Traumatic brain injury (TBI), which is defined as a physical injury to brain tissue that temporarily or permanently impairs brain function, is a global health concern and a growing socioeconomic problem. TBI is the leading cause of mortality and disability among individuals under the age of 45, with young adult males accounting for approximately 75% of cases. Due to the complex pathophysiology associated with TBI, there is currently no effective pharmaceutical treatment available for widespread clinical use. Consequently, individuals who suffer debilitating TBI often require lifelong medical care and support.

TBI is commonly classified based on the clinical severity of the injury, ranging from mild to severe. The Glasgow Coma Scale (GCS) has become the universally accepted severity classification system for TBI. Based on scores (ranging from 3-15) from eye, motor, and verbal tests, the GCS classifies TBI cases as mild (GCS 14-15), moderate (GCS 9-13), or severe (GCS 3-8). In addition to clinical severity, TBI has also been traditionally classified based on the mechanism of injury. Mechanism-based classification usually categorizes TBI as either closed or open head injuries. Closed head injury, also called blunt or non-penetrating brain injury, does not involve a breach of the brain’s dura mater; however, skull fractures may occur. Closed head injury is the most common type of TBI in the general population, and is typically caused by sports injuries, motor vehicle accidents, and physical assault. In contrast, open head injury involves the penetration of the scalp, skull, meninges, and often brain tissue itself. Such penetration injuries are more common amongst military personnel, and are usually caused by foreign objects such as bullets.

TBI might involve various types of gross or microscopic brain damage depending on the mechanism and severity of injury. Despite this heterogeneity, the associated damage of TBI is often categorized as resulting from either primary or secondary injuries. Primary injuries are induced at the moment of impact, when mechanical forces are applied to the brain. These forces most commonly affect the frontal, parietal, and temporal lobes, and result in focal and/or diffuse injury patterns. A focal injury pattern typically occurs following a direct blow to the head and may result in contusion, hemorrhage, and ischemic infarct. Diffuse injury patterns are typically a result of the stretching and/or shearing of white-matter tracts due to the differential motion of the brain within the skull. The severity of this diffuse pattern ranges from a brief disruption and misalignment of axonal neurofilaments to widespread axonal tearing. Secondary injuries result from processes that are initiated by the primary insult, and may develop over the hours, days, or weeks that follow. While different variations of TBI may initiate a range of secondary mechanisms, with variable extent and duration, these processes most commonly involve increased excitatory neurotransmitter release, calcium-mediated damage, mitochondrial dysfunction, free radical generation, hyperphosphorylated tau, amyloid plaques, and a neuroinflammatory response.

Depending on the severity and brain structures affected, various signs and symptoms may appear within the seconds to weeks following TBI. These might include a loss of consciousness, headache, vomiting or nausea, convulsions or seizures, dilation of one or both pupils, clear fluid draining from ears or nose, loss of bladder or bowel control, slurred speech, confusion, dizziness, sensory problems, sleeping abnormalities, memory loss, cognitive impairments, agitation, irritability, combativeness, disinhibition, impulsivity, anxiety, depression, mood swings, motor problems, and other unusual behaviors like paranoia or mania.

To date, improvements in TBI patient outcomes have resulted from advances in intensive care management, neurosurgical techniques, and rehabilitation. Unfortunately, these strategies often result in limited benefits after TBI. Given that TBI is an international health concern with limited treatment options and no effective pharmaceutical intervention, it is imperative that research is conducted to better understand the underlying pathophysiological mechanisms of TBI and improve TBI treatment strategies.