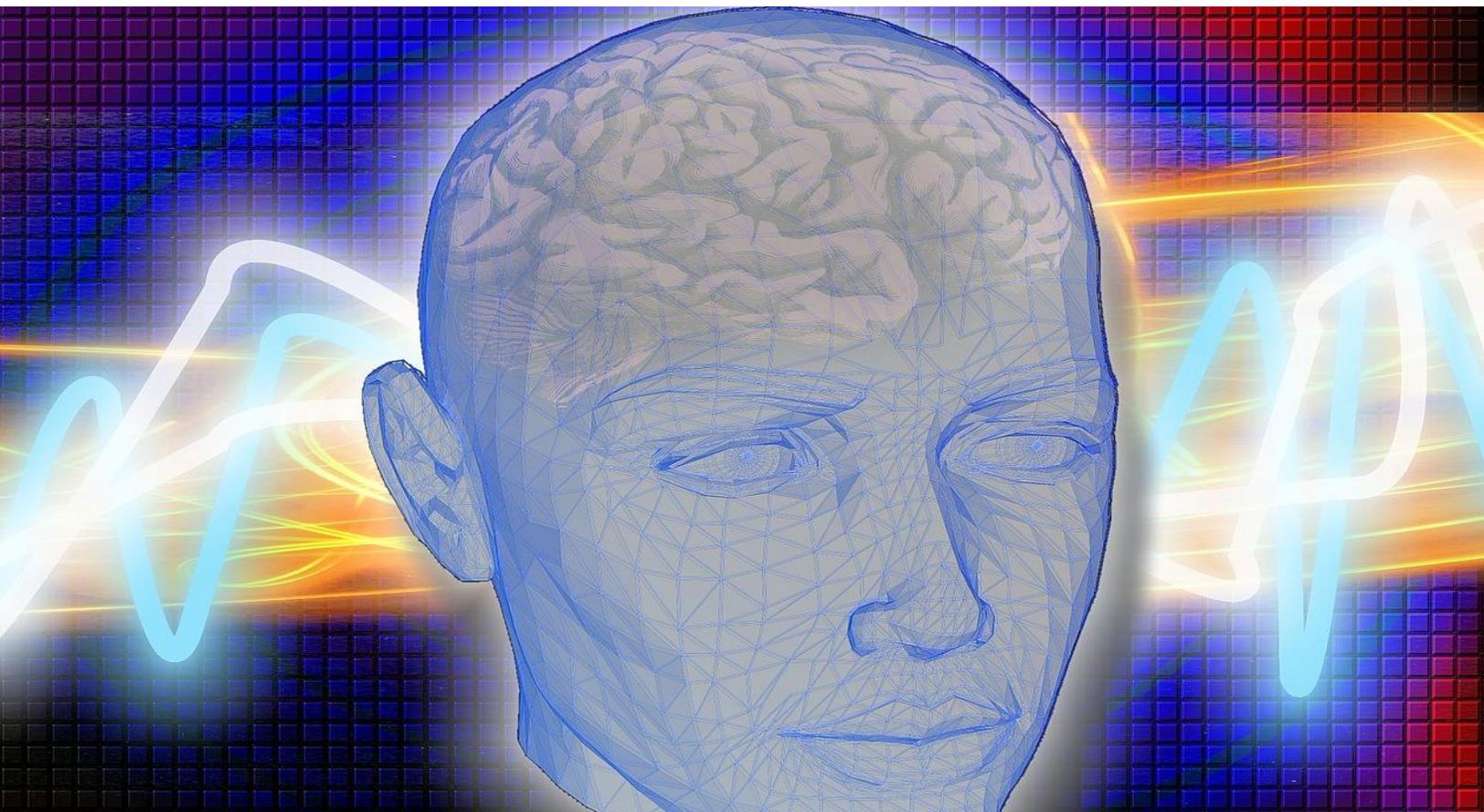


# Mild Traumatic Brain Injury (TBI)



# Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors

## Abstract

Traumatic brain injury (TBI) presents in various forms ranging from mild alterations of consciousness to an unrelenting comatose state and death. In the most severe form of TBI, the entirety of the brain is affected by a diffuse type of injury and swelling. Treatment modalities vary extensively based on the severity of the injury and range from daily cognitive therapy sessions to radical surgery such as bilateral decompressive craniectomies. Guidelines have been set forth regarding the optimal management of TBI, but they must be taken in context of the situation and cannot be used in every individual circumstance. In this review article, we have summarized the current status of treatment for TBI in both clinical practice and basic research. We have put forth a brief overview of the various subtypes of traumatic injuries, optimal medical management, and both the noninvasive and invasive monitoring modalities, in addition to the surgical interventions necessary in particular instances. We have overviewed the main achievements in searching for therapeutic strategies of TBI in basic science. We have also discussed the future direction for developing TBI treatment from an experimental perspective.

## Keywords

traumatic brain injury, management, intracranial hypertension, treatment strategies

## Epidemiology of Traumatic Brain Injury (TBI)

TBI continues to plague millions of individuals around the world on an annual basis. According to the Centers for Disease Control, the total combined rates for TBI-related emergency department visits, hospitalizations, and deaths have increased in the decade 2001–2010.<sup>1</sup> However, taken individually, the number of deaths related to TBIs has decreased over this same period of time likely secondary in part to increased awareness, structuralizing management and guidelines, and significant technological advancements in current treatment regimens. We should also acknowledge that there is a certain percentage of TBIs that never reach medical care, hence, the overall rates for TBIs are likely underreported.<sup>2</sup> The highest rates of TBI tend to be in a very young age-group (0–4 y) as well as in adolescents and young adults (15–24 y). There is another peak in incidence in the elderly (>65 y). The 2 leading causes of TBI overall are falls and motor vehicle accidents.<sup>3</sup> As a result of an overall increased number of TBIs, but lower rate of related deaths, we have a growing population of individuals living with significant disabilities directly related to their TBI.

## Pathophysiology of TBI

TBI pathogenesis is a complex process that results from primary and secondary injuries that lead to temporary or permanent neurological deficits. The primary deficit is related directly to the primary external impact of the brain. The secondary injury can happen from minutes to days from the primary impact and consists of a molecular, chemical, and inflammatory cascade responsible for further cerebral damage. This cascade involves depolarization of the neurons

with the release of excitatory neurotransmitters such as glutamate and aspartate that lead to increased intracellular calcium. Intracellular calcium activates a series of mechanisms with the activation of enzymes caspases, calpases, and free radicals that results in degradation of cells either directly or indirectly through an apoptotic process. This degradation of neuronal cells is associated with an inflammatory response that further damages neuronal cells and incites a breach in the blood brain barrier (BBB) and further cerebral edema. This entire process is upregulated and downregulated as well through several mediators. After the second injury phase follows the recovery period, which consists of reorganization in an anatomical, molecular, and functional level.

The volume of the intracranial compartment is comprised of 3 separate contents: the brain parenchyma (83%), cerebrospinal fluid (CSF, 11%), and blood (6%).<sup>4</sup> Each of these contents relies on one another for a homeostatic environment within the skull. However, when intracranial volume exceeds that of its normal constituents, a cascade of compensatory mechanisms takes place. An increase in intracranial volume can take place in the traumatized brain via mass effect from blood, both cytotoxic and vasogenic edema, and venous congestion. Brain tissue is incompressible. As a result, edematous brain tissue will initially cause an extrusion of CSF to the spinal compartment. Eventually, blood, especially that of venous origin, is also extruded away from the brain. Without proper intervention, and sometimes even with maximal intervention, the compensatory mechanisms fail and the end result is pathological brain compression and ensuing death.<sup>5</sup>

### **Concussion**

Concussive injuries are often viewed as mild TBIs without any gross structural damage secondary to a nonpenetrating TBI.<sup>6</sup> They usually follow direct blows to the head with subsequent acceleration/deceleration forces taking place. A concussive injury typically leaves the individual with varying levels of transient altered mental status, ranging from slight confusion to an actual state of unconsciousness for a few minutes. Routine neuroradiographic imaging such as computerized axial tomography scan (also called computerized tomography [CT] scan) and magnetic resonance imaging (MRI) do not show any immediate abnormalities. However, newer imaging techniques using MRI such as diffusion tensor imaging and functional MRI may result in earlier diagnosis of concussion. It has been postulated that mild degrees of axonal damage take place even in the face of a mild TBI.<sup>7</sup>

A very rare condition seen most often in athletes is second impact syndrome. The inciting event is often a concussion, however, the player may return to play prematurely and sustain a second concussive event amid continued recovery from their initial injury. The mechanism typically involves the rapid evolution of malignant cerebral edema, ensuing over a short-time course after the second injury takes place

often on the playing field. The mortality rate ranges from 50% to 100%.<sup>8</sup>

### **Chronic Traumatic Encephalopathy (CTE)**

Repetitive mild TBI may lead to a delayed manifestation known as CTE. This entity has gained popular attention in the media as one of the unfortunate consequences of CTE is psychiatric disturbances, ultimately leading to suicidal behavior in a number of high-profile athletes in professional sports. Other clinical manifestations of CTE include dysarthric speech, tremors, difficulty with attention, deficits in memory and executive functions, and incoordination and pyramidal signs.<sup>5</sup> CTE likely results from evolution of progressive neuronal loss.<sup>9,10</sup>

### **Extra-axial Hematomas**

Extra-axial hematomas consist of both epidural hematomas (EDH) and subdural hematomas (SDH). EDH classically result from a direct blow to the temporal region, at times causing a skull fracture, with resultant disruption of the middle meningeal artery. However, venous injuries, such as disruption of the transverse sinus, have also accounted for more posteriorly oriented EDH. EDH can rapidly grow in size, causing an individual to present with essentially normal mentation, followed by deterioration down the cascade of herniation syndromes once a critical level of intracranial pressure (ICP) is reached.<sup>11</sup>

While EDH are almost always encountered in the acute setting, SDH have varying presentations based on the age of the patient and the chronicity of blood products. SDH in the setting of trauma often take place via acceleration/deceleration of the surface of the brain against the undersurface of the skull, causing shearing injuries to the bridging veins.<sup>12</sup> Acute SDH can be quite dangerous for the patient in the context of trauma, as they generally involve a much higher degree of underlying brain injury than does an EDH. The underlying cerebral edema is often a significant contributing factor to ensuing midline shifting of structures and progression of herniation syndromes if left untreated. There are some SDH that go unnoticed to the patient for a period of time. As acute blood in the subdural space liquefies over time, subacute and chronic SDH can be encountered. In the subacute and chronic setting of subdural hematoma, the clinical presentation is not nearly as rapid and progressive as in the acute phase. More chronic-appearing SDH tend to be encountered in the elderly population, many times while they are on antiplatelet agents or anticoagulants. The usual presentation for subacute and chronic SDH's tends to be more insidious, with headaches, hemiparesis, speech problems, confusion, and altered mentation being most common. On rare occasion, a patient will present with significant neurological deterioration due to untreated unilateral or bilateral chronic SDH.

## *Contusions and Traumatic Subarachnoid Hemorrhage*

Contusions generally take place as a result of coup and contrecoup forces. Coup injuries occur at the site of impact, while contrecoup injuries typically take place on the contralateral side of impact, most often causing injury to the frontal lobe and anterior temporal lobe. Subarachnoid hemorrhage is most often caused by trauma and takes place when small capillaries tear and ultimately spill blood transiently into the subarachnoid space. Generally, traumatic subarachnoid hemorrhage is not as severe a brain injury as is spontaneous aneurysmal subarachnoid hemorrhage,<sup>13</sup> given the fact that in the latter, blood is projected into the subarachnoid space under arterial pressure.

## *Diffuse Axonal Injury (DAI)*

DAI is the ultimate form of axonal shearing injury. Significant rotational acceleration/deceleration forces are generally required for such an injury to take place.<sup>14</sup> Radiographically, it is often picked up on T2 and gradient echo sequences as subtle hemorrhagic foci seen in areas such as the corona radiata, corpus callosum, internal capsule, brainstem, and thalamus.<sup>15</sup> Depending on where the axonal shearing takes place, patients can have varying degrees of clinical presentations. A subset of patients with DAI may have altered consciousness for a few days, while others present with hemiparesis from internal capsule involvement. Others never regain consciousness due to loss of axonal integrity in parts of the reticular activating system.

## **Neurological Exam in the Brain-injured Patient**

In the assessment of the brain-injured patient, a detailed neurological exam must be completed after the primary and secondary surveys have been completed by the trauma or emergency room staff. An adequate understanding of the Glasgow Coma Scale (GCS)<sup>16</sup> is paramount in this setting, as it often dictates management based on current guidelines. In the nonintubated, nonsedated patient, a basic survey of neurological symmetry should be undertaken once a GCS score is established. Pupil size should be compared, as should motor strength and sensation. Other nuances of the neurological exam, although important, do not play a significant role in the immediate decision-making of the traumatic brain-injured patients. Although eye opening is one individual component of the GCS grading, clinicians tend to put more weight on this finding, as it often suggests a more reassuring neurological status in our experience if a patient opens his or her eyes spontaneously. Assessment of the intubated patient with a much lower GCS score can be more challenging. A quick method of examining the intubated, potentially sedated brain-injured patient entails establishing a GCS score as soon as possible. Checking for pupil reactivity, symmetry, as well as cough/gag, and corneal reflexes are

also important. Intubated patients are usually sedated to some degree and pharmacologically paralyzed for placement of the endotracheal tube. This is also the case in patients intoxicated with alcohol and/or recreational drugs. These pharmacological factors play a significant role in the neurological exam at face value but are generally unaccounted for in basic grading scales such as the GCS. In these circumstances, it is of the utmost importance to gather data in a brisk fashion, such as the sedative/paralyzing medications used, the timing of administration, their half-lives, and any other potential confounding factors to the neurological exam. Without these details, untoward decisions may be made based on a GCS score alone, which may not be in the best interest of the patient. A full neurological exam of sedatives should be the primary goal of the neurosurgeon once airway, breathing, and circulation have been addressed.

## **Medical Interventions for TBI**

### *Head Elevation*

Raising the head of a traumatic brain-injured individual generally has rapid effects. ICP is reduced by displacement of CSF from the intracranial compartment as well as promotion of venous outflow.<sup>5</sup> Although the mean carotid pressure is reduced during head of bed elevation, ICP is reduced and cerebral blood flow (CBF) is unaffected.<sup>17</sup>

### *Hyperventilation*

Hyperventilation lowers ICP by reducing the intraarterial carbon dioxide partial pressure (PaCO<sub>2</sub>), which subsequently results in vasoconstriction. This pattern of events ultimately results in the reduction of cerebral blood volume.<sup>18</sup> Prophylactic hyperventilation is not generally recommended, as vasoconstriction lowers CBF. In areas of preserved autoregulation, focal areas of ischemia can occur.<sup>19</sup> The use of hyperventilation in the setting of severe TBI is usually only used for brief periods during acute neurological deterioration.<sup>5</sup>

### *Seizure Prophylaxis*

Current TBI guidelines state that 1 wk of prophylactic anti-epileptics is acceptable to help prevent early seizures. However, there has not been any proven benefit in prevention of late-term seizures after a TBI, and hence, the antiepileptic is generally discontinued after 7 d.<sup>20</sup>

### *Hyperosmolar Therapy*

Hyperosmolar therapy in the setting of a TBI can be administered in the form a bolus or an infusion. It has been shown that the immediate effects of mannitol are actually due to alterations in blood rheology. As blood rheology improves and blood becomes less viscous, an increase in CBF takes place.<sup>21</sup> The body's autoregulatory

response to this is transient vasoconstriction, which ultimately limits the degree of CBF. Mannitol also does have osmotic diuretic properties, but this mechanism of decreasing ICPs is not thought to take place until after the primary effect.

### **Medically Induced Comatose State**

One of the last steps of maximal management is placing a patient in a medically induced comatose state usually by infusion of a benzodiazepine such as midazolam or infusion of a barbiturate such as pentobarbital. These medications are titrated to burst suppression on the continuous electroencephalogram. They work by significantly decreasing the metabolic demand in the brain. Prophylactic use of barbiturates for burst suppression is not currently recommended. It is, however, recommended for severe refractory intracranial hypertension after maximal medical and surgical ICP-lowering therapy have been exhausted.<sup>5,18</sup> Oftentimes, medically induced comatose states are used once a form of invasive intracranial pressure monitoring has been undertaken. Medications such as midazolam and pentobarbital pose a potential risk of altering blood pressure to patients.

### **Therapeutic Cooling**

It is thought that oxidative stress is a secondary effect of TBI. Therapeutic hypothermia has been shown in infants and children to decrease oxidative injury.<sup>22</sup> As the body's temperature cools, the cerebral metabolic demand decreases. This type of therapy also comes with risks such as alterations in blood sugar, platelet count, and coagulation factors. Platelet count and coagulation factors must be checked before any invasive procedure when an individual is brought to a hypothermic state. Therapeutic cooling in the context of severe TBI has had mixed results and is currently a second-tier therapeutic modality.<sup>23</sup>

### **ICP Monitoring**

Certain indications have been put forth as guidelines in regard to ICP monitoring in brain-injured patients. Some patients clinically present with signs of significant neurological compromise but without clear indications for emergent surgical intervention. Level II evidence exists for placing an ICP monitor in patients with a severe TBI, a GCS between 3 and 8, and an abnormal CT scan of the head. Level III evidence also suggests placing an ICP monitor in patients with a severe TBI and a normal CT scan of the head, if 2 or more of the following are noted upon admission: age over 40 y, unilateral or bilateral posturing, or systolic blood pressure <90 mm Hg.<sup>24</sup> The rationale behind placing an ICP monitor exists, because it is now known that secondary injuries to the brain have the ability to potentiate further deterioration.<sup>24</sup> If the primary impact, such as a subdural hematoma, does not

warrant immediate surgical intervention, both cytotoxic and vasogenic edema, as well as resulting cerebral hypoperfusion, may ensue. These secondary impacts may cause the abrupt demise of a patient, if the ICP is not closely monitored. Other parameters such as brain oxygen tension are now able to be monitored as well, giving clinicians another means of monitoring the injured brain.<sup>25</sup> The mainstay of ICP monitoring continues to be the external ventricular drain, which can be utilized for both therapeutic and diagnostic purposes.<sup>26</sup> If the patient's ventricles are too small and do not accommodate a ventricular drain, another option is to place a diagnostic fiberoptic ICP monitor.<sup>27</sup> New models are now being used on a more routine basis to monitor brain oxygen tension, as evidence exists that this parameter falls in cases of severe TBI. These different modalities help neurosurgeons decide on which patients can safely be managed with medical management alone and which patients will ultimately need neurosurgical intervention.

## **Surgical Intervention**

### **Craniotomy: Evacuation of Extra-axial Hematoma/Contusion**

Surgical intervention is generally warranted when there is significant mass effect from either an epidural or subdural hematoma or a contusion with a significant volume of blood.<sup>28</sup> The underlying brain injury associated with an EDH is usually quite minor, however, the rapidity with which an EDH can expand often makes this a neurosurgical emergency. The mainstay of treatment of an EDH is a craniotomy over the desired region, with evacuation of the hematoma and cauterization of the bleeding vessel, often the middle meningeal artery. Acute SDH are usually associated with a much more significant underlying brain injury. Not only does the extra-axial blood cause mass effect on the brain, but the underlying cerebral edema is often what pushes the patients over the edge to clinical deterioration. As a result of the oftentimes severe brain injury associated with an acute SDH, a decompressive craniectomy (DC) is performed. Standalone evacuation of the subdural hematoma without temporary removal of the bone flap in a patient with significant associated underlying cerebral edema can result in further delayed deterioration after the initial surgery has taken place. However, if the underlying brain injury is minimal and mass effect is mainly due to the hematoma itself, it may be reasonable to perform a craniotomy, with hematoma evacuation and duraplasty.<sup>28</sup>

SDH vary in age from acute (the most severe form) to subacute, chronic, and mixed. After a number of days, acute SDH generally enter into a process of liquefaction, making them amenable to minimally invasive surgical evacuation. While acute SDH's are actual clotted blood, subacute and chronic SDH's have a liquefied component. A bedside subdural bolt evacuating system can be placed once blood is out of the acute phase and has liquefied to a significant degree.

A very small incision is made over the area of the SDH, a handheld twist drill is then used to make a burr hole, the durra is opened, and the metal bolt is secured into the burr hole. A tube connected to a small suction device is then attached to the bolt and allowed to drain via self-suction. A limitation to this device is when there are multiple subdural septations and loculations, allowing chronic blood to be evacuated from only the pocket the bolt is overlying. In the case of a symptomatic mixed-density SDH, surgical intervention may be undertaken whereby a craniotomy is performed, followed by the SDH evacuation, and finally clearing of the subdural membranes responsible for the recurrent “leakage” of blood from neovascularized blood vessels.<sup>29</sup>

Most contusions that occur can usually be watched clinically and radiographically to ensure that they do not significantly expand. However, a small percentage of brain contusions do “blossom” to the point of requiring surgical intervention with a craniotomy and clot evacuation.

### *DC for Cerebral Edema*

Radiographically, some severe TBIs do not yield significant hemorrhages. However, upon close inspection, it can be noted that there is blurring of the gray–white junction, effacement of the ventricles, and obliteration of normally visible cisterns. Obliteration of the basal cisterns is an ominous sign that there is impending distal herniation, ultimately leading to the demise of the patient. If the edema is localized to one side of cerebral hemispheres, surgical intervention may consist of a hemicraniectomy, whereby a large bone flap is removed from the surrounding skull, and the durra is opened. Severe bilateral diffuse cerebral edema may warrant bilateral DC as a last resort surgical option to salvage the patient.<sup>30</sup>

### *Synopsis*

The clinical aspects of TBI can be quite complex, as is evidenced by the wide array of presentations and treatment strategies. Of utmost importance in the management of TBI patients is obtaining neuroradiographic imaging as well as a baseline neurological examination. The decision-making process for therapeutic maneuvers will essentially be based upon critical deviations from the initial scan and neurological status. Therapies for TBI range from medical management alone with frequent neurological exams, to invasive intracranial monitoring, and as a last resort to radical decompressive surgical interventions.

## **Therapeutic Studies in Animal Models of TBI**

TBI is a combination of anatomical and functional damage to the brain after direct mechanical insult from external forces. TBI-induced cerebral injury is a mixture of structural, cellular, and vascular injury. Reaction with a complex

molecular and cellular cascade is activated as a result of the structural damage from the initial impact.

In order to minimize the cerebral injury after the TBI, therapeutic intervention is directed to prevent the first impact damage and to restrict the molecular and cellular cascade of the continuous cell damage. So far, there are no effective treatments for the first impact damage. Numerous studies have been carried out in an effort to search for treatment to prevent further neuronal damage after TBI and to enhance neural network reorganization and functional recovery. Unfortunately, these experimental studies have not been successfully translated into clinical therapies. Many questions have been raised through these years such as whether we fully understand the pathological dynamics after TBI and whether TBI models are clinically relevant.

### *Animal Models of TBI*

Several animal models for TBI have been proposed and each of them has tried to mimic clinical TBI. Animal models of TBI that have been frequently used for research include fluid percussion injury (FPI), control cortical impact injury (CCI), weight drop impact acceleration injury (WDIAI), and blast injury model.<sup>31</sup>

*FPI.* FPI produces a TBI that is characterized by cerebral edema, intraparenchymal hemorrhage, and cortical neuronal injury. Lately, FPI model has been modified to lateral FPI model, which creates not only focal cortical contusion but it also transmits the traumatic injury into subcortical structures such as hippocampus and thalamus. The neuronal loss starts immediately after the impact and progresses up to 7 d post-TBI. The cascade of the molecular changes continues for months in the subcortical structures such as septum pellucidum, thalamus, amygdala, and striatum. This TBI model produces similar symptoms to humans and manifests severe neurobehavioral deficits that persist more than 1 y after TBI.<sup>31,32</sup>

*Control CCI.* Control CCI is a TBI model that provides a more controlled injury in terms of velocity force, time, and depth of injury as compared to the FPI model. This model creates cortical injury, SDH, axonal injury, and subcortical injury in the thalamus and hippocampus. The CCI model-induced brain injuries cause long-term neurobehavioral deficits that persist more than a year and are associated with cortical atrophy and reduced brain perfusion.<sup>31,33</sup>

*WDIAI.* WDIAI is a model that generates an open or closed head injury. The result of the first impact is cortical contusion with possible subcortical intracerebral hemorrhage. This leads to the formation of a necrotic cavity within 2 wk after injury. In this model, the recovery phase is ranged from 2 wk to 3 mo. The closed head injury of this model causes neurologic deficits, neurodegeneration, inflammatory response with microglial activation, BBB breakdown, and

DAI. The pathology features of this model contain similar components as seen in human TBI that is caused by motor vehicle accidents or sport injury.<sup>31</sup>

**Blast injury.** Blast injury model is created by high-velocity ballistic penetration or a stub of a blast. The anatomical and morphological characteristics of the blast injury are related to trajectory of the injury with intraparenchymal hemorrhage and subsequent cavity formation. Moreover, this model also generates additional TBI components such as inflammation with BBB breakdown, cerebral edema, neurodegeneration, tauopathy, and axonal degeneration.<sup>31,34</sup>

### **Exploration of Therapeutic Strategies in Animal Models of TBI**

Animal model not only helps us understand the pathological progression after TBI, but it also allows us to develop putative interventions for preventing secondary injury, enhancing brain repair and improving recovery after TBI.<sup>31</sup> Neuroprotection, neurovascular regeneration, and neurorestoration have been proposed to be therapeutic strategies for TBI. As mentioned earlier, TBI leads to a cascade of primary and secondary neuron loss, which is clinically manifested with different degrees of neurological deficits depending on the location and the severity of the neuron loss. Numerous studies have targeted the reduction or prevention of the TBI-induced neuronal loss. Treatment that shows neuroprotective effects on TBI in animal models requires intervention within a few hours after the first impact.<sup>35–37</sup> However, a large number of clinical trials using neuroprotective treatment have not shown promising results. The therapeutic potential of neuroprotection, therefore, has become questionable in TBI research. Several neuroprotective approaches that have been used for TBI clinical trials or animal models are outlined below.

**Calcium channel blockers.** Increased intracellular calcium is a very important element in the cascade of the cellular damage after TBI. Using 2 types of calcium channel blockers (L-type and N-type) to neutralize intracellular calcium has shown benefits in preventing TBI-induced cellular death.<sup>38–41</sup>

The neuroprotective effect of nimodipine was reported in 1984<sup>38</sup> based on the regulation in brain perfusion and prevention of further neuronal damage. Nimodipine is an L-type calcium channel blocker and has been shown to improve outcomes in the patients with spontaneous subarachnoid hemorrhage.<sup>39</sup> However, a systematic review contradicted those results and revealed that the mortality and morbidity displayed no significant difference between placebo and nimodipine treatment in TBI patients.<sup>40</sup>

Ziconotide (SNX-111) is an N-type calcium channel blocker. It has been shown that administration of ziconotide during the period of 15 min to 6 h after TBI improves mitochondrial function in patients<sup>41</sup>; however, significant side effects such as hypotension were also observed. Another

N-type calcium channel blocker, SNX-185, was reported to show neuroprotective effects when directly injected to hippocampal CA2 and CA3, 24 h after TBI.<sup>41</sup>

**Osmotherapy.** Hyperosmolar agents are used in patients with severe TBI to control ICP. Hyperosmolar saline injection displayed beneficial effects in TBI patients. Mannitol, one of hyperosmolar agents, has been shown as having a significant effect on reducing ICP in TBI patients in a dose-dependent manner. Mannitol treatment also resulted in improvement of blood perfusion and reduction of inflammatory response after the TBI.<sup>41</sup>

**Amantadine.** Amantadine is a dopamine agonist used for Parkinson's disease. Amantadine can distribute in frontal lobes and acts as an N-methyl-D-Aspartate (NMDA) receptor antagonist. It has been proposed that amantadine may protect the neurons against glutamate excitotoxicity in the acute phase of TBI. Many studies have demonstrated that amantadine in dose of 100–400 mg/d may increase the arousal and improve cognitive function when given within 12 wk after the TBI.<sup>37,42</sup>

**Erythropoietin (EPO).** EPO is a secreted glycoprotein with a molecular weight of 30-kD. The role of EPO in the regulation of erythropoiesis has been initially identified in the hematopoietic system.<sup>43</sup> EPO may also play a role in the central nervous system as the expression of both EPO and its receptor, EpoR, are widespread in the brain.<sup>44,45</sup>

Although the molecular weight of EPO is larger than the molecular threshold of the BBB, exogenous EPO has been found in the brain parenchyma where it may play a role in neuroprotection after brain injury.<sup>46</sup> Several studies have demonstrated that EPO shows antiexcitotoxic, antioxidant, antiedematous, and antiinflammatory effects in TBI.<sup>47–50</sup> Brain injury causes upregulation of EpoR expression.<sup>45</sup> Reduced number of neural progenitor cells (NPCs) and increased apoptosis has been found in the mice lacking the EPO receptor.<sup>51</sup>

EPO/EpoR signal pathway has been shown to be involved in neuroprotection in pathological conditions.<sup>50,52</sup> Expression of the receptors for EPO is significantly increased in neurons, glia, and endothelial cells after TBI.<sup>41</sup> EPO appears to promote neuroprotection through binding to EpoR and activating JAK-2/NF- $\kappa$ B and PI3K signaling pathway.<sup>41,53</sup> Additionally, JAK-2 phosphorylation activates PI3K/AKT and Ras/MAPK pathways and promotes STAT-5 homodimerization, which has been shown to have antiapoptotic and neurotrophic effects.<sup>54–56</sup> However, a recent double-blind randomized controlled clinical trial has revealed that EPO does not reduce the number of patients with severe neurological dysfunction and that the effect of EPO on mortality remains uncertain in moderate or severe TBI.<sup>57</sup> Clearly, more clinical trials need to be performed to confirm the results collected from the experimental studies.

**S100B protein.** S100B protein is a calcium-binding protein produced by glial cells. S100B protein has been detected in serum after the opening of the BBB after brain injury. S100B shows a dose-dependent dual effect in neurons. In small doses, S100B acts as a neurotrophic factor for neuroprotection. However, in high doses, S100B increases neuroinflammation and worsens the neural survival.<sup>41</sup>

**Hypothermia.** In 1945, Fay reported possible benefits of hypothermia on severe cerebral trauma.<sup>58</sup> Since then, many studies have shown that hypothermia improves outcome in animal models of TBI.<sup>59–64</sup> Temperature management in the brain is very important after cerebral injury.<sup>65,66</sup> Deep hypothermia (below 30 °C) appears to show no benefits for TBI while mild to moderate hypothermia (32 to 35 °C) displays neuroprotective effects.<sup>67,68</sup> However, the neuroprotective mechanisms of hypothermia after TBI remain poorly understood. Several beneficial effects of hypothermia have been determined, including the effects on regulation of metabolism, excitotoxicity, inflammatory mediators, or autophagy.<sup>68–74</sup> Neuroprotective effects of hypothermia have been proposed to be associated with the reduction of brain oxygen consumption and glucose metabolic rate, preservation of high-energy phosphate compounds, and maintaining of tissue pH in the brain.<sup>75</sup> Recent studies have shown that therapeutic hypothermia significantly alters genomic transcripts and microRNA responses and regulates protein synthesis and translation in rat models of TBI.<sup>76–78</sup> The hypothermia-induced changes in gene, microRNA, and protein responses following TBI may target the delayed responses that regulate the secondary brain damage. Although the robust neuroprotective effects of therapeutic cooling have been demonstrated in animal models of TBI, it still remains controversial whether hypothermia treatment could really provide permanent protection or delay the injury processes.<sup>69</sup>

**DC.** DC is a neurosurgical procedure, which allows a swelling brain to expand without being compressed. DC has been used to reduce ICP in the conditions of brain tumor, stroke, and severe TBI.<sup>79</sup> DC as a treatment of TBI was originally reported by Emil Theodor Kocher.<sup>80</sup> However, due to the controversial findings in both clinical and experimental studies, DC is recommended as a third-tier therapy for the treatment of elevated ICP by most national and international guidelines.<sup>80,81</sup> The role of DC on brain edema formation and secondary injury after TBI has been examined in animal models of TBI. Using a controlled cortical impact model of TBI in mice, Zweckberger and coworkers reported that early craniectomy prevented secondary brain damage and significantly reduced brain edema formation.<sup>82</sup> A recent study suggested that DC might affect AQP4 expression and reduce brain edema formation after TBI.<sup>83</sup> However, Szczygielski and coworkers reported opposite findings. They found that surgical decompression promoted brain edema formation and contusional blossoming and exacerbated functional

impairments in mice with closed head injury.<sup>84</sup> The different results may be attributed to different injury severity from different TBI models. The outcomes of craniectomy application are highly correlated with the severity of the initial injury.<sup>79</sup> Although the results of experimental studies are controversial, DC still exhibits an important role to save the lives of patients with TBI and improve neural functional outcomes. Further studies need to be performed to confirm which kind of TBI is suitable for DC and which physiological and pathological mechanisms are related to functional outcomes after DC in TBI patients.

### Neurovascular Regeneration

Neuronal and vascular regeneration have been proposed to play a role in brain recovery after brain injury. Neurogenesis in adult brain has been shown to occur in the subgranular zone in the dentate gyrus (DG) of the hippocampus and subventricular zone. In animal models, it has been described that TBI induces the neurogenesis in cerebral cortex, DG, and CA3. Thymosin  $\beta$  4 (T $\beta$ 4) is an important G-actin-sequestering molecule in cells. In animal models, T $\beta$ 4 injection increases proliferation of NPCs. Moreover, T $\beta$ 4 also enhances angiogenesis and promotes NPC differentiation.<sup>35</sup>

In the subventricular zone and subgranular zone, there is a particular group of astrocytes that can go through division and differentiation into new neurons. These newborn neurons have been proposed to play a role in replacing the neurons in the olfactory bulb or in the cortex and hippocampus after TBI. In animal models, it has been shown that the number of regenerated neurons in young animals is greater than those of aged animals. The process of NPC proliferation and differentiation has a peak at 2 to 5 d after TBI, while some studies extend this time frame to 14 d.<sup>85</sup>

TBI causes changes in vascular density in the cortex, DG, and CA3 in animal models. T $\beta$ 4 treatment increases the vascular density in the cortex, DG, and CA3. This increased vascular density is associated with neurogenesis and synaptogenesis. The entire process of angiogenesis, neurogenesis, and synaptogenesis may contribute to TBI recovery.<sup>35</sup> Recently, Zhang et al.<sup>86</sup> reported that a T $\beta$ 4 active peptide fragment, N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), enhanced angiogenesis and neurogenesis, and increased the number of dendritic spines in the injured brain.

S100B appears to be a stimulator for neurogenesis after TBI. Using animal models of TBI, a number of studies have shown that intraventricular administration of S100B in the acute or subacute phase of TBI promotes neurogenesis in the hippocampus and subventricular area and improves cognitive function and spatial learning.<sup>41,87</sup> It has been shown that nitric oxide enhances neurogenesis and angiogenesis through the mediation of guanylyl cyclase and formation of guanylate cyclase.<sup>88</sup> Induced neurovascular regeneration lays the foundations for neural plasticity and functional recovery.

## Neurorestoration

**Cell-based therapy for TBI recovery.** In the past few decades, stem cell-based therapy opened a new therapeutic avenue for neurological disorders and Central Nervous System (CNS) injuries. Preclinical studies utilizing stem cells and progenitor cells as treatment for spinal cord injury,<sup>89–91</sup> stroke,<sup>92,93</sup> and brain injury<sup>94,95</sup> have shown beneficial effects in improving recovery. Currently, different cell types have been used as putative therapies for TBI recovery. It has been revealed that enhancing neurogenesis, angiogenesis, and immunoregulation by secreting chemokine and growth factors are involved in the functional recovery induced by stem cell/progenitor cell-based interventions.<sup>96–99</sup> Several clinical trials in cell-based treatment for TBI recovery have demonstrated safety of this therapeutic approach.<sup>100,101</sup> However, the administration route, dose, and time window still remain controversial.

The therapeutic effects of mesenchymal stem cell (MSC) transplantation in TBI recovery have been demonstrated in animal models. MSCs were mainly isolated from the bone marrow, umbilical cord, and adipose tissue.<sup>99,101,102</sup> The administration dose of MSCs ranges from 0.1 to 20 million cells per kg body weight.<sup>96</sup> The approaches of lateral ventricle and intravenous injection have been utilized.<sup>96</sup> The timing for MSC transplantation in experimental animal models has been intensively studied within 24 h after TBI. Recently, a clinical study has showed significant improvements in neurological function of patients with sequelae of TBI after umbilical cord MSC transplantation.<sup>101</sup> Although it remains to be fully understood how MSCs transplantation improves functional recovery after TBI, emerging evidence has suggested that neurorestoration is most likely the mechanism underlying the MSCs transplantation-induced TBI recovery rather than neuroreplacement. It has been shown that MSCs release growth factors such as Fibroblast growth factor 2 (FGF-2), Vascular endothelial growth factor (VEGF), Brain-derived neurotrophic factor (BDNF). These growth factors enhance neurogenesis, angiogenesis, and synaptogenesis.<sup>41,103</sup> The efficacy of MSCs transplantation in the acute phase of TBI is contradictory. Extensive studies are needed to further validate the therapeutic effects of MSCs transplantation in the acute phase of TBI in animal models before this approach is translated into clinical trials.

Neural stem cells (NSCs)/NPCs are also most frequently used in experimental TBI. NSCs/NPCs reside in the mammalian brain at the ependymal lining, subventricular zone, and hippocampus.<sup>104</sup> Recently, promoting endogenous NSCs or NPCs proliferation and differentiation have been shown to stabilize the cortical microenvironment and enhance post-TBI functional recovery.<sup>105–108</sup> Exogenous NSC transplantation also promotes neuroprotection, enhances hippocampal neurogenesis, and improves functional outcomes.<sup>109</sup> In animal models, the number of cells for transplantation ranges from 0.15 to 25 million cells per kg body weight.<sup>96</sup> The most common delivery method used for NSC transplantation is stereotactic injection to the brain. Although the timing for transplantation ranges from

immediately after TBI to a few weeks later,<sup>110–112</sup> Shear et al.<sup>113</sup> reported that NSC transplantation at 2 d after TBI showed better outcome than at 2 wk after TBI. It has been shown that the benefits of NSC/NPC transplantation may attribute to differentiating into functional neurons and replacing lost neurons.<sup>114,115</sup> Recent studies have shed new light on the interaction between NSCs/NPCs and immune system. The cross-talk between immune cells and transplanted NSCs/NPCs not only enhances endogenous regenerative responses, but it also promotes functional integration of grafted NSCs/NPCs.<sup>116</sup> Gao et al. reported that grafted human NSCs promoted the switch of microglia/macrophages into an anti-inflammation phenotype which may contribute to stem cell-mediated neuroprotective effects after severe TBI in mice.<sup>117</sup> Although there is no clinical trial concerning NSC transplantation for TBI recovery, the clinical study in traumatic cervical spinal cord injury has shown the safe outcomes.<sup>118</sup>

Transplantation of embryonic stem cells (ESCs) in TBI has also been studied. Molcanyi et al.<sup>119</sup> reported that post-traumatic inflammatory response inhibited the survival and integration of transplanted ESCs after TBI. Riess et al.<sup>120</sup> revealed that ESC transplantation improved neurological outcomes but it had the risk of tumorigenesis.

Although preclinical studies indicate stem cell-based interventions may be a promising approach for TBI, long-term risks and benefits of this approach still need to be further investigated.

**Enriched environment (EE) intervention for TBI recovery.** Neurorehabilitation plays a crucial role in integrating TBI patients into a functional lifestyle. TBI survivors are often left with long-term depression. Exposure to positive environments plays a significant role in improving emotional well-being for TBI patients.

Numerous studies have examined the effects of exposing animals to EEs after neurological insults. An EE consists of housing animals in a larger cage and allowing animals to have more opportunities for social interaction, sensory stimulation, and exploratory behavior.<sup>121</sup> Rats exposed to an EE have shown benefits in both neurobehavior and neuroanatomy.<sup>121–131</sup> Using animal models of TBI, multimodal interventions including exposure to an EE have yielded positive results.<sup>132,133</sup> It has been shown that EE exposure improves spatial memory recovery after cerebral ischemia.<sup>134</sup> In olfactory bulbectomized rats, exposure to an EE results in antidepressant effects.<sup>135</sup> In rats with striatal lesion, EE has also proven beneficial for neural graft function and morphology.<sup>136</sup> It has also been reported that visually defected rats may regain some degree of visual acuity after exposure to an EE.<sup>17</sup> The prophylactic effects of EE exposure prior to undergoing a TBI has also shown positive results.<sup>137</sup> Spinal cord-injured rats also display functional recovery once exposed to an EE.<sup>126</sup>

Translating the research on EEs to the clinical arena in humans has significantly positive implications in

neurorehabilitation. Individuals sustaining TBIs are known to have a high incidence of depression. EE intervention plays a key role in rehabilitative motivation for the individuals.

## Conclusive Remarks

Although there is lack of effective treatment for TBI recovery today, the efforts for developing therapeutic strategies on TBI recovery have been continuously made over the past several decades. Standard medical and surgical interventions always play a significant role in the acute management for TBI patients. Given increased population of TBI survivors due to the advent of better acute management guidelines in the acute phase of TBI, the number of TBI survivors with various disabilities has risen. This calls for major research of TBI to be shifted into the area of neurorestoration and neurorehabilitation.

## Declaration of Conflicting Interests

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# Evaluation and Treatment of Mild Traumatic Brain Injury: The Role of Neuropsychologist

**Abstract:** Awareness of mild traumatic brain injury (mTBI) and persisting post-concussive syndrome (PCS) has increased substantially in the past few decades, with a corresponding increase in research on diagnosis, management, and treatment of patients with mTBI. The purpose of this article is to provide a narrative review of the current literature on behavioral assessment and management of patients presenting with mTBI/PCS, and to detail the potential role of neuropsychologists and rehabilitation psychologists in interdisciplinary care for this population during the acute, subacute, and chronic phases of recovery.

**Keywords:** mTBI; concussion; PCS; neuropsychology; cognitive rehabilitation

## 1. Introduction

In 2013, an estimated 2.5 million traumatic brain injury-related emergency department (ED) visits occurred in the United States [1]. Although estimates across analyses vary, it is generally thought that 75%–90% of these injuries would be classified as mild [2,3]. These percentages likely underestimate the total number of mild traumatic brain injuries (mTBI) since patients do not always present to the ED following a mTBI, with some patients following up with general practitioners and others not seeking any medical care [2,4]. As a result, a high percentage of mTBIs in the United States and worldwide may go underdiagnosed or unidentified. The purpose of this article is to detail the role of neuropsychologists and rehabilitation psychologists in the interdisciplinary care of patients with a history of mTBI. Our review focuses primarily on civilian adults who have sustained a mTBI, since the additional factors associated with assessment and treatment of children, adolescents, veterans, and/or athletes is beyond our intended scope. Despite this population focus, much of the information covered is likely generalizable across the mTBI population at large. In this review, we aim to provide education on neuropsychological evaluation and treatment of this often underdiagnosed and underserved population.

## 2. Defining Mild Traumatic Brain Injury

Adding to the complication of the likely underdiagnosis of mTBI is the lack of an interdisciplinary consensus regarding what constitutes a mTBI [4–6]. The American Congress of Rehabilitation Medicine (ACRM) was the first to establish diagnostic criteria of mTBI as involving “a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: i) any period of loss of consciousness; ii) any loss of memory for events immediately before or after the accident; iii) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and iv) focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: loss of consciousness of approximately 30 min or less; after 30 min an initial Glasgow Coma Scale (GCS) of 13–15; and posttraumatic amnesia (PTA) not greater

than 24 h" [7] (p. 86). In their report to Congress, the US Centers for Disease Control and Prevention (CDC) posited a comparable, though less specific conceptual definition of mTBI as "any period of observed or self-reported: transient confusion, disorientation, or impaired consciousness; dysfunction of memory around the time of injury; loss of consciousness lasting less than 30 min" as well as "observed signs of neurological or neuropsychological dysfunction" [2] (p. 2). More recently, the World Health Organization (WHO) task force on Mild Traumatic Brain Injury put forth a definition based on a review of the literature that varied from the ACRM diagnosis by simplifying the classification of altered mental status to "confusion or disorientation" and changing the "focal neurological deficit(s)" criteria of the ACRM definition to: "Other transient neurological abnormalities, such as focal signs, seizure, and intracranial lesion, which are not requiring surgery." In addition, the WHO definition allows for the GCS score of 13–15 to be assessed after the typical 30-min timeframe, which accounts for a possible delay in assessment by a qualified healthcare provider [8] (p. 115). The lack of consensus in terminology complicates matters further, with the research literature using terms like concussion, mild head trauma, and mild head injury interchangeably. For clarity, this review will use the term mTBI exclusively.

### 3. Acute Identification and Evaluation of Mild Traumatic Brain Injury

In addition to the lack of a standard definition of mTBI, there is much variability in acute medical management of this common condition. In their evaluation of 41 guidelines related to mTBI, Peloso and colleagues [9] only categorized three as being evidence-based and reported that "in the absence of clear evidence, experts frequently disagree" [9] (p. 111). Blostein and Jones [10] surveyed 35 level I trauma centers in the United States regarding their evaluation and discharge of patients with suspected mTBI. They found that less than half of the centers had a standardized protocol in place for evaluating all patients with suspected mTBI. Foks and colleagues [11] found a similar lack of consistency in mTBI evaluation and management when they surveyed 71 neurotrauma centers in Europe and Israel. Powell and colleagues [12] found that over half of the 197 patients identified as having a mTBI by study personnel were not documented with that diagnosis by medical personnel in the ED. Within the Veteran population, Pogoda and colleagues [13] showed that clinical judgment differed from ACRM-based criteria for mTBI history in 24% of the cases seen for a comprehensive TBI evaluation, with the majority of these disagreements indicating that clinician judgment on mTBI diagnosis was inconsistent with ACRM-based criteria (Clinician N/ACRM Y). This outcome of Clinician N/ACRM Y reportedly occurred more often when veterans reported higher affective symptoms accompanied by lower reported cognitive and physical symptoms. The lack of consistent guidelines regarding acute ED evaluation and management of patients suspected as having sustained a mTBI likely contributes to the estimates that "50%–90% of patients with mTBI often go unidentified or undiagnosed in the hospital ED" [14] (p. 272). Patients who go undiagnosed may be at a higher risk for a "complicated recovery" [12] (p. 1554) because they are not provided with psychoeducation regarding possible consequences of mTBI and the expected recovery trajectory [12].

Even in the instance of a positive diagnosis of mTBI in the ED, many researchers have shown a lack of standardized guidelines regarding when to hospitalize, when to discharge home from the ED, and when to make a referral for outpatient follow-up [11]. Patients who are discharged directly from the ED are often expected to have a better recovery than patients who require hospitalization after mTBI; however, research reported by de Koning and colleagues [15,16] indicates that one in five patients who were directly discharged from one of three level-I trauma centers after mTBI had unfavorable outcomes at six months. Further, only a quarter of these patients followed up with an outpatient neurologist within the first six months of injury due to persisting symptoms. These unfavorable results may be due, in part, to the lack of clear guidelines regarding outpatient follow-up after direct discharge from the ED. Similarly, Foks and colleagues found that the majority of patients with a history of mTBI in Europe do not receive routine follow-up care [11]. Contributing to these concerns is the finding that many discharge instructions failed to address the possibility that patients may develop persisting post-concussive symptoms [4]. Overall, these findings suggest a need to

develop more clear guidelines regarding discharge instructions and psychoeducation for all patients diagnosed with a mTBI, regardless of whether or not they required hospitalization. Further, additional research is needed to provide more clarification as to when and for whom follow-up care is appropriate.

#### **4. Mild Traumatic Brain Injury Symptoms**

As discussed above, there is a dearth of information provided to patients with mTBI discharged from the ED regarding symptom expectations. During the acute and subacute phases of recovery from a mTBI, patients generally report symptoms that fall into one of three symptom clusters: somatic (e.g., physical and/or sensory), cognitive, and affective (e.g., emotional). Commonly reported somatic symptoms include headache, sleep disruptions, dizziness, nausea, visual disturbance, photophobia, and phonophobia. Common cognitive symptoms include problems with attention and memory, slow processing speed, difficulty multitasking, increased distractibility, losing one's train of thought, and feeling foggy. Affective symptoms often reported by patients with mTBI include increased irritability, emotional lability, anxiety, and depression [17,18]. Fatigue is a frequent complaint after mTBI. Research regarding fatigue suggests that it is a multidimensional symptom, with many factors contributing to and exacerbating fatigue, including somatic symptoms, sleep disturbance, cognitive exertion, chronic situational stress, and mental health [19–22].

Similar to the cycle of symptom exacerbation observed in fatigue, many somatic, cognitive, and affective symptoms following mTBI interact with and exacerbate each other. Kay and colleagues [23] described a dysfunctional feedback loop that may result in the maintenance of numerous symptoms even after medical signs resolve. For example, when cognitive difficulties during the early phase of recovery co-occur with pain symptoms or emotional factors, a feedback loop may develop whereby the pain and emotional factors start to elicit secondary cognitive complaints. Over time, the interaction between these symptoms strengthens to the point that persisting pain and emotional factors will continue to elicit subjective cognitive complaints even after the primary cognitive complaints have resolved. Other researchers have identified the associations between mTBI symptoms as well. Wood and colleagues [24] found that patients with mTBI history who scored higher on measures of anxiety sensitivity and/or alexithymia tended to score higher on the Rivermead post-concussion symptom questionnaire at two weeks post injury than patients scoring lower on these measures. In a different study, cogniphobia, defined as "fearful avoidance of a specific headache trigger, mental exertion" [25] (p. 1), was found to be associated with worse memory test performance in a group of patients with mTBI history who reported more severe post-traumatic headaches [25]. The development of these dysfunctional feedback loops "may serve to maintain a variety of symptoms beyond the resolution of the original organic deficit" [26] (p. 552).

#### **5. The Controversy regarding Persisting Post-Concussive Symptoms**

While the majority of patients with mTBI history are asymptomatic within a couple of weeks post-injury, a small minority (10%–20%) of patients continue to report detrimental symptoms for months and even years post-injury [5]. This group of patients with unfavorable outcomes following mTBI is sometimes termed the "miserable minority" [26] (p. 551), and the condition is termed post-concussive syndrome (PCS). The outcomes of this patient group have generated much controversy, with the emergence of two polar opinions among professionals as to whether these persisting symptoms are the result of neurogenic factors (e.g., neurological residuals of the original mTBI) or psychogenic factors (e.g., pre-morbid psychopathology or personality characteristics) [5,27,28]. Others take the more balanced perspective that these two opinions are "complimentary and capable of being integrated" [27] (p. 1120).

The controversy regarding this patient group has resulted in many researchers attempting to determine the etiology of their symptoms. Numerous studies have reported that patients with a premorbid psychopathology history are more likely to report post-concussion symptoms beyond one month post-injury [17,29,30]; however, the same researchers have shown that premorbid psychopathology no longer predicts post-concussion symptoms at the one year mark [29] and others

have shown no association between premorbid psychopathology and post-concussion symptom reporting [31]. Premorbid personality traits, including perfectionism, grandiosity, individuals with unmet dependency needs, and borderline traits, have been identified as possible risk factors for development of PCS after mTBI [23,26]. Patients who present to the ED with moderate to severe somatic complaints (e.g., headache, light sensitivity, blurred vision) tend to have less favorable outcomes at 12 months post-injury [32]. Similarly, patients who are highly symptomatic at one month often continue to be highly symptomatic at one year [29]. Injury characteristics like mTBI severity and extra-cranial bodily injuries predict future PCS symptom development [14,29]. Biological factors that have been identified in prolonging mTBI recovery include genetics, older age, female sex, prior mTBI history, and poorer physical health, to name a few [14,29,30,32,33]. Various psychosocial factors thought to contribute to poorer outcome post-injury include: disability or unemployment at time of injury, marital status, education level, occupational skill level, cognitive reserve, financial and recreation setbacks secondary to injury, involvement in litigation, substance abuse, and other life stressors [29,30,32,33].

Uomoto and Fann [34] found that symptomatic patients with mTBI history tended to overestimate their injury severity level and their residual cognitive impairment when compared with patients who had sustained a moderate or severe TBI. In addition, the patients with mTBI history tended to “view their injury as having a more global impact across important areas of their life” [34] (p. 336). Iverson and colleagues [35] evaluated the so-called “good old days” bias (p. 17) with regard to patients with a history of mTBI and found that, in comparison to healthy adults, these patients report fewer, less severe premorbid symptoms. Furthermore, they found that patients who failed performance validity testing (TOMM) reported fewer premorbid symptoms and more debilitating post-concussion symptoms than patients with mTBI history who passed validity testing [35].

The literature presents different viewpoints on neurogenic versus psychogenic causes of PCS, and to date the reasons for symptom persistence after mTBI are not fully understood. However, many psychologists engage in patient-centered care, and therefore are able to evaluate, target, and treat the individual needs of each patient experiencing PCS, regardless of symptom etiology. In the sections that follow, the authors will provide a brief review of the evaluation and intervention methods available for patients with mTBI history within the field of neuropsychology, rehabilitation psychology, and cognitive rehabilitation.

## 6. Neuropsychological Evaluation Following Mild Traumatic Brain Injury

The purpose of a neuropsychological evaluation is to assess the cognitive and functional deficits resulting from a neurological disorder or injury. As part of a comprehensive evaluation, the neuropsychologist conducts a thorough clinical interview that reviews the presenting condition and associated symptoms as well as premorbid patient characteristics and psychosocial history factors that may be contributing to the clinical presentation. Information from individuals who know the patient well is often pursued to gain additional insight regarding the patients’ pre- and post-morbid behaviors. The information gathered from these clinical interviews is integrated with the results of cognitive testing and self-report measures to construct a holistic view of the etiology of the patient’s present complaints. Perhaps the most important phase of the neuropsychological evaluation is when the patient, the patient’s family, and the referring provider are given feedback and psychoeducation regarding the evaluation findings and provided with recommendations for treatment.

This detailed, holistic approach to evaluating the patient is especially helpful when it comes to working with patients recovering from a mTBI since, as discussed above in Section 5, there are many confounding factors that are likely contributing to and exacerbating the symptomatic presentation. If a neuropsychological evaluation is conducted shortly after a mTBI, the treatment team can be informed of any factors that may prolong the patient’s recovery and develop interventions to help mitigate these factors. In addition, earlier evaluation ensures that the patient receives psychoeducation regarding mTBI and the expected recovery trajectory, the importance of which is discussed in more detail below in Section 7.1.

### 6.1. Cognitive Dysfunction after a Mild Traumatic Brain Injury

After a mTBI, cognitive dysfunction is often seen in the domains of attention, processing speed, executive functions, and/or memory, although there is differential recovery across these domains over time [23,27]. The observed deficits can be relatively subtle and are influenced by numerous factors, including injury severity, time since injury, and the specific neuropsychological measures used [36]. With regard to the influence of time since injury, Karr and colleagues conducted a systematic review of meta-analyses and found that multiple studies report a return to cognitive baseline by 90 days post-injury [37]; however, some patients who have developed a more chronic PCS continue to show neuropsychological impairments on testing [25,33]. There is also great variability across neuropsychological tests with regard to their ability to capture cognitive deficits secondary to mTBI [37].

### 6.2. Neuropsychological Evaluation of Mild Traumatic Brain Injury

As discussed above a comprehensive neuropsychological evaluation consists of a clinical interview of the patient and collaterals, when available; a thorough test battery that capture all cognitive domains; and self-report measures to evaluate the patient’s mood and current symptoms. With regard to an evaluation of a patient with a mTBI, thorough assessment of attention, processing speed, executive functions, and memory is necessary to capture any current cognitive deficits. Mood measures should assess for symptoms of depression, anxiety, irritability, and emotional lability. Finally, inclusion of a self-report measure that captures symptoms that are common after a mTBI is recommended since the patient may have trouble relaying all of their symptoms during the clinical interview. These measures also provide the patient with a method for ranking the severity of the symptoms at the time of the evaluation. When interpreting cognitive test performance, the neuropsychologist looks for patterns of deficits across the tests, since one test score indicative of impairment does not necessarily translate into diagnosis of a cognitive deficit. Consideration is also given to the “sterile,” distraction-free testing environment, which may mitigate the “real-world” impact of cognitive dysfunction following mTBI that the patient experiences in his or her daily life [38]. Table 1 details a sample mTBI battery used by one of the authors (C.P.) in her evaluations of patients with mTBI history; however, this battery is only given as an example of a comprehensive neuropsychological evaluation. Providers are encouraged to develop batteries based upon the individual needs of their patients as well as the referral question.

**Table 1.** Sample mTBI Neuropsychological Evaluation Test Battery.

Functional Domain	Neuropsychological Tests
Pre-Morbid Estimate	Test of Premorbid Functioning (TOPF)
Performance Validity	Reliable Digit Span California Verbal Learning Test-Second Ed. (CVLT-II): Forced Choice
Motor	Grooved Pegboard
Attention/Working Memory	Wechsler Adult Intelligence Scale- Fourth Ed. (WAIS-IV): Digit Span, Arithmetic Neuropsychological Assessment Battery (NAB): Orientation, Numbers & Letters Continuous Performance Test of Attention Paced Auditory Serial Addition Test (PASAT)
Processing Speed	Trail Making Test A WAIS-IV: Symbol Search, Coding Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference: Color Naming, Word Reading
Language	WAIS-IV: Similarities, Vocabulary, Information Animal Naming Boston Naming Test Complex Ideation
Visuospatial	WAIS-IV: Block Design, Matrix Reasoning NAB: Visual Discrimination Rey Complex Figure Test (RCFT): Copy

**Table 1. Cont.**

Functional Domain	Neuropsychological Tests
Memory	CVLT-II NAB: Story Learning, Shape Learning RCFT
Executive Functions	Trail Making Test B Controlled Oral Word Association Test (COWA-FAS) DKEFS Verbal Fluency: Category Switching DKEFS Color-Word Interference: Inhibition, Inhibition/Switching Tower of London-Second Ed. Wisconsin Card Sorting Test-64 Card Version
Mood Self-Report	Beck Depression Inventory-Second Ed. (BDI-II) Beck Anxiety Inventory (BAI) Patient Health Questionnaire: Somatic Symptom Scale
Neurobehavioral Symptom Self-Report	Neurobehavioral Symptom Inventory

## 7. Neuropsychological Intervention Following Mild Traumatic Brain Injury

While several decades of research have established an increasingly clear picture of typical mTBI symptoms and the complexity of persisting PCS, research on effective interventions for this population has yielded mixed results, and therefore has not yet supported professional consensus on mTBI treatment. Despite the relative dearth of well-controlled prospective research studies in this population, the existing literature does provide preliminary support for a number of behavioral interventions for management and amelioration of symptoms following mTBI. Given the complexity and variability of presenting problems after mTBI as detailed above, treatment must account for multiple factors including cognitive, emotional, and somatic symptoms. Neuropsychologists and rehabilitation psychologists are uniquely suited to manage care for these concerns holistically, given our expertise on psychological and cognitive functioning, as well as an established presence in Neurology and Rehabilitation departments. The following section provides an overview of neuropsychological interventions for individuals who have sustained a mTBI.

### 7.1. Early Intervention in the Acute Phase Following Mild Traumatic Brain Injury

Most individuals who sustain a mTBI spontaneously recover fully within the first few weeks or months, but a significant minority continue to experience persistent symptoms for months or years following injury [39,40]. A small but significant body of research has addressed the question of whether psychoeducational and supportive interventions in the acute phase after mTBI can prevent progression to persistent PCS. These interventions are based on the theory that persistent PCS is associated with attribution of symptoms to the mTBI and negative expectations about recovery [41]. Such interventions typically involve education on post-concussive symptoms, reassurance and education on the expectation for complete recovery, and guidance regarding rest and gradual resumption of typical activities. Psychoeducational early interventions have the strongest empirical support of any post-mTBI interventions, with several systematic reviews concluding they are well supported [42–44]. One recent systematic review with stringent methodological exclusion criteria [45] found that only two studies in the entire corpus of research on mTBI treatment met its standards; one supporting telephone-based early educational intervention [46], and one supporting recommendations for bed rest in the acute recovery phase [47].

Acute care for mTBI is typically provided by medical professionals, including ED staff and primary care physicians [48,49]. Individuals are often not referred for consultation with a neuropsychologist until their symptoms persist beyond the typical period of spontaneous recovery. However, it is our opinion that the literature on early intervention after mTBI supports earlier consultation with psychology or neuropsychology, particularly for individuals at highest risk for developing persistent PCS. Psychological distress and psychosocial stressors are associated with greater likelihood of

progression to persistent PCS [23–26], and neuropsychologists and rehabilitation psychologists are well equipped to provide early educational interventions that address the interplay of cognitive, emotional, and somatic symptoms. Psychologists also can provide psychotherapeutic intervention when appropriate, including validation of the individual’s experience and instillation of hope. When a neuropsychological evaluation is feasible, neuropsychologists can tailor preventative education to the individual’s neuropsychological profile. In short, early consultation with Neuropsychology may be beneficial to more comprehensively address the needs of the subset of patients who are most at risk for persisting PCS. Current research supports early psychoeducational and supportive services after mTBI [42–44]; we would argue for broad application of such services, as these interventions are brief, relatively low cost, and may prevent progression to PCS, hence decreasing the individual burden of disability as well as the societal burden of more resource-intensive services.

### *7.2. Neuropsychological Treatments for Persisting Post-Concussive Symptoms*

A relatively smaller amount of research has examined interventions for the significant minority of individuals who continue to experience post-concussive symptoms for months or years. Awareness of PCS has increased in recent decades, due in part to high frequency of mTBI in the conflicts in Iraq and Afghanistan, as well as well-publicized cases involving athletes. The research literature on specific treatments for PCS is limited, and systematic reviews have consistently concluded that the existing literature is limited by methodological inconsistency [43–45]; however, clinicians can also refer to the much larger literature on treatment of specific symptoms common to PCS, such as cognitive rehabilitation for attention deficits, or cognitive behavioral therapy for symptoms of depression and anxiety. Thorough discussion of specific interventions is beyond the scope of this review, but we strive to provide a brief overview of the types of treatments for PCS that may be provided by neuropsychologists and rehabilitation psychologists.

**Cognitive Rehabilitation:** Cognitive rehabilitation comprises an eclectic set of therapeutic approaches that are tailored to the individual’s neuropsychological profile and functional goals [50]. The first step in treatment planning is a thorough neuropsychological assessment. Based on this assessment, the clinician may draw from a number of therapeutic approaches, incorporating not only strictly cognitive interventions but also emotional, behavioral and social interventions as needed. Broadly, cognitive rehabilitation interventions can be categorized as “bottom-up” interventions, which build or restore basic skills using rote practice, or “top-down” interventions, which use metacognitive skills, or “thinking about thinking,” to promote effective self-management of cognitive difficulties. Top-down approaches can be further subdivided into internal strategies, such as self-monitoring and self-regulation, and external strategies, such as reminders and organizational systems. In clinical practice, treatment typically involves a combination of these approaches. The following paragraphs provide a brief overview of cognitive rehabilitation interventions relevant to mTBI and PCS. Clinicians are advised to refer to the ACRM Cognitive Rehabilitation Manual [51] for more comprehensive guidelines on the interventions outlined here.

Individuals with persistent PCS often present with cognitive deficits in attention regulation, executive functions, and memory [20]. Systematic reviews of cognitive rehabilitation in PCS have reached varying conclusions, and no true meta-analyses have been possible to date due to substantial variability in interventions, outcome measures, and study designs. The most recent systematic review at the of time of this writing reviewed interventions for mTBI in military/veteran populations and found good support for the efficacy of cognitive rehabilitation [43]; similarly, a 2009 consensus conference on services for military service personnel and veterans with mTBI history strongly endorsed cognitive rehabilitation interventions [52]. The civilian literature on mTBI remains limited, and most systematic reviews have not resulted in firm support for cognitive rehabilitation interventions in treatment of cognitive symptoms in mTBI/PCS [44,53]. However, there exists a substantial literature on cognitive rehabilitation interventions for attention, executive functions, and memory, which can be assumed to be applicable to individuals with PCS, according to their neuropsychological profile.

Deficits in attention regulation (e.g., working memory, multi-tasking, distractibility) are among the most common features of PCS. Based on systematic reviews of the cognitive rehabilitation literature, Cicerone and colleagues [54] recommend cognitive remediation of attention deficits after TBI as a “practice standard”. Specifically, “remediation of attention deficits after TBI should include direct attention training and metacognitive training to promote development of compensatory strategies and foster generalization to real world tasks” [54] (p. 521). Computer-based interventions are classified as a “practice option” in conjunction with therapist-guided treatment to promote functional application of skills. Evidence-based treatments for remediation of attention include Attention Process Training [55], n-back working memory remediation [56], and Time Pressure Management [57]. These interventions should be implemented with explicit focus on the development of proactive compensatory strategies to manage attentional resources.

Remediation of executive functions may have especially far-reaching effects, as executive skills (e.g., planning, prioritizing, problem-solving) are applicable across rehabilitation disciplines and to all aspects of daily living. The Cicerone et al. reviews [54,58] recommend metacognitive strategy training, including self-monitoring and self-regulation skills, as a practice standard; this approach may be applied to self-regulation of cognition, emotion, and behavior, and is useful as a component of other rehabilitation interventions. Training in problem-solving strategies is a “practice guideline” for executive dysfunction after TBI, and group-based interventions are a “practice option”. Most structured treatments for executive functions follow a four-step sequence: building awareness; anticipation of difficulties and planning accordingly; task execution and self-monitoring; and self-evaluation following the task [51]. Structured interventions include goal management training [59], problem-solving training [60], and the Cognitive Orientation to Occupational Performance (Co-Op) [61]. The specific elements within each of these steps vary, but the process of anticipation, execution, and evaluation is common across interventions.

Difficulties with memory are among the most common subjectively reported cognitive problems. In individuals with mTBI, memory difficulties often represent a “downstream” effect of attentional and/or executive deficits impacting the acquisition and retrieval of memories, rather than a true memory encoding or retention deficit. Therefore, memory may be positively impacted by attentional and executive training. For further specific rehabilitation of memory, the Cicerone et al. reviews [54,57] recommend memory strategy training as a practice standard for mild memory impairments after TBI, including both internal and external strategies. Internal, or metacognitive, memory strategies include association techniques such as visualization or “peg” methods associating new material with well-known information, and organizational techniques such as acronym/rhyming mnemonics or contextualization/chunking of information [62]. External strategies include memory notebooks, strategically placed external cues/reminders, as well as ever-evolving use of smartphones and other technological aids.

It is important to note that attention, executive functions, and memory are mutually interdependent processes [50,58], and many interventions explicitly target several cognitive domains simultaneously. Combined attentional-executive interventions typically consist of metacognitive strategy training grounded in the patient’s functional goals, and may also incorporate direct skill training, though isolated use of rote skill training without metacognitive skills is not recommended [58]. Integrated treatment of executive skills and attention regulation has been shown to improve functional outcomes [63,64] as well as modulate prefrontal cortical activity as observed through fMRI [65].

Psychotherapy: Individuals with PCS typically present with emotional dysregulation, and often meet diagnostic criteria for clinical psychological disorders including depression, anxiety, post-traumatic stress, and substance use disorders [40]. Neuropsychological assessment should include screening measures for mental health conditions at a minimum, and may include more comprehensive psychological assessment if necessary. In some cases, psychological treatment may be necessary either as a prerequisite to, or concurrent with, other interventions, since individuals in acute psychological

distress may have difficulty participating actively in other rehabilitation interventions, and emotional distress may exacerbate other cognitive and somatic symptoms.

One systematic review on behavioral health interventions post-mTBI [66] examined four categories of psychological interventions: cognitive-behavioral therapy (CBT) for PCS; educational interventions; cognitive rehabilitation interventions with a psychotherapeutic element; and mindfulness/relaxation training programs. They found adequate support for CBT, and concluded that the literature on integrated rehabilitation/psychotherapeutic programs and mindfulness/relaxation was too limited at that time to make recommendations. In a recent review of post-concussive treatment among veterans and military service personnel, several studies were identified that showed promising early results for the feasibility of psychotherapeutic interventions in individuals with mTBI, though recommendations were limited by small sample sizes and lack of control groups [51]. Some individuals may experience decrements in perceived quality of life and life satisfaction after mTBI [67], indicating a need for psychotherapeutic support for coping and adjustment.

**Integrated Treatment Options:** An increasing number of brain injury treatment programs are structured to integrate psychoeducation, cognitive rehabilitation, and psychotherapy, “operating from an assumption of comorbidity” [43]. From a neuropsychological perspective, this approach makes logical sense, as changes in the brain have broad impacts across cognitive, emotional, social and behavioral functioning. Particularly, deficits in executive functions have broad impacts upon the awareness, monitoring, and regulation of thoughts, feelings, and behaviors. Accordingly, integrative treatment programs apply the core concepts of metacognition and self-regulation to all aspects of rehabilitation. The most recent systematic review of cognitive rehabilitation by Cicerone and colleagues identifies “comprehensive-holistic neuropsychological rehabilitation” as a distinct category of post-TBI intervention, and it is recommended as a practice standard for individuals with moderate to severe TBI [54]. Research on comprehensive-holistic interventions with mTBI is limited, but a few studies have shown promising outcomes [63,68,69].

Beyond comprehensive neuropsychological intervention, care for individuals with persistent PCS often involves interdisciplinary collaboration across specialties. In a rehabilitation setting, this may include: physical therapists, who may address vestibular/balance dysfunction and neck/back problems; occupational therapists, who treat vision problems, upper extremity coordination, and provide compensatory strategies for activities of daily living; and speech therapists, who often address attentional and executive aspects of communication such as complex comprehension and verbal organization. Depending on the patient’s functional needs, the treatment team may also include vocational, educational, or recreational specialists. Some patients may also benefit from additional alternative medicine or complementary therapies such as acupuncture [70] or meditation [71]. The treatment team should be assembled to address the patient’s individualized needs while integrating care for cognitive, emotional, and somatic concerns.

### *7.3. Tracking Progress and Outcomes*

Measuring progress and outcomes from neuropsychological rehabilitation for mTBI, whether for clinical or research purposes, is challenging given the variability of baseline symptoms, the subjectivity of many common presenting problems, and the lack of a reliable relationship between objective measures (e.g., neuropsychological tests, neuroimaging), and subjective sense of progress or success. The fundamental goal of any rehabilitation intervention is to improve independence and quality of life, but there is not yet consensus in the field on how best to measure these subjective variables.

Regarding objective and standardized measures, formal neuropsychological re-evaluation can be especially helpful in the earlier stages of recovery, or after provision of direct cognitive remediation interventions, in order to track recovery and/or treatment efficacy. This can involve a full formal re-evaluation, or selective periodic re-administration of tests that are sensitive to change over time. Self-report instruments can provide a structured and normed measure of subjective symptoms, and repeat administration of self-report measures (or specific relevant items) can help to track the

impact of the treatment on subjective concerns. Some research studies use generalized functional variables such as return-to-work as objective measures of real-world outcomes.

In clinical practice, the most meaningful gains are not necessarily captured well by neuropsychological tests or by broad variables such as return-to-work. Therefore, it is often both practical and therapeutic to identify client-centered treatment goals, which then serve both as a mechanism of change and as a way to measure progress. The process of setting realistic goals and benchmarks for progress can in itself be therapeutic, as it sets realistic expectations and promotes a sense of self-efficacy. One approach to setting clear, achievable personalized goals is Goal Attainment Scaling (GAS) [72], which can be incorporated into executive interventions such as goal management training [73]. Goal setting is a collaborative process, and must involve both client selection of relevant goals and therapist assistance in clarifying and defining realistic and measurable goals [74]. Attainment of goals defined at the onset of treatment, or lack of progress towards those goals, can provide a collaborative basis upon which to terminate or extend treatment. Clear documentation of goals and outcomes also serves to monitor treatment efficacy and contributes to the growing evidence base behind neuropsychological rehabilitation.

## 8. Conclusions

Proper identification and treatment of mTBI and post-concussive syndrome is challenging due to lack of consensus in the health care system regarding mTBI diagnosis and management, complexity of symptom presentations and comorbidities, heterogeneity with regard to symptom development and spontaneous recovery, and the dearth of prospective, controlled studies examining services for PCS. However, the existing literature does provide growing support for the efficacy of neuropsychological evaluations and interventions across stages of recovery from mTBI, from early preventative interventions to compensatory strategy training in the chronic phase. In order to provide comprehensive and patient-centered care, neuropsychologists and rehabilitation psychologists can be a valuable addition to the interdisciplinary teams caring for patients with a history of mTBI.

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