediate the benefit of exogenously administered EPO therapy.[10]

Summary of pre-clinical evidence. Review of the experimental TBI literature suggests that EPO is a promising therapy. A literature search identified 23 studies all showing efficacy of EPO in rodent models of TBI.[8–10,91–110] These studies comprised both rat and mouse models across brain injury models including CCI, FPI, impact acceleration, focal closed head injury, Feeney weight drop, and combined injury. Studies in large animal models of TBI were not identified. Route of administration, dosing, and therapeutic window are favorable. The studies indicate that any parenteral route of administration shows efficacy (IV, intraperitoneal, or subcutaneous). A dose of 5000 IU/kg appears to be optimal, with doses of 1000 or 3000 IU/kg also showing efficacy.

The therapeutic window may be prolonged, with some studies suggesting benefit with a first dose as late as 24 h post-injury.[8] EPO significantly increased production of newly generated neurons and preserved hemispheric brain volume when administered 6 weeks after an experimental stroke.[111] The most comprehensive study of treatment time window in TBI, however, identified 6 h as the latest time point for successful initial dosing, at least from the point of view of cytoprotection.[95] Studies have shown benefit from a single dose, two doses, three doses, or daily treatment for 14 days.[8–10,91–110]

Benefit has been shown across many outcomes. In single dose regimens in rat TBI models, hematocrit (HCT) increased from baseline values of $\sim$45% to between 52% and 60% with increases most prominent on 4 to 14 days after administration.[9,109] Carbamylated EPO analogs that have no effect on HCT do not bind to the EPO receptor, yet show similar efficacy to EPO in CCI models.[9] The EPO analog darbepoietin has a longer half-life than EPO and has shown benefit in CCI.[96]

Summary of clinical development. There is an ongoing, single center Phase III clinical trial of EPO in severe TBI that began in 2006 (NCT00313716) and a Phase III multicenter study of EPO in severe TBI in adults (NCT00987454) that began recruiting in 2010. A small 10 patient Phase I trial of darbepoetin alfa in adults with severe TBI was completed (NCT00375869), but results are not yet available. Concern for the use of EPO in TBI has resulted from increased HCT and increased mortality in clinical testing in adult patients with stroke, from 9.0% to 16.4% ($p < .01$) (NCT00604630).[112] Of note, many patients received recombinant tissue plasminogen activator (63%) in the study, and the excess mortality was only seen in this group. The side effect of polycythemia may not be a concern in severe TBI or polytrauma, given that HCT is often reduced in patients with these conditions, and EPO could reduce transfusion risk.

Consistent with that possibility, a Phase II clinical study of EPO in 80 adults with subarachnoid hemorrhage (NCT00140010) revealed a significant reduction in the incidence of severe vasospasm, reduced delayed ischemic deficits, a shortened duration of impaired autoregulation, an improved discharge outcome, and a reduction in the number of blood transfusions with EPO treatment.[113] For mTBI, this would not be the case, and hyperviscosity could be a concern.

A recent non-randomized retrospective study showed that administration of EPO to 89 patients with severe TBI initiated within 14 days after TBI was safe and beneficial and resulted in lower hospital mortality.[114] Likewise, EPO administration in humans has proved to be effective in chronic conditions, such as bipolar depression[115] and schizophrenia. EPO was beneficial and decreased loss of gray matter in chronic schizophrenia.[116]

Evidence-based assessment of setting for suitable clinical development. There is already considerable clinical development of EPO in severe TBI. The pre-clinical data provide evidence for subacute administration as well in TBI. Most of the pre-clinical evidence was generated in the CCI model with moderate to severe insults, but some of the studies were performed in the impact acceleration model, suggesting that efficacy might also be seen in mTBI.

Discussion of gaps in knowledge. Given that EPO features a number of beneficial effects on regeneration within the scope of its mechanism of action (e.g., neurogenesis, angiogenesis), there is need for pre-clinical testing of EPO specifically in mTBI and in the specific setting of delayed therapy in the post-acute and chronic phase. Given concerns with regard to erythropoietic effects, EPO analogs devoid of erythropoietic effects might be desirable for mTBI and delayed or chronic therapy. EPO is a potentially appealing drug for TBI plus polytrauma and/or hemorrhage, where the combination of benefit on TBI and reduction of need for transfusion could be synergistic. A clinical trial of EPO in the setting of TBI plus polytrauma and/or hemorrhage would be logical if either of the current Phase III clinical trials in severe TBI is promising.

5. Glyburide

Mechanism of action. The sulfonylurea receptors are members of the adenosine triphosphate binding cassette (ABC) transporter superfamily. These proteins, Sur1/*Abcc8* and Sur2/*Abcc9,* associate with other pore-forming subunits to form ion channels. One of the best understood protein interactions is the association between Sur1 and the ATP-sensitive K^+ channel Kir6.2/*Kcnj11* to form K_{ATP} channels in pancreatic β cells and neurons. Sur1 also associates with non-selective cation channels to form $NC_{Ca\text{-}ATP}$ channels, which are not expressed in normal tissues but are upregulated after injury. Sur1 is increased in endothelial cells and neurons after multiple types of injury to the brain.[117] Glyburide is a sulfonylurea that binds Sur1 and blocks K_{ATP} channels and is widely used clinically as an insulin secretagogue. It is FDA-approved for the treatment of patients with adult onset diabetes.

Summary of pre-clinical evidence. More than 10 pre-clinical studies from multiple laboratories indicate that glyburide reduces inflammation, hemorrhage, and vasogenic edema. The models used in previous studies include CCI, experimental subarachnoid hemorrhage, spinal cord injury, and middle cerebral artery occlusion. Glyburide has been associated with reduction of secondary hemorrhage[118] and reduction of hippocampal injury and improved performance on the MWM.[119] In these studies, glyburide was administered within a few minutes of injury. Longer, more clinically relevant time windows have not been systematically studied. In ischemia models, however, starting therapy as late as 10 h after injury resulted in histological and behavioral benefit.[117,119,120]

Summary of clinical evidence. Two retrospective studies have attempted to examine the effect of sulfonylurea use in ischemic stroke in humans. Patients with diabetes treated with sulfonylureas experienced better recovery from non-lacunar stroke compared with those not receiving sulfonylureas, although there were no differences in stroke severity at baseline.[121] Another study indicated that sulfonylurea use was associated with reduced in-hospital mortality and reduced likelihood of neurologic worsening.[39] A recently completed Phase IIa trial of IV injected glyburide (NCT01268683) in 10 patients with large anterior circulation strokes suggested a reduction in malignant edema and need for osmotherapy, compared with historical controls.[117] A Phase II trial of glyburide (RP-1127) in moderate or severe TBI recently started. Treatment begins within 8 h of injury and continues for 72 h. In this study, the primary outcome measure is change in MRI-defined edema and/or hemorrhage over the course of treatment.

Evidence-based assessment of setting for clinical development. Glyburide is a promising compound for further clinical development. It appears to target injury mechanisms such as cerebral edema and secondary hemorrhage, which can be detected and reliably measured by neuroimaging methods such as MRI. The current ongoing study uses an appropriate design for Phase II clinical trials and is among the first to use an MRI biomarker as the primary outcome measure for a TBI trial. Given that cerebral edema and secondary hemorrhage are also common after complicated mTBI, the use of similar trial design in this large population of TBI patients may be a promising approach.

Discussion of gaps in knowledge. Additional pre-clinical work is needed to better define the time window for glyburide efficacy, which may be at least 6 h after injury in stroke models. Use of MRI in pre-clinical models to directly measure the effects of glyburide on cerebral edema and microhemorrhages in a manner that can be directly translated to early phase human studies also seems important. Finally, Phase II clinical trials of glyburide in patients with complicated mTBI and MRI evidence of cerebral edema and microhemorrhage would be useful in extending the use of this promising therapy to a large population of patients.

6. Growth hormone

Mechanism of action. Growth hormone (GH) is a 191-amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotrophic cells within the lateral wings of the anterior pituitary gland. GH is regulated by neurosecretory nuclei of the hypothalamus, under the primary control of GH-releasing hormone. GH is released in a pulsatile manner with about 50% of daily GH secretions occurring during the early hours of the morning, primarily during the third and fourth non-rapid eye movement sleep cycles. GH has anabolic effects mediated through GH receptors. GH deficiency/insufficiency (GHD/GHI) is the most common anterior pituitary abnormality after TBI. It can occur as a result of either direct pituitary or indirect hypothalamic injury. It is estimated to occur in approximately 20% of patients with TBI, including Operation Iraqi Freedom/Operation Enduring Freedom veterans with blast-related mTBI.[122–127] Prospective studies have demonstrated both normalization of early (<3 months) GHD/GHI as well as late (>12 months) onset of GHD/GHI after TBI, however.[128] GH is FDA-approved for a variety of pediatric GH deficiency conditions and is also FDA-approved for adult patients with acquired GHD.

Summary of pre-clinical evidence. GH potentially has both neuroprotective and neuroregenerative effects beyond replacement effects in TBI-associated GHD/GHI. Manipulating the GH axis has been shown to improve motor function, enhance learning and memory retention after TBI in rats,[129] and to improve spatial learning and memory in a mouse model of AD.[130,131] GH-mediated increases in insulin-like growth factor-1 (IGF-1) corrects impairments of endothelial progenitor cells, the circulating cells responsible for repairing damaged vascular walls.[132] GH and/or IGF-1 receptors are present in the choroid plexus, thalamus, hypothalamus, pituitary, putamen, hippocampus, and parahippocampal areas, suggesting a functional role of GH in the brain.[133] The GH axis is neuroprotective in other (i.e., non-trauma) animal models of neurologic damage, including AD[134] and radiation injury.[135] GH has direct autocrine and/or paracrine neuroprotective effects in chick and quail retinal ganglion cells by regulating cell survival.[136] This antiapoptotic effect of GH is mediated by the caspase, protein kinase B (Akt), extracellular signal related kinase (ERK), and tropomysin-related kinase (Trk) pathways.[137] Systemically, the wound healing effects of recombinant human GH (rhGH) administration are well established.[138–140]

Summary of clinical evidence. Three small recent studies have demonstrated cognitive improvement in GHD/GHI TBI patients treated with rhGH.[141–143] An aggregate of 57 patients with GHD/GDI were treated with daily subcutaneous rhGH injections for either 8 or 12 months (chronic TBI patients, $n=36$) or 3 months (chronic TBI patients, $n=21$). The patients were treated a mean of 11 years post-TBI. All had GHD documented by either the glucagon or arginine stimulation tests. In the High Study, the dose of rhGH was titrated until a normal IGF-1 plasma level was achieved.[142] In the other two studies, GH was administered at a constant dose, 1 mg/day.[141,143] All three studies noted improved cognitive outcomes in the GH-treated group compared with the placebo controls. All three studies noted no adverse events or safety issues with drug administration. Earlier studies using supraphysiologic GH administration after acute medical illnesses in Europe were aborted because of increased mortality rates in the GH-treated group.[144,145] These studies suggest that it may not be safe to use GH in the acute stages after TBI. There have been no clinical trials of GH in TBI patients without documented GHD/GHI.

Evidence-based assessment of setting for suitable clinical development. There is sufficient pre-clinical data to justify a Phase II/III trial of GH after TBI, especially in the post-acute and chronic stages. There is pre-clinical and pilot study evidence to support its use in TBI patients both with and without GHD/GHI. There is still some uncertainty about the best biomarkers to use,

although IGF-1 has been most widely used. Further, there is uncertainty as to the optimal stimulation tests and thresholds to define GH deficiency and insufficiency. Additional biomarkers remain to be established, but neuroimaging methods such as MRI may prove helpful in discriminating its neuroregenerative effects from its replacement effects.

Discussion of gaps in knowledge. There is preliminary evidence for the use of GH treatment in both acute and chronic TBI associated with GH deficiency, but there have been no Phase III clinical trials to date establishing its efficacy. Further, there have been no clinical trials in patients with TBI without documented GHD/GHI. Several additional gaps remain: (a) the standardization of GH biomarkers in the acute and chronic stages after TBI; (b) the standardization of stimulation tests to assess hypothalamic-pituitary-adrenal (HPA) function after TBI; (c) the optimal timing and dosing of GH therapy after TBI; (d) safety of GH administration in the acute period when administered at physiologic rather than supraphysiologic doses; (e) the mechanism of action for GH-related neurocognitive improvements in TBI-associated GHD/GHI; (f) potential for additive benefits if co-administered with other mediators of the HPA or other TBI therapies.

7. Lithium

Mechanism of action. Lithium is the primary drug for the treatment of patients with bipolar disorder. It exerts neuroprotective effects through reduction of excitotoxicity, ischemic damage, and apoptosis. Other neuroprotective actions involve the attenuation of several pathways involving pro-inflammatory cytokines, β-APP-cleaving enzyme-1 (BACE-1) expression, β-amyloid accumulation, microglial activation, cyclooxygenase-2 activity, glycogen synthase kinase-3β (GSK-3β) activity, and matrix metalloproteinase-9 expression, as well preservation of the BBB.[146–150]

Summary of pre-clinical evidence. A total of five studies in pre-clinical TBI models were identified by a literature search.[146–150] Yu and colleagues[147] administered lithium 15 min after TBI, and thereafter for up to 3 weeks. Lithium attenuated Aβ load, amyloid precursor protein (APP) load, BACE-1 overexpression, and Tau protein phosphorylation.[147] Functionally, lithium treatment improved spatial learning and memory evidenced by behavioral improvement in the Y-maze and MWM. This same research team also showed that lithium after TBI reduced lesion volume and that the therapeutic window was at least 3 h after injury.[148]

Lithium attenuated TBI-induced neuronal death, microglial activation, cyclooxygenase-2 induction, and matrix metalloproteinase-9 expression. Lithium also preserved the integrity of the BBB. Lithium reduced anxiety-like behavior in an open-field test, and improved short- and long-term motor coordination in rodents. The investigators noted that lithium increased serine phosphorylation and thus inactivation of GSK-3β, suggesting this as the underlying neuroprotective mechanism of lithium. Dash and coworkers[150] found that TBI in a rodent model caused a rapid increase in lipoprotein-related protein-6 (LRP6) phosphorylation, resulting in decreased β-Catenin phosphorylation. Daily lithium selectively inhibited GSK-3 and resulted in inactivation of post-TBI GSK-3β load, and decreased Akt activity.

Zhu and associates[149] administered daily lithium in rodents before and after a moderate TBI and found that lithium treatment decreased cerebral edema, neuronal and hemispheric volume loss, and levels of the pro-inflammatory cytokine, interleukin-1β, and improved spatial learning and memory performance in the MWM. Shapira and colleagues[146] demonstrated that mTBI increases serine phosphorylation of GSK-3β, which coincided with increased serine phosphorylation of its upstream kinase protein kinase B and accumulation of its downstream target ß-Catenin in the hippocampus, manifesting as depression. Pre-treatment with lithium prevented this TBI-induced depression.[146–150]

Summary of clinical evidence. Six small case studies were identified in the literature.[151–156] The severity of TBI varied widely and treatment timing ranged from 6 weeks up to 17 years post-injury and follow-up ranged from several days to months post-treatment. Aggression and agitation were the primary behavioral problems, and poor impulse control, mood change, decreased self-care, and suicidal behaviors were also noted. The daily dose of lithium varied from 600 to 1200 mg per day. The outcomes were varied, with improvement in some cases but deterioration in others. None of these studies involved neuroimaging, brain volumetric analysis, or post-mortem histology.

Evidence-based assessment of setting for suitable clinical development. The pre-clinical studies suggest that the potential applications of lithium are both in the acute (via early inflammatory and apoptotic pathways) and chronic (via tau expression) treatment of mild, moderate, and severe TBI. These data are few, scattered, and only one used a model of mTBI, however. The chronic toxicity of lithium could be a potential limitation to prolonged, chronic therapy.

Discussion of gaps in knowledge. There has been borderline sufficient pre-clinical and insufficient clinical work to support further studies of lithium in patients with either mild or severe TBI. Additional pre-clinical investigation is needed in models of mTBI as are more clinical studies examining early administration before clinical manifestation of TBI.

8. Methylphenidate and atomoxetine

Mechanism of action. Methylphenidate increases synaptic DA by blocking DA transporters and inhibiting DA reuptake.[157–162] Methylphenidate also enhances synaptic norepinephrine levels by blocking norepinephrine reuptake.[163,164] Atomoxetine inhibits norepinephrine transporters[165] and increases extracellular norepinephrine and DA.[163,166] Both methylphenidate and atomoxetine are FDA-approved in the United States for the treatment of patients with attention deficit hyperactivity disorder.

Summary of pre-clinical evidence in TBI models. A number of pre-clinical studies specifically examining the effects of methylphenidate in TBI animal models were identified. Methylphenidate has been shown to promote striatal dopaminergic neurotransmission after TBI and enhance spatial learning and retention and motor performance.[167–169] There may be sex-specific differences in behavioral performance and response to methylphenidate in rats after TBI.[169,170] Atomoxetine also enhances performance in the MWM after TBI.[171]

Summary of clinical development of methylphenidate and atomoxetine in TBI

Methylphenidate. Fifteen RCTs have used methylphenidate in TBI with the majority of trials enrolling participants with mild to severe TBI in the subacute or chronic phases of TBI (i.e., weeks to

years post-injury). Treatment duration ranged from a single dose to 30 days. Clinical studies were generally small, and 14 of the 15 RCTs enrolled ≤40 participants. Two trials focused solely on adverse events and safety, and both concluded that methylphenidate appeared to be safe for use in TBI.[172,173] Overall, results of neuropsychological testing to assess executive function are mixed with relatively few replications. There have been reported improvements in sustained arousal and/or attention,[174–176] and a positive finding for the ''two-back'' test used during fMRI,[174] but negative results for improvement on the Porteus maze [177] and Stroop Interference task.[178]

Results of an effect of methylphenidate on attention were also somewhat mixed, with 6 of 11 studies reporting positive findings on at least one outcome measure[173,175–177,179,180]; the other five studies reported negative results [178,181–183] or did not report individual results.[184] Five of seven RCTs that assessed processing speed and reaction time have reported a positive result on at least one assessment,[173,175–177,181] and two studies reported negative findings.[178,183] With regard to memory testing, one study reported positive results in the Wechsler Memory Scale, one study reported negative results on the serial digit learning test, and one investigation did not report an individual result in this domain.[177,178,184]

Among the eight RCTs that assessed behavioral symptoms and related constructs in TBI after treatment with methylphenidate, one reported improvement in the Hamilton Depression Scale but not the Beck Depression Inventory.[181] Four other studies reported positive findings for behavioral and other related outcomes, but some of these reports constituted the only RCT using individual assessment instruments.[175,176,181,182] Four RCTs assessing these areas reported negative findings[173,177,183] or did not report individual results.[184] In one study that used patients with moderate or severe TBI (≤48 h post-injury), treatment with methylphenidate significantly decreased intensive care unit stay.[185] Little additional data are currently available on the use of methylphenidate in the acute phase of TBI. Another RCT compared methylphenidate ($n=10$) with sertraline ($n=10$) or placebo ($n=10$), and reported that both methylphenidate and sertraline significantly improved depressive symptoms compared with placebo; methylphenidate also decreased daytime sleepiness and was well-tolerated.[181]

Ongoing clinical trials using methylphenidate in TBI include an active study in mild to severe TBI (NCT00453921; estimated enrollment 160), and an active RCT with methylphenidate or galantamine in TBI and/or PTSD (NCT01416948; estimated enrollment 159).

Atomoxetine. There are currently no completed RCTs with atomoxetine in the literature, but an RCT with atomoxetine for the treatment of patients with attention disorders in moderate and severe TBI at least 1 year after injury is listed in ClinicalTrials.gov as ongoing (NCT00702364; estimated enrollment 60).

Evidence-based assessment of setting for suitable clinical development

Methylphenidate. Although these 15 RCTs are very heterogeneous in methodology, target population, duration of treatment, and end points, and report somewhat mixed findings, some reports nonetheless suggest that methylphenidate could play a useful role in the therapeutics of TBI. Additional investigation in larger cohorts is clearly needed, however, to obtain a more comprehensive understanding of its therapeutic potential, because studies are difficult to compare, multiple assessments were used, and sample sizes were small. The crossover design used by the majority of these RCTs is also a limitation. Overall, 10 of the 13 RCTs that did not focus solely on safety and adverse events yielded promising results for at least one outcome measure (although a descriptive summary of this nature is limited, and potentially overestimates positive findings as each RCT reported several end points and generally did not adjust for multiple comparisons). The safety profile appears to be favorable.

Atomoxetine. There is currently only one pre-clinical study focusing on atomoxetine in TBI; no RCTs using atomoxetine in TBI have been published to date.

Discussion of gaps in knowledge.

Although a number of RCTs have used methylphenidate for TBI, their methodologies varied widely and the clinical populations were very heterogeneous (15 total RCTs; two of these 15 RCTs focused solely on adverse events and safety). Standardization of end points would be useful, because multiple outcome measures have been reported to date. Duration of treatment in these 15 total RCTs was also variable, ranging from a single dose of methylphenidate to 30 days of treatment. In addition, the crossover design used by 10 of the 15 RCTs is suboptimal. The numbers of patients participating in RCTs using methylphenidate in TBI is also relatively small: 14 of 15 RCTs included ≤40 participants (with 6 randomizing ≤20 participants). The largest RCT included 80 participants. Larger studies are warranted. In addition, more extensive pre-clinical investigations with methylphenidate in animal models of TBI would potentially be useful, and the utilization of neuroimaging approaches in clinical populations also holds promise.

For atomoxetine, pre-clinical data in TBI are currently very limited, and RCT data are not yet available. Additional research is warranted.

9. Minocycline

Mechanism of action.

Minocycline is a lipid permeable member of the tetracycline family of antimicrobials. It can be administered both IV and orally, has a long half-life (16–18 h), and readily crosses the BBB.[186] Minocycline also shows anti-inflammatory, antiapoptotic, and antioxidant activity at doses greater than needed for antimicrobial activity. Thus, minocycline has the additional advantage that it can potentially prevent infections after TBI or TBI in the context of polytrauma.

Summary of pre-clinical evidence.

Minocycline has shown efficacy in a variety of animal models of neurodegenerative diseases including TBI, cerebral ischemia, amyotrophic lateral sclerosis, PD, Huntington disease, multiple sclerosis, and AD.[186] In these models, minocycline is used at a six-fold higher dosage than is needed for antimicrobial action. At these higher levels, minocycline has anti-inflammatory, antiapoptotic, and antioxidant activity. As an anti-inflammatory drug, minocycline inhibits the action of microglia, T cells, and neutrophils. Minocycline also blocks caspase-dependent and caspase-independent apoptosis, directly scavenges reactive oxygen species, and inhibits metaloproteases. These multiple drug actions are believed to underlie the ability of minocycline to limit TBI.[186]

Minocycline has shown efficacy in multiple laboratories using different pre-clinical models of TBI including weight drop, CCI, and whole body blast when given between 45 min and 4 h after injury. Minocycline has protected both grey and white matter and reduced lesion volume when administered between 30 and 45 min post-

injury.[187–189] In addition, myelin content was maintained when minocycline was given 1 h after injury.[82] In a model of whole body blast TBI, minocycline was effective at attenuating a variety of serum biomarkers of neuronal and glial injury and neuroinflammation when dosed between 1 and 4 h after injury.[190] In a direct comparison of progesterone, N-acetyl cysteine (NAC), simvastatin, cyclosporine, and minocycline, only minocycline improved acquisition of an active place avoidance task, although the effects were not maintained at the 24 h post-test suggesting that minocycline did not restore long-term memory.[82] Interestingly, coapplication of minocycline with NAC restored memory after CCI.[82]

Summary of clinical development of minocycline. Minocycline showed some efficacy in a Phase II study of spinal cord patients, and serum biomarkers of inflammation confirmed minocycline as an anti-inflammatory drug.[191] Minocycline was administered at a high dose, demonstrating its tolerance and safety at elevated dosage levels. Minocycline was safe, but did not show efficacy in the treatment of HIV-associated cognitive impairment or PD.[192,193]

Evidence-based assessment of setting for suitable clinical development. Minocycline has shown efficacy and safety in a variety of pre-clinical studies of TBI. The therapeutic window of minocycline also shows that it could be an effective treatment in the acute phase of TBI. Additional pre-clinical work is needed to test whether minocycline remains effective when tested 1–7 days after injury. Pre-clinical evidence suggests that minocycline is a promising drug to treat patients with TBI 1 to 24 h post-injury. Thus, minocycline is a promising candidate for clinical trials.

Discussion of knowledge gaps. Minocycline addresses many of the gaps identified in the testing of drugs to treat patients with TBI. The therapeutic window of minocycline needs to be tested systematically, but it is encouraging that it shows efficacy when dosed hours after injury.

10. NAC

Mechanism of action. NAC is FDA-approved as an antidote for acetaminophen overdose and as a mucolytic for cystic fibrosis and other bronchopulmonary diseases. NAC is available by prescription, as well as in the form of an over-the-counter dietary supplement. It can be administered orally, IV, or by aerosol. NAC is readily deacetylated in the liver to cysteine. Both NAC and cysteine are potent antioxidants that largely scavenge cytosolic radicals. Cysteine more readily crosses the BBB than NAC, and more lipophilic derivatives of NAC have been developed with better brain penetration.[194,195] In the brain, cysteine also acts by increasing levels of the endogenous antioxidant glutathione[194,195] and extracelullar levels of glutamate.[196]

Summary of pre-clinical evidence. In animal models of TBI, NAC has shown strong antioxidant activity by increasing glutathione levels and decreasing markers of oxidative damage.[197] NAC also showed anti-inflammatory activity by decreasing the activation of NF-κB, while lowering Iinterleukin (IL)-1β, tumor necrosis factor (TNF)-α, and intercellular adhesion molecule (ICAM)-1 levels.[198,199] It is unclear how the anti-inflammatory action of NAC is related to its antioxidant activity. NAC has been shown to reduce lesion volume while simultaneously reducing levels of the putative neuroprotective enzyme heme oxidase.[198,199]

NAC also showed efficacy in the treatment of experimental spinal cord injury.[200] A caveat of these animal studies is that NAC was administered within 15 min after injury. The two animal studies that began dosing NAC 1 h after injury had no effect on reduction of brain edema, lesion volume, or the ability of rats to learn a complex task 1 week post-injury.[82,201] NAC administered 1 h after injury, however, had some efficacy in preventing myelin loss.[82] NAC also synergized with minocycline to restore memory in the CCI model of TBI.[82]

Summary of clinical evidence. The ability to increase extracellular glutamate underlies the testing of NAC in clinical trials for the management of a variety of psychiatric diseases and drug addiction. NAC is presently being tested in clinical trials for a variety of neurologic and psychologic disorders based on its antioxidant, anti-inflammatory, and neuromodulatory actions.[196] A recent small randomized, placebo-controlled clinical trial conducted in a military field hospital in Iraq enrolled 81 persons who had been exposed to ordnance blast and suffered post-concussive symptoms.[202] Treatment lasted 7 days, and there was a significant increase in symptom resolution in the NAC treated group compared with placebo (odds ratrio 3.6, $p=0.006$). This promising study should be replicated in a larger population. NAC is also being studied in combination with probenecid in children with severe TBI to determine whether probenecid increases levels of endogenous antioxidants in the serum and CSF (NCT01322009).

Evidence-based assessment of setting for suitable clinical development. Both pre-clinical and clinical studies suggest that NAC has both antioxidant and neuromodulatory activity while having minimal adverse effects. There is insufficient evidence demonstrating that NAC has a sufficient potency or a useful therapeutic window to be an effective treatment of patients with TBI.

Knowledge gaps. The antioxidant properties of NAC are well established and justify assessing endogenous antioxidants in serum and CSF as a biologic readout in pre-clinical and clinical TBI studies. The therapeutic window of NAC has not been well established.

11. Progesterone

Mechanism of action. Progesterone is a steroid that is made in the brain, in addition to its synthesis in the reproductive organs and adrenal glands. Similar to other neurosteroids, progesterone appears to be enriched in human brain compared with blood, with progesterone levels in human brain exceeding peripheral plasma levels by more than five-fold; there do not appear to be sex differences in brain levels.[203–206] Progesterone has pleiotropic effects, and thus has multiple candidates for mechanisms of action with regard to its potential therapeutic efficacy in TBI. It is therefore possible that a combination of these candidate mechanisms contributes to its beneficial actions in pre-clinical TBI models and potentially in clinical populations.

Multiple pre-clinical models of TBI have demonstrated neuroprotective properties of progesterone and have shown that it enhances behavioral and functional outcomes, decreases cerebral edema, apoptosis, pro-inflammatory cytokines, and other markers of inflammation, and prevents neuronal cell death. Progesterone also enhances myelination[207] and neurogenesis[208] and impacts aquaporin expression, and modulates neurotrophin expression, among other actions. In addition to these candidate mechanisms of action, progesterone can also be metabolized to other neurosteroids

that act at membrane-bound ligand-gated ion channel receptors, including inhibitory gamma-aminobutyric acid $(GABA)_A$ receptors. For example, allopregnanolone is a progesterone metabolite that enhances $GABA_A$ receptor responses and exhibits pronounced neuroprotective effects. This is relevant to progesterone therapeutics, because oral progesterone administration in humans significantly increases downstream allopregnanolone levels several-fold.[209] Several investigations suggest that allopregnanolone has neuroprotective actions and that these effects may be more potent than those of progesterone.[210,211] Emerging pre-clinical data suggest that combinations of progesterone with other agents such as vitamin D may potentiate its neuroprotective effects.[3,212]

Summary of pre-clinical evidence in TBI models. More than 50 pre-clinical studies examining progesterone and TBI in animal models have been conducted. In addition, there is a substantial body of relevant scientific literature that examines the effects of progesterone in ischemic stroke and intracerebral hemorrhage-induced injury, among other injuries. The considerable majority of these TBI pre-clinical investigations support a role for progesterone in the management of multiple components of TBI pathophysiology. Investigations have been conducted primarily in rat and mouse models; in a number of cases, multiple independent laboratories have replicated supportive findings.

Progesterone has been shown pre-clinically to decrease brain edema after TBI,[213–223] reduce apoptosis,[213,224–228] and reduce pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α.[213,219,229–231] Progesterone also enhances CD55 production after TBI, potentially resulting in the inhibition of complement convertases and contributing to the inhibition of inflammatory processes.[232] In addition, progesterone reduces tissue loss and lesion size,[219,233–235] protects against lipid peroxidation,[236] enhances superoxide dismutase activity,[237] and levels of neurotrophin factors,[224] inhibits neuronal calcium signaling,[238,239] reduces neuronal loss,[221,240] decreases intracranial pressure,[217] modulates aquaporin 4 expression,[241] decreases mitochondrial dysfunction,[221] reduces astrocytic accumulation,[242,243] and alters NFκ-B signaling pathways after TBI.[213,219,229,244,245] In addition, progesterone impacts the Toll-like receptor signaling pathway,[245,246] alters cell proliferation,[247] and decreases axonal injury following TBI.[226]

Clearly there are multiple mechanistic possibilities for the potential therapeutic utility of progesterone in TBI. Given these pleiotropic actions of progesterone, it is perhaps not surprising that progesterone administration results in altered expression of more than 500 genes, many involved in inflammatory and apoptosis pathways, in a cortical contusion model of TBI compared with controls.[248] These results are consistent with findings from multiple research groups showing the anti-inflammatory and antiapoptotic effects of progesterone in rodent studies of TBI.

Importantly, many pre-clinical investigations also demonstrate that progesterone enhances functional and behavioral recovery.[228,249] These include improved spatial learning and memory in behavioral paradigms such as the MWM,[212,234,235,240,250] improved locomotor activity and outcomes,[213,214,250] decreased anxiety-like behaviors in the elevated plus maze paradigm,[214] and enhanced motor and cognitive performance on the rotarod and Barnes maze, respectively.[226] Because improvements in functional and behavioral outcomes in rodent models of TBI do not always correlate with other investigational variables such as edema, lesion size, inflammatory markers, or histopathological findings, the above reports of improvements in functional and behavioral end points are important components in the accruing scientific literature in this area.

Although the large majority of investigations using progesterone in animal models of TBI support a possible therapeutic role for this molecule, a small number of investigations report data that are potentially non-supporting.[82,233,234,251] Currently, the supporting pre-clinical evidence for a potential role for progesterone in TBI therapeutics is far more extensive than non-supporting studies.

Summary of clinical evidence. To date, two Phase II RCTs using progesterone in TBI have been conducted by independent research groups. Building on the foundations of these two positive Phase II studies, two Phase III RCTs are ongoing. In addition, a RCT with the metabolite allopregnanolone is now under way. The first randomized controlled Phase II trial using progesterone for TBI enrolled participants with moderate or severe TBI, who were assigned to either IV progesterone ($n = 77$; 0.71 mg/kg IV loading dose in first hour, then 0.5 mg/kg IV for 11 h; followed by an additional series of five 12-hour IV infusions; total treatment duration 3 days) or placebo ($n = 23$), in a 4:1 ratio, within 11 h of injury. Participants had sustained blunt trauma and had a GCS score of 4–12 post-resuscitation. Participants randomized to progesterone had a mortality rate at 30 days that was more than 50% lower than the mortality rate in participants randomized to placebo (rate ratio 0.43; 95% confidence interval 0.18–0.99). Progesterone appeared to be well-tolerated.[252]

The second randomized controlled Phase II trial using progesterone for TBI was a single-site study conducted at the Neurotrauma Center, Clinical Medical College of Hangzhou, China.[253] It enrolled 159 participants with severe TBI who were assigned to either intramuscular (IM) progesterone ($n = 82$; 1.0 mg/kg IM progesterone, then once every 12 h IM for a total of 5 days of treatment) or placebo ($n = 77$), in a 1:1 ratio, within 8 h of injury. Participants had sustained an acute severe TBI and had a GCS score ≤ 8 post-resuscitation. At follow-up, mean group differences were reported in GOS and Functional Independence Measure scores with the progesterone group showing significantly improved scores compared with healthy controls.

There are currently two ongoing Phase III RCTs investigating progesterone in acute TBI, and one Phase II RCT investigating allopregnanolone. The SyNAPSe (NCT00822900) and ProTECT III (NCT01143064) studies are both multi-site randomized controlled Phase III clinical trial investigating IV progesterone in moderate and severe acute, and severe TBI, respectively. A Phase II single-site RCT (NCT01673828) of IV allopregnanolone is also under way.

Evidence-based assessment of setting for suitable clinical development. There are currently two positive Phase II RCTs using progesterone in the scientific literature (one conducted in moderate and severe TBI, and one conducted in severe TBI). These encouraging clinical data, combined with substantial supportive pre-clinical literature, suggest that progesterone demonstrates promise in the treatment of patients with TBI. The results of the two ongoing Phase III RCTs undoubtedly will guide any future pharmacological development efforts with this molecule. In addition, a Phase III RCT using allopregnanolone, a progesterone metabolite, is newly under way. If one or both of the ongoing Phase III RCTs with progesterone are positive and this new therapeutic avenue for TBI accrues additional evidence, further characterization of the pleiotropic actions of progesterone and their specific roles in contributing to its efficacy are warranted. The investigation of other neurosteroid metabolites of progesterone as therapeutic candidates for TBI may also be a logical pharmacological development strategy and could also hold biomarker potential.

Discussion of gaps in knowledge. The precise mechanisms of action and/or combinations of mechanisms of action for progesterone as a potential therapeutic in TBI remain unclear. Although pre-clinical efforts are extensive, promising, and largely well-replicated, a more comprehensive understanding of progesterone's mechanism(s) of action would be beneficial to the field. Optimal dosing and duration of treatment with progesterone remain to be determined, and dose-finding and pharmacokinetic investigations will be very important. There is also considerable potential for the determination of biomarkers of clinical response with regard to progesterone, including metabolite profiling using mass spectrometry and neuroimaging approaches. Combination approaches may also be advantageous and merit additional investigation.

12. Simvastatin/other statins

Mechanism of action. Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMGA) reductase inhibitors, reduce serum cholesterol but also have potent effects in the brain relevant to mechanisms of TBI injury and recovery. Such effects target mechanisms that influence both the acute and chronic phases of TBI.[93,254–259] There is pre-clinical evidence of beneficial effects including those on acute injury processes such as brain edema, BBB integrity, cerebral blood flow, neuroinflammation, axonal injury, and cell death, in addition to effects on key facets of regeneration such as trophic factor production. A variety of molecular outcomes are influenced including TUNEL staining, CREB, Akt, eNOS, FOXO1, NF-κB, GSK3, cytokines, BrdU labeling, blood vessel formation, and vascular endothelial growth factor.[256,259] In some studies, however, paradoxical increases in brain tissue cytokine levels have been seen with statin treatment.[259]

Summary of pre-clinical evidence. Although a number of statins are available, most pre-clinical evidence supporting their efficacy comes from work with simvastatin and atorvastatin in rat and mouse models. A literature search revealed more than 20 pre-clinical studies on statins, primarily simvastatin, in experimental TBI models.[93,254–259] Most pre-clinical studies of statins in TBI have used oral administration; however, a few studies have used systemic delivery approaches. Early studies focused on atorvastatin and contributed to the initiation of a current clinical trial of atorvastatin in mTBI.[260–262] Studies with simvastatin and atorvastatin have been performed in multiple models including CCI, FPI, and closed head injury, although the majority of studies have been in CCI.

Several studies have compared atorvastatin and simvastatin, and benefits on behavior and histology have been reported with both agents. One study used systemic administration of statins and suggested that both statins had similar benefits on behavior but that atorvastatin offered better protection against neuronal death than simvastatin.[263] Atorvastatin was also favored over simvastatin because of its longer half-life and active metabolites.

In contrast, Lu and colleagues[264] reported that simvastatin resulted in less hippocampal CA3 cell death and improved MWM performance after CCI in rats when compared with atorvastatin. Sierra and coworkers[265] compared nine statins on measures of regard to BBB penetration, lipophilicity, HMG CoA reductase inhibition, and protection versus neurodegeneration from Tau, and concluded that simvastatin was best. How these findings translate to TBI is unclear, but the favorable BBB permeability profile of simvastatin may be important. Nevertheless, both simvastatin and atorvastatin attenuate neurofibrillary tangle deposition in models of chronic neurodegenerative diseases.[265,266]

Regarding dosing, most studies have used oral administration. The therapeutic window for acute administration is favorable with benefit shown with treatment initiated even at 24 h after TBI. Dosing has generally used 1 mg/kg with atorvastatin or 1–3 mg/kg with simvastatin via the oral route, and treatment is usually 7 to 14 days in duration. Surprisingly, studies using systemic administration of statins in experimental models of TBI have used higher does than those used with oral administration, but in both cases, the doses used in experimental TBI have been higher than those generally used in the clinical treatment of hypercholesterolemia.

Summary of clinical development. Atorvastatin is currently in a Phase II safety and efficacy clinical trial in adults with mTBI (NCT01013870). A 7-day treatment regimen is being used, and the Rivermead Post-Concussion Symptoms Questionnaire administered at 3 months post-injury represents the primary outcome. This study is being conducted as part of the Mission Connect consortium. Certainly statins have a long track record for clinical use, and both simvastatin and atorvastatin are FDA-approved drugs.

Evidence-based assessment of setting for suitable clinical development. The pre-clinical data provide evidence for acute or subacute administration in severe TBI. Pre-clinical evidence, however, is again lacking for testing of efficacy with delayed administration of statins weeks or months after injury.

Discussion of gaps in knowledge. Given the large body of studies in pre-clinical models of severe TBI, the safety record of statins, and surprisingly long therapeutic window of 24 h in many studies, a clinical trial of acute statin treatment in severe TBI is warranted, likely with simvastatin. Pre-clinical studies of delayed chronic administration of statins after TBI are needed.

Conclusion

TBI is an increasingly prevalent and complex challenge for the U.S. military as well as for the larger society. Despite substantial and ongoing investments in both pre-clinical and clinical studies, there remain significant gaps in knowledge ,and there is a paucity of therapies to limit the disabling consequences of TBI or to foster neuroregeneration. The Neurotrauma Pharmacology Workgroup was tasked by the U.S. Department of Defense to review the state of the science and identify research gaps. While there is much promising work under way, there are significant opportunities to focus resources in areas such as mTBI, the post-acute and chronic period of all TBI severities, and on therapies targeting mechanisms of neurorepair and neuroregeneration. In addition, while it is likely that polypharmacy will eventually be needed to achieve maximal recovery after TBI, the challenges combination therapy presents are only beginning to be addressed. The way forward will require sustained support of research efforts and focused commitment to excellence.

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Author Disclosure Statement

Dr. Kochanek holds three co-provisional patents: (1) Method of Inducing EPR Following Cardiopulmonary Arrest; (2) Validation of a Multiplex Biomarker Panel for Detection of Abusive Head Trauma in Well-Appearing Children; (3) Small Molecule Inhibitors of RNA Binding MOTIF Proteins for the Treatment of Acute Cellular Injury. Dr. Marx is a co-applicant or applicant on pending patent applications focusing on neurosteroids and derivatives in CNS disorders and for lowering cholesterol (no patents issued, no licensing in place). Dr. Marx is an unpaid scientific consultant for Sage Therapeutics. For the remaining authors, no competing financial interest exist.

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