

Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury is defined as isolated head injury producing a Glasgow Coma Scale score of 13 or greater and occurs in the context of sports, recreational activities and vehicle accidents. These patients are usually asymptomatic on presentation. Most patients recover quickly, with a predictable clinical course of recovery within the first one to two weeks following traumatic brain injury. 5%-20% of the patient's physical, cognitive or behavioral post concussive symptoms may be persistent. Radiological investigations including computer tomography scans should be obtained and magnetic resonance imaging can be very valuable in patients who have sustained mild traumatic brain injury. If there are any concerns about the safety of the discharged patient with mild injury, a brief inpatient observation period of 12 to 24 hours is advisable. Careful neurologic examination must be made to determine the presence of delayed complications if the patient returns for second time. Far from diagnosis and observation of symptoms, we will review the differential diagnosis studies, imaging options, cognitive-behavioral findings and molecular trials for mild traumatic brain injury.

Keywords: Mild traumatic brain injury; Mild brain injury treatment modalities; Mild brain injury concepts

Introduction

Traumatic brain injury [TBI] is the foremost cause of death in children and young adults. The medical and surgical treatment options for TBI can be complex and usually requiring a multidisciplinary approach with trauma, intensive care and neurosurgical specialists. Key points for the management of TBI are the prevention and treatment of elevated intracranial pressure and secondary brain injury for preservation of cerebral perfusion pressure, and maintenance of cerebral oxygenation [1].

The clinical features mostly associated with mild traumatic brain injury [MTBI] are loss of consciousness, transiently altered mental state, retrograde amnesia and focal neurological deficits [2]. The frontal lobe is the most common site of focal lesions after MTBI [3].

The adult mammalian central nervous system [CNS] has a limited capacity for nerve regeneration and structural plasticity. The severe clinical consequences of CNS injury are due to the fact that, in contrast to most other tissues, the CNS lacks the ability to reconstitute itself by neuronal cell proliferation, and CNS neurons fail to regrow severed axons [4,5].

In this review we would like to browse through MTBI modalities from different aspects.

Prognostic Factors

MTBI is defined as isolated head injury producing a Glasgow Coma Scale [GCS] score of 13 or greater. MTBI occur in the context of sports, recreational activities and vehicle accidents. These patients are usually asymptomatic on presentation. Most patients recover quickly with a predictable clinical course of recovery within the first one to two weeks following TBI. 5%-20% of the patient's physical, cognitive or behavioral post concussive symptoms may be persistent [Table 1]. Symptoms include headaches, dizziness, nausea, appetite, sleep, vision, hearing, changes in coordination and balance. Fatigue, anxiety, depression, irritability, problems with memory, concentration and decision making are the most common examples for cognitive and behavioral symptoms. Women, older adults, less educated persons, and those with a previous mental health disease diagnosis are more likely to have persistent symptoms [6].

3% of all patients with MTBI sustain a sudden, unexpected neurologic deterioration, whereas less than 1% have surgically significant lesions. Determining which patients who have experienced a mild head trauma are at risk for an intracranial lesion and, therefore, require acute neuroimaging has proved difficult in research studies. Results have been conflicting, likely because of the use of different methods, definitions, and outcomes of MTBI. Head CT scans should be obtained on patients who have sustained MTBI. In most adult patients, skull radiographs are not recommended if the patient is deemed to require neuroimaging. CT is the preferred study as it yields information about both the skull and the brain. In rare instances, skull radiographs may be useful in patients who cannot undergo CT. If there is a history of loss of consciousness or amnesia for the event, many centers prefer to take CT images [7]. Magnetic resonance imaging [MRI] now is the most reliable tool to delineate MTBI and may give information on the anatomical basis of brain injury depending on the site of cerebral

Physical symptoms after MTBI	Cognitive and behavioral symptoms after MTBI	Delayed symptoms after MTBI
Headaches	Fatigue	Worsening headache
Dizziness	Anxiety	Repeated vomiting
Nausea	Depression	Loss of consciousness
Appetite	Irritability	Confusion
Sleep	Problems with memory	Agitation
Bad vision	Concentration	Seizure
Hearing problems	Decision making	Difficulty walking or balance
Changes in coordination and balance		Weakness
		Numbness
		Change in vision.

Table 1: Postconcussive symptoms.

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Received July 25, 2013; Accepted November 26, 2013; Published December 04, 2013

Citation: Selcuk O, Zeynep F, Basar A (2013) Mild Traumatic Brain Injury. J Neurol Neurophysiol 4: 172. doi:10.4172/2155-9562.1000172

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trauma. Some clinics recommend inpatient or prolonged observation to allow rapid identification of those patients whose conditions suddenly deteriorate after MTBI.

Major extra cranial injury [MEI] is common in TBI patients, but the effect on outcome is controversial. van Leeuwen et al. report a study to assess the prognostic value of MEI on mortality after TBI in an individual patient data meta-analysis of 3 observational TBI studies, a randomized controlled trial and a trauma registry. MEI meta-analysis was reported with 39274 patients. Mortality was 25% and 32% of patients in this series had MEI. MEI is an important prognostic factor for mortality in TBI patients. The effect varies by population, which explains the different reports in the literature [8].

Zhou et al. carry out a meta-analysis of cohort studies of sufficient rigor to determine whether the presence of the APOE4 allele contributes to initial injury severity and/or poor outcome following TBI. Study included a total of 2527 participants, 736 with and 1791 without the APOE4 allele. The association remained significant in sensitivity tests. This meta-analysis indicates that the presence of the APOE4 allele is not associated with the initial severity of brain injury following TBI but is associated with increased risk of poor long term outcome at 6 months after injury [9].

Most of the MTBI patients can be discharged safely after a normal examination. Approximately six hours of observation is advised [10]. Patients must be educated on the signs and symptoms of delayed complications of head injury which are worsening headache, repeated vomiting, loss of consciousness, confusion, agitation, seizure, difficulty in walking or imbalance, weakness, numbness and change in vision. If there are any concerns about the safety of the discharged patient with mild injury, a brief inpatient observation period of 12 to 24 hours is advisable. Careful neurological examination must be made to determine the presence of delayed complications if the patient returns for second time. It is not clearly indicated to repeat head CT in the presence of a nonfocal neurological deficit in neurologic examination, but this is often performed in many clinics [1].

Radiological Progress

Brain often appears to be normal on conventional CT and MRI scans in MTBI. Different imaging techniques must be chosen for the best diagnosis [Table 2] [11]. Conventional CT technics is not sensitive

to detect diffuse axonal injuries [DAI] and traumatic axonal injuries [TAI]. On the other hand special MRI techniques are very valuable in the diagnosis of diffuse axonal injury. MRI tractography is another tool to detect axonal injury and it is possible to find the injured fiber tracts as shown in the figure [Figure 1]. In MRI diffusion tensor imaging technique can visualize acute axonal shearing injury, which may have a prognostic value for the cognitive and neurological sequelae after TBI. Shenton et al. reviewed the incidence of MTBI and the importance of characterizing this patient population using objective radiological measures [11]. They suggest that more sensitive neuroimaging tools will improve the detection of brain abnormalities in MTBI. Newer and more advanced neuroimaging techniques to identify the areas of brain damage in MTBI will be important for documenting the biological basis of post-concussive symptoms, which are likely associated with subtle brain alterations and alterations which are undetected due to the lack of sensitivity of earlier neuroimaging techniques.

Bigler and Maxwell reported the potential insights into the neuropathology of MTBI that includes both an explanation of how the brain responds to an acute injury yet recovers but also how more permanent changes may occur. They showed that progression to axonal disconnection or secondary axotomy if it occurs in MTBI probably results in axonal fragmentation and functional disconnection of normally linked regions of cerebral cortex and other areas of gray matter. TBI increases the likelihood for chronic neuropsychiatric sequelae as well as the potential for ongoing deterioration, neuroimaging discoveries will hopefully result in increased research to understand the interacting cellular mechanisms that are active during such changes. It is also becoming clear that although modern imaging technologies allow more rapid and precise localization of macroscopic damage within the injured brain, neuroimaging findings have limits and do not fully reflect the underlying microscopic environment of the injured brain. The brain may itself possess mechanisms or approaches to compensate for the occurrence of small foci of damage such that a degree of improvement of posttraumatic cognitive activity may occur over months or years after TBI [12].

Cognitive and Emotional Perspective

Worldwide, millions of patients with TBI suffer from persistent and disabling intelligence impairment. Posttraumatic amnesia [PTA] duration is a promising predictor of intelligence following TBI. Konigs

Imaging technique	Function	Advantages offered
X-ray	Imaging of bony structures	Detecting fractures.
Computed Tomography (CT)	3D X-ray imaging of an object (e.g., brain and skull).	Detecting fractures, injuries and abnormalities for emergency surgical treatment
Magnetic Resonance Imaging (MRI)	Radiofrequency pulses to detect changes in spin signal of hydrogen atoms.	Detecting gray and white matter structures, brain stem areas, subacute hemorrhages and macroscopic areas of white matter damage. Better resolution for soft tissue.
Diffusion Weighted Imaging (DWI)/ Diffusion Tensor Imaging (DTI)	MRI sequence that uses the diffusion properties of water to detect microstructural tissue.	Detecting white matter integrity or damage, microscopic white matter damage and trace specific tracts of the brain
Susceptibility Weighted Imaging (SWI)	MRI technique used for susceptibility differences among structures (e.g., oxygenated vs. deoxygenated blood and iron).	Detecting areas of micro hemorrhage, gray- white matter junctions,
Magnetic Resonance Spectroscopy (MRS)	Produce a spectrum for individual chemicals or metabolites can be identified and concentrations can be measured.	Detecting structural damage or changes, neuronal health, neurotransmission, hypoxia and other brain functions.
Positron Emission Tomography (PET)	Uses radiotracers labeled with different isotopes that emit signals indicating areas of uptake or binding in the brain, most commonly used is 18-Fluorodeoxyglucose, an analog of glucose.	Detecting concentration of a chemical or protein in the brain such as the amount of glucose, which reflects activity, or the density of a type of protein such as beta amyloid, a hallmark of neurodegenerative disease.

Table 2: Imaging technical modalities for MTBI.

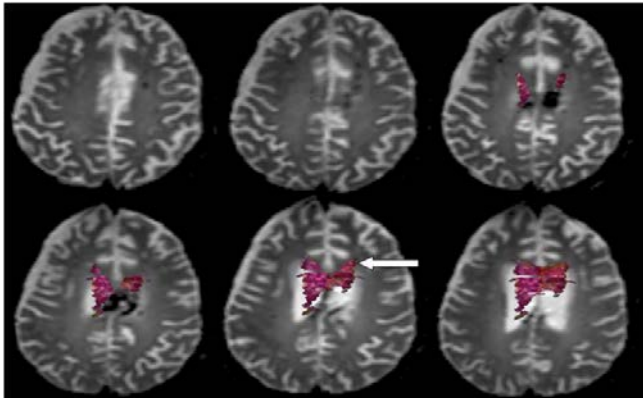


Figure 1a: Arrow shows injured tracts in MRI tractography in TBI.

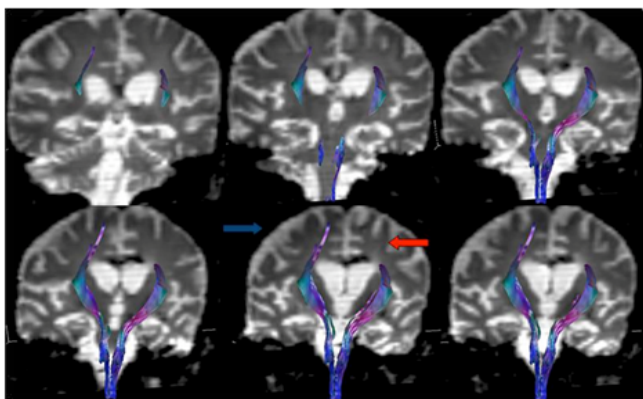


Figure 1b: Left arrow shows subdural hemorrhage and right arrow shows injured tracts on MRI tractography after TBI.

et al. made a study to determine the impact of TBI on value of PTA duration for intelligence impairment, using meta-analytic methods. Electronic databases were searched for peer-reviewed articles, published until February 2012. Studies reporting intelligence following TBI and injury severity by PTA duration were included. Patients with severe TBI exhibited large depressions in full scale IQ [FSIQ] in the subacute phase of recovery persisting into the chronic phase performance IQ [PIQ] was more severely affected than verbal IQ [VIQ] in the subacute phase but not in the chronic phase. Most importantly, longer PTA duration strongly predicted greater depressions of FSIQ and PIQ in the subacute phase and FSIQ, PIQ and VIQ in the chronic phase. PTA duration is a valuable predictor of intelligence impairment following TBI [13].

To investigate the neuropsychological effect of MTBI, Rohling et al. reanalyzed data from the 25 studies used in the prior meta-analyses, correcting statistical and methodological limitations of previous efforts and analyzed the chronicity data by discrete epochs. The effect of MTBI immediately post injury was largest on Verbal and Visual Memory domains. However, 3 months post injury all domains improved to show nonsignificant effect sizes. These findings indicate that MTBI has an initial small effect on neuropsychological functioning that dissipates quickly [14].

Simmons and Matthews suggest that MTBI is associated with deregulated functional activation in several prefrontal, parietal and temporal regions which are involved in decision-making and self-control in the results of their meta-analysis. More specifically, clusters

in the superior and middle frontal gyri, superior and inferior parietal lobules and superior temporal gyrus were differentially activated between MTBI subjects and controls. MTBI versus control individuals also showed differential activation in the medial frontal cortex, which is a central structure in the default mode network of the brain, which is involved in self referential processing. Taken together, these findings are in line with the interpretation that MTBI can affect a widely distributed network of structures that is involved in mental processes that are disrupted in mental disorders such as major depressive disorder [15].

Panayiotou et al. used meta-analytic techniques to integrate the available information on the emotional symptoms associated with MTBI. Small effect sizes were found across all domains [depression, anxiety, coping, and psychosocial disability]; however, significance depending upon the weighting method employed. The results indicate that MTBI had a small to negligible effect on emotional symptom reporting. This has implications for the etiology of PCS, the delivery of therapeutic interventions, and medicolegal disputations [16].

Clinical Molecular Trials of MTBI

Widespread diffuse axonal damage, decreased axonal transport and increased axonal disconnection due to cytoskeletal disintegration are some of the neuropathological changes in MTBI [17]. Neuronal cytoskeletal proteins are important structural components of the nervous system. These proteins, including neurofilament proteins are found in the neuronal perikarya, axons, and dendrites. Therefore, loss of neurocytoskeletal proteins has crucial detrimental effects after acute CNS injuries [18]. Protein loss has been demonstrated as early as 2 hours after trauma [19]. Current researches in this area of CNS trauma have focused on the prevention and reversal of cytoskeletal protein loss using therapeutic agents that act on the pathways assumed to be involved in neurofilament protein degradation [19].

Impact of lipid peroxidation by oxygen free radicals has been shown to rise in mild and severe brain injury. Lipid peroxidation in the cellular membrane is a chain reaction that destroys polyunsaturated fatty acids. Cell membrane integrity is essential for the maintenance of normal cellular function and degradation of the membrane results in increased permeability and dysfunctional ion transport. The latter leads to calcium influx and elevation of free intracellular calcium with subsequent activation of degradation enzymes and disintegration of the cytoskeletal system [20].

Many factors are suspected to contribute to cognitive dysfunction including neurotrophins, tumor necrosis factor- α , calcium influx in addition to increased free intracellular calcium with subsequent activation of degradation enzymes, calpain, caspase-3 proteases, activation of NMDA receptors, the inducible transcription factors c-Fos, c-Jun, JunB and Krox-24 [21].

Studies which have examined the effects of MTBI on neuronal cytoskeleton proteins have documented widespread changes in neurofilament [NF] proteins and microtubule associated proteins [MAPs] [22]. Research has also shown that modulating the severity of injury can produce regionally and temporally distinct patterns of MAP and NF loss [23].

Many researchers have demonstrated that a calpain mediated protein degradation occurs as early as 15 minutes after TBI [24]. Current researches in this area of CNS trauma have focused on the prevention and reversal of cytoskeletal protein loss using therapeutic agents that act on the pathways assumed to be involved in neurofilament protein degradation.

Microtubule-associated protein-2 [MAP-2] is one of the important neurofilament proteins and is one of the preferred substrates of calpain [25]. Several studies have demonstrated that activation of calcium activated neutral proteases and calpain play a major role in neuronal cytoskeletal degeneration after TBI [26]. Calcium is an early factor in the chain reaction of activating kinases, proteases, lipases and other enzymes which lead to cell death [27]. Calpains are activated by high levels of intracellular calcium that cause neuronal damage including ischemia and hypoxia [28]. Preferred substrates for calpain include cytoskeletal proteins [spectrin, MAP-2, neurofilament protein], protein kinases [PKC, CaMKII, and myosin light chain kinase] and proteins that regulate vascular contractility [caldesmon, calponin] [29]. Calpain-2 has millimolar sensitivity to intracellular calcium concentration and is primarily present in the axons. Calpain inhibitors prevent neurofilament protein degradation and attenuate neuronal degeneration after experimental brain injury in vivo [28]. However, the efficacy of calpain inhibitors to prevent protein loss after MTBI has been studied only in few studies [19,24].

Lipid peroxidation by oxygen free radicals has been shown to increase in mild and severe brain injury [30]. Mexiletine which significantly inhibits the increase of lipid peroxidation induced by cerebral subarachnoid haemorrhage or spinal cord injury is a class 1b antiarrhythmic drug that is widely used to treat ventricular arrhythmias [31]. The well-known action of this agent is sodium [Na]-channel blockage, which prevents cell depolarization [32]. However, experimental studies have shown that mexiletine can also activate ATP-sensitive potassium [K] channels and block calcium [Ca] channels [33].

One of the many explanations for the decreased anatomic plasticity after adult CNS injury is the presence of myelin associated inhibitory factors that block neurite outgrowth [34]. Currently the best characterized cells mediating inhibitory signals in axonal growth are oligodendrocytes. Nogo-A is a myelin associated neurite outgrowth inhibitory protein limiting neuronal regeneration and plasticity after CNS injury. It is a protein product of the Nogo gene which is expressed on the cell surface of oligodendrocytes. The presence of glia-derived inhibitory factor Nogo-A has been suggested to provide a nonpermissive environment for elongation of nerve fibers [35]. Following CNS lesions, reinnervation of denervated areas may occur via 2 distinct processes: regeneration of the damaged fibers or sprouting from adjacent intact fibers into the deafferented zone. Both regeneration and axonal sprouting are limited in the fully mature CNS of higher vertebrates but may be enhanced by neutralizing the neurite outgrowth inhibitory protein Nogo-A [36].

Neural cell adhesion molecules [NCAM] promote adhesion between the surfaces of neural cells during the acute inflammatory response to traumatic injury in the cerebral cortex [37]. NCAM is found in the gray and white matter and expressed on glial cells, especially on reactive astrocytes and neurons that have completed their differentiation [38]. N-cadherin is one of these adhesion molecules and it is found outside the cellular plasma membrane that promotes hemophilic adhesions [39]. Neurons lose their connections and transform into single cellular structures when antibodies to N-cadherin are applied [40]. Recent studies demonstrate that the cadherin cell adhesion molecules and their cytoplasmic partners can modulate axon dendritic spine contacts [41]. Cadherin activity is essential for synaptic plasticity and rearrangement [42].

Although much clinical and experimental work has investigated the etiology of the neuropathological changes that occur after mild head injury, the molecular events responsible for impaired cognition are poorly understood.

Lenzlinger et al. were the first to report an in vivo study supporting a beneficial effect of Nogo-A inhibition on cognitive function in a rat experimental model of TBI [42,43]. In this study, functional improvement was achieved with the intervention beginning 24 hours after the injury, making this beneficial treatment strategy potentially interesting for use in brain injured patients. Lenzlinger and coworkers reported significantly increased sprouting of corticospinal tract fibers following TBI [43]. In this study, the Nogo monoclonal antibody significantly attenuated cognitive deficits after TBI. In a similar study Atalay et al. [34,36] produced a mild cortical contusion instead of considerable parenchymal damage and they have applied the NEP 1-40 peptide immediately following cortical injury instead of 24 hours after head injury as was done in Lenzlinger's study [36]. In this study it was concluded that, early treatment might be a factor that promoted neuronal recovery. Emeric et al. [43] Reported anatomic plasticity in the motor cortex of adult rats after a unilateral aspiration lesion to the sensorimotor cortex and treatment with monoclonal antibody [mab] to IN-1 [Nogo-A] which permits neurite outgrowth from the intact, opposite cortex into deafferented subcortical targets [44]. After a 6-week survival period, a dramatic increase in movements of the lesion-impaired forelimb was demonstrated using intracortical stimulation in animals treated with Nogo-A mab compared to controls. These results showed that after adult cortical lesioning, treatment with Nogo-A mab induces functional reorganization of the motor cortex. Neuronal regeneration depends on an interplay between extrinsic cues and intrinsic properties of the lesioned neuron. Although the mechanisms that are responsible for regeneration failure in the adult mammalian CNS are not completely understood, research in this area is promising for brain injured patients. Inhibition of Nogo-A permit injured CNS nerve fibers to regenerate over long distances by neutralizing myelin associated growth inhibitory proteins in spinal cord and brain. This may be an important step toward a potential treatment because the Nogo-A monoclonal antibody could be applied to the injured cortex during initial emergency surgery immediately after open head injury or by intradural infusion pumps in the subacute stages of cortical injury.

NFs and MAPs are two important groups of protein heteropolymers in the neuronal cytoskeleton. Their integrity is necessary for normal neuronal function, primarily axonal and dendritic transport. NFs are members of the intermediate filament protein family of axons, and are composed of three main subunits referred to as NF-L, NF-M, and NF-H in vertebrates. NF-M is a 130-160 KD protein that is known to be the main constituent of all NFs in neuronal tissues [17]. According to Lee and Cleveland, NFs are the key determinants of conduction velocity, more importantly they play an essential role in the development and maintenance of normal axonal caliber [44,45]. Of the members of the MAP protein family, MAP-2 binds to and stabilizes microtubules, and regulates intermicrotubular spacing. Giving the roles of NFs and MAPs, it is apparent why disruption of the delicate balance between cytoskeletal elements may lead to interruption of intracellular transport and communication thus degrades the cellular structure and function [17]. Several studies have focused on the changes in MAP-2 and NF proteins that occur after moderate and severe experimental brain trauma [46]. However, few reports have investigated the effects of mild head trauma on these proteins, and those that have been done have not tested multiple levels of trauma. Caner et al. used graded levels of head trauma in the study, and demonstrated that disruption of NF160 increases in parallel with the force applied.

Cytoskeletal organization of neurons is one of the most important determining factor of outcome after mild head injury. MAP-2 is highly vulnerable to injury and its level is correlated with the outcomes of head

trauma. It is not possible to explain the protein degradation by lipid peroxidation alone. Inhibition of calpain proteases also play another important role; however cytoskeletal disruption is increased mostly by lipid peroxidation and MAP-2 protein destruction. Atalay et al. reported that the inhibition of lipid peroxidation by mexiletine significantly reduced the level of MAP-2 destruction early after mild closed head trauma. Although the calpain-2 inhibitor protected MAP-2 proteins significantly after trauma in the study, cytoskeletal organization was better preserved with mexiletine [17].

Ten clinical trials evaluating the efficacy and safety of methylphenidate in children and adults with TBI were reviewed. The effects of methylphenidate versus placebo on various aspects of attention, behavior, memory and motor function were tested. Patients with mild to severe TBI began treatment 1 week to 34 years after TBI. The adverse effects of methylphenidate were also evaluated in most of these studies. Exclusion criteria included patients who had other neurologic diseases, major mental illness, pregnancy, seizure, cardiac problems, history of alcohol or drug abuse [46]. To date, the published clinical trials that assessed the efficacy of methylphenidate in treating the neurobehavioral consequences that result after TBI have found that patients have shown improvements in different aspects of cognition. Improvements in memory, attention, learning, concentration and mental processing have been observed. Efficacy of methylphenidate on behavioral changes has not been demonstrated. One clinical trial demonstrated efficacy of methylphenidate on anger; the other studies did not demonstrate efficacy. Most patients treated in these clinical trials suffered from moderate to severe TBI and were several months to years after injury. Limitations to these clinical trials include short-term treatment and small sample size. Depending on the severity of TBI, the age of the patient and the region[s] of the brain affected, cognitive and behavioral changes may not resolve with natural recovery. These changes may worsen in severity and presentation over time. In fact, permanent changes can be seen after 12 to 24 months after injury. Patients were studied from 1 to 6 weeks in these studies, and some studies conducted one week to one year of follow-up upon discontinuation of methylphenidate. The majority of patients did not return for follow-up. Since these studies were conducted for short periods of time, it is not known whether a plateau effect is seen with continued use beyond 6 weeks or if methylphenidate would be required for the duration of the patient's life. The sample size for these studies ranged from 10 to 35. Small sample size decreases power and thus the likelihood to make a type II error is increased. The most commonly utilized regimen was 0.30 mg/kg twice daily and severe adverse events were not associated with this dose. Larger, double-blind and placebo-controlled studies are needed to determine optimal doses, during which phase of recovery to begin treatment, length of treatment, and longterm effects for patients with mild, moderate and severe TBI [46].

Conclusion

In the concept of traumatic brain injury a large number of studies are currently on the way. This type of injury is very complex and too many molecular pathways are involved than expected. This makes treatment difficult and the physicians must consider the multiple sides of this condition. Larger, double-blind, placebo-controlled studies are needed to determine mechanism and new treatment modalities of MTBI. Combined treatment options with multiple treatment modalities may offer our patients the better results.

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This article was originally published in a special issue, **Traumatic Brain Injury: Diagnosis & Treatment** handled by Editor(s). Dr. Douglas Mckay Wallace, University of Miami, USA