New Directions in Research and Therapies in Traumatic Brain Injury

Expert review:

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Abstract

Traumatic brain injury (TBI) is a significant cause of disability and death and its incidence is rising in some specific populations. TBI can result in various disabilities, cognitive problems and psychiatric disorders, depending on the location of the injury and premorbid patient conditions. Effective pharmacological and surgical treatments, however, are currently limited. Most randomised clinical trials for TBI treatments carried out to date have failed to show significant benefits. Initiatives such as the TRACK-TBI have highlighted the large variability in TBI treatment quality at different hospitals and widely differing death rates. This stimulated the establishment of the International Initiative for TBI Research (InTIBR), which aims to improve disease characterisation and patient management. The development of effective treatments for TBI and their evaluation requires an understanding of the complex neuroregenerative processes that follow an injury. In the case of haematoma in TBI, decompressive craniectomy can be a life-saving intervention but must be performed rapidly. The neurotrophic agent, Cerebrolysin® acts by mimicking neurotrophic factors (NTFs) and by stimulating the endogenous production of NTF in brain tissue. Experimental models show that this drug increases neurogenesis following TBI but these findings need to be converted into clinical practice. The potential of Cerebrolysin® in TBI was demonstrated in a large retrospective cohort trial in Romania (n=7,769 adults). Cerebrolysin® significantly improved Glasgow Outcome Scores (GOS) and respiratory distress (RDS) in patients with moderate or severe TBI at 10 and 30 days compared with controls. This and other experimental treatments have potential in TBI but, in developing such therapies, the design of clinical trials should closely reflect the reality of biological processes underlying natural recovery from brain injury.

Keywords

Traumatic brain injury, research, treatment, neurogenesis, cognitive decline, cognitive recovery, behavioural aspects, Cerebrolysin®

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Traumatic brain injury (TBI) is a condition with many unmet needs in medicine and public health.¹² It is a major cause of death and disability and also leads to extremely high direct and indirect costs to society.¹³ Current the incidence of TBI among some populations such as the elderly and military personnel is increasing.¹¹¹¹ TBI populations are heterogeneous in terms of mechanism of disease, baseline prognostic risk factors, clinical severity and evolution.³ This heterogeneity generates complex challenges. New pharmacological approaches together with more basic and clinical research are needed for better targeting TBI therapy for individual patients.³ Monomodal drugs have substantial limitations in TBI treatment and have little efficacy. Multimodal drugs, however, have shown promising results. A key example is the neurotrophic agent Cerebrolysin®, which has shown efficacy for the treatment of TBI in various studies.¹¹¹¹ This article provides an overview of major research progress in the pathology and diagnosis of TBI and the prospects for new drug treatments that were presented and discussed at the 21st International Mondsee Medical Meeting, which was convened at Salzburg, Austria in June 2014.
Research and Therapies in Traumatic Brain Injury

The Changing Landscape of Traumatic Brain Injury Research

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A critical factor in the field of brain injuries is the development of effective therapies. In the light of the enormous impact of TBI on society and healthcare systems worldwide, the failure of randomised clinical trials (RCTs) has created an urgent need for re-evaluation of the methodology used for the development of effective therapies. Clinical trials are characterised by two major flaws: they single out a single factor for treatment and fail to recognise heterogeneity in pathology, treatment and outcomes. Accordingly, most RCTs in this field showed no major breakthrough. Most advances in TBI care have resulted from observational studies, meta-analyses of individual patient data and international collaboration. Guidelines have also been of use, however, they lack individual patient perspective and therefore are not sufficient to guide effective treatments.

There is a need for a broader approach encompassing the existing heterogeneity as well as for re-orientation of clinical in TBI towards a comparative effectiveness research (CER), concept that includes personalised treatment requiring better characterisation of TBI in individual patients, as well as broader approaches.

Death rates in TBI are up to sixfold higher in some hospitals compared with others, which indicates large differences in treatment quality.

The TRACK-TBI study revealed that only one-third of all mild TBI patients will achieve full recovery. These factors stimulated the establishment of the International initiative for TBI Research (InTBIR) project. InTBIR is an international project that combines the efforts of the European Commission with US institutions (National Institutes of Health [NIH]/National Institute of Neurological Disorders and Stroke [NINDS], Canadian Institutes of Health Research [CIHR]) in which CENTER-TBI is the European component. The latter is an international multidisciplinary collaboration with 38 scientific participants and six associated participants. The core study (n=5,400) includes patients from three strata (emergency room, admission and intensive care unit [ICU], n=1,800 for each) and is being conducted at over 80 treatment centres in 21 countries. Patients of all ages are eligible but must have suspected TBI, indicated for computed tomography and must present <24 hours after injury. The project also includes a registry of patients (n=15,000–20,000) who were seen for TBI in participating hospitals. The registry involves simple data collection; the variables are collected during routine clinical care and outcomes are determined on hospital discharge. The analysis of data focuses on improved disease characterisation for accurate diagnosis (Precision Medicine) and CER approaches for defining effective clinical care.

**Figure 1: The Rationale of the International Initiative for Traumatic Brain Injury Research as a Ground-breaking Concept in Patient Management**
Traumatic Brain Injury

The benefits of the InTBIR project on TBI management are expected to include: improved disease characterisation leading to accurate diagnosis, targeted treatment and improved health of a patient (see Figure 1). The project is open to all countries; it contributes to a new culture of data sharing and international collaboration and encourages the utilisation of knowledge resources for the benefit of TBI patients.

Neurogenesis and Beyond – Brain Rejuvenation in Chronic Neurodegenerative and Acute Central Nervous System Diseases

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Ageing populations are creating enormous challenges for healthcare providers worldwide, including large increases in age-associated diseases, such as dementias, neurodegenerative diseases and stroke. Moreover, elderly people can suffer traumatic central nervous system (CNS) injuries from simple falls. Endogenous repair mechanisms such as neurogenesis are currently the focus of intense research activities aiming to regenerate or to rejuvenate the aged and damaged brain. In treating TBI and other neurological diseases, understanding self-repair mechanisms such as neurogenesis allows attempts to rejuvenate the aged brain and to restore function after CNS injuries. An important aim of current research is increasing the levels of neurogenesis and to lowering the inflammatory load in the aged brain.

Initial work has shown that restoring function in the ageing brain is feasible. A proof of concept study demonstrated rejuvenation of the aged brain following exposure to blood from a younger individual. Current investigations aim to elucidate the role of transforming growth factor-β (TGF-β) on leukotriene signalling for use as a target for brain rejuvenation. In addition, Cerebrolysin, a neurotrophic peptide drug in development, has been shown to rejuvenate the aged and diseased brain, and thus offers considerable potential in the treatment of spinal cord injury. Other experimental models show that Cerebrolysin and leukotriene receptor antagonists (such as montelukast, an asthma treatment agent) reduce neuroinflammation, stimulate neurogenesis and improve functional outcomes in the aged brain as well as in models of spinal cord injury. Other experimental models show that Cerebrolysin induces structural plasticity in ageing brain and also restores synaptic density, neurogenesis, learning and memory in Alzheimer’s disease models in mice.

Clinical data available to date suggest that Cerebrolysin is effective in the treatment of acute and neurodegenerative disorders. The usual failure of clinical trials in neurology can be attributed at least in part to their being focused solely on neuroprotection. Neuroprotection, however, is only a part of the complex rejuvenation process of the brain post-injury. The recovery from damage is based on natural, spontaneous processes leading to repair, regeneration and restoration of neurological structures and functions. Lateral ventricle neurogenesis is one example of such a natural process that can be further stimulated by pharmacological intervention.

In the experimental models of brain and spinal cord injuries, the leukotriene receptor antagonists (such as montelukast, an asthma treatment agent) reduce neuroinflammation, stimulate neurogenesis and improve functional outcomes in the aged brain as well as in models of spinal cord injury. Further clinical investigations are warranted for Cerebrolysin in order to optimise already existing treatment protocols. The significance of treatment regimen optimisation is well illustrated by a granulocyte colony-stimulating factor trial, which failed to show efficacy due to the poor understanding of the biology of recovery processes with the resulting inadequate treatment protocol employed in the trial.

Neuroregeneration in Both Experimental Brain Injuries and Clinical Trials

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Clinical management of brain injuries has focused on the prevention of secondary insults and once disabling deficits are established, treatments have proved disappointing. Cell therapies have proved effective in animal models of brain injuries, both in molecular and behavioural terms. However, clinical trial data are needed to confirm these findings. In order to achieve meaningful clinical effects, improvements are needed in the quality of the cells and associated molecular factors.

TBI treatment developed by Dr Wai Poon’s team at the Prince of Wales Hospital in Hong Kong is based on mesenchymal stem cell (MSC) therapy at both preclinical and pilot clinical research stages. The assessment of therapy efficacy includes: behaviour (motor rod, water maze, gait analysis); pathological examination (haematoxylin and eosin stain, immunohistochemistry); physiological factors (spikes, electrocardiogram [ECG]) and biochemical factors (biomarkers, gene expression). Several biomarkers are currently in clinical development.

Experimental stem cell therapies currently use various cell types: embryonic, foetal, adult bone marrow, adipose tissue and induced pluripotent stem cells (iPS cells). Proposed mechanisms of action of adult stem cells in CNS injuries are: engraftment and cell differentiation...
or cell fusion, suppression of apoptosis, modulation of inflammation, paracrine/endocrine effects and enhancement of angiogenesis. Possible routes of administration include: systemic infusion, direct implantation and topical application. Stem cells therapies, however, are in early phase development and safety concerns must be addressed in clinical investigations.

An example of cell therapy for brain injury is the use of green fluorescent protein-mesenchymal cells (GFP-MSCs) in a rat model. The GFP-MSC cells migrate to the place of injury and impact on recovery at molecular and cellular level. Most importantly, this therapy achieved improvements in functional outcome assessed as performance in the Morris Water Maze experiment. MSC therefore holds considerable potential in the treatment of neurological disorders.

There is a place for MSC-based therapies in axonal regeneration. However, experimental advances and better understanding have not yet converted into clinical practice. There is a need to develop better stem cell technology and to use this approach in combination with other agents, such as small molecules, which can enhance viability of the transplants as well as work in synergy with MSC for stimulation of endogenous repair mechanisms.

Recent findings emphasise that patients with severe TBI require analogue sedation and intubation, need to be relaxed and must undergo controlled respiration. Hypotension with a systolic pressure <90 mmHg and hypoxia (paO$_2$ under 60 mmHg and saO$_2$ under 90 %) must be avoided or treated urgently. In addition, an adequate cerebral perfusion pressure (CPP) must be maintained. Refractory intracranial hypotension should be treated with forced hyperventilation with a paO$_2$ below 30 mmHg, high-dosage barbiturates and decompressive craniectomy (a life-saving emergency surgical intervention). The therapeutic effect, if any, of hypothermia is currently being investigated in the ongoing Edinburgh Eurotherm Study. More recently, prospective, RCTs have been initiated with the clear statement of exact target values for intracranial pressure. Therefore, continuous multimodal measurement of cerebral perfusion and oxygenation of the brain is of great importance in the monitoring of therapeutic procedures in patients with severe brain trauma.

A complete decompressive craniectomy and venous drainage is important when a haematoma expands. Recent findings indicate that as soon as oedema subsides following a craniectomy, there is a need for rapid cranioplasty. The beneficial effects of cranioplasty on brain metabolism are related to: regulation of postural blood flow, cerebrovascular reserve capacity (CVR), cerebral glucose metabolism and improvement in cognitive functions.

A compelling need to optimally use time in surgical patients exists. Without fast intervention a patient’s health can rapidly deteriorate and additionally the financial burden of the TBI management rises. ‘Save the brain – not the bone!’ therefore, is one of the main messages for TBI emergency surgery.

One of the most important challenges of using neurological assessments such as the Glasgow Coma Scale (GCS) is to reduce the inter-rater variability to an absolute minimum thus maximising the reliability of the measure. A review of the use of the GCS in an injury assessment clearly showed that this is a matter that can make results of any trial obsolete. However, reduction of inter-rater variability is possible through planned training of the raters. There is, however, a chronic lack of clear operational rules and GCS training in TBI studies. For these reasons, a GCS Training Tool has been developed to achieve this goal. The tool is now available as a standalone version but also via Internet in different languages.

Preliminary trends from the study show clear difference between groups with and without training, with a trend towards an increase in the accuracy of GCS assessment after standardised training. As expected, there are notable differences between the different disciplines (neurosurgeon, neurologist, intensivist, traumatologist), different hospitals and countries. Neurosurgeons tend to overestimate bad situations and underestimate good ones. Intensive care personnel seem to achieve the highest benefit. Overall, benefits manifest quickly and appear stable, reliable and, above all, effective.

Standards and Recent Developments for the Treatment of Brain Injury – A Neurosurgical Procedure

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The Glasgow Coma Scale Training Tool and Results of a Validation Study

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Among TBIs, approximately 80% are mild (MTBI), and up to 15% of these patients have persisting clinical symptoms (poor memory, poor attention, headache, dizziness).\textsuperscript{50,51} Evidence suggests that about 50% of young adults with MTBI experienced moderate to severe disability at 1-year post-injury.\textsuperscript{52} In adults, MTBI frequently results in impairments of cognitive functions, emotions and brain mechanisms of behavioural control. All these symptoms often lead to problems with learning, social adaptation and unfavourable social and psychological consequences.\textsuperscript{53}

MTBI is defined by: conscious alertness, GCS $\geq 13$, brain concussion or brain contusion. Patients with brain contusions have significantly poorer cognitive functions than patients with concussions. Consequently, the safety and efficacy of Cerebrolysin, a multimodal and neurotrophic agent with both neuroprotective and neuroregenerative properties, has been evaluated in patients with MTBI related to contusions.\textsuperscript{11} Cerebrolysin is effective in the treatment of cognitive complications after stroke and in neurodegenerative disorders, such as Alzheimer’s disease and vascular dementia.\textsuperscript{54}

The ‘Cognitive effects of Cerebrolysin on MTBI patients presented with brain contusion: A preliminary study’ is an investigator-driven, double-blind, RCT that enrolled 32 MTBI patients within 24 hours after the onset of TBI.\textsuperscript{14} The inclusion criteria were: adults between 18 and 70 years old, to be alert and conscious, a GCS of $\geq 13$ and having abnormal imaging results (brain contusion). Patients were randomised to Cerebrolysin (30 ml once daily [OD] intravenous [iv] infusion for 5 days) or placebo (normal saline iv infusion OD). Results showed a strong trend towards improvement of cognitive functions in the Cerebrolysin-treated group in comparison with the placebo group. This included a statistically significant clinical benefit at 12 weeks as measured with the Cognitive Abilities Screening Instrument (CASI) (see Figure 2). Cerebrolysin therapy, therefore, can improve CASI scores and enhance cognitive recovery. The most significant impact was observed on improvement of MTBI patients’ long-term memory and drawing functions, an encouraging finding since many TBI patients suffer from long-term cognitive problems.

Cerebrolysin Enhances Cognitive Recovery of Mild Traumatic Brain Injury Patients

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Long-term cognitive impairment after critical illness (CIACI) is an increasingly recognised problem that affects patients 1 year after ICU discharge and is probably lifelong. The largest CIACI study, to date, included 821 patients; 40% had global cognition scores that were 1.5 standard deviations below the population means (similar to scores for moderate TBI or mild cognitive impairment).\textsuperscript{26} A further 26% had scores 2 standard deviations below the population means (similar to scores mild Alzheimer’s disease [AD]) after 3 months. These scores persisted in 34% and 24%, respectively, after 1 year. Deficits occurred in both older and younger patients, and a longer duration of delirium was independently associated with worse global cognition at 3 and 12 months.

Dementia prevention in ICU patients has enormous scope.\textsuperscript{34-38} A recent literature search found that 67 papers were published between 1999 and 2013 mainly by Hopkins (17 publications), Ely (14 publications) and Herridge (12 publications), and concluded that ICU patients are at high risk of developing long-term cognitive impairment or dementia. Imaging data from ICU survivors\textsuperscript{39,40} indicated that a longer duration of delirium was significantly associated with greater brain atrophy at hospital discharge ($p=0.03$) and at 3-month follow-up ($p=0.05$). Longer duration of delirium was also associated with significantly smaller superior frontal lobe ($p=0.03$) and hippocampal volumes at discharge ($p=0.001$). Larger brain atrophy at 3 months was associated with worse cognitive performances at 12 months and delirium duration in the ICU was associated with white matter disruption at both discharge and 3 months. Delirium, therefore, appears to be a major clinical variable connected with CIACI.\textsuperscript{53,54}

Cerebrolysin is currently the only neurotrophic agent in clinical use and acts by mimicking neurotrophic factors (NTFs) and by stimulating the endogenous production of NTF in brain tissue. Experimental studies
revealed neuroprotection and neuroregeneration properties. Results of clinical trials in stroke, TBI and dementia suggest the clinical efficacy of Cerebrolysin in these indications. The treatment of Cerebrolysin data associated with Alzheimer’s disease is of major clinical interest. The efficacy of Cerebrolysin persists for up to several months after treatment, suggesting not only symptomatic benefits, but also a disease-delaying potential. In TBI, acute Cerebrolysin treatment of mild TBI patients prevents development of cognitive decline 3 months post-injury. Clinical trials in stroke show a strong implication for CIACI prevention as a result of Cerebrolysin treatment. Cerebrolysin also induces early and accelerated recovery in motor, activities of daily living and cognitive functions. These data suggest that Cerebrolysin can support early mobilisation of patients, an important outcome for the majority of injured patients.

Combined data from clinical and preclinical studies, suggest that Cerebrolysin is a good candidate for the preventive treatment of CIACI and have provided the rationale for a clinical investigation entitled: ‘Changes in brain haemodynamics after neurotrophic factors compound Cerebrolysin treatment in severe traumatic brain injury survivors’. Initial unpublished results show that compared with untreated TBI patients, Cerebrolysin significantly improved hemodynamic parameters at 3 months and 1 year following treatment and showed a favourable safety profile in this group of patients.

Treating patients in the ICU with a Cerebrolysin regimen appears to be justified based on the experience of the author and on published clinical data (see Figure 3). The findings need verification in appropriately designed RCTs but, if positive, will support a major therapeutic breakthrough in the management of ICU patients.

The interplay between mechanisms of damage/cellular death and natural processes of neurorepair was hardly considered when designing single-target chemical treatments in neurology, resulting in the failure of clinical development programmes in recent years. Endogenous neuromodulation is a better therapeutic target since it more accurately reflects biological reality of neurological disorders. Pathophysiological mechanisms represent imbalances in normal neurobiological processes, and endogenous molecules (e.g. NTFs) are vital components of brain protection and recovery that alter DNA expression, generate post-lesional patterns of molecular synergism and rebalance major neurobiological processes. The concept of endogenous neuromodulation is essential to understanding the mechanisms of brain protection and recovery and in developing treatments. This concept can be illustrated by the example of nerve growth factor as potential natural enhancer or potential natural inhibitor of cellular death (see Figure 4). Cerebrolysin has similar actions to NTFs and therefore can stimulate natural defence activities within the injured nervous tissue.
Traumatic Brain Injury

The 'Early Cerebrolysin Treatment in TBI – a Multicenter, Cohort Trial’ included 7,769 adult patients with TBI (TBI), who were admitted at 10 departments of neurosurgery in Romania.\(^\text{44}\) Cerebrolysin-treated patients were assigned to two different drug regimens (20 ml or 30 ml/day), or to control treatment. In mild TBI, treatment with both Cerebrolysin regimens significantly improved Glasgow Outcome Scores (GOS) and respiratory distress (RDS) scores at 10 days compared with controls. However, no difference was seen in GOS and RDS scores at 30 days between Cerebrolysin and control patients, probably due to the generally good progress of mild TBI patients (so-called ‘ceiling effect’). In moderate and severe TBI, treatment with Cerebrolysin, both 20 ml and 30 ml/day regimens, significantly improved GOS and RDS scores at both 10 and 30 days compared with controls. Moreover, a significant dose-dependent effect was seen for Cerebrolysin on GOS score at 10 and 30 days. The results of this large retrospective study show significant beneficial effects of early Cerebrolysin treatment in TBI patients and justify a large prospective study to further support the use of Cerebrolysin in this indication.

Figure 4: Neurotrophic Factors in Brain Protection and Recovery

Behavioural and Psychiatric Aspects of Traumatic Brain Injury

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The most frequent TBI-related conditions with psychiatric relevance are affective alterations (e.g. depression, mania) and changes of personality.\(^\text{73}\) In addition, psychotic symptoms are reported relatively frequently.\(^\text{72}\) TBI patients are also often diagnosed with post-traumatic stress disorder (PTSD) and have an increased risk of substance-use disorders, such as alcoholism.\(^\text{71}\) This patient group greatly benefits from multi-professional support that is not only restricted to addressing physical but also mental health problems. The exact nature of the behavioural alterations and psychiatric symptoms is largely dependent on the type and localisation of the injury and also on premorbid patient characteristics (e.g. vulnerability, resilience). Thus, the inter-individual variability as well as the prognosis of each patient varies widely, so an individualised treatment approach is mandatory.

In recent years, diagnostic and therapeutic options for TBI have considerably improved and understanding of the pathophysiological mechanisms leading to the psychiatric symptoms is increasing.\(^\text{73}\) As improvements over time due to neuroplastic processes are often observed in this patient group, treatment options supporting such neuroregeneration and neuroplasticity are of considerable interest and are urgently needed. Nevertheless, psychiatric symptoms in TBI are often chronic;\(^\text{74}\) patients and their families require long-term support by an expert team.

Possible psychiatric consequences of TBI can be diverse, including combinations of: post-traumatic personality change, mood changes, anxiety, attentional deficits, thought and executive function disturbances, behavioural changes (e.g. impulsivity) and alteration of language. These changes have been further characterised in terms of gender, age and the milieu in which the recovery from trauma takes place. The variability of symptoms is related to many factors among which the site and the extent of injury as well as personal characteristics of each patient are probably the most prominent variables.

The development of pharmacological therapies that could aid recovery from the psychiatric consequences of TBI necessitates studying animal models that reflect as closely as possible the complex reality of challenges faced by TBI survivors. Imaging modalities such as diffusion tensor imaging (DTI) are increasingly employed in animal models\(^\text{25}\) and as surrogate analysis tools in clinical trials. Notable recent studies in this field include neuro-immune modulation experiments (with Ibudilast – inhibitor of glial cell activation); and modulation of neural plasticity (with Cerebrolysin).\(^\text{24,75}\)

Discussion and Conclusions

Approaches to TBI are advancing on several different levels. Improved techniques are becoming available for ensuring consistent patient assessment and managing behavioural problems; more successful treatments are in development and better clinical trial methodologies are becoming established. TBI is a heterogeneous condition that requires improved characterisation in order to aid understanding of the condition. The pathology of TBI is complex and much further studies are needed to adequately map the processes involved and develop means of manipulating them. In patients, improved use of assessment scales and multimodal monitoring is necessary to ensure more reliable and complete documentation in trials and in clinical practice.

Many experimental treatments for TBI arising from a reductionist approach have failed to rectify damage to brain tissue and address the long-term consequences of injury. More recent developments, however, using cell-based therapies or NTFs have produced more promising results. It is clear that to achieve successful restoration of nerve tissue and function requires a multimodal approach in which many genetic and biochemical pathways are activated to promote recovery. However, experimental cell-based neurotherapies have enabled structural recovery of the spinal cord but have not yet shown the same level of functional restoration. Further work using these cells in combination with pharmacological agents is needed.
The large multicentre cohort trial conducted in Romania showed that Cerebrolysin is effective in the treatment of mild to severe TBI and provided significant improvements in GOS and RDS scores after 10 and 30 days compared with controls. This result is encouraging and justifies further development of Cerebrolysin in this indication. In addition, other studies show that Cerebrolysin can be successfully used to treat CIACHI, which is often an additional long-term problem following neurological injury.

The design of clinical trials to investigate this and other therapies should closely reflect the reality of biological processes underlying natural recovery from brain injury. In addition, investigators must ensure that all medical personnel assessing patients in trials is well trained to provide correct and consistent results when using instruments such as the GCS to avoid higher inter-rater variability. Clinical trials should also address cognitive decline and the behavioural effects of TBI, which can severely affect the social and professional lives of patients for many years after the injury or permanently disable them.

Effective treatment of TBI is likely to remain a serious medical challenge and its incidence is likely to remain high, especially among military personnel and the older population. An enhanced understanding of the underlying process of brain tissue repair, better short- and long-term management of patients and the development of effective multimodal therapies are likely to reduce the effects of this often devastating condition.


