Emergency Medicine: Open Access
ISSN: 2165-7548

Tabish and Syed, Emerg Med (Los Angel) 2015, 5:1
DOI: 10.4172/2165-7548.1000229

Review Article Open Access

Recent Advances and Future Trends in Traumatic Brain Injury

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Received date: November 06, 2014, **Accepted date:** November 25, 2014, **Published date:** December 02, 2014

Abstract

Traumatic brain injury (TBI) has been called a silent epidemic and is a major health and socioeconomic problem. TBI is the leading cause of morbidity and mortality among young adults in developed economies and the incidence in the elderly population is increasing. In developing countries the incidence of TBI is high and rapidly increasing. The World Health Organization predicts that TBI and road traffic accidents will be the third greatest cause of disease and injury worldwide by 2020. TBI is a heterogeneous condition in terms of etiology, severity, and outcome. Currently, no effective TBI therapy exists, with patients treated through a combination of surgery, rehabilitation and pharmacological agents managing post-trauma conditions such as depression. Evidence-based guidelines and management protocols help to guide target-driven care and are associated with better outcome. Continuous attempts have been made worldwide to discover the best possible treatment, but an effective treatment method is not yet available. Evidence-based intensive care management strategies improves outcome. The most definite benefits in terms of survival after TBI come from admission to a specialist neurosurgical centre, with goal-targeted therapy and intensive care services. Early detection and objective characterization of abnormalities in TBI are important objectives of modern neuroimaging. Improved treatment will come through understanding the physical changes in the brain that occur at the microscopic and molecular levels when the brain is subject to trauma. Novel achievements in neuroprotection are now expected from developing antiapoptotic agents, from more potent antioxidants, cholinergic agents, alpha blockers, from researching various physiological substances, advances in molecular medicine including stem cell and gene therapy. A more analytical approach to understanding the complex array of factors that influence the incidence, severity, and outcome of TBI is essential. Future therapies that are currently under investigation hold promise. Unless systematic efforts are made towards prevention, management and rehabilitation, many more individuals, children and middle-aged adults will continue to die. There is a strong need to enhance TBI prevention and to improve treatment. Appropriate targeting of prevention and improving outcome requires a detailed understanding of incidence, causes of injury, treatment approaches and outcome results. Specific topics addressed in this paper include scientific understanding of the problem in its various dimensions, complexities and controversies regarding diagnostic and therapeutic modalities, outcome and impact of TBIs on rapidly transforming societies, challenges and opportunities in research and linking research to practice. Improved patient outcomes will depend on organised trauma response systems, particularly to prevent the potentially reversible effects of secondary brain injury strategies.

Keywords: Trauma; Brain injury; TBI research; GCS; Neuroimaging; Variations in care; Standardization of practice guidelines; PTSD; Violence; Ballistic trauma; Accidents

Background

Injuries are the neglected epidemic of modern society. Head injuries are the most serious and preventable major public health problem and a frequent cause of morbidity and mortality in young people and children. “Head trauma comes in a bewildering variety of types — each has its own special management considerations and prognostic implications. Traumatic Brain Injury (TBI) is considered a 'silent epidemic', as society is largely unaware of the magnitude of this problem” [1]. Variability in both diagnostic criteria and case ascertainment in TBI further contributes to the inconsistency of incidence estimation and confounds comparison between studies. Epidemiological patterns of TBI are changing, linked to consequences of prevention strategies and health-care delivery. Notwithstanding knowledge explosion and technological advances and better understanding of TBI physiology during the last two decades, treatment options remain relatively limited and are primarily directed towards the prevention of secondary brain injury. Being a highly complex subject, TBI has many controversies right from definition to the outcome of interventions. There has not been any significant breakthrough in research that could be linked to practice for reducing the burden of disease. Developed economies have the resources and infrastructure to treat patients according to existing evidence based protocols. The developing countries in their rapidly changing environments do not have even proper healthcare infrastructure like pre-hospital care of trauma care (level I-IV) and rehabilitation programme that further add to the loss of life and increased disability. Prevention is the key to reduce the morbidity and mortality.

Epidemiology

TBI, according to the World Health Organization (WHO), will surpass many diseases as the major cause of death and disability by the year 2020. “With an estimated 10 million people affected annually by TBI, the burden of mortality and morbidity that this condition imposes on society, makes TBI a pressing public health and medical problem. The burden of TBI is manifest throughout the world, and is especially prominent in Low and Middle Income Countries which face

a higher preponderance of risk factors for causes of TBI and have inadequately prepared health systems to address the associated health outcomes" [2,3].

Rates of TBI are highest in the very young (age group zero to four years) and in adolescents and young adults (15 to 24 years); there is another peak in incidence in the elderly (age >65 years) [4]. "Approximately 78 percent of TBI are treated in the emergency department only; 19 percent of patients require hospitalization, and 3 percent are fatal. Hospitalization rates are highest in patients older than 65 years. As with most traumatic injuries, the incidence of TBI is significantly higher in men compared to women, with ratios that vary between 2.0 to 1 and 2.8 to 1 [5]. For severe TBI, the gender ratio is more pronounced, 3.5 to 1. Lower socioeconomic status and underlying psychiatric and cognitive disorders are also risk factors for head injury" [6].

TBI is a major cause of death, especially among young adults, and lifelong disability is common in those who survive. "It is estimated that in the USA, around 5.3 million people are living with a TBI-related disability, and in the European Union, approximately 7.7 million people who have experienced a TBI have disabilities. Across Europe there is an average incidence of approximately 235 per 100,000, with most countries experiencing an incidence in the range of 150–300 / 100,000 per year" [7]. The severity of TBI is often classified using the Glasgow Coma Score (GCS). Patients with a score of 8 or less are classed as severe, 9–12 are moderate and scores of 13–15 are mild [8]; 90% of injuries are classified as mild [9]. Mild injuries can be associated with significant impairment, disability and long term morbidity [10]. Hospitalisation due to TBI is associated with an increased risk of epilepsy, depression [11], cognitive impairment [12] and death [13].

The overall incidence of TBI in developed countries is about 200 per 100 000 population per year. Population- based studies show that the incidence of TBI is between 180 and 250 per 100 000 population per year in the United States. Incidence is higher in Europe ranging from 91 per 100 000 in Spain to 546 per 100 000 in Sweden, in Southern Australia incidence is 322 per 100 000 and in South Africa 316 per 100 000. Many patients with mild TBI (not presenting to the hospital) or with severe TBI (associated with death at the scene of the accident or during transport to a hospital) may not, in fact, be accounted for in the epidemiological reports. Approximately 50% of TBIs are the result of motor vehicle, bicycle or pedestrian–vehicle accidents. Falls are the second-commonest cause of TBI (20–30% of all TBI), being more frequent among the elderly and the very young population. Violence-related incidents account for approximately 20% of TBI, almost equally divided into firearm and non-firearm assaults [14-16]. Estimates of TBI incidence show substantial variation between countries [17]. Data from the CDC indicate that each year in the USA, 1.7 million people sustain a TBI [18]. 1.4 million of these injured individuals are treated in emergency departments, with around 275,000 hospitalizations and 52,000 fatalities. A meta-analysis of reports from 23 European countries revealed a hospital admission incidence of 235 per 100,000 people [17].

The main difference between the American Congress of Rehabilitation Medicine (ACRM) and WHO Task Force definitions of TBI concern the inclusion of 'altered mental state'. For diagnosis of TBI, the ACRM definition requires "any alteration of mental state at the time of accident (dazed, disoriented, or confused)," whereas the WHO Task Force has changed this definition to "confusion and disorientation." The ACRM and WHO definitions focus on mild TBI, excluding patients with more-severe injuries, and thus ignoring the clinical reality that TBI severity lies along a continuum.

Scenario in Developing Countries

TBI is a leading cause of morbidity, mortality, disability and socioeconomic losses in developing countries. According to an estimate nearly 1.5 to 2 million persons are injured and one million succumb to death every year in India [19]. Road traffic injuries are the leading cause (60%) of TBIs followed by falls (20%-25%) and violence (10%). Alcohol involvement is known to be present among 15%-20% of TBIs at the time of injury. The rehabilitation needs of brain injured persons are significantly high and increasing from year to year.

The rapid industrialization and ever-increasing number of motor vehicles on roads in India during the past 25 years, coupled with poor safety regulations has resulted in increasing numbers of injuries and deaths due to road traffic crashes. After injuries occur, many challenges exist for appropriate and effective pre-hospital and trauma care including an inadequate transport system, and logistical and infrastructure deficiencies.

Population-based studies in countries such as South Africa (SA), Taiwan and India suggest even higher rates in developing countries accounted for primarily by road traffic accidents or motor vehicle accidents (MVAs) [20]. Males in South-East Asia and Africa have the highest and second highest incidences of road traffic injury-related fatalities in the world [21], and it can be assumed that a significant proportion, if not the majority, of these deaths are attributable to TBI. TBI is a critical public health and socio-economic problem throughout the world. Standardized epidemiological monitoring in TBI is essential [22].

A recent review of incidence rates for all age ranges, reported lowest rates for U.S (103/100,000) and highest rates for Asia (344/100,000), with 23 European countries reporting an average incidence rate of approximately 235/100,000 [23]. Rates vary from 280-1,373/100,000. The pattern of injury varies across regions: in high-income countries, individuals with TBI are generally motor-vehicle occupants, whereas in middle-income and low-income countries patients with TBI are often vulnerable road-traffic users such as pedestrians, cyclists and motorcyclists. Increased motorization combined with inadequate traffic education and slow implementation of traffic safety regulations is the main cause of the increasing incidence of TBI in low-income and middle-income countries. In high income countries, improved safety regulations have led to a decline in traffic-related TBI [24].

The success of safety regulations with regard to prevention of TBI was unequivocally demonstrated in Taiwan, where implementation of the motorcycle helmet law decreased the incidence of motorcycle-related TBI by 33% [25]. On analysis of patients recruited into the Medical Research Council CRASH trial, those who were injured in low-income and middle-income countries were younger and sustained more injuries in traffic incidents than their high-income country counterparts [26]. In high-income countries, alcohol consumption represents an important risk factor for TBI, and is suggested to be a contributory cause in up to 50% of all TBI admissions to intensive care units [27]. In developing economies, traffic safety education is an inescapable necessity.

The economic loss to developing countries due to TBIs is phenomenal, though unmeasured. The need for good quality scientific information for policy and programme development is essential.

National level data is not available for TBIs in India. The only epidemiological study undertaken in Bangalore, has revealed that the incidence, mortality and case fatality rates were 150/1,00,000, 20/1,00,000 and 10%, respectively. Every year in the city of Bangalore nearly 10400 people sustain brain injury, 2,000 people are hospitalized and about 1,000 people die from brain injuries. Several people live with various types of disabilities affecting physical, social and occupational areas of their life following a brain injury [19,28]. In India, nearly two million people sustain brain injuries, 0.2 million lose their lives and nearly a million need rehabilitation services every year. Nearly 10,000 people sustain brain injury every year in the city of Bangalore with more than 1,000 deaths. The data also showed that the majority of these individuals are males, in their early years (5 - 44 years) and often involved in road traffic injuries. The cost of managing one patient per day (in the Emergency Department only) is estimated at 2,152 INR. This is the lowest possible estimate and in actual values could be much higher. This does not include medical/surgical/ICU costs of inpatients, which constitute nearly one-third of the head injury patients. Road traffic injuries, falls, alcohol consumption and violence are main causes. The major categories of injured and killed road users were motorized two wheeler occupants, pedestrians and bicyclists. Collision of heavy vehicles with these categories of road users resulted in greater number of deaths and serious injuries. The majority of the TBIs were mild brain injuries and concussive head injuries. Contusions, haemorrhages and skull fractures accounted for one-third of brain injuries. Nearly one-third of the patients continued to experience various disabilities having an impact on their day-to-day activities. Nearly 25 percent of patients had incurred a total expenditure of more than 20,000 INR towards injury care. This included only the expenditure incurred by individual households and their family members as out-of-pocket expenses. Since much of the health care in public institutions is subsidized, the cost incurred by institutions has not been taken into account [19,28].

Signature Injury

TBI is a common consequence of modern warfare. Severe head trauma has been identified as a common cause of death in terrorist bombings and has been found to be a major cause of critical injury in a number of these events [29]. Most reported TBI among Operation Enduring Freedom and Operation Iraqi Freedom service members and veterans has been traced back to Improvised Explosive Devices, or IEDs, used extensively against Coalition Forces. In the military from 2000 through 2012, more than 266,000 service members sustained a TBI. Brain injury has become known as the signature wound of the wars in Iraq and Afghanistan. Most brain injuries are mild, and most people recover in a matter of weeks. During Operation Iraqi Freedom, explosive munitions were found to be the most common primary causative agent for the injuries in soldiers wounded in action [30]. Moreover, data from Operation Iraqi Freedom and Operation Enduring Freedom also demonstrate an increasing incidence of head and neck wounds, with a concomitant increase in brain injury, when compared to previous conflicts [31]. The incidence of head injury in the 1995 Oklahoma City bombing was 14% [32]. In the attack on the USS Cole in 2000, the incidence of head injury was 31% [33]. In the 2004 Madrid train bombings, 12% of the 250 injured that were treated at the closest hospital had head injury; among the 29 critically injured, 52% suffered head trauma [34]. The epidemiology of TBI in the military has changed with the advent of the use of body armor. The effectiveness of body armor may contribute to a higher incidence of TBI in survivors because there is decreased mortality secondary to torso wounds. The use of Kevlar™ helmets has greatly reduced the incidence of penetrating head injuries from projectiles, but the brain remains susceptible to concussive forces [33]. Moreover, the increased use of improvised explosive devices (IEDs) as weapons has contributed significantly to the incidence of TBI [34].

During the First Gulf War in 1991, about 20% of those treated for wounds had head injuries [35]. In the current conflicts in Iraq and Afghanistan, blasts are the most common cause of wounds and the leading cause of TBI [35]. Approximately two-thirds of army war zone medical evacuations are due to blast injury, and 88% of second echelon treatment site injuries are due to blast trauma [35]. Since the beginning of the current conflicts, over 1700 individuals have sustained TBIs. A descriptive analysis of 433 individuals with TBI seen at the Walter Reed Army Medical Center indicates that MTBI accounted for less than half of the sample; moderate and severe (including penetrating) brain injury accounted for 56%. Penetrating brain injury accounted for 12% of the total group, while closed TBI accounted for 88%. The number of those with serious brain injury has been estimated to exceed those with amputations by 500%, which is in marked contrast to the pattern of wounds in World War I and World War II [35]. At a regional Veterans' Administration hospital, the number of TBI admissions almost doubled over a 2-year period prior to June 2005 [33].

In Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), from October 2001 to January 2005, the Joint Theater Trauma Registry reported that of those with battle injuries, a total of 1,566 combatants sustained 6,609 combat wounds. The wounds were to the head (8%), eyes (6%), ears (3%), face (10%), neck (3%), thorax (6%), abdomen (11%), and extremities (54%). The proportion of head and neck wounds from2001 to 2005 was higher than the proportion suffered in World War II, Korea, and Vietnam wars. Furthermore, while gunshot wounds accounted for 18% of the injuries from 2001 to 2005, those sustained from explosions accounted for 78% of the injuries, the highest proportion seen in any large-scale conflict [36].

The severity and nature of brain injuries that occur depend partly upon the nature and quantity of the explosive used. Both open and closed brain injuries can occur as a result of a blast, and include penetrating brain injury, skull fracture, diffuse axonal injury, cerebral contusion, and epidural and subdural hemorrhage. There are a number of aspects of blast-induced brain injury that may be different from more "typical" injury mechanisms, such as motor vehicle accidents or falls. These include high rates of sensory impairment, pain issues, and polytrauma. The emotional context in which the injury occurred must also be considered in understanding the clinical presentation of these patients. Successful treatment of these individuals must use a multidisciplinary approach focused on the varied conditions that occur in those injured [37].

A polytrauma "triad" has been reported [38] with rates of chronic pain, PTSD, and persistent postconcussive symptoms (PPCS) present in 81.5%, 68.2%, and 66.8% of one sample, respectively. From this study, only 3.5% of the individuals seen were without chronic pain, PTSD, or PPCS, and 42.1% of the sample were diagnosed as having all three conditions concurrently. In the polytrauma population this introduces significant challenges for care and requires a multidisciplinary, integrated approach for success to be achieved [39]. The prevalence of polytrauma in the blast population may complicate the recovery for those who, under the best of circumstances, would otherwise have an uneventful recovery from their mTBI. Polytrauma patients, even without brain injury, have high rates of neurobehavioral

symptoms including memory difficulties, irritability, mood swings, suspiciousness, a motivation, and guilt [40]. Some pain conditions, namely headache, also occur frequently in the TBI population [41].

Military service-related injuries have serious long-term health and socioeconomic consequences

The overall rate of TBI among active duty service members more than doubled from 720.3 per 100,000 SMs to 1,811.4 per 100,000 SMs from 2000 to 2011. The TBI rate increased dramatically from 2006 to 2008 followed by slight increases in 2010 and 2011. As is experienced in the general population, the actual rate of TBI among military personnel is potentially underestimated by existing TBI surveillance efforts. This is especially true for identification of personnel who have sustained a mild TBI. The total burden of TBI among current and former military personnel, including medical costs, rehabilitation costs and lost productivity/income, is difficult to determine from existing data sources.

TBI care in the Military Health Service (MHS) varies by TBI severity, interval from injury to presentation, and physical location where the injury occurs. In late 2009, Concussion Care Centers were established in Afghanistan to provide supervised rest, education, treatment, and recovery for SMs with concussion. For patients not improving in primary care, specialty referrals and management in a dedicated TBI clinic are indicated. Since 2010, current DoD guidelines have mandated that deployed service members who are in specific, potentially concussive events will undergo standardized evaluation with MACE, which avoids reliance on self-reporting and broadens in-theater screening from symptom-based to incident-based and includes recommendations for a more detailed evaluation of those sustaining recurrent concussions. Certain studies have attempted to estimate the costs of TBIs that have resulted from OEF/OIF. One study estimated that the total lifetime cost of severe TBIs sustained in OIF through August 2005 to be $16 billion [42].

In 2008 the RAND Corporation released a report estimating TBI costs resulting from OEF/OIF. The report provided cost estimates for acute treatment and rehabilitation, mortality and suicide, and lost income. In the first year following injury, costs were estimated to be $27,260 to $32,760 per case for mild TBI and up to $408,520 for those with moderate to severe injury. The estimated overall cost for acute treatment of deployment-related TBIs in the hospital in 2005 ranged from $6.9 million to $14.3 million. The estimated cost of inpatient rehabilitation was $1.9 million and the estimated cost of outpatient rehabilitation ranged from $377,000 to $907,000. The estimated costs associated with mortality from deployment-related TBIs in 2005 ranged from $67 million to $89 million, unemployment associated with deployment-related TBI was $13 million, and reduced wages associated with deployment-related TBI was $1.2 million [43].

A Cross-sectional analysis of Soldiers and Marines evaluated for combat-related disability between October 1, 2004 and September 30, 2010 was performed. TBI cases were identified using the Veterans Affairs Schedule for Rating Disabilities code for TBI and compared with other combat-related disabilities. Combat-related TBI disability rates have significantly increased in both the Army and the Marine Corps since 2005. Significantly more unfitting conditions are present on average in combat-related TBI cases than in other combat-related disability cases. Combat-related TBI disability cases are more likely to be medically retired than other types of combat-related disability. Because veterans with combat-related TBI disabilities are likely to require chronic care for TBI-associated medical conditions, disability evaluation policy and programs must ensure that combat-related TBI disabilities are accurately identified and compensated, and the potential long-term care needs are addressed [44].

Diagnostic Criteria

Many patients with mild TBI in whom CT scans are normal show abnormalities on subacute MRI. Such abnormalities are strong predictors of poor neurocognitive and neuropsychiatric outcomes [45]. MRI may provide useful confirmatory evidence that the symptoms are attributable to an earlier TBI. These emerging technologies offer opportunities for improved disease characterization in TBI, which will aid 'precision medicine'—a concept recently advocated by the US National Academy of Science that will facilitate targeted management and individualized approaches to treatment of patients with TBI [46]. The initial GCS score and, therefore, the severity of the TBI help to predict the likelihood of death from the injury. The mortality rate is high in severe TBI and is low in moderate TBI [47].

Acute and long-term risk factors associated with youth and sports-concussions are a major concern, and there is increasing evidence that multiple mild TBIs may pre-dispose to early onset dementia, later substance-use disorders and mental illness [48,49]. In the United States, research shows that receiving care at a Level I trauma center can decrease the risk for death among seriously injured patients by 25 percent [50]. New technology in CT and MRI is allowing the acquisition of more accurate and detailed information on cerebral pathology post-TBI. This has greatly improved prognostic ability in TBI and enables earlier identification of pathology, making it potentially amenable to therapeutic intervention. Several MRI methods have excellent potential to help visualize metabolic, microstructural and functional network changes related to resting and cognitive states in addition to allowing better detection of microhemmorrhage. Multomodel techniques may emerge helpful orthogonal approaches to enhance the diagnostic precision of abnormalities. Neuroimaging is an essential tool to assist clinicians in diagnosis of TBI. Early imaging reduces time to detection of life-threatening complications and is associated with better outcomes. Advanced MRI (diffusion tensor imaging) allows visualization of white matter tracts and quantification of axonal damage.

Injuries from Sports

Each year in the United States, an estimated 38 million children and adolescents participate in organized sports, and approximately 170 million adults participate in some type of physical activity not related to work. The health benefits of these activities are tempered by the risk for injury, including TBI. CDC estimates that 1.1 million persons with TBIs are treated and released from U.S. Hospital Emergency Departments (EDs) each year, and an additional 235,000 are hospitalized for these injuries. TBIs can result in long-term, negative health effects (e.g., memory loss and behavioral changes). To characterize sports- and recreation-related (SR-related) TBIs among patients treated in U.S. hospital EDs, CDC estimated 207,830 patients with nonfatal SR-related TBIs were treated in EDs each year during this period. The highest rates of SR-related TBI ED visits for both males and females occurred among those aged 10--14 years. Increased awareness of TBI risks, prevention strategies, and the importance of timely identification and management is essential for reducing the

incidence, severity, and long-term negative health effects of this type of injury [51].

Developing Trauma Registry

Databases have been described as the engine of change in today's healthcare environment, especially in the trauma center. A trauma registry serves as a conduit for trauma data that drives the evaluation, prevention, and research of trauma care and can be used for quality control and planning. A trauma registry is an integral component of modern comprehensive trauma care systems. "Trauma registries have not been established in most developing countries, and where they exist, are often rudimentary and incomplete. Improvement in trauma care depends on the establishment of functioning trauma care systems, of which a trauma registry is a crucial component. Hospitals and governments in developing countries should be encouraged to establish trauma registries using proven cost-effective strategies" [52].

The Impact of Traumatic Brain Injury

Globally, in excess of 10 million people suffer TBI serious enough to result in death or hospitalization each year. It has been estimated that TBI accounts for 9% of global mortality and is a threat to health in every country in the world. For every death there are dozens of hospitalizations, hundreds of emergency department visits, and thousands of doctors [53].
Violence and injuries cost more than $406 billion in medical care and lost productivity each year [54].

A severe TBI not only impacts the life of an individual and their family, but it also has a large societal and economic toll. The estimated economic cost of TBI in 2010, is approximately $76.5 billion. The cost of fatal TBIs and TBIs requiring hospitalization, many of which are severe, account for approximately 90% of the total TBI medical costs [53]. A non-fatal severe TBI may result in an extended period of unconsciousness (coma) or amnesia after the injury. For individuals hospitalized after a TBI, almost half (43%) have a related disability one year after the injury [55].

Tabish et al, 2010, in a study [56] from a conflict zone (Kashmir) reported that the hospital
received 630 violence related civilian patients of which 393 were admitted. Of the 393 patients
admitted 157 (39.94%) had head injuries, 131 (33.33%) limb injuries, 28 (7.12%) chest injuries
and 24 (6.10%) abdominal injuries. Of all the injured admitted 159 (40.4%) were having major injuries of which 59 (37.10%) comprised head injuries, 24 (15.09%) chest trauma, 17 (10.69%) abdominal trauma and 51 (32.07%) limb injuries. Most of the injured were in the age group 13-24 years. Of the 393 patients, 59 patients had received head injuries, of which 38 (64.4%) had cerebral contusions, 11(18.60%) had fracture of skull bones mostly temporal or frontal bone and 10 (16.94%) had mutilated compound fracture skull bones and brain lacerations. When assessing the likely severity of gunshot wounds, numerous variables that affected management of trauma include: the particular type of weapon used, the caliber of the weapon, the type of the bullet and its propellant charge (i.e. a standard velocity), the range at which the victim was shot (i.e. wounds inflicted), the site of injury and the number of wounds inflicted. Frequently, victims of gunshot wound have been hit several times. An individual shotgun pellet is comparatively small, though victims are usually hit by large numbers of pellets simultaneously; the degree of injury is severe, particularly when the wound is inflicted at close range. The patients present with multiple pellets, sometimes hundreds causing diagnostic difficulties to the treating clinicians. We gradually developed protocols for such patients. Reduction in morbidity and mortality associated with severe head injury has been achieved with aggressive management protocols at SKIMS hospital" [56].

Tabish and Khan, 2009, in a study [57], in a conflict zone, have found that traumatic events can have a profound and lasting impact on the emotional, cognitive, behavioral and physiological functioning of an individual. The effects of trauma in terms of psychopathology are well understood in the case of adults, while as in the case of children they have only recently begun to be understood. In a turmoil situation, civilian casualties have been found to outnumber military casualties by 3:1. Post-Traumatic Stress Disorder (PTSD) is highly prevalent in general population in Kashmir. Most patients (67%) had co-morbid depression out of which 64.51% were males and 69.04% females. Majority of the PTSD cases had a co-morbid psychiatric disorder most commonly depression. Innovative community-based health programmes which are culturally and gender appropriate and reaches out to all segments of the population need to be developed. Substantial and sustainable improvements can be achieved only when a comprehensive strategy for mental health which incorporates both prevention and care elements is adopted [57].

In a 10-year retrospective study of the incidence and etiology of maxillofacial trauma associated with brain injury that required both oral and maxillofacial and neurosurgical intervention during the same hospital stay, at presentation to the Emergency Department the majority of the patients were diagnosed with severe traumatic brain injury and a Marshall CT class 2. Intracranial pressure monitoring was the most common neurosurgical intervention, followed by reconstruction of a bone defect and haematoma evacuation. Although it is a small population, our data suggest that maxillofacial trauma does have an association with traumatic brain injury that requires neurosurgical intervention (8.1%) [58]. Maxillofacial trauma is often associated with injuries to the cranium, especially in high-energy trauma. The management of such cases can be challenging and requires close cooperation between oral and maxillofacial surgery and neurosurgical teams. The most common treatment modality employed to manage complications was pharmacological, followed by antibiotic treatment, conservative treatment and decompression therapy. The mean hospital stay after the trauma for the patients with complications was 28 days. Thirteen patients (36.1%) were transferred to a rehabilitation centre, a nursing home, or a home for the elderly. Nine patients (25%) completely recovered from their complications and 4 patients (11.1%) died after the trauma [59].

Economic Burden of TBI

While a price cannot be put on the cost of the emotional and physical issues that arise as a result of a brain injury, a price can be put on the financial burden that results from a brain injury. The cost of TBIs in the United States is estimated at more than $48.3 billion annually: over $31.7 billion in hospitalization costs and another $16.6 billion+ in costs associated with fatalities. The CDC (the Centers for Disease Control and Prevention) estimates the total cost of acute care and rehabilitation for TBI victims in the United States is about $10 billion per year, not including indirect costs to families and society (e.g., lost earnings, work time, and productivity for family members, caregivers, and employers, or the costs associated with providing social services). It is estimated that over a lifetime, it can cost between

$600,000 and $1,875,000 to care for a survivor of severe TBI [60]. According to the CDC, the annual estimated direct and indirect medical costs of TBI are close to $76.5 billion in the United States. But TBI is a global problem [61].

TBI is a major cause of long-term disability in industrialized and developing countries across the world. An estimated 10 million people will be affected annually by TBI, and by the year 2020, it will surpass many diseases as the major cause of death and disability [62]. The WHO has predicted that road accidents alone, which account for many instances of TBI, will constitute the third largest contributor to the global burden of disease and disability (after heart disease and depression) [63].

In terms of long term outcomes and recovery, it has been recognized that disturbances of cognition, mood, and behavior constitute the most debilitating aspects of brain injury [64]. The term neurobehavioral disability [65] has been employed to encompass the diverse range of disabilities that often result in wholesale changes in a person's character or personality. These changes in personality are often reported by family members as constituting the greatest source of stress and burden, which has an impact on psychosocial outcome [66]. A range of factors can reflect psychosocial outcomes, such as employment status, social functioning, activities of daily living, financial status, cognitive impairment, and emotional disorders. Concepts of functional outcome are based on three dimensions; the need for assistance with self-care; employment or productivity; and social relationships.

Faul et al's 2007 cost-benefit analysis [67] estimated that the implementation of the Brain Trauma Foundation treatment would have a positive impact on long-term neurologic disability burden to family, work, and society as a whole. The medical savings were estimated to be $11,280 per patient compared to the estimated cost to society of $164,951. They estimated the total societal cost savings to be $3,837,577,538.

A 2009 Missouri study [68] estimated the social cost in terms of years of potential life lost as well as indirect costs (ie, lost productivity) using present discounted value of future earnings discounted at 3% per annum. The authors calculated that the total productivity lost due to TBI related deaths was almost $1.1 billion annually with the rate three times higher for males than females. The highest productivity cost losses were due to motor vehicle crashes at $513 million.

Rockhill et al's 2010 study [69] examined the associated healthcare costs of mild TBI and psychological distress in children and adolescents. The authors concluded that both mild TBI and psychological distress were linked to higher total healthcare costs in the 3 years following an accident in children under 15 years. The 3-year incremental cost associated with psychological distress in a TBI patient was estimated to be $3529 compared to the incremental cost associated with psychological distress in a nonTBI patient of $2769.

Runge et al. [70] estimated annual direct cost burden of TBI (mild, moderate, and severe) to be $302 million (2009 prices), whereas Schulman et al. [71] estimated the same direct cost burden as $98 million or $2.8 billion (indirect costs; 2009 prices). Worthington et al 40 estimated cost savings of between £863,000 and £1.190,000 admitted within 12 months of injury; £539,000–£755,000 admitted within 2 years of injury; and £388,000–£539,000 for admissions after 2 years (2009 prices) for all types of TBI. Faul et al. [67] estimated total cost savings of approximately $4.2 billion (2009 prices) for severe TBI.

The monetary cost of brain injuries varies significantly. It is estimated that a **mild head injury** costs $85,000, a moderate injury costs $941,000, and a severe injury costs $3 million. Overall, it is estimated that the cost of TBIs in the United States weighs in at $48.3 billion annually. About $31.7 billion of that is spent on hospitalization costs, while the additional $16.6 billion goes toward costs associated with fatalities. According to the Center for Disease Control, **acute care** and **rehabilitation of brain injury patients** in the United States costs about $9 billion to $10 billion per year. This does not include indirect costs to society as well as to families, including costs associated with lost earnings, work time, and productivity, as well as the costs linked to providing social services. While costs vary according to the extent of the injury and its specific **long-term effects**, it is estimated that the cost of caring for a survivor of severe traumatic brain injury is between $600,000 and $1,875,000 over a lifetime [72].

Hospital Stay

Advances in medical science in recent years may have resulted in better outcomes and higher survival probability for Acquired Brain Injury (ABI) patients with more patients directed to rehabilitation centers to augment their recovery [73]. However, TBI patients admitted to the post-acute settings are medically complex have longer length of stay (LOS) and are at increased risk of re-hospitalization. The Canadian Institute of Health Information (CIHI) reported that the median LOS in rehabilitation centers for patients with brain dysfunction 36 days versus 21 days for average rehabilitation patient [74]. Patients with head injuries also had prolonged stays in other sub-acute facilities with the median LOS in complex continuing care of 92 days versus 40 days for all patients cared for in the same setting [75]. The main finding of this study is that direct medical costs in the ABI population are substantial with mean cost in the first year post-injury per TBI and nTBI patient being $32132 and $38018 respectively. Although most expenses occur in the first follow-up year ABI patients continue to use medical services in the second and third year with emphasis shifting from acute care and rehabilitation towards homecare physician services [76].

Nosocomial Infection

Infection occurs commonly among patients hospitalized after TBI and has been associated with increased intensive care unit and hospital lengths of stay and an elevated risk of poor neurological outcome and mortality. Patients with neurological injury, such as stroke and TBI, appear to be particularly susceptible to infection. Although aspiration due to a decreased level of consciousness may explain the development of pneumonia among some patients, research also suggests that catecholamines released as a result of brain injury-induced sympathetic activation may modulate cells of the immune system and induce systemic immunosuppression [77]. While this immune suppression may protect the brain from further inflammatory damage, it may also increase susceptibility to infection among those with acquired brain injury [78]. It is estimated that approximately 50% of patients with severe TBI develop at least one infectious complication during hospitalization [74]. Among those who develop infection, the most frequent location is the lung, with reported incidences of pneumonia ranging between 41% and 74% [79]. Moreover, sepsis has been found to affect between 10% and 41% of patients with severe TBI during hospitalization [80]. As patients with severe TBI (GCS ≤8) have a significantly higher incidence of infection and sepsis compared to patients with mild or moderate TBI (GCS >8), the risk of infection

may correlate with severity of brain injury [81]. Among ICU patients, reported risk factors for infection include mechanical ventilation, presence of indwelling invasive devices, administration of immunosuppressive drugs, long-term or repeated use of antibiotics, and decreased host defenses due to poor chronic health status and/or acute disease processes [82]. A better understanding of the risk of infection among patients with TBI could assist healthcare providers in identifying patient subgroups that may benefit from preventative or early treatment efforts and may provide evidence to support priority setting for the allocation of scarce healthcare resources and research funds [81].

Pathophysiology

An estimated 10 million people will be affected annually by TBI. This makes TBI a pressing public health and medical problem. An incidence rate of between 150–170 per 100,000 is demonstrated in Latin America and sub-Saharan Africa due to road traffic accidents compared to a global rate of 106 per 100,000 [62]. Motor Vehicle Accidents (MVAs) are the leading cause of TBI in the general population. MVAs account for approximately 50% of all TBIs. In the United Kingdom, MVAs are the third most common cause of TBI, after falls and assaults. Falls are the second leading cause of TBI. Falls account for 20-30% of all TBIs. Firearms are the third leading cause of TBI (12% of all TBIs) and are a leading cause of TBI among individuals aged 25-34 years. Work-related TBIs constitute an estimated 45-50% of all TBIs. Incidence varies from 37 cases per 100,000 people for military employees (57% are related to transportation) to 15 cases per 100,000 people for civilians (50% are because of falls). Alcohol is a major factor in many TBIs and often is associated with the leading causes of TBI [82].

TBI induces secondary biochemical changes that contribute to delayed neuroinflammation, neuronal cell death, and neurological dysfunction. Attenuating such secondary injury has provided the conceptual basis for neuroprotective treatments. Despite strong experimental data, several clinical trials of neuroprotection in TBI patients have failed. These failures likely reflect methodological differences between the clinical and animal studies, as well as inadequate pre-clinical evaluation and/or trial design problems. However, recent changes in experimental approach and advances in clinical trial methodology have raised the potential for successful clinical translation. neuroprotective therapies for TBI.

Primary injury is the result of immediate mechanical damage that occurs at the time of injury. Primary injuries can manifest as focal injuries, or they can be diffuse (as in diffuse axonal injury). A combination of vascular and tissue damage leads to cerebral contusion. Diffuse axonal injury also could occur as a result of ischemia. In addition, primary blast exposure can lead to some axonal injury, which can be detected using diffusion tensor imaging (DTI) [83]. Neuropathologic findings in patients with diffuse axonal injury were graded by Gennarelli and colleagues, as follows [84]. Grade 1 - Axonal injury mainly in parasagittal white matter of the cerebral hemispheres, Grade 2 - As in Grade 1, plus lesions in the corpus callosum and Grade 3 - As in Grade 2, plus a focal lesion in the cerebral peduncle. Gunshot wounds and missile/nonmissile projectiles cause many penetrating head injuries. High velocity missiles tend to cause the most profound damage.

Secondary types of TBI are attributable to further cellular damage from the effects of primary injuries. Secondary injuries may develop over a period of hours or days following the initial traumatic assault. Excitatory amino acids (EAAs) are significantly elevated after a TBI [85]. Secondary injury is the result of biochemical and physiological events which ultimately lead to neuronal cell death. Several biochemical derangements responsible for secondary injury have been demonstrated, including perturbation of cellular calcium homeostasis, [86] increased free radical generation and lipid peroxidation, [87] mitochondrial dysfunction, [86] inflammation, apoptosis, and diffuse axonal injury [88]. The period of evolution of secondary injury provides a window of opportunity for therapeutic intervention with the potential to prevent and/or reduce secondary damage and to improve long-term patient outcome.

Head injury causes cell death and neurological dysfunction first by both direct physical tissue disruption (primary injury), as well as from delayed and potentially reversible molecular and cellular pathophysiological mechanisms that cause progressive white and grey matter damage (secondary injury) [89]. Such delayed injury begins within seconds to minutes after trauma, may continue for weeks or months or potentially years, [89] and eventually may be responsible for a significant component of the chronic neurodegeneration and neurological impairment following TBI [90]. The primary injury can be described as the mechanical damage occurring at the time of trauma to the neurons, axons, glia and blood vessels through shearing, tearing and stretching. Such events pave the way for secondary pathophysiological cascades that include biochemical, metabolic and physiological changes such as spreading depression, ionic imbalance, release of excitatory neurotransmitters, mitochondrial dysfunction, and activation of inflammatory and immune processes [91] among others. Some of the more important secondary injury mechanisms involve activation of neuronal cell death pathways, microglial and astrocyte activation, and neurotoxicity.

Observational studies [92] have identified the following common features associated with minor head trauma in children evaluated in emergency departments: loss of consciousness (LOC) occurs in approximately 5 percent of children <2 years of age with minor head trauma, headache is a frequent complaint, occurring in up to 45 percent of children, at least one episode of vomiting is reported in approximately 13 percent of patients following minor head trauma, among unselected populations of children with head trauma, immediate posttraumatic seizures occurred in ≤0.6 percent, skull fractures occur in up to 10 percent of children younger than two years of age following minor head trauma. Most skull fractures in this population are linear. Among children with linear skull fractures, 15 to 30 percent have associated intracranial injuries. Most children with skull fractures will also have overlying scalp hematomas. Other findings of skull fracture include a palpable skull defect, cerebrospinal fluid rhinorrhea or otorrhea, posterior auricular hematoma (Battle's sign), hemotympanum, and periorbital hematomas ("raccoon eyes") [92].

More recently, there has been increased recognition of the frequency and consequences of concussive brain injury in athletes and military personnel [93]. TBI represents perhaps the most heterogeneous of neurological disorders; in addition to severity, differences across patients may reflect location, invasive *versus* non-invasive insults, focal *versus* diffuse, presence or absence of intracranial bleeding, as well as differences in gender, genetic predisposition, and presence or absence of certain co-morbidities. Thus, although the animal models of TBI have generated valuable information on delayed biochemical changes that lead to behavioral

dysfunction and provided the experimental basis for treatment strategies, clinical trials of drugs showing preclinical improvements have uniformly failed, reflecting in part the major methodological differences between preclinical and clinical modeling and evaluation [89]. Strong reservation about animal modeling include questions about how well they simulate clinical pathophysiology, especially diffuse axonal injury; use of anesthetics resulting in potential drug-drug interaction issues; failure in most cases to demonstrate that proposed preclinical mechanisms reflect those in humans, use of genetically identical subjects and failure to address gender, injury severity, species, strain or age-related differences in most pre-clinical evaluations; and choice of outcomes that differ from those used clinically. Another major methodological issue has been the historical focus on using treatments directed toward single injury mechanisms, although clearly secondary injury is multi-factorial. More recently, the focus has shifted to address the need to modify multiple targets, either through combination therapies or through use of single agents that modulate multiple key secondary events [94].

TBI induces secondary biochemical changes that contribute to delayed neuroinflammation, neuronal cell death, and neurological dysfunction. Attenuating such secondary injury has provided the conceptual basis for neuroprotective treatments. Despite strong experimental data, more than 30 clinical trials of neuroprotection in TBI patients have failed. In part, these failures likely reflect methodological differences between the clinical and animal studies, as well as inadequate pre-clinical evaluation and/or trial design problems. However, recent changes in experimental approach and advances in clinical trial methodology have raised the potential for successful clinical translation [94].

Variations in Care of TBI Patients

Trauma presents with variety of injuries and problems that demand rapid evaluation, discussion, improvisation and intervention to save life and prevent permanent disability. Gunshot and blast injuries are common cause of brain injury during war time with increased incidence during peace also. Mild TBI is common and, while typically benign, has a risk of serious short and long-term sequelae. Important considerations in the management of mild TBI include: identification of immediate neurologic emergencies, recognition and management of neurologic sequelae and prevention of cumulative and chronic brain injury. Civilian are the major targets in recent war situations and account for more than 80% of those wounded and killed [96].

TBI must not be considered an acute or static disorder, but a complex and chronic neurodegenerative condition. Interestingly, the delayed nature of such injury has suggested the existence of a substantially longer therapeutic window for intervention after TBI, which challenges the traditionally-accepted view that TBI-induced damage can only be reversed within a few hours of trauma. Despite considerable success in elucidating secondary injury mechanisms, more than 30 phase III prospective trials of targeted drug therapies that showed promise in experimental models, have failed to generate favorable results under clinical settings [94].

Complications from closed head injuries are the single largest cause of morbidity and mortality in patients who reach the hospital alive. Of patients who require long term rehabilitation, head trauma is usually the primary injury. Although the mechanisms vary, head injuries are the major cause of morbidity and mortality in childhood trauma victims, accounting for an annual mortality rate of 1 per 1000 in this age group [96].

Because a head injury occurs every 15 seconds and a patient dies from head injury every 12 minutes, a day does not pass that an emergency physician is not confronted with a head injured patient. Severe head injury is associated with high mortality and morbidity [97]. A study [98] reveals that "mode of injury in majority of patients was Road Traffic Accident 44.4% followed by fall from height 32.2%, assault 18.8%, blast injury 3.8% and fire arm injury 0.8%. Majority of patients were having normal Glasgow Coma Scale (GCS). Conservative treatment was given in majority of patients 90.5% followed by surgical treatment 9.5%. Majority of patients improved 93.6% and 6.4% expired after treatment".

Tabish et al, in a 2004 study [97] of TBI patients, majority of patients belonged to age group 0 to 10 years (25.5%) and maximum deaths (8) were seen in age group 51 to 60 years. Maximum number of patients were males (75.9%) and (71.1%) TBI patients were from rural areas. (26.7%) reached this hospital within a period of one hour. (66%) were shifted through ambulance service. 6.4% expired after treatment. Factors responsible for improved outcome in severe head injury patients are improvement in early recognition, resuscitation and triage, coupled with prompt computed tomography (CT) scanning and aggressive surgical management [96]. The quality of survival after severe and moderate head injury is highly dependent on the adequacy of cognitive recovery. Outcome assessments are usually based on the integrity of neurological function and give little information regarding cognitive abilities [96,97].

A GCS of 8 is considered representative of a severe brain injury, 9–13 moderate brain injury, and 14–15 mild brain injury. Patients presenting with severe brain injury have the highest mortality rate, typically reported in the range of 39–51%. These patients are also at highest risk for the development of intracranial hypertension and thus are most likely to benefit from intervention to control intracranial pressure (ICP). Thus, this group of patients will most likely benefit from early intervention to minimize secondary brain injury [96,97].

Despite the availability of evidence-based guidelines for the management of head-injured patients, considerable variations in care remain. There are considerable variations in care among centers. The establishment of guidelines for the management of head injury based on available scientific data may lead to improvement in the standard of care. The striking differences in mortality rates between the aggressive and nonaggressive centers call for the prospective evaluation of aggressive management strategies for head-injured patients [98-100].

Existing and Evolving Therapeutic Interventions

The current medical management of TBI patients mainly includes specialized prehospital care, intensive clinical care and long-term rehabilitation, but lacks clinically proven effective management with neuroprotective agents to limit secondary injury or enhance repair [101]. The enormous burden of TBI, however, clearly supports the need for such neuroprotective and/or neurorestorative agents or approaches. Combined treatments may provide better benefits. These potential combinations include agents (e.g., pharmaceuticals or cytokines) or cells (e.g., MSCs, neural stem cells) or other approaches (physical or electric stimulation) [102].

Many preclinical studies have tested therapeutic efficacy of drugs in animal TBI models by targeting secondary injury mechanisms

including calcium channel blockers, corticosteroids, excitatory amino acid inhibitors, N-methyl D-aspartate (NMDA) receptor antagonist, free radical scavengers, magnesium sulfate, and growth factors Several phase-II clinical trials have shown favorable effects including polyethylene glycol-conjugated superoxide dismutase (PEG-SOD), moderate hypothermia, nimodopine, and triamcinolone [103]. All the compounds or approaches that have been tested thus far in phase-III trials have failed to clearly show efficacy [104]. The efficacy of existing neuroprotective treatments for TBI remains uncertain [105]. Hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Until more evidence from well-conducted trials becomes available, clinicians should continue to exercise caution when considering administering hypothermia for treatment of TBI [106]. High ICP is still the most frequent cause of death and disability after severe TBI. There is no evidence to support the routine use of decompressive craniotomy (DC) to improve mortality and quality of life in TBI adults with high ICP [107].

Most treatments of TBI are aimed at ameliorating secondary insults arising from the injury; these insults can be characterized with respect to time post-injury, including early, intermediate, and late pathological changes. Early pathological responses are due to energy depletion and cell death secondary to excitotoxicity, the intermediate phase is characterized by neuroinflammation and the late stage by increased susceptibility to seizures and epilepsy. Current treatments of TBI have been tailored to these distinct pathological stages with some overlap. Many prophylactic, pharmacologic, and surgical treatments are used post-TBI to halt the progression of these pathologic reactions [107].

Recent Advances

Recent advances have identified several therapeutic classes showing promise for the treatment of TBI. These includes erythropoietin (EPO), carbamylated form of EPO (CEPO), statins, bone marrow stromal cells (MSC), methylphenidate, progesterone, dexanabinol, and rivastigmine [108]. TBI induces neurogenesis in the subgranular zone (SGZ) of the dentate gyrus (DG) in rat and mouse and treatments that enhance neurogenesis promote cognitive function after TBI [109]. Calcium channel blockers (calcium antagonists) have been used in an attempt to prevent cerebral vasospasm after injury, maintain blood flow to the brain, and thereby to prevent further damage [110]. These results do not lend support to the finding of a beneficial effect of nimodipine on outcome in patients with traumatic subarachnoid hemorrhage, as reported in an earlier review by Langham et al. [111]. Corticosteroids have been used to treat head injuries for more than 3 decades because they are thought to reduce ICP [112]. The effect of corticosteroids on the risk of death was reported in 17 included trials. The largest trial, with about 80% of all randomized participants, found a significant increase in the risk ratio of death with steroids and an increased risk of death or severe disability. The increase in mortality with steroids in this trial suggests that steroids should no longer be routinely used in people with TBI [113].

Mannitol is sometimes effective in reversing acute brain swelling [114], but its effectiveness in the ongoing management of severe TBI remains unclear. Four eligible randomized controlled trials were identified [115]. Magnesium is a potential therapeutic tool because of its activity on NMDA-receptors, calcium channels and neuron membranes [116]. There is currently no evidence to support the use of magnesium salts in patients with acute TBI [117]. The hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. The Brain Trauma Foundation/American Association of Neurological Surgeons guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI [118]. There remains significant interest in the benefits of hypothermia after TBI and, in particular, traumatic axonal injury (TAI), which is believed to significantly contribute to morbidity and mortality of TBI patients [119,120].

Decompressive craniotomy (DC) is used to treat elevated ICP that is unresponsive to conventional treatment modalities [106]. In addition to infusion of hypertonic solutions, e.g., mannitol, and other medical measures. DC by surgical removal of a portion of the cranium (craniotomy) has been used for many decades as an intuitive strategy for the treatment of post-traumatic ICP increase. DC should be recommended only as a third tier therapy for the treatment of pathologically elevated ICP [106]. Early DC prevents secondary brain damage and significantly reduces brain edema formation after experimental TBI [120].

Excitatory Amino Acid (EAAs), mainly glutamate, is released into the synapse in supra-physiological concentrations and overstimulate mainly the NMDA receptor [121]. Neuroprotective therapy is aimed at interrupting the excitotoxic cascade in brain tissues before neuronal toxicity is irreversible [122], leading to a reduction in severity of damage. The dopaminergic agonist amantadine has effects on both dopamine and NMDA channels and has been the subject of considerable interest and clinical use in acute TBI [123]. The release of kinins is thought to be an important factor in the development of cerebral vasogenic edema and the detrimental role of beta 2 receptor (B2R) in the development of the inflammatory secondary injury and of the neurological deficits resulting from diffuse TBI [124]. There is no reliable evidence that B2R antagonists are effective in reducing mortality or disability after TBI. Barbiturates are believed to reduce ICP by suppressing cerebral metabolism, thus reducing cerebral metabolic demands and cerebral blood volume [125].

There is evidence that progesterone affords protection from several forms of acute central nervous system injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury. Progesterone appears to exert its protective effects by protecting or rebuilding the blood-brain barrier, decreasing development of cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis [126].

The results demonstrated that methylphenidate (monoaminergic agonist) is likely to improve memory, attention, concentration, and mental processing, but its effects on behavior have not been determined [127]. However, there is, at present, insufficient evidence to support the routine use of mono-amino acids to promote recovery from TBI [128].

Recombinant factor VIIa (rFVIIa, NovoSeven) is a hemostatic agent that has been shown to limit intracerebral hemorrhage (ICH) expansion in patients with spontaneous ICH (sICH) [129]. The similarities of hemorrhage progression in sICH and traumatic ICH (tICH) as well as the possibly related secondary injuries, provide an appropriate rationale for exploring the use of rFVIIa in TBI [130]. Free radical scavenger, Polyethylene glycol (PEG)-conjugated SOD (PEG-SOD or pegorgotein) has been demonstrated to be the only agent showing efficacy in a Phase II trial of TBI patients receiving 10,000 U/kg of PEG-SOD [131].

Intraperitoneal administration of Erythropoietin (rhEPO) crosses the blood brain barrier to protect against brain injury [132]. These

peptides have promise for treatment of brain injury because they do not have side effects of increased hematocrit by EPO.

Statins, potent inhibitors of cholesterol biosynthesis, also benefit brain injury. Atorvastatin administration after brain injury significantly reduces neurological functional deficits, increases neuronal survival and synaptogenesis in the boundary zone of the lesion and in the CA3 regions of the hippocampus, and induces angiogenesis in these regions in rats subjected to TBI [133]. Simvastatin treatment increases phosphorylation of Akt, glycogen synthase kinase-3β (GSK-3β), and cAMP response element-binding proteins (CREB); elevates the expression of brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) in the DG; increases cell proliferation and differentiation in the DG; and enhances the recovery of spatial learning [134]. Amnesia is a common sequelae following TBI, for which there is no current treatment. Statins promote rapid recovery of spatial memory after TBI in animals.134 When administered in combination with bone marrow stromal cells (MSCs), atorvastatin increases MSC access and/or survival within the injured brain and enhances functional recovery compared with monotherapy [135]. Statins induce neuroglial differentiation of human MSCs [136]. A combination therapy of MSCs and atorvastatin amplifies endogenous cellular proliferation [135]. These cholesterol-lowering agents might be used in conjunction with MSC transplantation in the future for treating neurological disorders and injuries.

Nitric Oxide (NO) activates soluble guanylyl cyclase, leading to the formation of cyclic GMP (cGMP). Increases in cGMP levels enhance proliferation of endothelial cells and motor neurons.125 Increased cGMP production may facilitate neuroprotection and neurorestoration after TBI. cGMP levels in brain may be increased by cGMP production via increases in NO or inhibition of cGMP hydrolysis using phosphodiesterase 5 inhibitors, e.g. Sildenafil. NO promotes angiogenesis, and neurogenesis, and increases neuroblast migration after brain injury such as stroke [137].

The S100B protein belongs to a multigenic family of low molecular weight calcium-binding S100 proteins [138]. S100B is primarily produced by glial cells [139]. S100B acts as a neurotrophic factor and a neuronal survival protein. S100B is released after brain insults, and serum levels are positively correlated with the degree of injury and negatively correlated with outcome [140]. Cerebrospinal S100B may be useful as one of the outcome predictors in cases of severe TBI in adults [141], but is not a reliable prognostic index in pediatric TBI [142], S100B has been shown to improve memory function [143].

Neuronal tissue has limited capacity to repair after injury. Cellular therapies using neural stem/progenitor cells are promising approaches for the treatment of brain injury. However, the clinical use of embryonic stem cells or fetal tissues is limited by ethical considerations and other scientific problems. Bone Marrow Stromal Cells (MSCs) could represent an alternative source of stem cells for cell replacement therapies. MSCs are mesoderm-derived cells, primarily resident in adult bone marrow. MSCs can give rise to neuronal cells as well as many tissue-specific cell phenotypes [144]. MSC treatment significantly improves neurological functional recovery after TBI [145].

Research efforts are currently focusing on more specific therapeutic modalities, such as the inhibition of the complement cascade. Enriched Environment (EE) - physical exercise and training, training/learning - leads to improved long-term recognition memory and increases hippocampal neurogenesis. Adult-generated neurons participate in modulating memory function. EE is a very effective treatment which improves motor function and spatial learning after TBI [146]. Exercise could provide a simple and effective means to maintain brain function and promote brain plasticity.

Issues in TBI Research

The selection of appropriate therapeutic window of drug administration is essential in animal studies, but often lacks clinical relevance. Often, preclinical studies evaluating the efficacy of pharmacological agents for TBI do not assess the pharmacokinetics or pharmacodynamics related to the drugs administered, and thus do not attempt to optimize or identify effective brain concentrations required. Moreover, the specificity of the treatment target is often questionable because the pharmacological agents have secondary treatment effects and may modulate other molecular pathways. The use of structurally different modulators with similar effects or simultaneous studies with knockout models may help to solve this problem.

It is equally important that demonstrated effects should be robust, not only significant, and should be demonstrated across multiple experimental models and species. Studies should be replicated across laboratories. Behavioral, as well as histological or imaging outcomes should be demonstrated. Dose-response, brain penetration, pharmacokinetic and pharmacodynamic studies should be performed in animals, with optimal dosing and dose schedules established. Finally, the therapeutic window for any proposed treatment should be at least 6–8 hours [147]. It has been observed that most of the failed clinical trials used treatments targeted single proposed injury mechanisms such as excitotoxicity mediated by ionotropic glutamate receptors. However, secondary injury reflects a cascade of often interactive factors/mechanisms. Combination drug therapies in TBI would be very expensive, and experimental studies have demonstrated that combinations of highly effective treatments may show poorer outcomes that optimal treatment with single agents, potentially reflecting unanticipated drug-drug interactions [147]. The current experimental research focus is on development of single treatment strategies that have multipotential effects on various secondary injury mechanisms.

Naturally occurring hormones such as corticosteroids, thyrotropin-releasing hormone and progesterone were some of the first agents to be evaluated for their multipotential pharmacological effects in TBI models. Progesterone has been shown to exhibit neuroprotective effects in animal models of TBI [148]. It attenuates glutamate excitotoxicit, membrane lipid peroxidation, apoptotic pathways, and diffuse axonal injury. Two randomized, double-blinded, placebo-controlled phase II clinical trials for progesterone have been conducted that showed trends towards improvement in outcomes by progesterone treatment [149,150].

However, experimental TBI studies have resulted in mixed results and a systematic review noted that many of the experimental studies were of poor methodological quality, therapeutic window studies were narrow, and there was statistical evidence of bias in the experimental TBI as opposed to experimental stroke work in the field [151].

There have been two phase III multi-center clinical trials. The ProTECT phase III trial (NINDS/NIH) used initiation of progesterone via intra-venous (i.v.) administration within 4 h of TBI, continuing for 72 h in patients with moderate to severe TBI [152].

The SyNAPSE phase III trial (BHR Pharma) involves administration of i.v. infusion of BHR-100 (progesterone) initiated within 8 h in severe TBI patients [153]. The ProTECT trial was recently terminated, because of lack of data supporting effectiveness. The other clinical trial continues.

Future Trends

An effective TBI treatment could improve the quality of life for the millions of people worldwide who suffer these injuries each year. Progesterone, now being studied in two Phase III clinical trials, currently provides the best hope for a potentially approvable TBI treatment in the near term. Progesterone is the only investigative treatment for TBI to date that potentially hits multiple pathways, exerting its neuroprotective effects by protecting or rebuilding the blood-brain barrier, decreasing development of cerebral edema (brain swelling), down-regulating the inflammatory cascade and limiting cellular necrosis and apoptosis (programmed cell death) [153]. Human data is also very promising. Two independently conducted, randomized, double-blind, placebo-controlled Phase II clinical trials assessed the efficacy of progesterone in TBI patients, and both demonstrated that progesterone improved outcomes. The ProTECT™ trial in the United States and Xiao et al in China each showed a roughly 50 percent reduction in mortality in the progesterone-treated group as compared to placebo and statistically significant functional improvement in survivors [154,155]. Two Phase III clinical trials are underway to test progesterone as an acute treatment for moderate-to-severe TBI. A second Phase III clinical trial, the NIH-sponsored multicenter trial known as ProTECT™ III at Emory University, is currently studying the safety and efficacy of progesterone for moderate-to-severe TBI patients [156].

A number of agents beyond progesterone and surgeries or applications to treat TBI are being tried. Tranexamic acid, being studied in the CRASH-3 study, is an antifibrinolytic agent hypothesized to reduce intracranial bleeding after injury. In this study has enrolled nearly 500 of the 10,000 patients targeted world-wide. The study includes patients with moderate to severe TBI (GCS 3-12) within 8 hours of injury. Three Phase II studies are underway and may hold promise for the more distant future. INTREPID 2566 is examining a synthetic tripeptide analogue in moderate–to-severe TBI. RP-1127 is examining the ability of glyburide to limit swelling and edema following TBI. The DASH TBI Study is investigating whether decreasing adrenergic or sympathetic hyperactivity after TBI alters outcome after injury. The recently completed DECRA trial examined bilateral decompressive craniectomy in TBI with intracranial hypertension refractory to first line therapies. It failed to demonstrate improved neurologic outcome. The RESCUE-ICP study related to decompressive craniectomy continues enrollment at present. This study does include higher ICP pressures. The POLAR Phase III study is currently enrolling patients to investigate whether early cooling of patients with severe TBI is associated with better outcomes [157].

Advances in TBI research so far have created new opportunities for improved surveillance and for effective, acute and long-term medical care and rehabilitation. However, critical gaps remain in surveillance, epidemiology, clinical diagnosis, management, and rehabilitation, including a need to continue developing standard surveillance definitions, clinical definitions, and data collection methods as new knowledge and technology emerge. Researchers remain optimistic that a potential treatment could be relatively close. An acute TBI treatment could improve the quality of life for the millions of people worldwide who suffer these injuries each year. Progesterone, now being studied in two Phase III clinical trials, currently provides the best hope for a potentially approvable TBI treatment in the near term.

Clinical Decision Rules in Children

The priority for the evaluation of children with apparently minor head trauma is to identify those patients with TBI who may require immediate intervention, admission for monitoring or close follow-up, while limiting unnecessary neuroimaging. Those with minor head trauma, no combination of clinical findings is both highly sensitive and specific for clinically important traumatic brain injuries (ciTBI). Most children with minor head trauma do not need computed tomography (CT) of the head CT to exclude ciTBI. The decision to obtain a head CT should be made using clinical predictors to determine risk of ciTBI. Children who have minor head trauma and who are at an increased risk for ciTBI that may require neurosurgical intervention or intensive care or monitoring should be initially imaged with unenhanced CT. Head CT identifies essentially all ciTBI. It can be rapidly obtained in most hospitals. The decision to obtain a head CT for children with minor head trauma must balance the importance of identifying a significant, but rare ciTBI with the estimated risks of late onset malignancy associated with radiation exposure from CT. The risk of death or major disability if a ciTBI is missed is considerable and immediate [158]. "The estimated lifetime risk of cancer mortality from a head CT is substantially higher for children than for adults because of a longer subsequent lifetime and the greater sensitivity of some developing organs (eg, brain or bone marrow) to radiation. Estimates suggest that the lifetime risk of death due to cancer caused by radiation from one head CT is 1 in 1500 in a one year old infant and 1 in 5000 in a 10 year old child" [159]. However, the latency period for development of cancer may be decades. Thus, the probability of ciTBI as determined by clinical findings is a key factor for identifying the optimal approach in individual patients. For infants and children with minor head trauma, absence of high-risk signs or symptoms of ciTBI, especially the performance of neuroimaging and observation, be guided by the use of the Pediatric Emergency Care Applied Research Network (PECARN) low-risk clinical decision rules rather than other rules because it was derived in the largest cohort and is the only rule to be validated.

Several other clinical decision rules for children with minor head trauma have been derived. Of these, CHALICE and CATCH were derived in the largest and most heterogeneous cohorts. However, no other clinical decision rule, including CHALICE or CATCH, has either been validated or achieved similar results during implementation [160]. Unlike PECARN, which sought to identify children at low risk who would not require imaging, the CHALICE rule, derived from a prospective study of 22,772 patients, has identified 14 high-risk criteria for ciTBI that serve as indicators for head CT. During derivation, the rule had a sensitivity of 98 percent (95% CI 96-100 percent) and a specificity of 87 percent [160]. Although not prospectively validated, the CHALICE rule has been implemented in the United Kingdom, and other investigators have suggested use of the CHALICE rule instead of the PECARN rule. The rapid identification and stabilization of children with severe traumatic brain injury is essential. Effective initial management of conditions that contribute to secondary brain injury (ie, hypoxia and hypotension) and prompt transfer to a facility that can provide pediatric trauma care are important determinants of outcome.

In a study by Tabish et al (2000) [161] undertaken to evaluate the frequency distribution, causes, pattern, management and outcome of patients suffering from trauma due to ballistic injuries in Kashmir over a period of 7 years, the type of injury was predominantly bullet with only a small percentage of blast and stab injuries. The common complications included septicemia, pleural effusion, wound infection and urinary tract infection. Head injuries were most common, seen in 22.6% of patients. The gross death rate was 14.7%. Innovative approaches of Emergency Medical Care Services must be created to minimize morbidity and mortality due to trauma [162]. Yattoo and Tabish, 2005, in a study [161] of children below 15 years admitted to hospitals with a diagnosis of head injury revealed that the highest incidence of head injury was seen at ages 6—10 years. Head injury rates were higher in males than in females. The leading causes include falls and motor vehicle accidents. The study underpins the development of effective injury prevention strategies warrants an interdisciplinary approach that draws on public health, biomechanics, engineering, behavioural sciences, law enforcement, medicine, and urban planning. Eliminating risk factors and establishing appropriate state-wide trauma care facilities will go a long way to reduce morbidity and mortality.

Because children younger than two years of age are more difficult to assess, may be asymptomatic despite having a ciTBI, are at risk for abusive head trauma, and are more prone to skull fractures than older children, the following criteria is for neuroimaging: perform imaging in infants and children younger than two years of age with high risk for intracranial injury or with suspected skull fracture should have a head CT [163,164] and intermediate-risk patients may be managed with close observation for four to six hours after the injury, or they may be evaluated immediately by head CT. Imaging studies should be avoided in children <2 years of age at very low risk for brain injury. These patients should have a normal neurologic examination, no history of seizure, and no persistent vomiting. The risk for clinically important TBI is less than 0.02 percent in these patients [165]. Criteria to guide decisions about neuroimaging in children two years of age and older are derived from several large multicenter observational studies [163,165] and a metaanalysis of observational studies [166]. Children ≥2 years of age with one or more of the following signs and symptoms appear to be at the highest risk for ciTBI and should have CT of the head performed [163,165] focal neurologic findings, skull fracture, especially findings of basilar skull fracture, seizure, persistent altered mental status, prolonged loss of consciousness, for children with signs and symptoms that have been variably associated with intracranial injury, close observation for four to six hours after the injury is an alternative to immediate CT of the head. Those who are at an increased risk for ciTBI that may require neurosurgical intervention or intensive care or monitoring should be initially imaged with unenhanced CT. Skull radiography is of little or no added value if a head CT is performed [167]. Patients at high risk for ciTBI should undergo prompt neuroimaging. Those at intermediate risk may undergo neuroimaging or observation with performance of imaging if persistent, worsening or new symptoms occur during observation. Infants and children at low risk for ciTBI should not undergo neuroimaging. For infants and children with minor head trauma and absence of high-risk physical findings of ciTBI, the performance of neuroimaging or emergency department (ED) observation, be guided by the use of the Pediatric Emergency Care Applied Research Network (PECARN) low-risk clinical decision rules rather than other rules [167].

Issues Regarding Evaluation

Tabish et al (2004), in a study [168] of 485 consecutive patients of TBI, revealed that 280 with GCS of 13, 14, and 15 were subjected to routine early CT scan of head after 4 hours of reporting to Emergency Department. Patients with penetrating head injury were excluded. 15 % of patients had abnormal CT Scans and only 4% needed surgical intervention. Though a small number of patients harbour potentially lethal intracranial lesions yet, most of these cases are salvageable if diagnosed early and proper treatment. The study reveals that the current practice in some countries of risk stratification of adult mild head injury (MHI) based on skull radiography need to be replaced by slightly modified versions of the Canadian CT rule/NICE guidelines. This will result in a large reduction in skull radiography and will be associated with modest increases in CT and admissions rates. Early CT Scanning can detect intracranial lesions and will reduce unnecessary hospital admissions. Early diagnosis and appropriate management improves outcomes. CT scanning is the examination of choice in mild TBI patients in the acute phase. This study supports other similar studies suggesting the need for replacing of risk stratification of adult MHI based on skull radiography by slightly modified versions of the Canadian CT rule/NICE guidelines. This will result in a large reduction in skull radiography and will be associated with modest increases in CT and admissions rates. Early CT Scanning can detect potentially lethal intracranial lesions and will reduce unnecessary hospital admissions. The lives will be saved by early diagnosis and proper management. Moreover, it saves bed days for the hospital leading to availability of beds for new emergency admissions. It could lead to decrease in the number of admissions annually thus reserving hospital beds for patients with greater needs. Patients with mild head injury can be managed more cost effectively with a CT strategy instead of admission for observation at the acute stage. The CT strategy costs €196 less per patient. Costs for acute care of patients with mild head injuries are considerable. Model calculations indicate that use of computed tomography during triage for admission would be less expensive than admission for observation. CT is more cost effective for acute care of patients with mild head injury, being about a third less expensive than admission for observation [168].

Evidence-based Clinical Guidelines

The most common causes of injury are falls (41%), assaults (20%), and road traffic accidents (13%). Falls are the leading cause of TBI among people aged 65 years and older, whereas transportation accident leads among persons aged 5-64 years. Firearms surpassed motor vehicles as the largest single cause of death associated with TBI in the United States. The outcome of these injuries varies greatly depending on the cause. Death results from 91% of firearm-related TBIs, but only 11% of fall-related TBIs are fatal. Only a few analyses of the monetary costs of these injuries are available" [169,170].

The care of patients with TBIs is complex and demanding, requiring the integration of skills from numerous different specialties. These patients often have prolonged hospitalizations, which may be marked by numerous complications. In an attempt to provide a consistently high standard of care as well as maintaining cost efficiency to all severely impaired TBI patients, a multidisciplinary clinical pathway (CP) to help guide their care needs to be followed. The CP facilitates patient progression and communication between the various caregivers. This limits duplication of workloads and also decreases length of stay parameters and complications, therefore limiting costs [171].

Evidence-based intensive care management strategies improves outcome. The most definite benefits in terms of survival after TBI come from admission to a specialist neurosurgical centre, with goal-targeted therapy and intensive care services. Detailed Analysis of prognostic factors in TBI forms an important part of the IMPACT project (Maas et al., 2007a). A series of papers have confirmed the prognostic effects of many known predictors (e.g., age, GCS, pupil response, and CT parameters), have disclosed the predictive value of hitherto insufficiently recognized parameters (e.g., race and laboratory parameters), and have identified potential candidates for therapeutic intervention (e.g., blood pressure and laboratory parameters). Notwithstanding the relevance of these univariate analyses, the ultimate value of predictors can only be established in multivariable analysis, adjusting for the influence of other variables [172].

Treatment of severe TBI (GCS score, 3-8) follows current trauma life-support guidelines. Stabilization begins with applying the basic elements of resuscitation: securing the airway, achieving adequate oxygenation and ventilation, and avoiding or rapidly treating hypotension. Early airway management involves providing proper airway position, clearance of debris while keeping cervical spine precautions in place, and orotracheal intubation. Hypercarbia and hypoxia must be avoided. In the initial resuscitation period, efforts should be made to maintain eucapnia at the low end of the normal reference range (PaCO2 of 35-39 mm Hg) and prevent hypoxia (PaO2 < 60-65 mm Hg) to prevent or to limit secondary brain injury. Efforts should be made to avoid hyperthermia [173,174].

A study to assess the effectiveness of adopting the Brain Trauma Foundation (BTF) in-hospital guidelines for the treatment of adults with severe TBI indicated that widespread adoption of these guidelines could result in: a 50% decrease in deaths; a savings of approximately $288 million in medical and rehabilitation costs; and a savings of approximately $3.8 billion—the estimated lifelong savings in annual societal costs for severely injured TBI patients [175].

The current functional classification used in clinical trials of TBI involves a 15-point Glasgow Coma Scale (GCS). A more comprehensive and symptom-based classification is required, which includes evaluation of specific behavioral outcomes such as cognitive and motor functions, quality of life, and physiological- and imaging-based biomarkers.

Traumatic brain injury (TBI) induces secondary biochemical changes that contribute to delayed neuroinflammation, neuronal cell death, and neurological dysfunction. Attenuating such secondary injury has provided the conceptual basis for neuroprotective treatments. Despite strong experimental data, more than 30 clinical trials of neuroprotection in TBI patients have failed. In part, these failures likely reflect methodological differences between the clinical and animal studies, as well as inadequate pre-clinical evaluation and/or trial design problems. However, recent changes in experimental approach and advances in clinical trial methodology have raised the potential for successful clinical translation. Here we critically analyze the current limitations and translational opportunities for developing successful neuroprotective therapies for TBI [176].

Advances in Research in TBI

Research in TBI is challenging because of the heterogeneity between patients regarding causes, pathophysiology, treatment, and outcome. As clinical research has been hampered by non-standardised data collection, restricted multidisciplinary collaboration, and the lack of sensitivity of classification and efficacy analyses, multidisciplinary collaborations are now being fostered. Approaches to deal with heterogeneity have been developed by the IMPACT (International Mission on Prognosis and Clinical Trial Design in TBI) study group. These approaches can increase statistical power in clinical trials by up to 50% and are also relevant to other heterogeneous neurological diseases, such as stroke and subarachnoid haemorrhage. Rather than trying to limit heterogeneity, we might also be able to exploit it by analysing differences in treatment and outcome between countries and centres in comparative effectiveness research. This approach has great potential to advance care in patients with TBI.177

There are three main directions of research: first, standardisation of data collection; second, prognostic analysis and development of prognostic models; and third, improvements in the design and analysis of randomised clinical trials. Although randomized controlled trials remain the prime approach for investigating treatment effects, these can never address the many uncertainties concerning multiple treatment modalities in TBI. “Pooling data from different studies may provide the best possible source of evidence we can get in a cost efficient way. Standardisation of data collection and coding is essential to this purpose. Analysing individual patient data across studies may well be key to advancing the clinical field of TBI, and improving treatment. Much uncertainty exists regarding the benefit and risk of many treatment modalities in TBI. This uncertainty is reflected in the paucity of class I and II evidence underpinning authoritative guideline recommendations. Pooling data from multiple studies can provide an alternative source of evidence that can be realistically obtained in a cost-efficient way. Relating differences in trauma organization and treatment approaches to outcome will permit both better targeting of prevention and exploration of reasons for observed differences. Standardization of data collection and coding is essential to facilitate sharing of results and to analyze data across studies” [178].

Problems with TBI data collection include the fact many patients with mild TBI may not present to the hospital, and the ones who do present may be discharged at the emergency department (ED) without adequate documentation. Severe TBI with associated death at the scene of the accident or during transport to a hospital also may not be accounted for completely in data collection for TBI epidemiologic studies. Differences in diagnostic tools and admission criteria also may affect the above-defined severity classifications. The use of different definitions that may not clearly define the type of injury makes the epidemiology of TBI difficult to describe. Another variable is the difference in findings from diagnostic imaging at different time intervals (eg, when early epidural hematoma is present, the CT scan may be normal, but if the scan is later repeated, it may show evidence of pathology) [179]. There is variation in the stratified incidence rates of TBI, some general trends are universal. By focusing preventive and educational efforts on these high-risk groups, it may be possible to maximize the positive impact on this significant public health problem.

A class of novel cyclic dipeptides (diketopiperazines) has shown remarkable neuroprotective potential both *in vitro* and in rodent TBI models. One of the agets, 35b, shows strong neuroprotective effects across TBI models, improving functional recovery and reducing lesion volume after fluid percussion injury (FPI) in rats [180,181]. Another class of diketopiperazines, cyclo-l-glycyl-l-2-allylproline (NNZ 2591), improved functional recovery and histological outcomes, and attenuated apoptotic pathways and microglial activation in rats after

hypoxic-ischemic brain injury [182]. 35b treatment reduced the expression of multiple cell cycle members, as well as calpain and cathepsin, while increasing expression of two potent endogenous neuroprotective factors-brain derived neurotrophic factor (BDNF) and heat shock protein (HSP) 70 [181]. These mutipotential drugs exhibit a clinically relevant therapeutic window of at least 8 h, show good brain penetration after systemic treatment and have a favorable safety profile- making them promising candidates for future clinical trials.

The up-regulation of sulfonylurea receptor 1(SUR1)-regulated $NC_{Ca\text{-}ATP}$ channels in microvascular endothelium has been implicated in models of CNS ischemia and trauma a secondary injury mechanisms [183]. Administration of the SUR1 antagonist glibenclamide reduced edema, secondary hemorrhage, inflammation, apoptosis and lesion size, and improved functional recovery after experimental TBI [184]. Given that glibenclamide is already used in humans as a hypoglycemic therapy, it has fast-track potential for clinical trials.

Results showed that the expression of Sirt3 was significantly increased at both mRNA and protein levels after H_2O_2 treatment in primary cultured cortical neurons. Down-regulation of Sirt3 using specific targeted siRNA exacerbated the H_2O_2-induced neuronal injury, whereas overexpression of Sirt3 exerted protective effects through attenuating ROS generation and activation of endogenous antioxidant enzymes. The increased expression of Sirt3 induced by oxidative stress might be an endogenous protective mechanism, which is partly dependent on the preservation of mitochondrial calcium homeostasis and enhancement of mitochondrial biogenesis. Thus, metabolic rescue observed upon overexpression of Sirt3 may represent an appropriate strategy to avoid neuronal death in a broad range of oxidative stress related brain disorders [185].

Low level of antioxidant and high content of polyunsaturated fatty acids result in limited antioxidant defense in the brain (Cherubini et al., 2008; Nazıroğlu, 2011). Glutathione peroxidase, a selenium containing enzyme, is responsible for the reduction of hydro and organic peroxides in the brain (Nazıroğlu and Yürekli, 2013). Reduced glutathione is a hydroxyl radical and singlet oxygen scavenger that participates in a wide range of cellular functions (Nazıroğlu, 2013; Senol et al., 2014). Vitamin E, alpha-tocopherol, is the most important antioxidant in the lipid phase of cells (Nazıroğlu, 2007). Vitamin C, ascorbic acid, as a free radical scavenger, also transforms vitamin E to its active form (Cherubini et al., 2008; Nazıroğlu, 2011). Vitamin A, retinol, serves as a prohormone for retinoids and is involved in signal transduction at cytoplasmic and membrane sites (Cherubini et al., 2008; Nazıroğlu, 2011) [186].

In TBI, secondary events occur after primary events like shearing of nerve cells and blood vessels, cause post-traumatic neurodegenerations with an increase in reactive oxygen species and reactive oxygen species-mediated lipid peroxidation (Cornelius et al., 2013). Three different types of metabolic disturbances occur after traumatic brain injury: inflammation, ischemia and calcium ion entry (Campolo et al., 2013). Ischemia/reperfusion negatively influence outcome as oxygen and glucose deprivation reduces cerebral oxidative metabolism. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is a major complex that produces reactive oxygen species during the ischemic period (Niesman et al., 2014). Concurrently with these metabolic disturbances, also after TBI, several factors like extravagated blood products, tissue debris, intracellular components, prostaglandins, reactive oxygen-nitrogen species trigger inflammation (Cornelius et al., 2013). Once blood-brain barrier is disrupted, neutrophils, monocytes, and lymphocytes accumulate in the injured brain area, and microglia are activated by Ca^{2+} entry, all these initiate inflammatory response [186].

"Melatonin, a hormone secreted from pineal gland and synthesized from tryptophan or formed as the metabolic end product of serotonin, is a non-enzymatic antioxidant and neuroprotective agent (Espino et al., 2012; Nazıroğlu et al., 2012b). As an antioxidant, melatonin scavenges the free radicals and/or stimulates the enzymes of antioxidant defense system (Reiter et al., 1997). The efficacy of melatonin for post-traumatic brain injury has been shown in *in vivo* and *in vitro* studies (Esposito and Cuzzocrea, 2010; Campolo et al., 2013). Melatonin has been shown to counteract oxidative stress-induced pathophysiologic conditions like cerebral ischemia/reperfusion injury, neuronal excitotoxicity and chronic inflammation (Reiter et al., 1997; Ekmekcioglu, 2006; Celik and Nazıroğlu, 2012; Espino et al., 2012; Nazıroğlu et al., 2012b). We proposed the hypotheses that modulation of oxidative stress in blood and the cerebral cortex by means of treatment with melatonin may cause an increase in antioxidant vitamin level" [186]. Melatonin supplementation has protective effect on oxidative stress and antioxidant redox system in the cerebral cortex and blood. Melatonin can regulate reduced glutathione and antioxidant vitamins levels and glutathione peroxidase activity in the cerebral cortex. Therefore, use of melatonin in traumatic brain injury may be a potential approach to arresting or inhibiting the oxidative stress caused by excitotoxic agents [186].

Statins or 3-hydroxy-3methylglutaryl coenzyme A (HMGCoA) inhibitors attenuate cholesterol biosynthesis and have multipotential neuroprotective effects. Statins have shown neuroprotection in TBI models. They limit production and expression of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and intracellular adhesion molecule 1 (ICAM-1); reduce glial cell activation and cerebral edema, and increase blood-brain barrier integrity [187]. These anti-inflammatory effects exhibited by the statins may in part be mediated by inhibition of toll-like receptor 4 and nuclear factor κB (NF κB) [188]. One of the primary advantages of statins is that these drugs have a wide therapeutic window, with treatment 24 h after TBI improving functional deficits and neuronal recovery. A clinical trial with rosuvastatin in TBI patients showed improvement in amnesia and disorientation-related outcomes [189]. Phase II clinical trials for the administration of rosuvastatin and atorvastatin to TBI patients have been planned [89].

In TBI models cyclosporin A reduces axonal damage and decreases lesion size [190]. A randomized, placebo-controlled, double-blind clinical trial of cyclosporin A in patients with severe TBI showed significantly reduced glutamate concentration and lactate/pyruvate ratios, and increased mean arterial pressure and cerebral perfusion pressure [190]. Phase III trials for cyclosporin A are being planned [89]. As an immunosuppressant drug, cyclosporin A may exhibit adverse effects on the immune system after prolonged use [191]. Other potential limitations include poor brain penetration and a biphasic dose-response curve.

Substance P (SP) is a neuropeptide released following TBI and contributes to edema and functional deficits [192]. Attenuation of TBI-induced SP generation, by preventing its release or antagonizing the neurokinin-1 (NK-1) receptor, reduced inflammation and maintained the integrity of the blood-brain barrier [192]. Administration of the SP (NK-1) antagonist *N*-acetyl-l-tryptophan

after experimental TBI reduced vascular permeability and edema formation, and improved motor and cognitive outcomes [193].

TBI induces cell cycle activation (CCA) in neurons and glia that can result in apoptosis of post-mitotic cells, as well as the proliferation and activation of mitotic cells such as astroglia and microglia. In proliferating cells, the cell cycle is controlled by complex molecular mechanisms and progression through distinct phases that require sequential activation of a large group of Ser/Thr kinases called the cyclin-dependent kinases (CDK) and their positive regulators (cyclins) [194]. CCA following TBI may initiate multiple secondary injury mechanisms that contribute to neuronal apoptosis and delayed neurotoxicity. Central or systemic administration of the semi-synthetic flavonoid and non-selective CDK inhibitor flavopiridol reduced lesion size, improved cognitive and sensorimotor outcomes and inhibited caspase-mediated cell death [195]. Roscovitine, a more selective inhibitor of CDKs, improved functional recovery, reduced lesion size, attenuated apoptotic pathways, and inhibited progressive neurodegeneration and chronic neuroinflammation in multiple models of TBI [196]. More recently, an N6-biaryl-substituted derivative of roscovitine, called CR8, was synthesized [197]. Central as well as systemic administration of CR8, at a dose 10 times less than previously required for roscovitine, significantly improved cognitive outcomes, reduced lesion size and improved neuronal survival after CCI in mice [198]. Several of these CDK inhibitors have been extensively studied as treatment for various neoplasias. Although they are highly toxic when administered chronically, only short-term treatment is necessary for optimal treatment of experimental TBI.

Metabotropic glutamate receptor member 5 (mGluR5) is highly expressed in microglia and astrocytes as well as in neurons. The mGluR5 selective agonist (RS)-2-chloro-5- hydroxyphenylglycine (CHPG) inhibits caspase-dependent apoptosis across many *in vitro* models. CHPG also strongly attenuates microglial activation, an effect mediated in part through inhibition of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [199]. Early treatment with CHPG, administered intracerebroventricularly (i.c.v.), shows strong neuroprotection after TBI [200]. CHPG administered one month after CCI in mice significantly reduced expression of reactive microglia expressing NADPH oxidase subunits; decreased hippocampal neuronal loss and lesion progression, as measured by repeated T2-weighted magnetic resonance imaging; white matter loss, as measured by high field *ex vivo* diffusion tensor imaging at four months; and significantly improved motor and cognitive recovery [201]. These findings not only highlight the neuroprotective potential of this novel pharmacological treatment for TBI, but also markedly extend the currently-accepted therapeutic window for neuroprotection.

Programmed neuronal cell death contributes to secondary injury and delayed tissue loss after TBI. Both caspase-dependent and caspase-independent apoptotic mechanisms have been strongly implicated in post-traumatic neuronal cell loss. Caspase-dependent mechanisms are activated in response mitochondrial cytochrome c release into the cytosol where it forms a caspase-activating complex (apoptosome) with Apaf-1 further causing sequential activation of caspase-9 and caspase-3 (the main executioner caspases) [202]. Caspase-independent mechanisms may be initiated by mitochondrial release of other cell death modulators such as the apoptosis-inducing factor (AIF) [203]. The AIF-mediated cell death pathway involves its translocation to the nucleus, a step that depends on its interaction with cyclophilin A (CypA), which transports AIF from the cytosol to the nucleus [203]. Constitutive CypA knockouts were observed to improve long-term functional outcomes, reduce lesion size, improve neuronal recovery and attenuate microglial activation in the CCI model [204]. Both caspase-dependent and AIF-dependent modulation strategies improve outcome after experimental TBI, and combined treatment approaches had additive protective effects.204 Seventy kilodalton (kDa) HSPs (HSP70s) are stress-induced molecules that are induced in response to CNS and have neuroprotective properties [205]. Sabirzhanov et al. [206] showed neuroprotective effects of HSP70 overexpression by transfection with HSP70-expression plasmids in multiple *in vitro* models of neuronal cell death. The neurons transfected with HSP70 construct demonstrated significantly reduced expression of markers of caspase-dependent as well as AIF-mediated cell death [206] Induction of HSP70 using geranylgeranylacetone, before or after TBI in mice, significantly improved outcome [207].

Although autophagy has been shown to be up-regulated after TBI, its function in this context remains controversial [208]. Treatment with the anti-oxidant gamma-glutamylcysteinyl ethyl ester (GCEE) after TBI in mice reduced oxidative stress, attenuated autophagy and improved functional outcomes and TBI-induced oxidative stress was observed to be contributing to the overall neuropathology by mediating autophagy [208]. In contrast, apamycin-induced inhibition of the mammalian target of rapamycin (mTOR) [209]. A potential role for modulating autophagy as a neuroprotective strategy requires further study.

Both pathophysiological changes and neurological impairment after experimental TBI can be attenuated by physical activity [210]. The mechanisms underlying the therapeutic effects of exercise may include up-regulation of brain-derived neurotrophic factor (BDNF), leading to enhanced neuronal plasticity as well as anti-apoptotic and anti-inflammatory effects [211]. Other factors implicated include cyclic-AMP response-element-binding protein (CREB), protein kinase C (PKC), calcium-calmodulin-dependent protein kinase II (CAMKII), mitogen-activated protein (MAP) kinase I and II (MAPKI and MAPKII) and synapsin-I following [210-211]. An important variable appears to be the timing of initiation of exercise as a function of injury severity, which can affect the neurotrophic factor response to injury. Late initiation of exercise beginning at 5 weeks after CCI in mice, but not early initiation of exercise at 1 week, significantly reduced working and retention memory impairments at 3 months, and decreased lesion volume [212]. The improvement in cognitive recovery is associated with attenuation of classical inflammatory pathways, activation of alternative inflammatory responses and enhancement of neurogenesis.

Right Care at the Right Time

Timely access to care is critically important for patients with traumatic injuries or emergent conditions. Although health outcomes depend on many factors (e.g., severity of injury), trauma patients who do not receive appropriate and timely care are at increased risk of death. Globally a large number of patients particularly people living in poverty and in rural areas do not have access to a Level I or II trauma center within one hour of being injured [56,57,96,97]. All levels of trauma centers (Level I to Level IV) and hospitals are critical components of trauma systems. Since all injuries do not need to be treated at a trauma center, “Field Triage Decision Scheme: The National Trauma Triage Protocol" (Decision Scheme), recommended by CDC need serious consideration to help emergency medical responders better and more quickly determine if an injured person needs care at a trauma center. The Decision Scheme is based on current best practices in trauma triage. Widespread use can help

ensure that injured people get the right level of care as quickly as possible [213].

Future Trends in TBI Research

The brain is made up of billions of cells that interconnect and communicate. The neuron is the main functional cell of the brain and nervous system. One area of research that shows promise is the study of the role of calcium ion influx into the damaged neuron as a cause of cell death and general brain tissue swelling [214]. The use of stem cells to repair or replace damaged brain tissue is a new and exciting avenue of research. Researchers are investigating the ability of stem cells to develop into neurotransmitter-producing neurons, specifically dopamine-producing cells. Researchers are also looking at the power of stem cells to develop into oligodendrocytes, a type of brain cell that produces myelin, the fatty sheath that surrounds and insulates axons. At present, stem cell research for TBI is in its infancy, but future research may lead to advances for treatment and rehabilitation. Novel achievements in neuroprotection are now expected from developing antiapoptotic agents, from more potent antioxidants, cholinergic agents, alpha blockers from researching various physiological substances, molecular biology and gene therapy. Translational regulation that alters mRNA expression and transplantation-based approaches might significantly improve the brain function in the individuals with brain injury. Some researchers are looking at the role of plasticity in memory, while others are using imaging technologies, such as functional MRI, to map regions of the brain and record evidence of plasticity [214]. There is a need to look deep inside the brain to see the subtle alternations that occur after the traumatic injury. The focus of advanced research should be on a unified understanding of the human brain, from genes to behaviour and in health and disease; a map to enable diagnosis of neurological and psychiatric diseases, to understand brain diseases and develop new drugs, and even personalised medicine. Recent advances in clinical trials design, including adaptive design methodology, as well as appreciation for the need for larger sample sizes and more extensive preclinical pharmacological evaluation, may serve to increase the likelihood of successful clinical translation in the future.

Looking Ahead

Many survivors of TBI live with significant disabilities, resulting in major socioeconomic burden as well. In 2000, the economic impact of TBI in the United States was estimated to be $9.2 billion in lifetime medical costs and $51.2 billion in productivity losses [215,216]. One of the major advances over the past two decades in the care of patients with severe head injury has been the development of standardized approaches that follow international and national guidelines [216]. The intent of these guidelines has been to use existing evidence to provide recommendations for current care in order to lessen heterogeneity and improve patient outcomes. There is evidence that treatment in centers with neurosurgical support, especially in settings where protocol-driven neurointensive care units operate based on the above-referenced guidelines, is associated with better patient outcomes [217]. Treatment of severe TBI should be centralized in large trauma centers that offer neurosurgical treatment and access to specialized neurocritical care. The management of the patient with severe head injury is often complex and requires a multi-disciplinary approach and lends itself to protocol-based treatment and standardized hospital order sets derived from the previously referenced guidelines. The primary goal of prehospital management for severe head injury is to prevent hypotension and hypoxia, two systemic insults known to be major causes of secondary injury after TBI. Changes in prehospital management that aim to normalize oxygenation and blood pressure have improved outcomes [218].

There are interventions that can be effective to help limit the impact of TBI. These measures include primary prevention, early management, and treatment of severe TBI. Paradigm shifts in our approaches to prevention, management and post-injury care for TBI are essential. There is a great need for the development of high-quality epidemiological monitoring databases for reliable estimation of incidence, prevalence and outcome parameters. Long-term follow-up of large cohorts could provide definitive information about the cognitive consequences of acute TBI. Huge database with health sector can be a powerful tool both for advocacy and for action. To meet the challenges of TBI there is a strong need to devise evidence-based protocols, establish pre-hospital care and trauma centres in developing countries (where TBI patients can be transported within 'golden hour'), and invest in research to ensure that the millions of people injured each year gets the right care, at the right place, at the right time. The right care can help people continue to live to their full potential, despite having experienced a severe injury.

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