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PERSPECTIVE

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The latest and greatest in TBI treatments

By Molly M. McKibben

Traumatic brain injury (TBI) is a major public health issue with serious social and economic effects worldwide. Some studies have estimated that 1.5 million people in the United States sustain traumatic brain injuries each year. Anyone can experience a traumatic brain injury, and some groups are at greater risk from suffering long-term consequences or even death after injury. Despite the fact that the vast majority of TBI are classified as mild, in developed countries, TBI ranks highest amongst medical conditions in terms of its economic, medical, and social damage to society.

Yet despite its seriousness, TBI was under-researched and understudied for many years. Thanks largely to the rising awareness of TBI's effects on professional athletes as well as the Department of Defense's recognition of the high occurrence of TBI amongst service members, research teams, organizations, and institutions have accelerated their interest in understanding the biological mechanisms underlying the injury and developing new treatment strategies over the last decade.

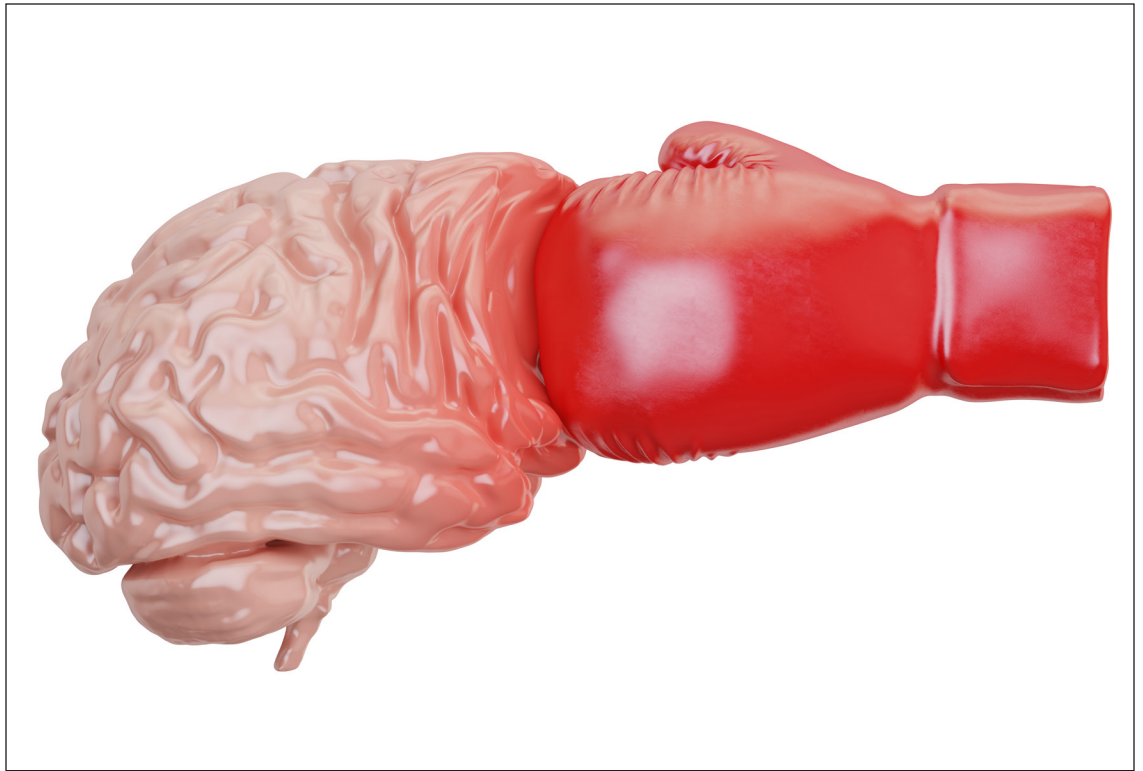
The brain has limited intrinsic healing capacities after an injury. A traumatic brain injury has two parts - a primary injury and secondary injury. The primary injury occurs with the immediate result of energy dissipation within the substance of the brain after the initial insult. The secondary in-

jury is the result of the reactive biochemical events that occur in the brain after the primary injury. The secondary injuries can progress into prolonged secondary damages which can last as little as a few hours and as long as a lifetime. Because primary injuries involve acute structural damages and brain cell death that generally can't be reversed, TBI treatment research has focused mainly on minimizing secondary injuries and their consequences.

The vastness and unique characteristics of the brain make it diffi-

cult to develop treatments that are helpful to large groups of patients. The human brain has 86 billion neurons that form 100 trillion connections to each other. Given that secondary injuries involve a cascade of events that can affect multiple brain regions, it's hard to develop treatments that target just the damaged areas and don't affect the healthy portions. The treatment options that are prescribed to patients haven't changed dramatically in recent years. The mainstay of any treatment plan for a TBI sufferer is time at a comprehensive integrated

inpatient brain injury rehabilitation program. A good program should have a multi-disciplinary approach and include things like cognitive rehabilitation therapy, speech and language therapy, physical therapy, occupational therapy, vocational rehabilitation services, neuropsychological and psychiatric treatment, and, depending on the person's symptoms, treatment with a neuro-ophthalmologist or neuro-optometrist. After time in an inpatient program, a TBI patient should then transition to living at home with family who can support them and



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continue care in an outpatient/day program, or have in-home or community-based services on a regular basis.

Medication is a treatment option that is rapidly evolving for TBI patients. New research on blood biomarkers (molecules that indicate the state of someone's health) is aiding researchers in identifying which medications will be most effective for a specific person based on which of the secondary injuries (excitotoxicity, inflammation, etc.) their brain is undergoing. While they are not able to reverse the loss of neural function on their own, the majority of drugs that exist to treat TBI have neuroprotective qualities. Thus, they can help reduce inflammation, axonal damage, and mitochondrial dysfunction. However, many medications show promising effects in preclinical studies and Phase I and II trials but fail to be successful in Phase III trials. In fact, more than 30 clinical trials of TBI pharmaceutical agents have failed over the past three decades.

Supplements have been shown to have beneficial outcomes when administered to patients who have sustained mild traumatic brain in-

juries. For instance, lipoic acid is an antioxidant that has been shown to decrease neuronal cell death when administered after a TBI; vitamin D combined with progesterone has been shown to reduce markers of inflammation in the brain and neuronal cell death; persons who were given vitamin E after a TBI had improved cognition and reduced oxidative stress; and patients who took zinc showed a reduction in oxidative stress and inflammation, and a reduction in depression and anxiety.

Alternative therapies like acupuncture and acupressure are recommended by some practitioners and have been found to have some therapeutic benefit (improved motor and speech functions), but the randomized, controlled studies that actually reviewed their efficacy were found to have a high risk of bias. Hyperbaric oxygen therapy, which involves 100% oxygen administration to the patient, has also been approved clinically for TBI treatment. While it has been shown to diminish inflammation and improve neovascularization, the Department of Defense funded studies to consider its efficacy and found no effectiveness.

The two most promising emerging treatments for TBI are neuromodulation and cellular therapy. Neuromodulation involves the external alteration of nerve activity in the brain through delivery of a distinct stimulus such as a magnetic field or electric current. Three kinds of neuromodulation have shown to be effective and safe: transcranial magnetic stimulation (TMS), peripheral nerve stimulation (PNS), and vagus nerve stimulation (VNS); however, more research needs to be done on these treatments since limited rigorous studies have been performed out of concerns for patients having seizures.

Cellular therapy involves using stem cells to repair, replace, or regenerate damaged tissues in the brain. The stem cells play two important roles in TBI treatment: (1) modulating inflammation, and (2) regeneration. Eleven studies of cellular therapy as a treatment for TBI over the last 10 years have found that it is safe and leads to neurological improvement in TBI patients. More research needs to be done to determine the appropriate dosage, timing of implantation, and method/location of implantation.

Scientists and doctors are still figuring out what happens in the brain during trauma. This state of continuing education and the focus on treating just the parts of the person's brain affected by trauma means that research into the most effective treatment for TBI is a constant work in progress. Options exist for patients, and hopefully with more time and more funding for clinical studies, more targeted treatments will become available soon.

Molly McKibben is a partner at *Greene, Broillet & Wheller LLP*.

