Understanding Traumatic Brain Injury

& the Role of Polychromatic Light Therapy

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Epidemiology of Traumatic Brain Injury (TBI)

In 2003, the Center for Disease Control and Prevention (CDC) issued a report to the United States Congress proclaiming there exists a "silent epidemic" in America: traumatic brain injury (TBI).[1] Shortly following that report an increased awareness of head injuries in sports developed, particularly football. TBI was eventually declared the "signature injury" of the Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) offensive in the Middle East.

The official estimate of the incidence of traumatic brain injuries in the United States is approximately 1.7 million documented cases per year. This number refers only to those who sought medical attention, so some authors speculate the actual number is likely much higher.[2] It is probable, according to other published reports, an equal number of TBIs occur yearly and do NOT seek medical attention. That would translate to estimates ranging up to 3.8 million new TBI cases per year.[3] Of the documented TBI cases, approximately 80% fall into the mild category and the other 20% into the moderate to severe category.[4] Given that non-documented cases by definition consist of non-life threatening and/or less severe head injuries, it is probable that mild traumatic brain injuries constitute closer to 90% of all TBIs sustained each year in the United States.

What is a Mild Traumatic Brain Injury?

There are those who say no brain injury should be considered "mild." This is because as many as 10-15% of people with "mild" TBIs have been shown to go on to develop permanent brain damage.[5]

The following definition of mild traumatic brain injury (mTBI) comes from the American Congress of Rehabilitation Medicine[6] and the World Health Organization[7]:

"An occurrence of an injury to the head resulting from blunt trauma or acceleration or deceleration forces with one or more of the following conditions attributable to the head injury during the surveillance.

1. Any period of observed or self-reported transient confusion, disorientation or impaired consciousness under 30 minutes.

2. Any period of observed or self-reported dysfunction of memory (amnesia) around the time of injury lasting less than 24 hours.

3. Observed signs of other neurological or neuropsychological dysfunction such as:
    a. Seizure activity following head injury.
    b. In infants and young children, irritability, lethargy or vomiting following head injury, or

c. Symptoms among older children and adults such as headache, dizziness, irritability, fatigue or poor concentration when identified soon after injury."

There are two very important points to take away from the above criteria:

1. Loss of consciousness (LOC) is not required in order to sustain a mTBI, rather, simply a brief alteration in the state of consciousness and/or memory issues.

"Getting your bell rung" is a common aphorism used in sports to minimize the seriousness of a mild TBI. In rear-end collisions resulting in whiplash injury to the neck, with no external blow to the head, patients often report having been "dazed and confused."

2. It is not necessary to hit your head in order to sustain a brain injury.

How does that happen? In the example of a rear-end automobile collision in which whiplash occurs, the brain is thrust forward and backward within the skull generating acceleration/deceleration forces. This can cause either a coup/contrecoup injury of the brain banging against the inside of the skull or shear forces resulting in diffuse axonal injury.

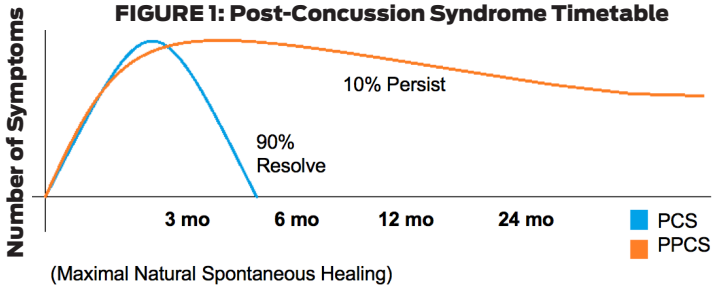
Both the current International Code of Diagnoses (ICD-10) and the Diagnostic and Statistical Manual for Mental Disorders (DSM-V) developed criteria for the diagnosis of PCS. While slightly different symptomology is identified, both require experiencing three or more of the symptoms found in Table 1 following TBI.

Table 1: PCS Diagnostic Criteria

PCS Diagnostic Criteria		
Symptom	**ICD-10**	**DSM-V**
Fatigue	✓	✓
Irritability	✓	✓
Dizziness	✓	✓
Headache	✓	✓
Sleep problems	✓	✓
Concentration problems	✓	-
Memory problems	✓	-
Problems tolerating stress/emotion	✓	-
Affect changes, anxiety, or depression	-	
Changes in personality	-	
Apathy	-	

It is normal following mild head injuries to develop symptoms of Post-Concussion Syndrome (PCS). Normally, a person will recover from the PCS of a mild TBI within 90 days. Therefore, it is not inappropriate for a medical provider in the acute setting to state an individual sustaining a mild TBI will "probably" recover completely. Some authors believe the normal period of recovery to be on the order of six months. However, if symptoms of PCS persist longer than six months, the individual is diagnosed with persistent post-concussive syndrome (PPCS). Although many of the individuals in this group may still spontaneously recover, the likelihood becomes much less. In fact, some 10-15% of individuals sustaining an initial mild TBI will go on to develop permanent brain deficits. Unfortunately, these individuals are sometimes referred to as the "miserable minority."

FIGURE 1: Post-Concussion Syndrome Timetable



(Maximal Natural Spontaneous Healing)

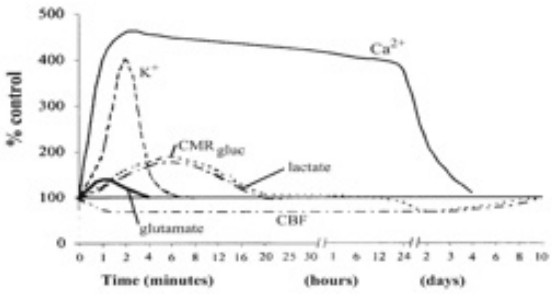
The numbers are staggering, if one does the math on the incidence of TBI in the United

States. There are approximately 2.5 to 5 million new cases per year times a conservative estimate of 90% falling into the mild category with a minimum of 10% of these going on to develop permanent symptoms of PCS. This equates to a minimum of 200,000 and upwards to as many as 400,000 new cases of permanent brain damage arising from individuals sustaining only mild TBIs veach year.

Remember, it is completely appropriate to tell a patient who has sustained a mild TBI that he or she has a 90% likelihood of recovering completely. However, developing PPCS puts patients at an increased risk for developing permanent brain damage. FIGURE 1 illustrates the relative timelines between PCS and PPCS.

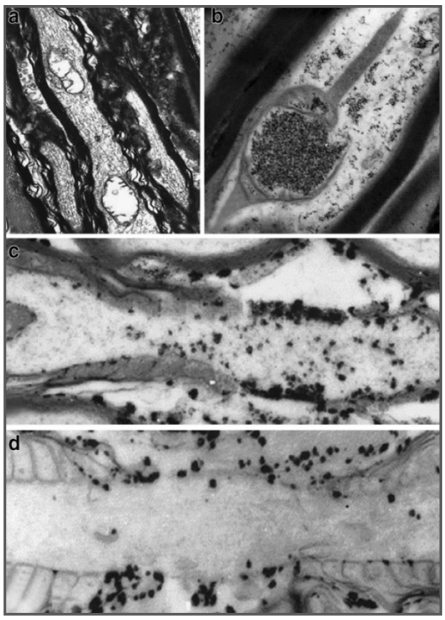
FIGURE 2: Pathobiology of Traumatic Brain Injury

1) Neurometabolic Cascade



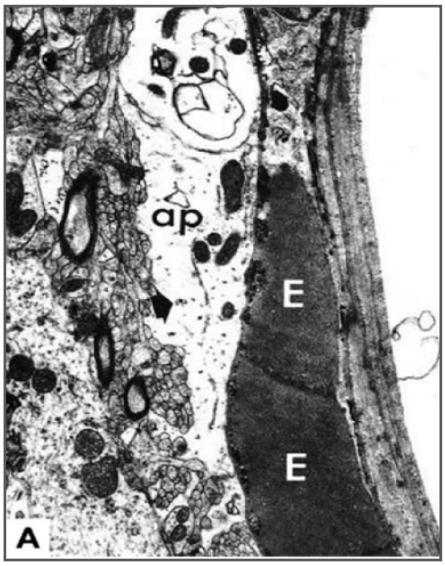
Giza & Hoyda (2000)

2) Axonal Injury



Bigler & Maxwell (2012)

3) Vascular Injury



Bigler & Maxwell (2012)

Brain Injury as a Disease Process

In cases of severe TBI with serious primary injuries such as skull fractures, subdural or subarachnoid bleeding and/or penetrating injuries with associated mass swelling, obvious brain damage occurs. TBI, particularly mild (LOC less than 30 minutes) or moderate (LOC greater than 30 minutes), is no longer being viewed as an isolated event in which the brain is simply momentarily stunned, shocked or where the worst symptoms occur first with day-by-day improvement expected. Recent scientific advances into the exact cellular mechanisms involved in TBI indicate that rather than being an instantaneous, spontaneously resolving event, mTBI is actually a complex disease process that unfolds over time.[8]

Mild to moderate brain injuries fundamentally involve disruptions of the neurovascular unit (NVU) commonly called the blood-brain barrier. It is this disruption that evolves and worsens over the subsequent hours, days, weeks and months that results in development of the so-called secondary or "invisible injuries."[8] The disruption of the NVU results in the stimulation of microscopic cellular processes known as the neurometabolic cascade.[9] This results in alterations in sodium/potassium pump functioning, calcium influx into the mitochondria, an increase in neuro-excitatory amino acids such as glutamate and aspartate, decreased cerebral blood flow (CBF), and brain edema.

In addition, disruption of the NVU leads to leakage of fluid into brain spaces (edema) and the release of cytokines and other reactive oxygen species (ROS), which initiates the neuroinflammatory response.[10] In cases of PPCS, this process can continue for months. In some cases, triggering the neuroinflammatory response leads to the build-up of tau proteins. This in turn can lead to a condition known as Chronic Tau Encephalopathy (CTE), a devastating sequela to a TBI often resulting in dementia, severe depression, and death. This condition has and is affecting many of our professional football players as well as other professional athletes (boxers, hockey players, soccer players, etc.) exposed to repetitive brain injuries.

Diagnosing Mild TBI: The Role of Imaging

When an individual sustains a mTBI, whether in sport, a fall, a blow or an accident, it is not uncommon, depending on the severity of the initial symptoms, to seek medical attention at a doctor's office or emergency room. A history and physical examination will take place and, quite often, a CT scan of the head is ordered. It is important to know, the primary purpose of a head CT scan in the acute setting is to rule out possible fractures or bleeding within the head which could evolve into more immediate serious, potentially life-threatening medical conditions. However, cellular abnormalities that occur in mTBI are beyond the detection capability of either CT or MRI. Therefore, the scan result will often be interpreted as "negative."[11] In addition, if significant orthopedic injuries or other internal injuries are also present, the TBI typically go undiagnosed.

When a "closed head injury" or a "concussion" is diagnosed (these terms, in the current vernacular, are synonymous with a mild traumatic brain injury) the patient is commonly instructed to follow-up with their primary care physician in a few days. Then, at the patient's initial follow-up visit, he or she is usually told the symptoms of PCS will likely resolve in a few weeks or so.

What happens if a person's symptoms persist and warrant a diagnosis of PPCS? What are the options at this point? Often, six to nine months later, a mTBI patient with persistent symptoms will be referred to a neurologist who will typically order MRI scan. In the case of a patient with a mTBI, the scan results are usually negative, the patient is diagnosed with a concussion or mild TBI, sent home with various pills and told to get counseling. Sometimes, given the normal MRI, patients are mistakenly told "nothing is wrong" with them. Unfortunately, this often occurs in the face of a patient being totally disabled from their PPCS. Patients at this time, either directly from the TBI or indirectly from loss of function, employability, and self-esteem, become hopeless and increasingly depressed. In many worst-case scenarios, patients are sometimes told they are "faking." This is where my professional hypothesis becomes important for clinicians to remember: **Having a normal or negative medical test of any type does not necessarily mean there is nothing wrong with the patient.** This is where a more sensitive type of brain scan that looks at the functional status of a person's brain cells should come into play; either positron emission tomography (PET) or single photon emission computed tomography (SPECT).

What is Brain SPECT Imaging?

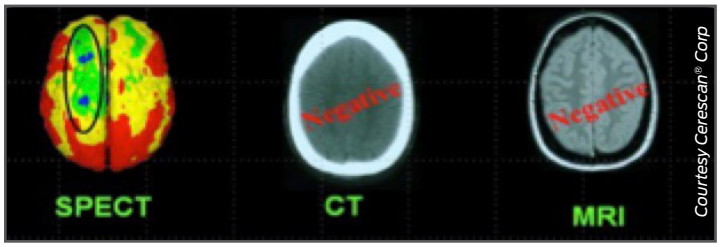
FIGURE 3: SPECT Imaging Device

SPECT is a nuclear medicine procedure which uses a radiopharmaceutical that **emits** a gamma ray (**photon**) which is captured by a gamma camera. (FIGURE 3) This gamma camera transduces the gamma ray emissions into an electical signal which is run through a **computer** program to generate sliced images (**tomograms**) of the brain. Instead of looking at the anatomic structure of the brain like the CT and MRI, the tomograms depict the relative blood flow of the brain which is a very close approximation to the metabolism of the brain cells, which tells us how they are functioning. If brain cells have been damaged at the microscopic level by elements of the neurometabolic cascade, they will not function normally. When a person's brain cells are not functioning or metabolizing, they do not demand normal amounts of blood flow. This alteration in blood flow is detected with brain SPECT imaging. Also, when brain cells are not functioning as they should, patients aren't and likely can't feel or function normally, even when their head CT or MRI scan is "negative."

FIGURE 4 provides an excellent example of an actual patient that I performed a SPECT scan on approximately 15 years ago. She was involved in a motor vehicle accident in which she sustained a mTBI.

Immediately after the accident, she developed symptoms of PCS and was transported by emergency vehicle to the nearest emergency department. There, she was evaluated and the CT scan you see in the middle of FIGURE 4 was obtained and reported as "negative." The patient was sent home with a diagnosis of a concussion and told to follow-up with her primary doctor in several days. Her primary doctor confirmed the diagnosis of concussion, prescribed pain pills for her headache, and sent her home with the instructions that she would likely recover in a few weeks.

FIGURE 4: Diagnostic Scans of Actual Patient



Unfortunately, she did not get better in a few weeks or even a few months. At this point, she had now developed PPCS. The patient was then referred to a neurologist who proceeded to obtain an MRI scan which you see on the right in FIGURE 4. It was also interpreted as being "normal" and the patient was told there was "nothing wrong" with her.

The patient languished with PPCS, becoming increasingly depressed and non-functional. She suffered with her TBI. After two years, stating that something was "dreadfully" wrong, she finally consulted an attorney. The astutue attorney had heard of SPECT technology and referred her to a physician who ordered a SPECT scan. The results are displayed on the far left in FIGURE 4. In that image, the red color indicates areas of normal brain blood flow. Yellow represents areas of blood flow that are 95% below normal, green, 97% below normal and

blue 99% below normal. As you can see, SPECT imaging made her otherwise "invisible injury" visible and clearly depicts rather large areas of hypo-functioning brain cells. Although her brain cells were not technically "dead" such that they might have been visualized on CT or MRI scans, they are nonetheless markedly hypoactive and damaged from the afore mentioned intracellular neurometaboic cascade processes.

The patient went on to receive a substantial monetary judgment from her brain injury, now documented using SPECT technology. She was finally able to get the proper supportive care that she needed from her disabling brain injury. The TBI story does not end here. Now, it is time to examine and discuss light therapy.

The Role of Polychromatic Light Therapy in the Treatment of TBI

Although sunlight has been used for centuries as a specific therapy for various maladies, a Nobel Prize was awarded in 1903 for the use of "concentrated light" to treat the skin of lupus patients.[12] Then, with the discovery of laser technology in 1961 by Dr. Endre Mester at Stemmler University in Budapest, it was first noted that light of certain wavelengths and coherences could exert specific biologic effects on mammals. Since then, scientific research has demonstrated the existence of various biological and biochemical structures and enzymes capable of accepting and using specific wavelengths of light to initiate various biological responses in all mammalian species. This process is generally referred to as photobiomodulation (PBM).

One of the simplest and most common everyday examples of PBM at work is the use of light therapy in newborn care units to treat physiologic jaundice. In newborns, high levels of circulating estrogen from the mother competes with the natural breakdown product of the newborn's hemoglobin in the baby's liver. This natural breakdown product is unconjugated bilirubin. When this builds up in the baby's bloodstream it causes jaundice and remains in the circulation, unable to be excreted in either urine or feces until it is converted in the baby's liver to conjugated bilirubin. Light in the blue wavelength (400 – 500 nm) is absorbed by a light accepting portion of the unconjugated bilirubin and converts it to conjugated bilirubin which is easily excreted and the jaundice improves. Thus, bilirubin is one of many naturally occurring "photoacceptors" in the human body.

Another photoacceptor is cholesterol which, when impacted by certain wavelengths of sunlight on our skin, converts a form of cholesterol into Vitamin D. Dr. Mester discovered that coherent light in the form of laser was capable of speeding the growth rate of hair on the wounds of his experimental animals exerting yet another biologic effect. It turns out, the body has many other photoacceptors (in addition to the photoreceptors of the eye). The three primary photoacceptors are:

1. Cytochrome C Oxidase - an enzyme in the respiratory chain of all mitochondria in all living mammalian cells.
2. Nitric Oxide synthetase - an enzyme in the lining the endothelium of the vasculature of all living mammals.
3. Hemoglobin - contained within red blood cell of all living mammals.

The human body contains literally billions of photoacceptors prepared to receive light and exert various biological reactions. Humans are truly beings of light.

What is Polychromatic Light Therapy (PLT)?

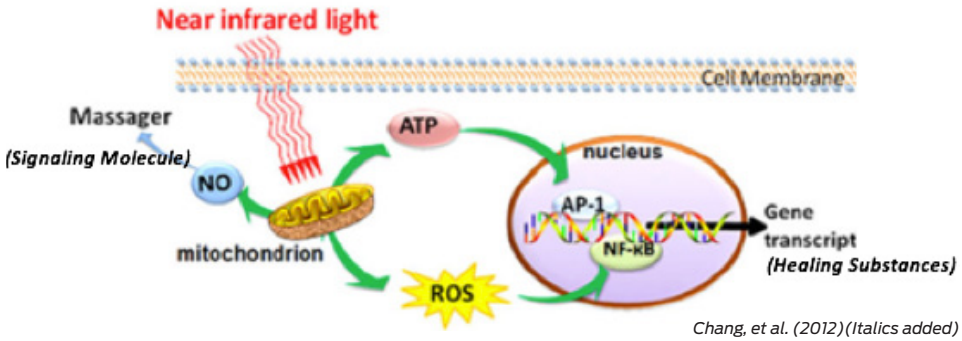
Numerous studies have demonstrated light, whether blue (400-500 nanometers), red (600-700 nanometers) or near infrared (800-1000 nanometers), impacts mammalian photoacceptors and triggers the release a chemical called nitric oxide (NO).[13] [14] Nitric oxide has been called the "miracle molecule" of the human body and found to be the messenger molecule of the cardiovascular system. For their discovery of this mechanism of action of NO within mammalian systems, Robert Furchgott, PhD, Louis Ignarro, PhD, and Ferid Murad, MD, PhD, were awarded the Nobel Prize in Physiology and Medicine in 1998.

Nitric oxide serves as an intracellular signalling molecule triggering the nucleus to produce many downstream healing substances which have been shown to have anti-inflammatory, analgesic, angiogenic, and neurogenic effects. (FIGURE 5) This is the mechanism of action of photobiomodulation.

"Polychromatic light therapy is the simultaneous application of two or more wavelengths of color (blue, red, or infrared) via light emitting diodes directly to the skin to trigger a biological response."

Nitric oxide has been demonstrated to cause a local vasodilatation of the vasculature resulting in increased local blood flow to the tissue to which the light is applied bringing with it an increase in oxygen, glucose, and the body's natural healing substances. Although the vasodilatation may last only 4 or 5 hours, once the nucleus has been activated to initiate the manufacture of the healing substances, it has been shown that these can continue to exert healthful effects for many weeks.

FIGURE 5: Cellular Mechanisms of PLT



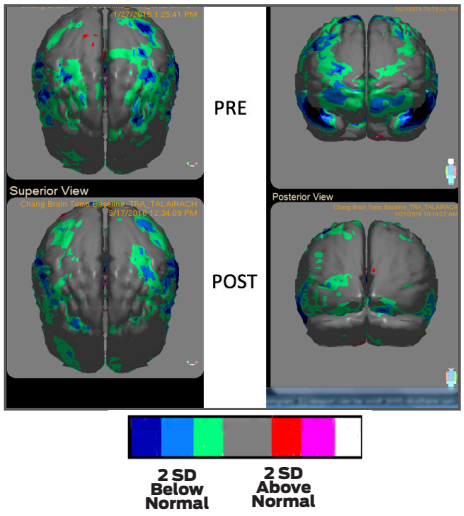
Chang, et al. (2012)(Italics added)

PLT and TBI

FIGURE 6: InLight Medical Polychromatic LED Therapy Pads

Historically, brain damage caused by stroke or TBI was taught in medical schools to be irreversible events. In addition, it was taught that the brain was incapable of generating new brain cells. Current scientific breakthroughs now reveal neither historical dogma are true. Further, it has been demonstrated in multiple studies that near infrared LED light is capable of penetrating the human skull.[15-17] In a small demonstration project, five Veterans with documented mTBI applied InLight Medical polychromatic light LED therapy (PLT) pads with Progressive Multi-Pulse™ technology (FIGURE 6) to their heads for a minimum of 20 minutes, 3 times per week for 12 weeks. Brain SPECT imaging was obtained before and after the PLT application. The results were impressive. Each Veteran reported a marked improvement in their symptoms. In addition, there were significant increases in the SPECT imaginging of brain blood flow. (FIGURE 7) To learn more about this demonstration project, please refer to InLight Medical's award-winning documentary, Light Up to Live (LightUpToLive.com).

FIGURE 7: Pre & Post Effects, Brain Blood Flow (SPECT Imaging)



Courtesy Cerescan® Corp

The results of this demonstration project are in line with other published studies by Dr. Michael Hamblin and his group out of Harvard Medical School demonstrating improved psychological functioning following treatment with polychromatic (red and near infrared) LED light for traumatic brain injury.[18, 19] The Harvard Medical School studies have also demonstrated positive results using PLT with LEDs for depression and Alzheimer's disease. Finally, this author has recently participated in an IRB-approved scientific study measuring not only the effects of InLight Medical's PLT with Progressive Multi-Pulse™ technology on the psychological functioning of Veterans with TBI, but has also obtained pre and post measurements of changes in brain blood flow as measured by brain SPECT imaging.[20] That study is now complete and the findings are being submitted for publication.

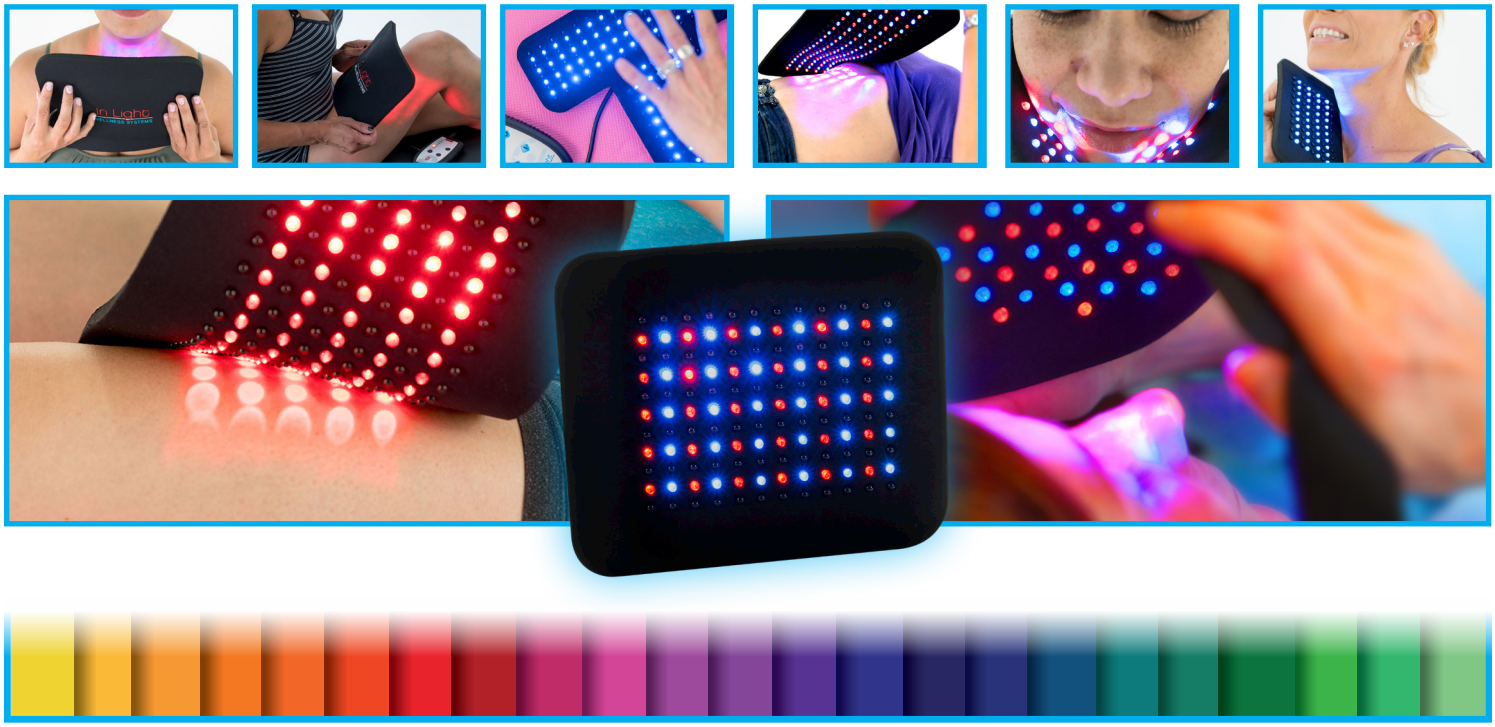
In Summary:

1. Mild traumatic brain injury (mTBI) is common.
2. Loss of consciousness and blunt trauma is not required to sustain a mTBI.
3. More than 10% of mTBI cases result in permanent, progressive brain injury.
4. "Normal" CT and/or MRI structural imaging results does not rule out the existence of mTBI.
5. The 2014 American College of Radiology guidelines recommends brain SPECT

imaging for the evaluation of mTBI in the chronic setting.

6. Polychromatic Light Therapy (PLT) using LEDS is capable of penetrating the human skull.
7. PLT has been shown in thousands of peer-reviewed scientific studies to impact photoacceptors throughout the body, particularly in the mitochondria and the endothelial lining of the vasculature, and cause the release of nitric oxide.
8. Nitric oxide has been shown in thousands of scientific studies to serve as an intracellular signaling molecule, which triggers the manufacture of various healing substances wherever it is applied.
9. Low-level polychromatic LED technology has been shown in peer-reviewed scientific studies to reverse the pathologic changes associated with traumatic brain injury, stroke, Alzheimer's, Parkinson's, depression and anxiety.

Further research, including placebo-controlled, double-blind studies, delving into more specific details of most effective wavelengths, power densities, frequency of light application, pad location, and doses of light is warranted based on the body of research to date. Because of the low cost, convenience, safety and effectiveness of light emitting diode (LED) PLT for many of the brain disorders mentioned above, it is easy to see the very high benefit to risk ratio for its use in various clinical settings. PLT with LEDs is gradually working its way into the mainstream practice of medicine, as it already has in Europe and Asia.[21] Look to InLight Medical with its safe, convenient, LED PLT with Progressive Multi-Pulse™ technology to be leading the way.



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